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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

Hindered Rotation of the Methyl Groups in Propane. The Heat Capacity, Vapor Pressure, Heats of Fusion and Vaporization of Propane. Entropy and Density of the Gas

BY J. D. KEMP* AND CLARK J. EGAN

Evidence proving the existence of a high potential barrier which hinders the rotation of the methyl groups about the single carbon–carbon bond in ethane[1–3] has made apparent the need for more experimental data on the hindering potentials in similar molecules. Accordingly, the entropy of propane gas has been obtained experimentally from calorimetric data with the aid of the third law of thermodynamics, and has also been calculated as a function of the height of the potential barrier by means of spectroscopic and molecular structure data. The contributions of a hindered rotator to the entropy, energy, and heat capacity have been given by Pitzer.[4] The height of the potential barrier was determined as that necessary to bring the spectroscopic entropy value into agreement with the experimental entropy value.

Purification of Propane.—C. P. propane, of 99.9% purity, from the Ohio Chemical Company, was bubbled through 12 *N* sodium hydroxide and 36 *N* sulfuric acid. It was then passed through a tube containing phosphorus pentoxide and condensed in a previously evacuated bulb. The liquid was subjected to two successive fractionations in a vacuum-jacketed fractionating column, the middle 30% being retained each time. From the course of the heat capacity curve just below the melting point, the amount of liquid-soluble solid-insoluble impurity was estimated to be less than 0.001 mole per cent. The method of making this calculation has been described previously.[5] A less accurate value of 0.002 mole per cent. impurity was calculated from the change of the melting point in heating from 5 to 20% melted.

Apparatus and Measurement of Amount. The Density of Propane at 1 Atmosphere and 298.10°K.—The calorimetric apparatus and procedure have been described previously.[6,7] Gold Calorimeter IV was used for the investigation. The volume of the propane was determined by means of the 5-liter measuring bulb described by Giauque and Johnston.[8]

A gas density determination was made after each of the three heats of vaporization. The volumetrically measured propane was condensed and weighed in a glass bulb containing pentane, which reduced the vapor pressure of the propane. The molal volume of propane, V, at T near 298°K. and P near 1 atm. was found to be

$$V = \frac{82.06T}{P} - 401 \pm 7 \text{ cc.} \qquad (1)$$

This gives 1.8325 ± 0.0007 g./liter for the density of propane gas at 298.10°K. and 1 atm.

(*) Present address: Standard Oil Co., Richmond, Calif.

(1) Kemp and Pitzer, *J. Chem. Phys.*, **4**, 749 (1936); THIS JOURNAL, **59**, 276 (1937).

(2) Howard, *Phys. Rev.*, **51**, 53 (1937).

(3) Kistiakowsky and Nazmi, *J. Chem. Phys.*, **6**, 18 (1938).

(4) Pitzer, *ibid.*, **5**, 469 (1937).

(5) Johnston and Giauque, THIS JOURNAL, **51**, 3194 (1929).

(6) Kemp and Giauque, *ibid.*, **59**, 79 (1937).

(7) Giauque and Egan, *J. Chem. Phys.*, **5**, 45 (1937).

(8) Giauque and Johnston, THIS JOURNAL, **51**, 2300 (1929).

Vapor Pressure.—The procedure used in the measurements of vapor pressure has been described previously.[6] The observations have been represented by the equation

liquid propane, 166 to 231°K., (0°C. = 273.10°K.)

$$\log_{10}P_{(\text{Int. cm. Hg})} = -(1325.358/T) + 9.64920 - 0.0118950T + 0.000013420T^2 \qquad (2)$$

A summary of the measurements is presented in Table I. The calculated and observed values are compared in columns 3 and 4. Temperatures have been given to 0.001° because of the high relative accuracy. The absolute temperatures may be in error by several hundredths of a degree. Column 5 contains values of the rate of change of pressure with temperature calculated from equation (2).

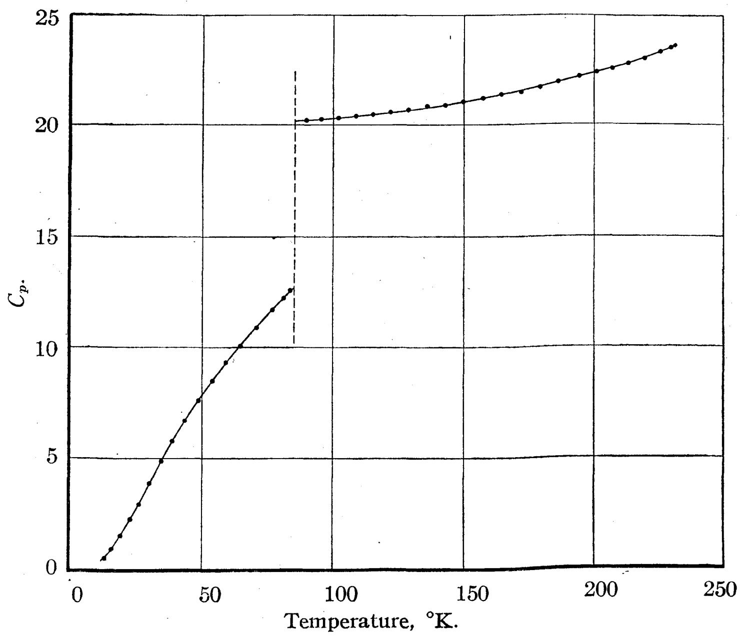

Fig. 1.—Heat capacity of propane in cal./deg. per mole.

Table I

Vapor Pressure of Liquid Propane

(0°C. = 273.10°K.)

T, °K.	$P_{\text{int. cm.}}$ obsd.	$P_{\text{obsd.}} - P_{\text{calcd.}}$	$T_{\text{obsd.}} - T_{\text{calcd.}}$	$\frac{dP}{dT}\ \frac{\text{cm.}}{\text{deg.}}$
166.140	1.161	−0.003	+0.028	0.108
173.270	2.200	+ .002	− .011	.187
179.792	3.739	.000	.000	.292
187.297	6.544	.000	.000	.466
195.081	11.103	− .002	+ .003	.720
202.860	17.992	.000	.000	1.067
209.876	26.833	− .013	+ .009	1.472
214.932	35.166	.000	.000	1.827
220.209	45.913	+ .001	− .000	2.257
225.048	57.889	− .015	+ .006	2.708
228.756	68.619	− .032	+ .010	3.092
231.412	77.271	+ .014	− .004	3.392

Table II

Melting Point of Propane

(0°C. = 273.10°K.)

Time	% melted	T, °K., resistance thermometer	T, °K. thermocouple
0:00		Stopped supply of heat	
0:55	5	85.428	85.43
1:27	5	85.424	85.43
2:00	5	85.426	85.43
2:15		Stopped supply of heat	
3:40	20	85.434	85.43
4:15	20	85.430	85.45
5:15	20	85.430	85.44
5:30		Stopped supply of heat	
7:00	40	85.436	85.45
7:30		Stopped supply of heat	
9:00	65	85.439	85.46
Accepted value		85.45 ± 0.05°K.	

The boiling point calculated from equation (2) is 231.04 ± 0.05°K. (0°C. = 273.10°K.).

Melting Point.—The melting point was observed with various percentages of the propane melted. The results are summarized in Table II. Table III contains a summary of the melting and boiling point temperatures observed by other experimenters.

Heat Capacity of Propane.—No measured values of the heat capacity of condensed propane below the boiling point could be found in the literature.

The heat capacity measurements are given in Table IV. 1.0004 absolute joules was taken equal to 1 International joule and 4.185 absolute joules equal to 1 calorie. A graphical

Table III

Melting and Boiling Point Temperatures of Propane

M. p., T, °K.	B. p., T, °K.	Observer
	228.1	Olszewski[9] (1894)
	229.0	Burrell and Robertson[10] (1915)
83.2	228.6	Maass and Wright[11] (1921)
	230.98	Dana, Jenkins, Burdick and Timm[12] (1926)
	230.8	Francis and Robbins[13] (1933)
86.0	230.93	Hicks-Bruun and Bruun[14] (1936)
85.45	231.04	This research

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[9] Olszewski, *Ber.*, **27**, 3305 (1894).

[10] Burrell and Robertson, This Journal, **37**, 2188 (1915).

[11] Maass and Wright, *ibid.*, **43**, 1098 (1921).

[12] Dana, Jenkins, Burdick and Timm, *Refrig. Eng.*, **12**, 387 (1926).

[13] Francis and Robbins, This Journal, **55**, 4339 (1933).

[14] Hicks-Bruun and Bruun, *ibid.*, **58**, 810 (1936).

representation is shown in Fig. 1. Table V contains values of the heat capacity taken from a smooth curve through the data.

TABLE IV

HEAT CAPACITY OF PROPANE

Molecular weight, 44.092;[15] 1.6779 moles in calorimeter.

T, °K.	C_p cal./deg. per mole	ΔT	Series
13.29	0.514	3.375	II
16.36	.865	2.795	II
19.60	1.504	3.705	II
23.11	2.257	3.315	II
26.57	2.970	3.609	II
30.51	3.864	4.221	II
34.58	4.870	3.915	II
38.85	5.785	4.590	II
43.68	6.682	5.132	II
48.91	7.593	5.219	II
54.48	8.471	4.899	II
59.16	9.328	5.447	II
64.87	10.08	5.947	II
70.96	10.87	6.373	II
77.05	11.69	5.733	II
81.32	12.21	2.673	II
83.60	12.42	1.851	III
83.84	12.60	2.551	II
84.75	12.70	0.438	III
85.14	13.14	.343	III
85.45	Melting point		
89.67	20.20	5.339	I
95.48	20.25	6.134	I
101.91	20.33	6.642	I
108.45	20.41	6.326	I
115.11	20.50	6.879	I
121.92	20.59	6.600	I
128.85	20.68	7.119	I
135.90	20.84	6.827	I
142.74	20.89	6.578	I
149.69	21.06	7.089	I
156.80	21.19	6.840	I
164.34	21.35	7.910	I
171.97	21.47	7.031	I
179.04	21.68	6.769	I
185.85	21.90	6.547	I
194.23	22.17	6.243	I
200.89	22.42	6.041	I
207.04	22.52	5.885	I
213.05	22.80	5.707	I
219.20	23.00	5.539	I
224.91	23.29	5.401	I
229.76	23.48	3.941	I
231.04	Boiling point		

Heat of Fusion.—No measured values of the heat of fusion were found in the literature. The present measurements of the heat of fusion of propane are summarized in Table VI.

TABLE V

HEAT CAPACITY OF PROPANE

Molecular weight, 44,092. Values taken from smooth curve through observations.

T, °K.	C_p cal./deg. per mole	T, °K.	C_p cal./deg. per mole
15	0.662	90	20.20
20	1.592	100	20.31
25	2.635	110	20.42
30	3.765	120	20.55
35	4.960	130	20.71
40	5.995	140	20.87
45	6.923	150	21.05
50	7.765	160	21.25
55	8.570	170	21.47
60	9.342	180	21.73
65	10.08	190	22.03
70	10.77	200	22.35
75	11.42	210	22.70
80	12.04	220	23.07
85	12.64	230	23.49
85.45	Melting point	231.04	Boiling point

TABLE VI

HEAT OF FUSION OF PROPANE

Molecular weight, 44.092

Temp. interval, °K.	Corr. heat input per mole	$\int C_p dT$	ΔH cal./mole
81.974–87.775	972.5	130.4	842.1
82.208–87.423	958.3	116.3	842.0
85.082–87.952	917.7	75.1	842.6

Average value = 842.2 ± 0.8 cal./mole

Heat of Vaporization.—The propane was vaporized from the calorimeter into the 5-liter measuring bulb mentioned previously. A constant pressure regulating device described by Giauque and Johnston[8] was used. The individual measurements are summarized in Table VII, and are compared with the value calculated from equation (2) and Berthelot's equation.[7] The value measured by Dana and co-workers[12] is also included.

TABLE VII

HEAT OF VAPORIZATION OF PROPANE

Boiling point, 231.04°K.; molecular weight, 44.092.

No. moles vaporized	Time of energy input, min.	ΔH at 760 mm. cal./mole
0.21634	38	4488
.21871	39	4487
.21865	39	4485

Average value = 4487 ± 4

From vapor pressure equation 2.
This includes a Berthelot correction of −180 cal./mole 4475
Value of Dana, Jenkins, Burdick and Timm 4475 ± 45

Entropy from Calorimetric Data.—The calculation of the entropy of propane at the boiling point, 231.04°K., from the calorimetric data is summarized in Table VIII.

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(15) Int. At. Wt. Committee, THIS JOURNAL, **59**, 219 (1937).

TABLE VIII

ENTROPY OF PROPANE FROM CALORIMETRIC DATA

0–15 °K., Debye extrapolation, ($h c \nu / k$ = 128)	0.25
Solid, 15–85.45 °K., graphical	9.702
Fusion, 842.2/85.45	9.856
Liquid, 85.45–231.04 °K., graphical	21.063
Vaporization, 4487/231.04	19.421
Entropy of actual gas at boiling point	60.29 ± 0.1
Correction for gas imperfection	0.16
Entropy of ideal gas at 1 atm. and 231.04 °K.	60.45 cal./deg. per mole

The correction for gas imperfection was obtained from the expression[7]

$$S_{\text{ideal}} - S_{\text{actual}} = (27RT_c^3P)/32T^3P_c$$

The values of the critical pressure and temperature were taken as T_c = 369.9°K. P_c = 42.01 atm.[16]

Magnitude of the Potential Barrier.—Although it would be more logical to evaluate the entropy due to the two degrees of freedom concerned with the internal rotation of the methyl groups and thereby estimate the magnitude of the potential barrier, it is more convenient to calculate an entropy value with the assumption of free internal rotation and evaluate $S_{\text{free}} - S_{\text{experimental}}$. With this quantity and a table of $S_{\text{free}} - S_{\text{hindered}}$ as a function of the potential barrier, the magnitude of the barrier may be obtained.

The values of the natural constants used were those given in the "International Critical Tables." The following data from the electron diffraction measurements of Bauer[17] were used to calculate the rotational contribution to the entropy.

$$\text{C–C} = 1.50_3 \pm 0.02\ \text{Å}.$$
$$\text{C–H} = 1.08_1 \pm 0.02\ \text{Å}.$$
$$\text{C–C–C} = 114^\circ 12'$$

The remaining H–C–H angles were assumed to be tetrahedral, namely, 109°28′. Kassel[18] has derived the partition function for freely rotating propane. The expression for the rotational entropy

$$S_{\text{free rotation}} = R/2 \ln (I_x - 2K \sin^2\alpha)(I_y - 2K \cos^2\alpha)(I_z)(K)^2 + 5/2\, R \ln T - R \ln \sigma + 447.599$$

may be separated into the usual expression

$$S_{\text{external rotation}} = R/2 \ln I_xI_yI_z + 3/2\, R \ln T - R \ln 2 + 267.649$$

plus

$$S_{\text{free internal rotation}} = R/2 \ln(I_r)^2 + R \ln T - R \ln 9 + 179.950$$

where the reduced moment

$$(I_r)^2 = (K)^2 \left(1 - \frac{2K \sin^2\alpha}{I_x}\right)\left(1 - \frac{2K \cos^2\alpha}{I_y}\right)$$

K = moment of inertia of a methyl group. α = one-half of the C–C–C angle. I_z = moment of inertia about the axis through the center of gravity and perpendicular to the carbon plane. I_y = moment of inertia about the axis which bisects the C–C–C angle in the carbon plane. I_x = moment of inertia about the axis through the center of gravity and perpendicular to both y and z axes.

From the above data the moments of inertia times 10^{40} g. cm.^{2} were found to be I_x = 26.9; I_y = 96.8; I_z = 108.2; K = 5.18; I_r^2 = 18.93. The symmetry number σ was taken equal to 18.

Kohlrausch and Köppl[19] have summarized the Raman data on propane. They have also included the results of Bartholomé[20] on the infrared spectrum of propane. The three vibrations of the carbon skeleton have been identified at 373, 867 and 1053 cm.$^{-1}$. For the calculation of the vibrational contribution to the entropy, the remaining frequencies were estimated as follows: seven at 950 cm.$^{-1}$, seven at 1440 cm.$^{-1}$ and eight at 3000 cm.$^{-1}$.[21]

The sum of the translational, rotational and vibrational entropies of freely rotating propane was calculated to be 63.85 ± 0.25 cal./deg. per mole at one atmosphere at the boiling point, 231.04°K. The disagreement of this value with the experimental value, 60.45 ± 0.10 cal./deg. per mole, indicates that the rotation of the methyl groups in propane is hindered rather than free. Although lack of equilibrium in the crystal at low temperatures has caused discrepancies in the experimental and spectroscopic entropy values of several molecules, the reasons for this lack of equilibrium are known and such an explanation for the disagreement in the case of propane as in the cases of ethane,[1] tetramethylmethane[22] and methylamine[23] seems very improbable. Pitzer,[21] by interpolating the values of the barriers present in similar molecules, has predicted a hindering potential of 3400 cal./mole for propane.

The difference, $S_{\text{free}} - S_{\text{experimental}}$, was found to be 3.40 ± 0.3 cal./deg. per mole at the boiling point. This amount of entropy corresponds to a

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(16) Beattie, Poffenberger and Hadlock, *J. Chem. Phys.*, **3**, 96 (1935).

(17) Bauer, *ibid.*, **4**, 406 (1936).

(18) Kassel, *ibid.*, **4**, 276 (1936).

(19) Kohlrausch and Köppl, *Z. physik. Chem.*, **B26**, 209 (1934).

(20) Bartholomé, *ibid.*, **B23**, 152 (1933).

(21) Pitzer, *J. Chem. Phys.*, **5**, 473 (1937).

(22) Aston and Messerly, THIS JOURNAL, **58**, 2354 (1936).

(23) Aston, Siller and Messerly, *ibid.*, **59**, 1743 (1937).

barrier of 3300 ± 400 cal./mole,[24] which is in excellent agreement with the predicted value mentioned above. The entropy at 298.10°K. has been calculated to be 64.7 ± 0.3 cal./deg. per mole from molecular and spectroscopic data, the experimental value of the potential barrier and the experimental value of the entropy at the boiling point. This value at 298.10°K. is the entropy to be used in thermodynamic calculations.

In these calculations the nuclear spin entropy, $8 R \ln 2 = 11.015$ cal./deg. per mole, has been neglected. Table IX contains a summary of the calculations.

TABLE IX

CALCULATION OF THE MAGNITUDE OF THE POTENTIAL BARRIER IN PROPANE

	$T = 231.04°$K. $P = 1$ atm.	$T = 298.10°$K. $P = 1$ atm.
	cal./deg. per mole	
$S_{\text{trans.}} = 3/2\, R \ln M + 5/2\, R \ln T - R \ln P - 2.300$	36.02	37.28
$S_{\text{external rotation}} = R/2 \ln I_x I_y I_z \times 10^{120} + 3/2\, R \ln T - R \ln 2 - 6.851$	20.46	21.22
$S_{\text{free internal rotation}} = R/2 \ln I_r^2 \times 10^{80} + R \ln T - R \ln 9 - 3.050$	6.32	6.83
$S_{\text{vibrat.}} = \Sigma_{\nu_1 \text{ to } \nu_{25}} S_{\text{Einstein}}$	1.05	2.22
	63.85 ± 0.25	67.55
Calorimetric entropy	60.45 ± 0.10	
$S_{\text{free}} - S_{\text{hindered}}$	3.40 ± 0.3	2.86
Entropy of propane with a potential barrier of 3300 cal./mole (nuclear spin entropy not included)		64.7 ± 0.3

Summary

The heat capacity of condensed propane has been measured from 15°K. to the boiling point. The melting point was found to be 85.45 ± 0.05°K., the boiling point 231.04 ± 0.05°K., the heat of fusion 842.2 ± 0.8 cal./mole and the heat of vaporization 4487 ± 4 cal./mole.

Vapor pressure measurements have been made on liquid propane and the results have been represented by the equation (liquid propane, 166 to 231°K. (0°C. = 273.10°K.))

$$\log_{10} P_{(\text{Int. cm. Hg})} = -(1325.358/T) + 9.64920 - 0.0118950T + 0.000013420T^2$$

The density of propane gas at 298.10°K. and one atmosphere was found to be 1.8325 ± 0.0007 g./liter.

At one atmosphere at the boiling point the experimental entropy of propane (ideal gas) was evaluated as 60.45 ± 0.10 cal./deg. per mole.

The entropy of propane calculated with the assumption of free internal rotation minus the experimental entropy, $S_{\text{free}} - S_{\text{experimental}}$ (at the boiling point), was found to be 3.40 ± 0.3 cal./deg. per mole, which corresponds to a potential barrier of 3300 ± 400 cal./mole hindering the internal rotation of the methyl groups.

The entropy of propane (ideal gas, with a 3300 cal./mole barrier) at one atmosphere and 298.10°K. was found to be 64.7 ± 0.3 cal./deg. per mole (nuclear spin entropy not included). This is the entropy value to be used in thermodynamic calculations.

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[24] Refer to Table I of ref. 4.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Vapor Pressure Studies. I. Evidence for the Validity of Raoult's Law. The Systems Benzene–Diphenyl, Benzene–Benzyl Benzoate, Ethyl Acetate–Benzyl Benzoate

BY H. H. GILMANN[1] AND PAUL GROSS

Attention recently has been drawn[2] to the paucity of direct experimental evidence which is available in support of Raoult's law. In view of its importance for modern solution theory and because of the difficulty of giving a general theoretical foundation to the law, the desirability[3] of adding to this evidence has been emphasized.

In connection with a study of the stability of addition compounds in non-aqueous systems as indicated by partial pressure determinations, partial pressure data were also obtained for certain binary systems consisting of a volatile and a non-volatile component. Some of these cases furnish evidence bearing on the validity of Raoult's law.

The systems in question are benzene–diphenyl, benzene–benzyl benzoate and ethyl acetate–benzyl benzoate. Benzyl benzoate boils at 324°

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[1] Part of a thesis of H. H. Gilmann submitted in partial fulfilment of the requirements for the Ph.D. in Chemistry.

[2] Guggenheim, *Trans. Faraday Soc.*, **33**, 161 (1937).

[3] Hildebrand, THIS JOURNAL, **59**, 794 (1937).

According to Rechenberg[4] it has a vapor pressure of 4.5 mm. at 156°. By means of a log p *vs.* $1/T$ plot the data given by Rechenberg above 156° were extrapolated to 95°, the highest temperature investigated here. The vapor pressure found thus was 0.3 mm. Since the partial pressure of the benzyl benzoate from the solutions could be no greater than this, its contribution to the total vapor pressure would be negligibly small. The measurement of the total vapor pressure of the systems containing benzyl benzoate would therefore be a direct determination of the partial pressure of the volatile component, benzene or ethyl acetate. A test of Raoult's law with systems of this type has the definite advantage that it involves fewer assumptions than earlier tests such as that of Zawidski with systems involving two volatile components. These necessitated the assumption of the validity of the gas laws and of Dalton's law of partial pressures in order to calculate the partial vapor pressures from the composition of the liquid condensate of the vapor phase which had been determined analytically.

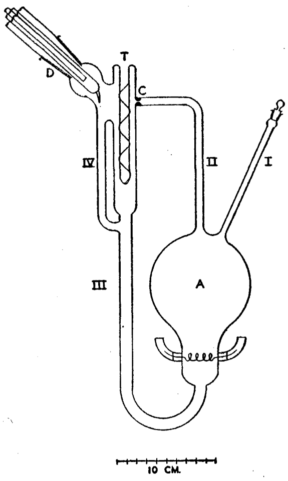

Fig. 1.

The same considerations apply to the system benzene–diphenyl in the range of temperatures between 50 and 80°. Here the partial pressure of the benzene can be placed equal to the total pressure of the solution with but negligible error. At the highest temperatures measured, 90–95°, the vapor pressure of the diphenyl is no longer negligible. However, even in these cases an estimate of the contribution that the partial pressure of its vapor makes to the total indicates that it is of the same magnitude as the experimental error. These cases will be considered in detail later.

Apparatus and Method

The total vapor pressures were determined by an ebulliometric method using a modification of the apparatus of Swietoslawski.[5] The principle of this is based on the earlier apparatus of Cottrell and need not be reviewed here. The precise boiling point elevation measurements of Washburn and Reade[6] and the extensive tests of his own apparatus by Swietoslawski[7] show that this method gives true values for the vapor–solution equilibrium and that it is capable of great precision. Our experience confirms this. The apparatus is shown in Fig. 1. The large bulb A (600 cc.) is filled through the stoppered side-tube I with a solution of known composition to a point just below the end of tube II. The solution is boiled by the platinum heating coil and also, if necessary, by external heating by means of gas micro burners heating the lower portion of A. A stream of mixed vapor and bubbles rises in II and is ejected through the constriction C onto the thermocouple well T. The volatile component is condensed in an efficient inner jacket condenser attached to D so designed as to have a minimum hold-up of returning condensate. The latter is by-passed through tube IV to prevent cooling of the vapor equilibrium chamber surrounding T. The return tube III is brought into the bottom to promote mixing and circulation. This and the heating coil which prevents bumping at low pressures are modifications in Swietoslawski's original design.

A pressure control system, containing a large thermally insulated reservoir of 30-liter capacity to minimize pressure variations, was attached to the upper end of the condenser. Pressures were read with a baromanometer similar in design to that of Germann[8] employing tubes of 13-mm. i. d. and with an electric device for setting the zero position in the arm connected to the pressure system. The scale was ruled on a strip of plate glass on a Geneva Society dividing engine and checked with a cathetometer. Pressures could be read to 0.2–0.3 mm. Atmospheric pressure readings taken at intervals with the baromanometer were compared with those of a "Greene Precision Barometer" which had a 0.75-inch (1.9-cm.) diameter mercury column and were found to be in agreement within the precision of the readings on the baromanometer. All pressures are corrected to sea level at 34° latitude and 0°.

Temperatures were determined by means of a 24-junction copper–constantan thermocouple designed according to the recommendations of White.[9] This was calibrated by the Bureau of Standards at six temperatures, the cold junctions being at zero. The Bureau's certificate furnished a four constant equation to represent the dependence of e. m. f. on temperature. A three constant equation of the type recommended by Adams[10] was found to fit their calibration data somewhat better and was therefore used. The hot junctions of the thermocouple were placed in the glass well T and covered with "Nujol" to about 1 cm. depth to ensure good thermal transfer from the walls of the well. E. m. f.'s were read with a Leeds and Northrup calibrated Type K potentiometer.

As an over-all check on the pressure and temperature readings the boiling temperatures of redistilled water under five different pressures from 352.6 to 751.8 mm. were determined and found to agree within 0.01° with those given in "International Critical Tables" in all but one case which differed by 0.02°. The vapor pressures of benzene from 40 to 80° and those of ethyl acetate from 40

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[4] Rechenberg, "Einfache und fraktionierte Destillation," 2 Aufl., Schimmel & Co., Miltitz, 1923, p. 305.

[5] Swietoslawski, *Bull. soc. chim.*, [4] **71**, 717 (1927).

[6] Washburn and Reade, This Journal, **41**, 729 (1919).

[7] Swietoslawski, *J. Chem. Ed.*, **51**, 469 (1928).

[8] Germann, This Journal, **36**, 3456 (1914).

[9] White, *ibid.*, **36**, 2292 (1914).

[10] Adams, *J. Wash. Acad. Sci.*, **3**, 469 (1913).

to 90° were determined. Since these compounds were carefully purified and the data in the literature, especially for ethyl acetate, show some disagreement it seems worth while to record our observed values here. Table I gives the values for benzene and Table II those for ethyl acetate.

TABLE I

t	p, mm.
36.73	157.8
40.90	188.5
45.13	223.9
50.19	272.1
55.09	326.7
60.63	389.9
64.89	461.2
69.67	544.7
74.98	646.0
79.78	753.0

TABLE II

t	p, mm.
39.46	183.7
53.35	324.1
67.96	557.1
77.04	758.6
83.01	919.8
87.58	1061.4

Large scale smoothed curves of the values in Tables I and II were drawn and the values for each even ten-degree interval found. These values are listed in the columns headed 100% in Tables V and VI. These were compared with the best values in the literature listed in "International Critical Tables." The benzene values agreed within 1 mm. with those of Young at 40, 50 and 60° and with those of Smith and Menzies at 65, 70 and 80°. The ethyl acetate values agreed within 1 mm. with those of Rechenberg[11] at 40, 60, 70, 80 and 90° but differed by 2.2 mm. at 50°, 3.4 mm. at 60°, and 2.0 mm. at 80° from those in "International Critical Tables." At 60 and 90° the difference from the latter values was less than 1 mm.

TABLE III

Mole % Benzene 69.93, Diphenyl 30.07

t	48.50	58.65	58.76	68.33	68.49	77.98	78.09	86.51	92.66
p, mm.	179.3	261.6	264.3	364.6	367.0	497.3	499.0	641.3	762.6
t	50	55	60	65	70	75	80	85	90
p, mm.	192	232	275	327	386	453	530	614	709

TABLE IV

Mole % Benzene 69.93, Diphenyl 30.07

t	55.26	59.63	69.55	79.88	90.26	95.65
p, mm.	232.2	271.8	381.8	530.6	722.7	841.1

t	55	60	65	70	75	80	85	90	95
p, mm.	233	274	327	386	453	532	615	712	826

In view of the purity of our substances and the comparisons cited for water, benzene and ethyl acetate we estimate that in the determination of the vapor pressures of pure substances the method will probably not result in errors greater than 0.03° in temperature, and 1.5 mm. in the pressure values. The errors in the case of the solutions will be discussed later.

Materials

Benzene.—A good grade was purified as follows: (a) shaken with concentrated sulfuric acid until no coloration was perceptible, (b) washed with water, then with 25% sodium hydroxide solution and then with water, (c) shaken with mercury, (d) washed with water and then dried over calcium chloride and phosphorus pentoxide, (e) distilled in a large Dufton column and the fraction distilling between 80.15 and 80.17° was then (f) fractionally recrystallized, that with melting point 5.42–5.46° being stored over sodium for use.

Diphenyl.—This was recrystallized twice from absolute alcohol, dried, and then distilled twice under about 7 mm. pressure at 112°. The product so obtained had a melting point of 68.95°.

Ethyl Acetate.—Eastman Kodak Company best grade was distilled and the fraction between 77.00 and 77.18° was dried over phosphorus pentoxide for three weeks. It was then distilled in the Dufton column, the large fraction distilling between 77.14 and 77.16° being used.

Benzyl Benzoate.—This was fractionally distilled under reduced pressure. Attempts at distillation at ordinary pressure as recommended by Berkeley[12] resulted in slight cracking and so were abandoned. The melting point of each fraction was determined and the best fractions redistilled. The best fractions from this redistillation melted from 19.10 to 19.20° and these were used.

Data

Samples of the actual data obtained are given in Tables III and IV. These values of the pressure at different temperatures for each solution of fixed composition were plotted and a smooth curve drawn through the points. From this the pressures at 10° intervals were found and these are tabulated in Tables V, VI and VII under the corresponding compositions in mole per cent. In the row immediately below each value of the mole per cent. (N) is tabulated the value of the quantity 100 Δ defined by the equation

$$\Delta = (p/p_0) - N$$

Here p is the observed pressure at the mole per cent. in question and p_0 is the vapor pressure of the pure volatile component at the temperature concerned, as listed in the row marked 100 mole per cent. Δ is the difference between the mole fraction computed from Raoult's law and the actual composition of the solution and is a measure of the deviations from the law. These deviations are averaged for constant temperature in the last row at the bottom and for constant composition in the last column at the right of each table.

Before discussing the significance of the data a closer evaluation of the possible errors of the

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[11] Rechenberg, Ref. 4, p. 190.

[12] Berkeley, *J. Chem. Soc.*, **109**, 520 (1916).

TABLE V

SYSTEM BENZENE–DIPHENYL, PARTIAL PRESSURE OF BENZENE IN MM.

Mole % C_6H_6	t....50	60	70	80	90	95	Av. 100 Δ
69.93	192	274	386	531	710	826	
100 Δ	1.18	0.32	0.25	0.21	−0.39	0.01	0.39
78.58	215	309	435	593	802	923	
100 Δ	1.05	0.65	0.51	−0.25	−0.03	−0.43	.49
84.79	228	333	472	645	855	1007	
100 Δ	−0.35	0.59	1.03	0.41	−1.05	0.48	.65
88.96	241	352	492	672	913	1052	
100 Δ	0.30	1.30	0.50	0.19	0.46	0.12	.48
93.00	249	363	511	704	.....	.....	
100 Δ	−0.78	0.08	−0.09	0			.24
100.00	270	390	550	757	1021[a]	1181[a]	
Av. 100 Δ	0.73	0.59	0.48	0.21	0.48	0.26	

[a] Calculated from the equation given in "I. C. T.," Vol. III, p. 221.

TABLE VI

SYSTEM BENZENE–BENZYL BENZOATE, PARTIAL PRESSURE OF C_6H_6 IN MM.

Mole % C_6H_6	t....50	60	70	80	90	95	Av. 100 Δ
50.14	132	191	269	364	493	583	
100 Δ	−1.25	−1.17	−1.23	−2.06	−1.85	−0.77	1.39
61.90	169	240	337	465	627	730	
100 Δ	0.69	−0.36	−0.63	−0.47	−0.49	−0.09	0.46
73.57	199	291	405	558	745	864	
100 Δ	0.13	1.04	0.07	0.14	−0.60	−0.41	.40
80.22	216	317	443	608	822	945	
100 Δ	−0.22	1.06	0.32	0.10	0.29	−0.20	.37
91.22	248	358	503	688	932	1074	
100 Δ	0.63	0.58	0.24	−0.34	0.06	−0.28	.36
100.00	270	390	550	757	1021	1181	
Av. 100 Δ	0.38	0.84	0.50	0.62	0.66	0.35	

TABLE VII

SYSTEM ETHYL ACETATE–BENZYL BENZOATE, PARTIAL PRESSURE OF ETHYL ACETATE IN MM.

Mole % ethyl acetate	t....50	60	70	80	90	95	Av. 100 Δ
50.27	154	224	324	451	608	705	
100 Δ	3.95	3.19	4.00	3.81	3.35	3.47	3.63
67.50	199	295	424	589	798	932	
100 Δ	2.57	2.91	3.52	3.12	2.87	3.54	3.09
79.81	228	341	488	681	929	1079	
100 Δ	0.47	1.57	1.93	1.84	2.09	2.43	1.72
89.43	261	376	543	751	1025	.....	
100 Δ	2.47	0.31	1.53	0.62	0.96		1.18
100.00	284	419	597	834	1134	1312[a]	
Av. 100 Δ	2.36	1.99	2.75	2.10	2.57	3.15	

[a] Interpolated from a log p vs. $1/T$ plot of the values given in "I. C. T.," Vol. III, p. 219.

method as a whole in the case of the solutions is desirable. Further errors in addition to those previously evaluated as inherent in the pressure and temperature measurements, are of two sorts. The first involves the assumption that the contribution to the observed pressure of the partial pressure of the benzyl benzoate or diphenyl is negligible. This is clearly the case for benzyl benzoate whose vapor pressure is below 0.5 mm. even at 95°. The case of diphenyl requires further consideration. The only vapor pressure data at low temperatures for diphenyl available in the literature are those quoted by Montillon, Rohrbach and Badger[13] for temperatures above 69.2°. From a smoothed curve through these values the following vapor pressures were found: 0.56 mm. at 70°, 1.3 mm. at 80°, 2.5 mm. at 90° and 3.3 mm. at 95°. These figures measure the es-

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(13) Quoted in inches of mercury in *Ind. Eng. Chem.*, **23**, 764 (1931), as data from the Swann Chemical Company.

caping tendency of the pure diphenyl. Since the maximum concentration in the solutions is only 30 mole % diphenyl its escaping tendency will be materially lower in all cases. To attempt to estimate the actual partial pressures would beg the question at hand so that we will use the above figures to estimate the error due to the volatility of the diphenyl, realizing that they represent an extreme and improbable upper limit. At 50, 60, 70, and 80° this greatest possible contribution to the total pressure would be of the same order or less than the other errors in the method already discussed. At 90 and 95° the total pressure could be 0.4% greater than the partial pressure of benzene for the 30 mole per cent. diphenyl solution. These values could result in errors in the calculated mole per cent. of benzene from 0.2 to 0.3% at 90 and 95°. These estimates apply only to the highest diphenyl concentration at these temperatures. For all lower concentrations at these temperatures these greatest possible errors due to this cause would be materially smaller. Again it must be emphasized that these figures are based on the improbable premise that the partial pressure of diphenyl is the same from its 30 mole per cent. solution in benzene as its vapor pressure as a pure liquid.

The second type of errors are those due to the possible errors in the composition of the solution phase. The errors in weighing the components of a given solution were much less than one per mille and due precautions were taken that no serious loss of the volatile component occurred on transfer to the ebulliometer. This was weighed at the beginning and end of each run and only inappreciable losses in weight were found, indicating that the condenser was effectively stopping loss of the volatile component. Any possible error due to the segregation of a small, more or less constant fraction of the volatile component as it drained down from the condenser was minimized by the large volume of solution employed. The fact that reasonable differences in the rate of heating did not affect the boiling temperatures also indicated that any error due to such fractional condensation was small.

An over-all check on the reliability of the method was obtained by making two sets of duplicate runs with solutions of identical composition in which different pressures and temperatures were employed in each case. A sample of one pair of these runs is given in Tables III and IV together with the values of the pressures found independently from the smoothed curves for each run, for each 5° interval. The average discrepancy in the pressure readings for these two sets of duplicate runs was 1.0 mm. with one difference as great as 3 mm. These estimates indicate that the average error in terms of the pressures for these systems would be less than 2 mm. and that occasional errors of 3 mm. might occur. The presence of these errors could affect the values of p/p_0 by 1% or less on the average at the low pressures and by approximately 0.5 to 0.7% at the higher pressures. This might result in values of 100 Δ of these orders independent of any real deviation from Raoult's law. Furthermore, a very few values of 100 Δ of twice this amount might be expected. Examination of Tables V and VI indicates that the values of 100 Δ are on the whole less than these error limits would indicate. Therefore these two systems obey Raoult's law within the limits of error over the temperature and concentration ranges measured.

The deviations in the system ethyl acetate–benzyl benzoate as shown in Table VII are from two to three times greater than this experimental error and are all positive indicating a real, though small, positive deviation from Raoult's law in this system.

Discussion

Two assumptions are necessary for the derivation of Raoult's law on simple statistical grounds:[14] first, that the two molecular species have closely similar molecular fields and second, that they have the same size. In the system benzene–diphenyl the first of these conditions is fulfilled but not the second. Since benzyl benzoate contains the carbonyl and ether groups, both of which are polar and should have a different field than that of benzene, it might appear that neither of the conditions are fulfilled in the benzene–benzyl benzoate system. It is probable, however, that the major portion of the contacts with neighboring benzene molecules will be made by the phenyl rings and that these will shield the ester group and will to a large extent determine the character of the external molecular field of the molecule. Its field should thus be similar to that of the benzene.

The present measurements taken in conjunction with the solubility determinations of War-

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[14] Hildebrand, THIS JOURNAL, **59**, 795 (1937).

ner, Scheib and Svirbely[15] and the freezing point determinations of Washburn and Reade[16] indicate that the system benzene–diphenyl approximates fairly closely to the ideal over a large range of temperature. Furthermore, determinations of the lowering of the freezing point of benzene by benzyl benzoate made by Kendall and Booge[17] indicate that the system benzene–benzyl benzoate remains approximately ideal at considerably lower temperatures than those of the present measurements.

The system ethyl acetate–benzyl benzoate shows small but definite positive deviations from Raoult's law which persist substantially unchanged over a considerable temperature range. Two factors appear to be of importance in this case. In the first place contacts will be largely between the alkyl groups of the ethyl acetate and the phenyl groups of the benzyl benzoate. It is probable that the fields of these would be dissimilar as the solubility[14] of diphenyl in heptane deviates greatly from the ideal. Second, the shielding of the polar ester group in ethyl acetate is less complete than in benzyl benzoate. It is probable that this group accounts for an appreciable portion of the attractive forces between ethyl acetate molecules themselves. When these are surrounded in part by benzyl benzoate molecules it would seem probable that the separation between the polar ester groups in the two molecules of unlike size would be greater and their mutual attractions smaller. As a consequence the ethyl acetate molecules would show a higher escaping tendency.

If this analysis of the situation in these systems is correct it would indicate that differences in the volume of the components of a system are of secondary importance as determining its deviation from Raoult's law in comparison with differences in the effective molecular fields. The effective fields will be those of the component atoms or groups in the molecules which are most frequently in contact.

Summary

The total vapor pressures of the systems benzene–diphenyl, benzene–benzyl benzoate and ethyl acetate–benzyl benzoate have been determined from 50 to 95° over limited ranges of concentration. The bearing of these measurements on the validity of Raoult's law as applied to these systems is discussed. The benzene–diphenyl and benzene–benzyl benzoate systems follow Raoult's law within the limits of the experimental error. The ethyl acetate–benzyl benzoate system shows deviations several times larger than the experimental error, indicating a slight, but real, positive deviation from Raoult's law.

DURHAM, N. C. RECEIVED MARCH 31, 1938

[15] Warner, Scheib and Svirbely, *J. Chem. Phys.*, **2**, 591 (1934).

[16] Washburn and Reade, *Proc. Nat. Acad. Sci.*, **1**, 191 (1915).

[17] Kendall and Booge, THIS JOURNAL, **38**, 1712 (1916).

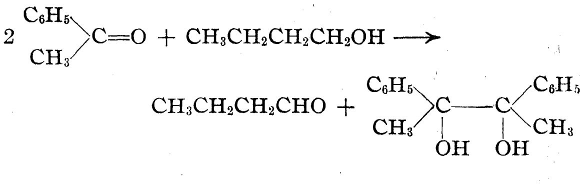
[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE]

Photochemical Interaction between Ketones and Alcohols

BY CH. WEIZMANN, ERNST BERGMANN AND YEHUDA HIRSHBERG

Ciamician and Silber[1] were the first ones to observe that ketones and (primary or secondary) alcohols, under the influence of light, may undergo a process of mutual oxidation and reduction. But although the amount of available experimental material is not small,[2] the elementary photochemical processes, apparently, have not yet been elucidated. In connection with other experiments which will be referred to later on, we have started an investigation of the questions concerned, primarily of the reaction products in some typical cases

Acetophenone and butanol on irradiation with the mercury arc give the pinacol of the former substance, butanol being dehydrogenated to form butyraldehyde according to the scheme



$$2\,(C_6H_5)(CH_3)C{=}O + CH_3CH_2CH_2CH_2OH \longrightarrow CH_3CH_2CH_2CHO + (C_6H_5)(CH_3)C(OH){-}C(OH)(C_6H_5)(CH_3)$$

Fifty per cent. of the theoretical amount of the aldehyde could be traced by titration according

[1] (a) Ciamician and Silber, *Ber.*, **33**, 2911 (1900); (b) **34**, 1537 (1901); (c) **36**, 1575 (1903); (d) **43**, 945 (1910); (e) **44**, 1280 (1911); (f) **45**, 1540 (1912); (g) **47**, 1806 (1914); (h) **48**, 190 (1915).

[2] (a) Baeyer and Co., German Patent 297,993 (1921); (b) Cohen, *Rec. trav. chim.*, **39**, 243 (1921); (c) Paternò, Chieffi and Perret, *Gazz. chim. ital.*, **44**, I, 151 (1914).

to Wagner.[3] It is interesting to note that both the diastereomerides of the pinacol, but to quite a different extent, are contained in surprisingly large yields in the solid product which is formed; their separation could be effected by fractional crystallization from light petroleum (b. p. 80–100°).

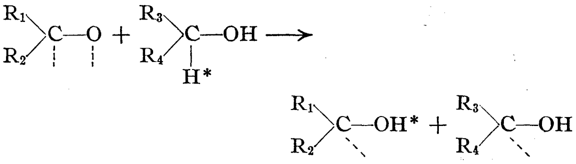
Acetophenone and cyclohexanol on irradiation gave the diastereoisomerides of acetophenonepinacol and cyclohexanone. Here, the cyclohexanone was determined in the mixture with excess cyclohexanol by Girard's reagent (trimethylammonium chloride acethydrazide)[4] which converts the ketone into a water-soluble, easily decomposable derivative. The amount of cyclohexanone found was as high as 80% of the theoretical yield.

In an analogous way acetophenone reacts with phenylmethylcarbinol to give the same mixture of pinacols. All these interactions parallel the known reaction between acetophenone and ethyl or isopropyl alcohol. In the same way, pinacol has been obtained from acetone and isopropyl alcohol.[2a]

The system cyclohexanone–cyclohexanol gives cyclohexanone pinacol only in poor yield. This substance[5] could not be obtained in an analytically pure state, but its identity has been proved by conversion into dicyclohexenyl.[6] Obviously, one cannot yet decide whether the above system is relatively inert or a complete exchange of two hydrogen atoms takes place, which would give again the original mixture of reactants.

Finally, the pair acetone–butanol was irradiated. Three substances have been isolated in pure state: two isomeric forms of *sym*-dipropylglycol, $C_3H_7CHOHCHOHC_3H_7$ (one liquid, one solid) as half-oxidation products of butyl alcohol and the trimeric form of butyraldehyde. In addition butyraldehyde and isopropanol were found in the first fractions of the reaction product. The question as to whether part of the acetone was converted into pinacol could not be decided, since no pure fraction consistent with its properties has been isolated. The balance of the concerned oxidation and reduction processes gave satisfactory results.

The characteristic feature of all these reactions is the reducing power of hydrogen H* on the carbon atom of a (primary or secondary) alcoholic group, $-CH^*OH$. That the hydrogen of the hydroxyl group itself is relatively insignificant may be concluded from the fact that ethers behave similarly toward ketones.[7] The primary step, however, in all these cases is most probably not the loosening of this hydrogen atom. This may be deduced from the following consideration. If irradiation would cause the loosening or dissociation of the C–H* bond—which is even for thermodynamical reasons highly improbable—then irradiation of an optically active secondary carbinol like phenylmethylcarbinol should lead to racemization, free radicals of the $C_6H_5CHCH_3$ type being configurationally unstable.[8] There is no change in rotation to be observed on irradiation of the optically active carbinol, but if a mixture of acetophenone and the carbinol is irradiated, the mixture of the epimeric acetophenone pinacols is found inactive, although one of them could have been formed in active state.[9] We therefore come to the conclusion that the first step in the irradiation of the above-discussed mixtures is the activation of the carbonyl compound, *e. g.*, leading to a diradical form.[10] This form reacts with the carbinol, splitting the C–H* bond and giving two radicals



which subsequently stabilize by symmetrical or unsymmetrical dimerization or by a second oxidation–reduction process. It is not easy to foresee which stabilization reaction will actually occur in a given case; here the relative stability of the intermediate radicals will play an important part.

It may well be that hemiacetal formation which takes place between carbonyl and hydroxyl compounds plays also a certain role in the course of the photocondensation, but it cannot be essential, since, according to the investigations of K. L.

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[3] Wagner, *Biochem. Z.*, **194**, 441 (1928).

[4] Girard and Sandulesco, *Helv. chim. acta*, **19**, 1095 (1936).

[5] Zelinsky, *Ber.*, **34**, 2801 (1901).

[6] De Barry-Barnett and Lawrence, *J. Chem. Soc.*, 1104 (1935).

[7] Ciamician and Silber, *Ber.*, **34**, 1541 (1901); **44**, 1554 (1911); **48**, 194 (1915); Paternò and Chieffi, *Gazz. chim. ital.*, **40**, II, 321 (1911); Bergmann and Fujise, *Ann.*, **483**, 65 (1930).

[8] Pauling and Wheland, *J. Chem. Phys.*, **1**, 362 (1933); Bergmann and Schuchardt, *Ann.*, **487**, 225 (1931).

[9] It is noteworthy that the part of the carbinol recovered unchanged from that experiment shows practically the original rotation, a slight decrease possibly being due to a certain complete hydrogen exchange between the ketone and the secondary alcohol.

[10] For this assumption, compare Bodenstein, *Sitzungsber. Preuss. Akad. Wiss.*, 73 (1931); *Z. physik. Chem.*, **B12**, 151 (1931); Farkas and Hirshberg, THIS JOURNAL, **59**, 2450 (1937); Hirshberg and Farkas, *ibid.*, **59**, 2453 (1937).

Wolf and Herold,[11] some of our pairs of compounds are unable to form hemiacetals.

The photochemical mobilization of the hydrogen in an alcoholic group is of interest with regard to the mechanism of ergosterol irradiation. At variance with the assumption of Spring[12] that this important reaction involves primarily epimerization at C_3, Windaus and Dimroth[13] were able to demonstrate that the secondary hydroxyl group at C_3 is actually not influenced by irradiation, while in the presence of eosin, which acts as hydrogen "acceptor," the well-known conversion of ergosterol into ergopinacol occurs.[13b,14] This reaction, undoubtedly, is rather complex in nature but here too, the primary step appears to be the loosening of the H* atom in the secondary alcoholic group in the presence of the activated "acceptor" molecule.

Experimental Part

Acetophenone and Butanol.—The irradiation product was fractionated. In the first fraction (b. p. 110–120°) butyraldehyde has been determined, as described above. The main part of this fraction was unchanged butyl alcohol: 0.74 g. was heated with 1.93 g. of *p*-nitrophthalic anhydride and 5 cc. of toluene for twelve hours on the water-bath. The solid product was collected and recrystallized from 20% acetic acid: leaflets, m. p. 146°, which were identified by mixed melting point as butyl hydrogen *p*-nitrophthalate.

The second fraction (b. p. 80–110° at 20 mm.) consisted of acetophenone, the third one (b. p. 205–210° at 25 mm.) was a viscous oil, which crystallized immediately on trituration with light petroleum (b. p. 40–60°). The solid product on recrystallization from light petroleum (b. p. 80–100°) gave first prisms, m. p. 123°, which were identified as acetophenone pinacol[15] by mixed melting point and analysis. The mother liquor was treated with petroleum ether, and the precipitate (m. p. 85–95°) recrystallized from petroleum ether (m. p. 80–100°); diamond-shaped crystals, m. p. 122–123°. This substance was again identified as isomeric acetophenone pinacol[16] by mixed m. p. and analysis.

Cyclohexanone and Cyclohexanol.—After removal of cyclohexanone and cyclohexanol, a viscous residue was obtained, boiling at 130–131° (20 mm.), 90° (0.04 mm.). It was identified by analysis and conversion into dicyclohexenyl.[6]

Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.7; H, 11.0. Found: C, 72.5, 72.4; H, 10.2, 10.5.

Acetone and Isopropanol.—The pinacol formed distilled at 60–65° (2 mm.) and was identified as its crystalline hydrate, m. p. 50°.[17]

Acetone and Butanol.—The reaction product was divided into five fractions: (a) b. p. 50–70° (760 mm.) acetone. (b) b. p. 78–80° (760 mm.). This fraction contained 29.1% isopropanol, as found after oxidation with chromic acid by Messinger's method for the determination of acetone,[18] which would not be present in this fraction, and 45% butyraldehyde. (c) b. p. 95–120° (760 mm.). This fraction was mainly butyl alcohol, but still contained 2.7% isopropanol. (d) b. p. 110–115° (25 mm.). Liquid *sym*-di-*n*-propyl-glycol. *Anal.* Calcd. for $C_8H_{18}O_2$: C, 65.7; H, 12.3. Found: C, 65.2; H, 12.3. (e) b. p. 140–150° (25 mm.). This fraction immediately separated crystals, which could be isolated by trituration with ice-cold petroleum ether (b. p. 40–60°). From the same solvent leaflets, m. p. 121°, with some sublimation, were obtained. Analysis showed that this substance was a solid isomer of the foregoing one. *Anal.* Calcd. for $C_8H_{18}O_2$: C, 65.7; H, 12.3. Found: C, 65.0; H, 12.3.

The mother liquor of the crystals was again distilled *in vacuo*, the first portion being rejected as containing some more of the above crystals. The fraction b. p. 95° (0.3 mm.), $n^{11.5}D$ 1.4640, was analytically identified as *p*-butyraldehyde. *Anal.* Calcd. for $(C_4H_8O)_3$: C, 66.7; H, 11.1. Found: C, 66.4; H, 11.1.

Experiments with Optically Active Phenylmethylcarbinol.—An equimolecular mixture of phenylmethylcarbinol ($[\alpha]_D$ +23.6°) and acetophenone (2 g. of each) was irradiated for about two hundred hours with a small mercury arc lamp and the mixture gradually turned yellow. Fractionation gave a mixture of the unchanged reactants (1.2 g.; b. p. 40–60° at 0.04 mm.) and a residue which crystallized on trituration with light petroleum (2.57 g.) and could be identified by the method of fractional crystallization indicated above[1] as mixture of the two acetophenone pinacols. While this mixture was optically inactive, the rotation of the liquid fraction amounted to α_D 9.05°. Under the assumption that this liquid product was still an equimolecular mixture of acetophenone and phenylmethylcarbinol, the specific rotation of the latter substance would be $[\alpha]_D$ +18.1°.

Irradiation of pure phenylmethylcarbinol for about two hundred hours failed to produce an appreciable decrease in rotation (19.2 ⟶ 18.6°), only a slight yellowish discoloration taking place.

Summary

The irradiation of the following pairs of compounds has been studied: acetophenone–butanol, acetophenone–cyclohexanol, acetophenone–phenylmethylcarbinol, cyclohexanone–cyclohexanol, acetone–butanol.

Optically active phenylmethylcarbinol is not racemized by ultraviolet light, but in the presence of acetophenone an optically inactive product is formed.

An activated ketone molecule reacts with the

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(11) K. L. Wolf and Herold, *Z. physik. Chem.*, **B5**, 124 (1929); **12**, 165, 194 (1931).

(12) Spring, *Chemistry & Industry*, **55**, 837 (1936).

(13) (a) Windaus and Dimroth, *Ber.*, **70**, 376 (1937). (b) Compare Dimroth, *ibid.*, **69**, 1123 (1936).

(14) Dehydroergosterol, lumisterol and dehydrocholesterol behave analogously. Windaus and Linsert, *Ann.*, **465**, 148 (1928); Urushibara and Ando, *Chem. Zentralbl.*, **109**, I, 2982 (1937).

(15) Beilstein, Vol. VI, p. 1011; Supplementary Vol. VI, p. 493.

(16) Ramart-Lucas and Salmon-Legageneur, *Bull. soc. chim.*, [4] **45**, 718 (1929).

(17) Beilstein, Volume I, Berlin, 1918, p. 488.

(18) Messinger, *Ber.*, **21**, 3368 (1888).

C–H bond of an alcoholic group, giving two configurationally unstable radicals. They stabilize by disproportionation or dimerization.

The significance of the results for the photochemical behavior of ergosterol is discussed.

REHOVOTH, PALESTINE RECEIVED MARCH 12, 1938

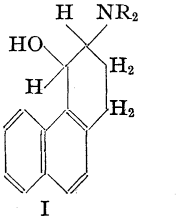
[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Studies in the Phenanthrene Series. XVII. Amino Alcohols Derived from 9-Hydroxy-1,2,3,4-tetrahydrophenanthrene[1]

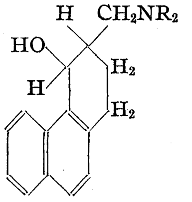
BY ALFRED BURGER

Some of the amino alcohols of types I and II derived from 1,2,3,4-tetrahydrophenanthrene[2] have been found to possess relatively favorable pharmacological properties.[3]

The 1,2,3,4-tetrahydroisoquinolino derivative of type I, for example, approaches codeine and pseudocodeine in analgesic action. The corresponding derivative of type II is weaker in analgesic effect, but does not exhibit any convulsant and emetic action. In morphine, the phenolic hydroxyl group is undoubtedly an important factor influencing the high analgesic effect of this alkaloid,[4] and therefore it appeared desirable to synthesize amino alcohols of types I and II carrying a phenolic hydroxyl group in one of the aromatic nuclei. The synthesis of the first group of amino alcohols with these structural features was planned as shown.

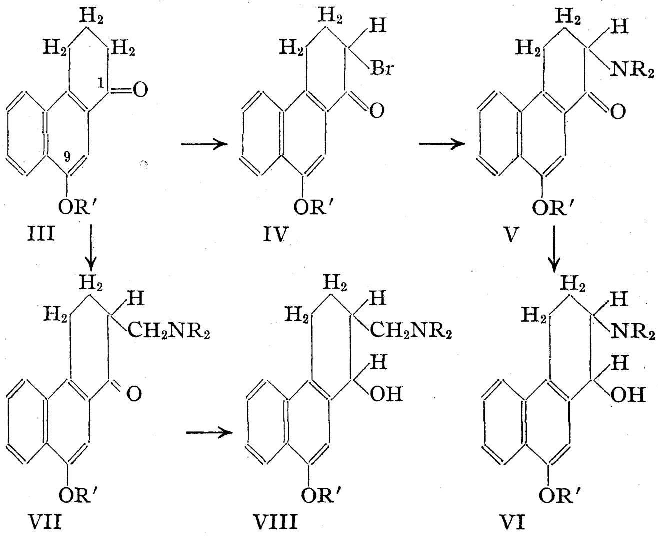


I



II

The starting materials for these syntheses, III (R′ = H, CH$_3$, CH$_3$CO) are relatively easily accessible.[5]



The preparation of IV (R′ = H, CH$_3$) did not offer any difficulties; only monobromo compounds were obtained. Attempts to exchange the bromine atom in IV (R′ = H) with secondary amines were without success. With R′ = CH$_3$, however, the reaction resulted in the expected amino ketones in yields that varied according to the secondary amine used. With piperidine the corresponding amino ketone V (R$_2$ = C$_5$H$_{10}$) was obtained in a yield of about 60%, while 1-hydroxy-9-methoxyphenanthrene appeared as a by-product. When diethylamine was used the amino ketone was formed in yields of about 30%; in this instance the formation of 1-hydroxy-9-methoxyphenanthrene by loss of hydrogen bromide and subsequent aromatization seems to be a main reaction, perhaps accompanied by the simultaneous formation of III.[6]

Unfortunately, catalytic hydrogenation under various experimental conditions did not furnish the corresponding amino alcohols VI, since the hydrogen absorption would not stop at this stage.

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[1] The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, the University of Virginia and the University of Michigan.

[2] (a) Mosettig and Burger, THIS JOURNAL, **57**, 2189 (1935); (b) Burger and Mosettig, *ibid.*, **58**, 1570 (1936).

[3] Mosettig, Eddy and co-workers, "Attempts to Synthesize Substances with Central Narcotic and, in Particular, Analgesic Action," Supplement to the U. S. Public Health Reports, in press.

[4] Edmunds, Eddy and Small, *J. Am. Med. Assoc.*, **103** 1417 (1934).

[5] Kon and Ruzicka, *J. Chem. Soc.*, 187 (1936).

[6] Compare footnotes 5 and 6 of Ref. 2a.

An excess of one to four moles of hydrogen was absorbed, and it was impossible to isolate any homogeneous reaction products.

The amino ketones of type VII were obtained by the Mannich method[7] in yields varying from 20–70%, depending on the nature of NR_2 and R′ (CH_3 or CH_3CO). Catalytic hydrogenation yielded the corresponding amino alcohols VIII. In each case only one of the two possible diastereoisomeric forms was obtained.

Further experiments that should lead to isomeric phenolic amino alcohols of types VI and VIII are in progress.

Experimental Part

Derivatives of 1-Keto-9-hydroxy-1,2,3,4-tetrahydrophenanthrene.—The reduction of β-[1-(4-methoxynaphthoyl)]-propionic acid[8] was carried out by the technique of Martin.[9] Five per cent. of glacial acetic acid by volume was added to the reaction mixture.[10] Commercial mossy zinc proved to be superior to other grades. The properties of the γ-[1-(4-methoxynaphthyl)]-butyric acid, obtained in a yield of 50%, agreed with those described by Martin[9] and by Kon and Ruzicka.[5]

It was hoped that the yield of the butyric acid derivative could be improved by reducing the methyl ester of β-[1-(4-methoxynaphthoyl)]-propionic acid catalytically. This ester was prepared from the acid with diazomethane in ether solution, or by the action of dimethyl sulfate in sodium hydroxide solution. It was recrystallized from dilute methanol, giving colorless needles, m. p. 42–43°.

Anal. Calcd. for $C_{16}H_{17}O_4$: C, 70.29; H, 6.28. Found: C, 70.46; H, 5.96.

In alcoholic solution, using a 16% palladium–charcoal catalyst, this ester absorbed more than two moles of hydrogen very slowly. Forty per cent. of the starting material was recovered unchanged, and the remaining acid, obtained by saponification of the mother liquors, was oily.

Hydrogen under high pressure at 100° in the presence of a chromite catalyst did not attack the ester in four hours. In other experiments (156, 185 and 210° for six hours, respectively) a mixture was obtained that melted from 104–108°. Repeated crystallization from methanol raised the m. p. to 120–122°. This substance appears in colorless leaflets, but is not entirely pure. Its behavior in alkaline solution and its analyses indicate that it represents a methoxytetrahydronaphthyl-γ-butyrolactone. No further efforts in this direction were made.

1 - Keto - 9 - acetoxy - 1, 2, 3, 4 - tetrahydrophenanthrene.—Ten grams of 1-keto-9-hydroxy-1,2,3,4-tetrahydrophenanthrene[5] was allowed to react with acetic anhydride (15 ml.) in pyridine solution (30 ml.) for forty-eight hours. Large crystals separated and were filtered. The mother liquor was evaporated in a vacuum, and the residue was combined with the crystals. The product was purified by distillation in a high vacuum, and recrystallization.

1 - Keto - 2 - bromo - 9 - methoxy - 1,2,3,4 - tetrahydrophenanthrene.—Ten grams of 1-keto-9-methoxy-1,2,3,4-tetrahydrophenanthrene was dissolved in 250 ml. of absolute ether, and 2.4 ml. of bromine was added. Two milliliters of a saturated ethereal solution of hydrogen chloride was added to initiate decoloration which was complete after about five minutes. The bromo ketone crystallized out, was filtered, washed with methanol and water, and purified by crystallization.

1 - Keto - 2 - diethylamino - 9 - methoxy - 1,2,3,4 - tetrahydrophenanthrene.—Eight grams of 1-keto-2-bromo-9-methoxy-1,2,3,4-tetrahydrophenanthrene was boiled under reflux with 20 g. of diethylamine in 80 ml. of benzene for five hours. A crystalline precipitate separated out after some time. Water was added to the reaction mixture, and the free diethylamino ketone was obtained by the addition of alkali to the aqueous solution. The crude diethylamino ketone melted at 90–95°. It was converted to the hydrochloride in acetone solution. From the benzene layer, 1-hydroxy-9-methoxyphenanthrene was obtained as described below.

1 - Hydroxy - 9 - methoxyphenanthrene.—The benzene layer (see above) was evaporated in a vacuum, and the residue was boiled with a 5% methyl alcoholic potassium hydroxide solution for ten minutes. The solvent was evaporated in a vacuum, the residue was dissolved in water and the filtered solution was acidified. The 1-hydroxy-9-methoxyphenanthrene precipitated as an oil which soon solidified (1.9 g.). It was purified by distillation in an oil-pump vacuum and crystallization from benzene–petroleum ether. Colorless needles were obtained, m. p. 131–132°.

Anal. Calcd. for $C_{15}H_{12}O_2$: C, 80.32; H, 5.40. Found: C, 80.76; H, 5.66.

1-Acetoxy-9-methoxyphenanthrene.—One and nine-tenths grams of 1-hydroxy-9-methoxyphenanthrene was boiled with 30 ml. of acetic anhydride and 2 g. of anhydrous sodium acetate for three hours. The mixture was decomposed with water, and the acetylation product was purified by distillation at 5 mm. pressure and crystallization from alcohol; fine, colorless needles, m. p. 154.5–155.5°; yield 2 g.

Anal. Calcd. for $C_{17}H_{14}O_3$: C, 76.66; H, 5.30. Found: C, 76.52; H, 5.04.

Attempts to oxidize this compound to 1-acetoxy-9,10-phenanthrenequinone failed.

1,9-Dihydroxyphenanthrene.—One part of 1-acetoxy-9-methoxyphenanthrene was boiled under reflux with twenty parts of a mixture of 48% hydrobromic acid and glacial acetic acid (1:1) for one hour. The reaction mixture was poured into water, and a pink crystalline precipitate separated out. It was dissolved in cold dilute potassium hydroxide solution which contained some sodium sulfite. The dihydroxy compound obtained by acidification was purified by distillation in a high vacuum and recrystallization from benzene. The compound was obtained as light brown plates which sinter at 181° and melt at 184–185° (evac. tube).

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(7) Mannich and co-workers, *Ber.*, **53**, 1874 (1920); **55**, 3510 (1922); *Arch. Pharm.*, **255**, 261 (1917); **275**, 54 (1937); Bodendorf and Koralewski, *ibid.*, **271**, 101 (1933).

(8) Fieser and Hershberg, THIS JOURNAL, **58**, 2314 (1936).

(9) Martin, *ibid.*, **58**, 1438 (1936).

(10) Private communication by Dr. E. B. Hershberg.

TABLE I

No.	Derivatives of 1,2,3,4-tetrahydrophenanthrene	Solvent	Appearance	Yield, %	M. p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	1-Keto-9-acetoxy-	*n*-Butanol	Colorless needles	83	159–160	$C_{16}H_{14}O_3$	75.56	75.15	5.55	5.34		
2	1-Keto-2-bromo-9-methoxy-	*n*-Butanol	Yellow plates	88	174–175	$C_{15}H_{13}BrO_2$	59.01	59.53	4.30	4.26		
3	1-Keto-2-bromo-9-hydroxy-[a]	Methanol	Yellow leaflets		Above 330	$C_{14}H_{11}BrO_2$	57.73	56.99	3.81	3.72		
4	1-Keto-2-diethylamino-9-methoxy—HCl	Alcohol–ether	Colorless light needles	27	128–138 (dec.)	$C_{19}H_{24}ClNO_2$					Cl, 10.63	10.27
5	1-Keto-2-piperidino-9-methoxy—HCl[b]	Alcohol–ether	Colorless	63	Sinters 246 258–261 (dec.)	$C_{10}H_{24}ClNO_2$	69.43	69.45	7.00	7.14	4.05	4.32
6	1-Keto-2-(1,2,3,4-tetrahydroisoquinolino)-methyl-9-methoxy—HCl	Methanol–ether	Yellow spears	46	176–177 (dec.)	$C_{25}H_{26}ClNO_2$					3.44	3.76
7	-Perchlorate[c]	Methanol–ether	Yellow		135–150 (dec.)	$C_{25}H_{26}ClNO_6$					2.97	3.12
8	1-Hydroxy-2-(1,2,3,4-tetrahydroisoquinolino)-methyl-9-methoxy-	Methanol	Colorless needles		137–138[d]	$C_{25}H_{27}NO_2$	80.38	80.63	7.29	7.32		
9	-Hydrochloride	Alcohol–ether	Colorless	90	211	$C_{25}H_{28}ClNO_2$	73.22	73.07	6.89	6.99		
10	1-Acetoxy-2-(1,2,3,4-tetrahydroisoquinolino)-methyl-9-methoxy—HCl	Alcohol–ether	Colorless		200–201 (dec.)	$C_{27}H_{30}ClNO_3$	71.73	71.98	6.70	6.41		
11	1-Keto-2-(1,2,3,4-tetrahydroisoquinolino)-methyl-9-acetoxy-[e]	Methanol	Almost colorless needles		144	$C_{26}H_{25}NO_3$	78.15	77.86	6.31	6.33		
12	-Hydrochloride	Alcohol–ether	Colorless rhombic plates	72	167–168 (dec.)	$C_{26}H_{26}ClNO_3$					3.22	3.21
13	1-Hydroxy-2-(1,2,3,4-tetrahydroisoquinolino)-methyl-9-acetoxy—HCl	Methanol–ether	Colorless prisms	90	234–235 (dec.)	$C_{26}H_{28}ClNO_3$	71.28	71.00	6.45	6.35		
14	1-Hydroxy-2-(1,2,3,4-tetrahydroisoquinolino)-methyl-9-hydroxy-[f]	Methanol	Colorless		213(dec.)(vac.)	$C_{24}H_{25}NO_2$	80.17	79.96	7.02	7.03		
15	-Hydrochloride[g]	Alcohol	Crystal powder	75	225–227 (dec.)	$C_{24}H_{26}ClNO_2$	72.79	72.63	6.62	6.56		
16	1-Keto-2-diethylaminomethyl-9-methoxy-	Methanol	Colorless prisms	41	83	$C_{20}H_{25}NO_2$	77.12	77.38	8.10	8.22	4.50	4.68
17	-Hydrochloride	Alcohol–ether	Colorless prisms		160–161	$C_{20}H_{26}ClNO_2$					4.03	3.97
18	1-Hydroxy-2-diethylaminomethyl-9-methoxy—HCl	Alcohol–ether	Colorless square plates	86	190 (dec.)	$C_{20}H_{28}ClNO_2$	68.63	68.48	8.07	7.92		
19	1-Acetoxy-2-diethylaminomethyl-9-methoxy—HCl	Alcohol–ether	Glittering prisms		165–166 (dec.)	$C_{22}H_{30}ClNO_3$	67.40	67.67	7.72	7.57		
20	1-Keto-2-diethylaminomethyl-9-acetoxy—HCl[h]	Alcohol–ether	Colorless prisms	20	146–147	$C_{21}H_{26}ClNO_3$					3.73	3.76

[a] Bromination of 1-keto-9-hydroxy-1,2,3,4-tetrahydrophenanthrene was carried out as in the case of no. 2. A mixture of chloroform and ether (5:1) was used as a solvent. The bromo compound turned dark at 190°, the light color returned at 210° and the sample did not melt below 330°. [b] Prepared analogously to no. 4. The free piperidino ketone, prepared from the hydrochloride, was recrystallized from methanol: brown needles which darken rapidly in air, m. p. 112–113°. Also in this case, 1-hydroxy-9-methoxyphenanthrene was obtained as a by-product in the preparation of the piperidino ketone. [c] Prepared from the free base with ethereal perchloric acid. [d] After drying at 100° in a high vacuum. [e] Prepared from no. 12 with dilute ammonium hydroxide solution. [f] Prepared by making the acid mother liquors of the crude no. 15 alkaline with sodium bicarbonate solution and extraction into ether. The pure substance melted at 195–196° (decomp.) in an open tube. Methylation with diazomethane in alcohol–ether solution yielded the methyl ether, m. p. 129–131°, identical (mixed m. p.) with no. 8. [g] One part of no. 13 was heated with 3 parts of an 8% methyl alcoholic potassium hydroxide solution for a few minutes, the solution was diluted with water and acidified with hydrochloric acid. The tarry hydrochloride precipitated out. It was separated from the mother liquor by decanting, and it crystallized on treatment with acetone. [h] The mother liquors from the preparation of this salt contained dark basic and non-basic by-products of elevated m. p.

Anal. Calcd. for $C_{14}H_{10}O_2$: C, 79.97; H, 4.80. Found: C, 80.13; H, 5.08.

1,9-Diacetoxyphenanthrene.—A sample of 1,9-dihydroxyphenanthrene was allowed to react with acetic anhydride in pyridine solution overnight. The diacetoxy compound was purified by distillation in the vacuum of an oil pump and crystallization from dilute alcohol, resulting in fine, colorless needles, m. p. 154–155°.

Anal. Calcd. for $C_{18}H_{14}O_4$: C, 73.44; H, 4.80. Found: C, 72.87; H, 4.80.

1,9-Dimethoxyphenanthrene.—One and six-tenths milliliters of dimethyl sulfate was added dropwise to a mixture of 0.3 g. of 1-hydroxy-9-methoxyphenanthrene, 1.45 ml. of 60% potassium hydroxide solution and 10 ml. of acetone, with vigorous stirring in the course of ten minutes.[11] After another ten minutes, the dimethoxy compound was precipitated with water and purified by distillation in an oil-pump vacuum and crystallization from methanol; colorless oblong plates resulted, m. p. 113–114°. The yield was nearly quantitative.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.63; H, 5.93. Found: C, 80.68; H, 6.38.

Preparation of Amino Ketones by the Mannich Reaction.—One mole of 1-keto-9-methoxy- or 1-keto-9-acetoxy-1,2,3,4-tetrahydrophenanthrene was boiled with 1.2 to 1.4 moles of the hydrochloride of the respective secondary amine and 3 moles of para-formaldehyde in 4 to 7 parts of isoamyl alcohol for four to five minutes. The hydrochlorides of the amino ketones precipitated as oils on addition of ether. These oily salts either solidified and could be filtered out, or, as in the case of the easily soluble diethylamino derivatives, they were extracted into water. The amino ketones were liberated and purified by crystallization or by conversion to a crystalline salt. The hydrochlorides of the less soluble amino ketones often can be separated from some unchanged hydrochloride of the respective secondary amine by their insolubility in cold water. Washing with acetone frequently removes colored impurities.

Preparation of Amino Alcohols.—The hydrochlorides of the amino ketones were hydrogenated, using a platinum oxide catalyst in methanol solution. One mole of hydrogen was absorbed in two to sixteen hours. The catalyst was filtered, and the solution concentrated in a vacuum. The hydrochlorides of the amino alcohols crystallized directly from the solution, or after addition of ether, and were purified by recrystallization.

The acetyl derivatives of the amino alcohols were obtained by allowing the free alkamines or their hydrochlorides to react with acetic anhydride in pyridine solution overnight. The solutions were then evaporated in a vacuum and the acetyl derivatives were converted into the hydrochlorides in the usual way.

Oxime of 1-Keto-9-methoxy-1,2,3,4-tetrahydrophenanthrene.—Ten grams of 1-keto-9-methoxy-1,2,3,4-tetrahydrophenanthrene, 6 g. of hydroxylamine hydrochloride, and 7.5 g. of barium carbonate in 170 ml. of alcohol were boiled for four hours. The barium salts were filtered from the hot solution, and the oxime was allowed to crystallize from the filtrate; yield, 9.7 g. of shining needles (from alcohol), m. p. 174–175°.

Anal. Calcd. for $C_{15}H_{15}NO_2$: N, 5.81. Found: N, 6.08.

1 - Amino - 9 - methoxy - 1, 2, 3, 4 - tetrahydrophenanthrene.—A solution of 9.5 g. of the oxime of 1-keto-9-methoxy-1,2,3,4-tetrahydrophenanthrene in 500 ml. of moist ether was allowed to react with 30 g. of aluminum amalgam for forty-eight hours. The mixture was filtered and the aluminum sludge was washed repeatedly with warm ether. The ethereal solution was extracted with dilute hydrochloric acid. An insoluble yellow hydrochloride (5.8 g.) precipitated and was filtered off. The clear aqueous solution was made alkaline, the oily amine was extracted into ether, and converted to the hydrochloride (1.1 g.) in the customary way. It was recrystallized from methanol as colorless needles, m. p. 291° (dec., evac. tube).

Anal. Calcd. for $C_{15}H_{18}ClNO$: C, 68.28; H, 6.88; N, 5.31. Found: C, 68.42; H, 7.39; N, 5.33.

The insoluble hydrochloride could be recrystallized from 400 parts of alcohol. It appeared as a poorly crystalline material that turned yellow on drying.

Summary

The synthesis of several tertiary 1-hydroxy-2-aminomethyl - 1, 2, 3, 4 - tetrahydrophenanthrenes, carrying in position 9 a phenolic hydroxyl, a methoxy or acetoxy group, is described. A number of derivatives of 1,9-dihydroxyphenanthrene were obtained from 1-hydroxy-9-methoxyphenanthrene, which is formed in a side reaction in the exchange of the bromine atom of 1-keto-2-bromo-9-methoxy-1,2,3,4-tetrahydrophenanthrene with secondary amines.

UNIVERSITY, VIRGINIA
RECEIVED MAY 9, 1938

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[11] *Cf.* Stevens and Tucker, *J. Chem. Soc.*, **123**, 2140 (1923).

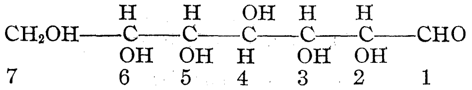
[Contribution from the National Institute of Health, U. S. Public Health Service]

A Suggestion for Naming the Higher Carbon Sugars[1]

By C. S. Hudson

When the initial syntheses by Emil Fischer of higher carbon aldoses in the heptose, octose and nonose series were in progress it became necessary to name the new sugars by some general plan. He named them (1) according to the hexose from which they were made (D-gluco, D-manno, D-gala, etc.) and (2) according to the number of carbon atoms in the sugar chain (heptose, octose, nonose); such is the historical origin of the names D-glucoheptose, D-galaoctose, etc.[2] Since the cyanohydrin synthesis yields two D-glucoheptoses from D-glucose, it was necessary for Fischer to distinguish between them, which he did later[3] by the provisional symbols α and β, given empirically in the order of isolation. Subsequently Philippe[4] synthesized several more of the higher carbon sugars obtainable from D-glucose and found it necessary in the octose and higher series to expand the α and β naming; in consequence certain sugars today are designated D-α,α,α- and D-α,α-β-glucononose; indeed theory predicts eight as the number of aldononoses obtainable from D-glucose and by present usage they are to be distinguished by the eight possible arrangements of α and β in a three-membered term. Fischer[5] also distinguished the two forms of methyl-D-glucoside (now known to be the pyranosides[6]) by the designations α and β, assigned empirically, and today this latter use has become universal for the ring forms of the sugars and their derivatives because in a large number of cases the designations have been correlated with the stereostructures according to the plan of nomenclature that the writer proposed in 1909.[7] It can hardly be questioned that the provisional naming of higher carbon sugars by the symbols α and β and combinations of them, given empirically, should at some stage of progress be replaced by a plan that names these sugars according to their configurations. This could not be done by Fischer nor by Philippe, because only two of the configurations were then known in full (the two D-glucoheptoses). Later the configurations of the two D-mannoheptoses, the two D-galaheptoses and two of the D-mannooctoses were established by Peirce,[8] and those of the two D-guloheptoses by LaForge.[9] The discovery of several independent rules of rotation correlating direction of rotation with configuration has supplied a simple way of learning the configurations of the remaining higher carbon sugars, and these methods have been applied to D-gulomethylose[10] and to two of the D-glucooctoses[11] and D-galaoctoses[12]; thus today we know the configurations of fourteen of the higher carbon aldoses (and two of the higher carbon aldomethyloses) and possess simplified methods for determining the configurations of all the others. Would it not be well therefore to introduce some new plan for naming higher carbon sugars of known configuration by which the name of the sugar will indicate its configuration with the minimum burden upon the memory? One might give configurational definition to the terms α and β, which would be the least possible change from the present names, but this would continue the present very confusing use of these symbols in two senses in the same name, for example, α-D-α-glucoheptose. The writer has been using for about twelve years in unpublished notes a system which avoids this confusion and, as some colleagues have looked upon it with favor, it is here published.

Consider the sugar that is now known as D-α-glucoheptose.



$$\begin{array}{lcccccc} & \mathrm{H} & \mathrm{H} & \mathrm{OH} & \mathrm{H} & \mathrm{H} & \\ \mathrm{CH_2OH}— & \mathrm{C}— & \mathrm{C}— & \mathrm{C}— & \mathrm{C}— & \mathrm{C}— & \mathrm{CHO} \\ & \mathrm{OH} & \mathrm{OH} & \mathrm{H} & \mathrm{OH} & \mathrm{OH} & \\ 7 & 6 & 5 & 4 & 3 & 2 & 1 \end{array}$$

D-α-Glucoheptose (D-Gluco-D-gulo-heptose)

It is made from D-glucose and its asymmetric carbon atoms 6, 5, 4 and 3, reading from the left, have the configuration that is carried over from D-glucose. Now read the configurations of carbon atoms 2, 3, 4 and 5 from the right; they are

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[1] Publication authorized by the Surgeon General, U. S. Public Health Service.

[2] Fischer, *Ber.*, **23**, 934 (1890).

[3] Fischer, *Ann.*, **270**, 64 (1892).

[4] Philippe, *Ann. chim. phys.*, [8] **26**, 289 (1912).

[5] Fischer, *Ber.*, **28**, 1145 (1895).

[6] Charlton, Haworth and Peat, *J. Chem. Soc.*, 100 (1926).

[7] Hudson, This Journal, **31**, 66 (1909).

[8] Peirce, *J. Biol. Chem.*, **23**, 327 (1915).

[9] LaForge, *ibid.*, **41**, 251 (1920).

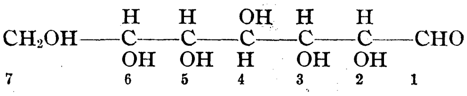
[10] Levene and Compton, *J. Biol. Chem.*, **111**, 335 (1935).

[11] Hudson, This Journal, **39**, 463 (1917); Hockett and Hudson, *ibid.*, **60**, 622 (1938).

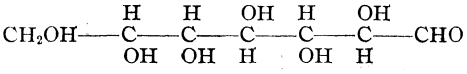
[12] Maclay, Hann and Hudson, *ibid.*, **60**, 1035 (1938).

the same as in D-gulose. This is more than a formal analogy because it is known from many examples that the higher carbon sugars have properties closely resembling those of the hexoses of like configuration for carbon atoms 2, 3, 4 and 5. It is suggested therefore that the sugar be named D-gluco-D-gulo-heptose. This name defines the configuration unequivocally, indicates that the sugar is made from D-glucose and reminds one that it may be expected to resemble D-gulose in properties.[13] Although the prefix gulo- does not require the D-symbol, since the D-gluco term is not compatible with an L-gulo term in a heptose, octose or nonose, it seems preferable to retain it because of its plain expression of the fact that the heptose resembles D- rather than L-gulose. Most of the higher carbon sugars of known configuration are listed below with the designation of the proposed new name, following the system just described.

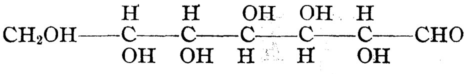
HEPTOSES


$$\begin{array}{lcccccl} & \mathrm{H} & \mathrm{H} & \mathrm{OH} & \mathrm{H} & \mathrm{H} & \\ \mathrm{CH_2OH}— & \mathrm{C}— & \mathrm{C}— & \mathrm{C}— & \mathrm{C}— & \mathrm{C}— & \mathrm{CHO} \\ & \mathrm{OH} & \mathrm{OH} & \mathrm{H} & \mathrm{OH} & \mathrm{OH} & \\ 7 & 6 & 5 & 4 & 3 & 2 & 1 \end{array}$$

(D-α-Glucoheptose)
D-Gluco-D-gulo-heptose


$$\mathrm{CH_2OH}—\overset{\mathrm{H}}{\underset{\mathrm{OH}}{\mathrm{C}}}—\overset{\mathrm{H}}{\underset{\mathrm{OH}}{\mathrm{C}}}—\overset{\mathrm{OH}}{\underset{\mathrm{H}}{\mathrm{C}}}—\overset{\mathrm{H}}{\underset{\mathrm{OH}}{\mathrm{C}}}—\overset{\mathrm{OH}}{\underset{\mathrm{H}}{\mathrm{C}}}—\mathrm{CHO}$$

(D-β-Glucoheptose)
D-Gluco-D-ido-heptose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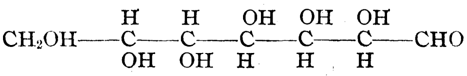
(D-α-Mannoheptose)
D-Manno-D-gala-heptose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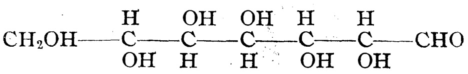
(D-β-Mannoheptose)
D-Manno-D-talo-heptose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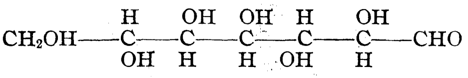
(D-α-Galaheptose)
D-Gala-L-manno-heptose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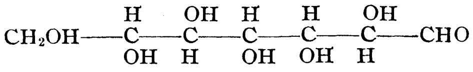
(D-β-Galaheptose)
D-Gala-L-gluco-heptose)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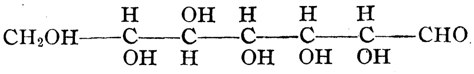
(D-α-Guloheptose)
D-Gulo-L-gala-heptose[14]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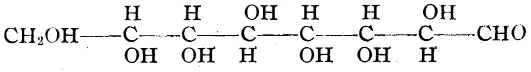
(D-β-Guloheptose)[14]
D-Gulo-L-talo-heptose

OCTOSES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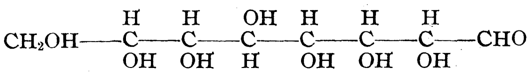
(D-α,α-Glucooctose)
D-Gluco-L-gala-octose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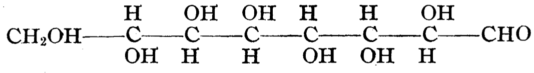
(D-α,β-Glucooctose)
D-Gluco-L-talo-octose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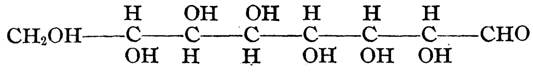
(D-α,α-Galaoctose)
D-Gala-L-gala-octose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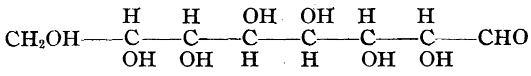
(D-α,β-Galaoctose)
D-Gala-L-talo-octose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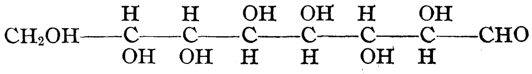
(D-α,α-Mannooctose)[15]
D-Manno-L-manno-octose


$$\mathrm{CH_2OH}—\overset{\mathrm{H}}{\underset{\mathrm{OH}}{\mathrm{C}}}—\overset{\mathrm{H}}{\underset{\mathrm{OH}}{\mathrm{C}}}—\overset{\mathrm{OH}}{\underset{\mathrm{H}}{\mathrm{C}}}—\overset{\mathrm{OH}}{\underset{\mathrm{H}}{\mathrm{C}}}—\overset{\mathrm{H}}{\underset{\mathrm{OH}}{\mathrm{C}}}—\overset{\mathrm{OH}}{\underset{\mathrm{H}}{\mathrm{C}}}—\mathrm{CHO}$$

(D-α,β-Mannooctose)
D-Manno-L-gluco-octose

The names of derivatives are readily formed in the usual way, for example: D-gala-L-gala-octitol, octopyranoside, octonic and octaric acids, octal, octosazone, etc.

In Fischer's era rhamnose and fucose were designated substituted pentoses (substitution of methyl for a hydrogen atom directly attached to

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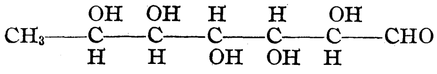
[13] I considered years ago the name D-glycero-D-gulo-heptose as an alternative for D-gluco-D-gulo-heptose, but discarded it in favor of the name that specifically indicates the hexose from which the higher carbon sugar is prepared.

[14] The D-guloheptoses were named by their discoverer (LaForge[9]) α and β as here written; LaForge proved their configurations by showing that D-α-guloheptitol is identical with D-β-galaheptitol. Isbell [*J. Research Nat. Bur. Standards*, **19**, 639 (1937)] recently has proposed reversal of the symbols in a plan which gives configurational definition to α and β; the disadvantage of this plan already has been mentioned.

[15] This configuration follows from the observation by George Peirce[8] that the sodium salt of D-manno-L-manno-octaric acid is optically inactive, but obviously it needs substantiation. The corresponding D-manno-L-manno-octitol was crystallized by Fischer and Passmore [*Ber.*, **23**, 2226 (1890)] but there is no mention of a rotatory measurement; the substance is probably inactive in accordance with the above provisional configuration of the sugar. We expect to be able to present data soon that will permit decision regarding the formula.

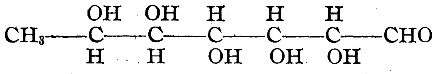
the carbon atom of the terminal group CH_2OH), a usage which persists in the class name methylpentose; the practice is now becoming general to consider them as 6-desoxyhexoses, under the class name methylose,[16] with an appropriate prefix to designate the configuration. Thus natural rhamnose is L-mannomethylose and natural fucose is L-galamethylose (or L-galactomethylose, if one chooses to use the full prefix). By combining this plan of nomenclature with that which is suggested in this article, the two 7-desoxyheptoses whose configuration is known may be given the following systematic names.

METHYLO-HEPTOSES[17] (OR 7-DESOXYHEPTOSES)



$$CH_3-\underset{H}{\overset{OH}{C}}-\underset{H}{\overset{OH}{C}}-\underset{OH}{\overset{H}{C}}-\underset{OH}{\overset{H}{C}}-\underset{H}{\overset{OH}{C}}-CHO$$

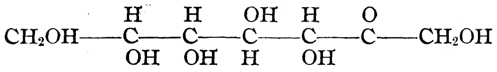
(α-L-Rhamnohexose of Fischer)
L-Manno-L-gala-methylo-heptose



$$CH_3-\underset{H}{\overset{OH}{C}}-\underset{H}{\overset{OH}{C}}-\underset{OH}{\overset{H}{C}}-\underset{OH}{\overset{H}{C}}-\underset{OH}{\overset{H}{C}}-CHO$$

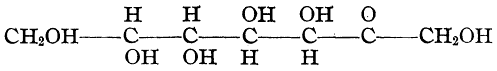
(β-L-Rhamnohexose of Fischer)
L-Manno-L-talo-methylo-heptose

The 2-ketoheptoses need to carry the name of the appropriate hexose only; the five known ketoheptoses are the following



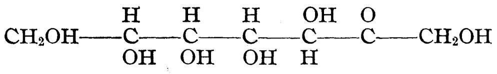
$$CH_2OH-\underset{OH}{\overset{H}{C}}-\underset{OH}{\overset{H}{C}}-\underset{H}{\overset{OH}{C}}-\underset{OH}{\overset{H}{C}}-\overset{O}{C}-CH_2OH$$

D-Glucoheptulose[18]
(Its mirror image is L-Glucoheptulose)[19]



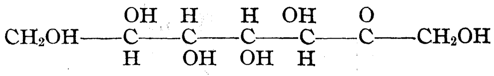
$$CH_2OH-\underset{OH}{\overset{H}{C}}-\underset{OH}{\overset{H}{C}}-\underset{H}{\overset{OH}{C}}-\underset{H}{\overset{OH}{C}}-\overset{O}{C}-CH_2OH$$

D-Mannoheptulose
(Originally named D-Mannoketoheptose)[20]



$$CH_2OH-\underset{OH}{\overset{H}{C}}-\underset{OH}{\overset{H}{C}}-\underset{OH}{\overset{H}{C}}-\underset{H}{\overset{OH}{C}}-\overset{O}{C}-CH_2OH$$

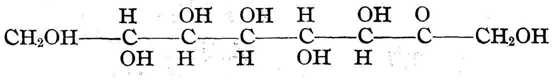
D-Altroheptulose[21]
(Originally named Sedoheptose)[22]



$$CH_2OH-\underset{H}{\overset{OH}{C}}-\underset{OH}{\overset{H}{C}}-\underset{OH}{\overset{H}{C}}-\underset{H}{\overset{OH}{C}}-\overset{O}{C}-CH_2OH$$

L-Galaheptulose[23]
(Originally named Perseulose)[24]

Beginning with the 2-keto-octoses, of which none are now known, prefixes of two hexoses would be required, leading for example to the unequivocal name D-gala-L-gluco-octulose for a ketose of the configuration



$$CH_2OH-\underset{OH}{\overset{H}{C}}-\underset{H}{\overset{OH}{C}}-\underset{H}{\overset{OH}{C}}-\underset{OH}{\overset{H}{C}}-\underset{H}{\overset{OH}{C}}-\overset{O}{C}-CH_2OH$$

In designating the α- and β-forms of ring derivatives (*e. g.*, the methyl glycosides) it seems to the writer advisable to follow the simplest rule that is adequate, which is to name the more dextrorotatory member of a pair in the D-sugar series as α (or, in full, α-D-); its enantiomorph is an α-L-form, which represents the more levorotatory member of a pair in the L-sugar series. I made this suggestion in 1909 and it has been generally adopted, but there recently has come from Isbell[25] the proposal to modify it and to reverse the α-β- naming in the arabinose and fructose series, and in a recent article Schlubach and Graefe[26] question the naming of a certain new methyl sorboside as an α-L-form because it closely resembles in certain peculiarities a β-D-methylfructoside. The recent experimental work of Jackson and Hudson[27] in correlating the configurations of carbon atom 1 in many of the aldohexopyranosides, aldopentopyranosides and an aldopentofuranoside furnishes proof of stereostructures which confirm in all cases the nomenclature that I originally proposed. The system of naming α- and β-methyl glycosides, etc., is best understood if one writes the skeleton stereostructures for the rings. The pyranoid forms are derived from the structures (I) and (II), as proved by Jackson and Hudson.

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(16) Votoček, *Bull. soc. chim.*, **43**, 18 (1928).

(17) The order methylo-heptose seems preferable to heptomethylose because, as pointed out in an analogous case by Freudenberg and Raschig [*Ber.*, **62**, 376 (1929)], hepto-methylosazone is an ambiguous name since it can apply to either the phenylosazone of a hepto-methylose or the methyl phenylosazone of a heptose; methylo-heptosazone is not ambiguous. To overcome the objection raised by Freudenberg and Raschig in the case of the name altro-methylose, it may be well to use altro-methylohexose instead. Rhamnose would then be L-manno-methylohexose and its osazone would be L-manno-methylo-hexosazone. The ambiguity could also be avoided by naming osazones with two words (*e. g.*, altromethylose osazone), as is in fact often done, especially with osazones from substituted phenylhydrazines.

(18) Austin, This Journal, **52**, 2106 (1930).

(19) Bertrand and Nitzberg, *Compt. rend.*, **186**, 925, 1172 (1928).

(20) LaForge, *J. Biol. Chem.*, **28**, 511 (1917).

(21) Ettel, *Collection Czechoslov. Chem. Communications*, **4**, 504, 513 (1932).

(22) LaForge and Hudson, *J. Biol. Chem.*, **30**, 61 (1917).

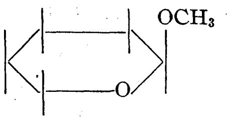
(23) This configuration for perseulose was made highly probable by LaForge;[20] definitive proof has been established recently by Raymond M. Hann and the writer and it will be published shortly.

(24) Bertrand, *Compt. rend.*, **147**, 201 (1908); **149**, 225 (1909).

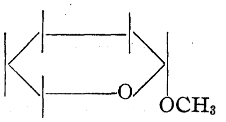
(25) Isbell, *J. Chem. Ed.*, **12**, 96 (1935); *J. Research Nat. Bur. Standards*, **18**, 505 (1937). Isbell appears to have considered only the pyranoid ring forms; if his plan were adopted it would require that in aldohexoses having *cis-trans* configuration for the hydroxyl groups on carbon atoms 4 and 5 (galactose, talose, gulose and idose) a pyranoside would be named α in the D series if it is the more dextrorotatory member of a pair, but a furanoside that is the more dextrorotatory member of its pair would have to be named a β-D-form, which seems objectionable; with septanosides and with tetrofuranosides it is not clear how one would name them by Isbell's plan. I warn against the confusion that must ultimately result if Isbell's modification of my simple, generally applicable rule is followed.

(26) Schlubach and Graefe, *Ann.*, **532**, 211 (1937).

(27) Jackson and Hudson, This Journal, **59**, 994 (1937).

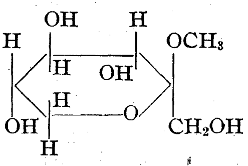


(I) $\left.\begin{matrix}\alpha\text{-D-}\\ \beta\text{-L-}\end{matrix}\right\}$ Methyl glycosides
(C_1 is dextrorotatory)

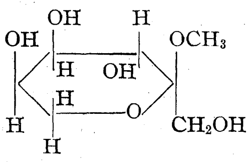


(II) $\left.\begin{matrix}\beta\text{-D-}\\ \alpha\text{-L-}\end{matrix}\right\}$ Methyl glycosides
(C_1 is levorotatory)

These skeleton structures permit one to write the stereo pyranoid formulas for any given case from the name of the substance; formula (I) pertains to α-D- and β-L-forms, where C_1 is dextrorotatory, and formula (II) to β-D- and α-L-forms, where C_1 is levorotatory. Thus the formulas for the methyl pyranosides of L-sorbose and D-fructose that were discussed by Schlubach and Graefe[26] take the forms (III) and (IV)

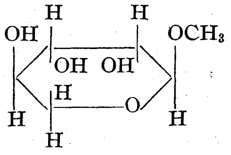


(III) β-Methyl-L-sorbopyranoside

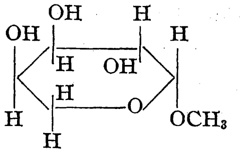


(IV) α-Methyl-D-fructopyranoside

and their close stereo similarity is apparent; their only difference is in respect to the configuration of their carbon atom 5, and it is to be concluded that their common peculiar behavior is independent of the stereo form of this particular carbon atom. The following is an interesting case in this connection. In acid methyl alcoholic solution D-lyxose finally reaches equilibrium when its α-methyl pyranoside is the predominating substance; under like conditions D-arabinose forms its β-methyl pyranoside principally; the stereo formulas (V) and (VI) show that the stereo form of carbon atom 3 for these substances has a great influence upon the stability of the grouping on carbon atom 1. The same influence from carbon atom 3 is noticed in the configurations of the more stable forms of the acetohalogen sugars and the fully acetylated forms, of ring configuration.

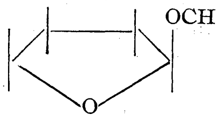


(V) α-Methyl-D-lyxopyranoside

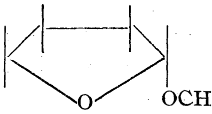


(VI) β-Methyl-D-arabinopyranoside

The skeleton formulas for the furanoid ring are (VII) and (VIII), as proved by Jackson and Hudson.

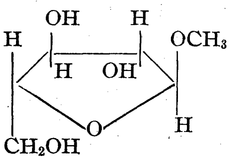


(VII) $\left.\begin{matrix}\alpha\text{-D-}\\ \beta\text{-L-}\end{matrix}\right\}$ Methyl glycosides
(C_1 is dextrorotatory)

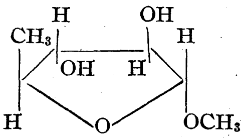


(VIII) $\left.\begin{matrix}\beta\text{-D-}\\ \alpha\text{-L-}\end{matrix}\right\}$ Methyl glycosides
(C_1 is levorotatory)

The known[28] α-methyl-D-arabinofuranoside is written as (IX) and the known[29] α-methyl-D-arabinomethylopentoside as (X); it is seen that closely approach mirror-image forms, which accounts for their opposite signs and near magnitudes of rotation.



(IX) α-Methyl-D-arabinofuranoside ($[\alpha]_D$ + 123)



(X) α-Methyl-L-arabinomethylopentoside ($[\alpha]_D$ −129)

Lastly, the skeleton formulas for the septanoid ring glycosides, etc., obviously are to be written in similar conventional form; detailed examples may be omitted.

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[28] Montgomery and Hudson, THIS JOURNAL, **59**, 992 (1937).

[29] Swan and Evans, *ibid.*, **57**, 200 (1935).

Summary

It is proposed to abandon the use of the symbols α and β as parts of the actual names of the higher carbon sugars and to designate these by the abbreviated names of two hexoses, one of which indicates the hexose that is used in the synthesis and the other of which shows the hexose that the new sugar resembles in its ring configurations. Examples are shown for the proposed names and for the use of the symbols α and β in designating the stereostructures of the pyranoid, furanoid and septanoid ring forms.

WASHINGTON, D. C. RECEIVED MARCH 3, 1938

[CONTRIBUTION NO. 239, DEPARTMENT OF CHEMISTRY, KANSAS STATE COLLEGE]

The Reaction of Kojic Acid with Aldehydes[1,2]

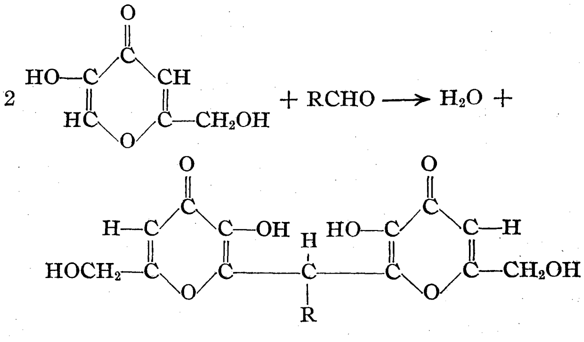
BY H. N. BARHAM AND G. NATHAN REED

Kojic acid, 2-hydroxymethyl-5-hydroxy-γ-pyrone, was first obtained by Saito[3] in a culture of *Aspergillus oryzae* grown upon steamed rice. Since then it has been found to be produced when different species of *Aspergilli* are grown upon a variety of organic substances.[4] The acid used in this research was produced in the laboratories of Kansas State College by the growth of *Aspergillus flavus* upon a glucose medium.

While investigating the properties of kojic acid it was observed that a solid reaction product was obtained readily with formaldehyde. This reaction was extended to other aldehydes until a series of solid derivatives was obtained which included derivatives from all of the normal, saturated, aliphatic aldehydes up to heptaldehyde, as well as acrolein, benzaldehyde, hydrocinnamaldehyde, cinnamaldehyde, and α-furfuraldehyde.

An investigation of these derivatives was made in order to establish their constitution. The molar quantities involved in their preparation, together with other quantitative data, indicated that the products were formed by the elimination of one molecule of water from two molecules of kojic acid and one molecule of aldehyde. The aldehyde products gave red colorations with ferric chloride, could be titrated with standard alkali and formed insoluble copper salts which contained the calculated per cent. of copper. Upon treating with thionyl chloride, chloro compounds were formed which could be produced also by the reaction of the corresponding aldehydes with 2-chloromethyl-5-hydroxy-γ-pyrone (obtained from kojic acid with thionyl chloride). Acetate esters were prepared and when hydrolyzed gave acetyl values corresponding to four hydroxyl groups per molecule. Attempts to hydrolyze the aldehyde products with dilute acid or alkali were unsuccessful. When the aldehyde products were treated with phenyldiazonium chloride and the resulting mixture neutralized with alkali, colored compounds were produced which appeared to be unstable diazonium salts of the phenolic hydroxyls. Under similar conditions, kojic acid coupled with phenyldiazonium chloride to form a stable dye.

It was concluded, therefore, that these aldehyde products were formed according to the equation



Experimental Data

Reagents.—The crude kojic acid obtained by concentrating the fermentation liquor was recrystallized twice from water, using Norite in the first recrystallization to decolorize the solution. The final purification was accomplished by chilling hot alcoholic solutions with rapid stirring. Prepared in this manner, the acid was obtained as fine, light cream-colored needles of m. p. 152–153°.

The formaldehyde used was a U. S. P. formalin solution. The other aldehydes were Eastman preparations.

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(1) Abstract of a thesis presented by G. Nathan Reed to the Graduate Council of Kansas State College in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

(2) Presented in part before the Division of Organic Chemistry of the American Chemical Society at the Rochester meeting, September, 1937.

(3) K. Saito, *Bot. Mag. Tokyo*, **21**, No. 249 (1907).

(4) A critical review of the literature upon kojic acid was made by Barham and Smits, *Trans. Kansas Acad. Sci.*, **37**, 91–113 (1934).

Preparation of the Aldehyde Products.—Although in the preliminary study slightly better yields were obtained from the use of two mols of kojic acid for each mol of aldehyde, in the actual preparation equimolar proportions were used because the products obtained in this way were easier to purify. A typical reaction mixture contained 10 g. of kojic acid and an equivalent amount of aldehyde dissolved in 100 cc. of ethyl alcohol. One cc. of concentrated ammonium hydroxide was added as a catalyst. The reaction mixture was refluxed one hour and then placed in an electric air-oven at 60–65° for from two to forty-eight hours depending upon the aldehyde used. By attaching a long glass tube to the reaction flask and passing this through the vent in the top of the oven, evaporation was prevented and the heating could be continued as long as required. Following this period in the oven, the reaction mixture was poured into a crystallizing dish and concentrated by surface evaporation. The solid material which formed was removed by filtration, washed with a little alcohol, and dried in a desiccator under reduced pressure.

The reaction of kojic acid and the aldehydes was always accompanied by the formation of resinous material. The quantity produced was influenced decidedly by the solvent, the catalyst, and the temperatures employed. Formaldehyde and kojic acid gave good yields with water as the solvent if no ammonium hydroxide was added, but in the presence of this catalyst resin formation was dominant. The remaining aldehydes did not react in water solutions. Likewise, the crystalline products were not formed when alcoholic solutions were used without ammonium hydroxide. On the other hand, using alcoholic solutions and ammonium hydroxide, the presence of any appreciable concentration of water favored the formation of these resins. Furthermore, the quantity of this resinous material was increased by lengthening the period of heating, especially at the boiling point of the alcoholic solutions. The particular conditions described above were selected in order to reduce to a minimum the amount of these resinous substances in the crude products.

The lower aldehydes reacted readily. Among the higher aliphatic aldehydes, the rate of reaction was influenced by the length and character of the carbon chain—those with an even number of carbon atoms reacted more easily than those with an odd number. The yields were good in most instances. Benzaldehyde reacted readily, giving good yields. Hydrocinnamaldehyde was somewhat slower in action while cinnamaldehyde reacted very slowly. Furfuraldehyde reacted readily but gave only fair yields. Acrolein reacted with extreme difficulty and the yields were very poor.

Purification of the Products.—The crude reaction products were purified by extraction with boiling chloroform or by recrystallization from alcohol. In the latter case, the alcoholic solutions were chilled in a freezing bath of salt and ice while stirring vigorously to prevent supersaturation. Repeated extractions or recrystallizations were necessary to eliminate the greater portion of the contaminating resinous substances but it is believed that traces still remained in spite of continued effort to remove them.

Physical Properties of the Products.—The purified products are light cream-colored, powdery solids. They are practically insoluble in cold water, while their solubility in hot water decreases rapidly as the molecular weight increases. All are somewhat soluble in alcohol with a pronounced tendency to give supersaturated solutions. They are slightly soluble in methyl alcohol and acetone, much less soluble in chloroform, and apparently insoluble in ether, ligroin, benzene, toluene, and carbon tetrachloride. They are soluble in alkali but insoluble in acids. The melting points of the products are given in Table I.

TABLE I

MELTING POINTS OF PRODUCTS

Aldehyde used	M. p., °C. (corr.)
Formaldehyde	248.3–249
Acetaldehyde	211.2–212
Propionaldehyde	217.5–218
Butyraldehyde	192.4–193
Valeraldehyde	185.6–187.2
Capraldehyde	144–147
Heptaldehyde	152.6–153.6
Benzaldehyde	242.4, dec.
Hydrocinnamaldehyde	182–183.5
Cinnamaldehyde	175–176
α-Furfuraldehyde	210–211
Acrolein	About 250[a]

[a] Yield too small to purify and determine m. p. carefully.

Combustion Analysis.—The combustion analyses of the aldehyde products are given in Table II. The calculated values are for a product formed by two mols of kojic acid and one mol of aldehyde with the loss of one mol of water.

TABLE II

ANALYTICAL RESULTS BY COMBUSTION

Aldehyde product	Carbon, % Calcd.	Carbon, % Found		Hydrogen, % Calcd.	Hydrogen, % Found	
Formaldehyde	52.70	52.78	52.85	4.05	4.42	4.22
Acetaldehyde	54.19	54.28	54.16	4.51	4.80	4.67
Propionaldehyde	55.55	55.71	55.28	4.94	5.11	5.02
Butyraldehyde	56.81	56.99	56.92	5.33	5.61	5.61
Valeraldehyde	57.95	58.01	57.98	5.68	5.81	5.94
Heptaldehyde	59.99	60.12	60.82	6.32	6.58	6.69
Benzaldehyde	61.31	61.96	61.35	4.30	4.52	4.43
Hydrocinnamaldehyde	63.00	62.50	62.31	5.00	5.06	5.05
α-Furfuraldehyde	56.35	55.99	56.01	3.87	4.08	4.04

Chemical Properties of the Products.—The aldehyde products gave a red coloration with ferric chloride. The intensity of the color produced decreased as the molecular weight increased, as would be expected from the solubilities. The products reacted readily with alkali and it is believed that they could be titrated with 0.1 N sodium hydroxide if an indicator were used which changed color at a pH of about 12. When the products were dissolved in standard alkali, back titrated with acid until neutral to phenolphthalein, and treated with an excess of copper acetate, insoluble copper salts were precipitated. These salts were analyzed for copper by igniting to copper oxide. The results given in Table III are for 1-g. samples of the aldehyde products and the calculated values are for products containing two phenolic hydroxyls and resulting from the reaction of two mols of kojic acid with one mol of aldehyde through the loss of one mol of water.

TABLE III

COPPER CONTENT

Product	Copper, % Calcd.	Copper, % Found
Formaldehyde	17.785	17.690
Acetaldehyde	17.115	17.084
Propionaldehyde	16.494	16.675
Butyraldehyde	15.916	16.090
Heptaldehyde	14.403	14.370
Benzaldehyde[a]	14.668	16.550

[a] Copper precipitate brownish in color and obviously contained some reduced copper.

The kojic acid–aldehyde products reacted readily with thionyl chloride. The unchanged thionyl chloride was removed from the reaction mixture with petroleum ether and the derivatives recrystallized from water. These derivatives did not show the presence of ionizable halogen but a sodium fusion revealed the presence of organic halogen. The chloro compound prepared in this manner from the butyraldehyde product melted at 180–184°. When 2-chloromethyl-5-hydroxy-γ-pyrone (prepared from kojic acid through the action of thionyl chloride) was treated with butyraldehyde, using the procedure outlined in the preparation of the aldehyde products, a product was obtained which melted at 183–185°. Apparently the same compound was prepared by these two reactions.

The acetates of the aldehyde products were prepared by treating with an excess of acetic anhydride and a few drops of concentrated sulfuric acid. If these mixtures were allowed to stand for twelve hours at room temperature, dark red solutions were formed. Upon decomposing the excess of acetic anhydride with water and evaporating the solutions before a fan, resinous products were obtained. The repeated extraction of these resinous products with water gave white solids which were purified by recrystallizing from ethyl alcohol or ethyl acetate. If the original reaction mixtures were treated with a large excess of ether, the acetates were precipitated immediately as crystalline solids. The melting points of the acetates were: from formaldehyde product, 105–107°; from acetaldehyde product, 134–136°; and from benzaldehyde product, 166–168°.

The acetates of the aldehyde products were hydrolyzed quantitatively by dissolving a weighed sample in a known quantity of standard alkali (an excess was always used), brought to colorless toward phenolphthalein with standard hydrochloric acid, and back titrated to full red with standard alkali. The net quantity of alkali used was determined by difference. The amount of alkali required for the liberated aldehyde product was determined by a blank. When this value was subtracted from the net quantity of alkali used, the difference was taken as a measure of the acetic acid produced upon hydrolysis. The values obtained for 1-g. samples of the acetates are given in Table IV and compared with the theoretical amounts of acetic acid calculated for diacetate and tetraacetate derivatives.

TABLE IV

HYDROLYSIS OF ACETATE ESTERS

Acetate prepared from	Total titration	No. of acetate groups	Required for nuclear OH	CH_3COOH by difference	Calcd.
Formaldehyde	123.8	2	46.1	77.7	56.62
product		4	37.7	86.1	86.70
Acetaldehyde	123.2	2	41.0	82.2	50.76
product		4	33.8	89.4	83.70
Benzaldehyde	117.0	2	41.2	75.8	43.86
product		4	34.8	82.2	74.1

A sample of the acetaldehyde product was dissolved in glacial acetic acid. The addition of an excess of ether to this solution precipitated a solid which, after recrystallizing from alcohol, required 49.50 cc. of 0.1 *N* sodium hydroxide to titrate a 1-g. sample to the full color of phenolphthalein. Since 50.80 cc. of 0.1 *N* sodium hydroxide was required to titrate a 1-g. sample of the original acetaldehyde product, it is evident that an oxonium salt was not formed by the aldehyde product.

The aldehyde products were not hydrolyzed either by refluxing for nineteen hours with dilute sulfuric acid or by stirring for forty-eight hours with 0.1 *N* sodium hydroxide.

Kojic acid did not react with benzal chloride in alcoholic solution. However, when the method of Friedel and Crafts was employed, using freshly distilled nitrobenzene as a solvent, a free evolution of hydrogen chloride was observed. After heating for two hours at 100–150° the reaction mixture was poured into an excess of water and the solid which precipitated removed by filtration. This solid was extracted repeatedly with ether and finally with alcohol. Evaporation of the alcohol gave a small amount of material which melted at 250–256° with decomposition; this compares favorably with the melting point of the crude benzaldehyde product.

When kojic acid was dissolved in alkali, cooled to 0–5°, treated with phenyldiazonium chloride, and the mixture made alkaline, a dark red solid was precipitated. This substance was stable. It could be dried and kept exposed to the air for an indefinite period of time. No apparent decomposition occurred when it was treated with moderately strong acid. When the same procedure was used with the aldehyde products, red and brown solids were obtained. However, these solids were unstable and turned dark upon drying in air. Apparently a gas was liberated during this decomposition. A freshly prepared sample of the colored compound obtained from the acetaldehyde product was suspended in cold, dilute (2:1) hydrochloric acid. After standing for a half hour at 0–5° the solution was filtered and the filtrate placed in a solution of "H-acid" (1-amino-8-naphthol-3,6-disulfonic acid). When this mixture was made alkaline an intense red color was produced which appeared to be identical with the color formed when "H-acid" was treated with phenyldiazonium chloride. The residue from the acid treatment melted at 188–198° and when mixed with an equal amount of acetaldehyde product the melting point rose to 201–210°. From these results, the colored compounds were assumed to be diazonium salts of the phenolic hydroxyls and not the products of true coupling reactions.

Discussion of Results

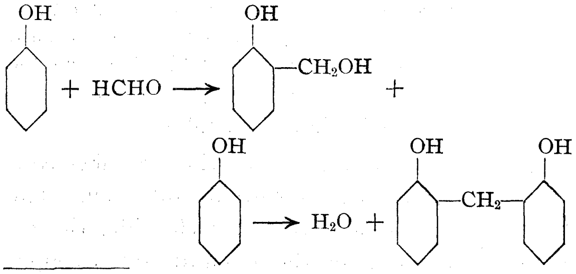
The qualitative analysis of the products consistently gave negative results for nitrogen. The production of color with ferric chloride, the reaction with alkali, and the precipitation of copper salts all indicate that the phenolic hydroxyls in position 5 are also present in the aldehyde products. Since these products do not hydrolyze readily they probably are not acetals. Further, the reaction with thionyl chloride points to the presence of the hydroxymethyl groups in the aldehyde products. These conclusions are all fully confirmed by the formation of tetraacetate esters.

This leaves position 6 as the most probable point of attack. It is known that when the Friedel and Crafts reaction is used with aromatic phenols, the hydrogen in the para position is replaced. However, when the para position is blocked, the reaction may occur at the ortho positions. If it is assumed that the hydroxymethyl group of kojic acid is para to the phenolic hydroxyl, then the only available point of attack is at position 6.

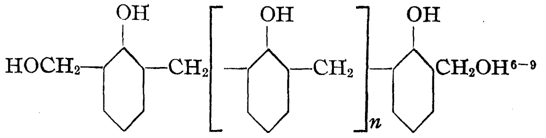
Further confirmation is given by the formation of the diazonium salts. Sidgwick[5] explains the coupling reaction of diazonium salts with phenols as forming a diazonium salt of the phenol which later rearranges by the diazo group passing to the para or ortho position. These diazonium salts of the phenol group are unstable, decomposing easily to give nitrogen, and when treated with dilute acids the original compounds are formed. Since both of these properties were observed in the products which were formed by the aldehyde products reacting with phenyldiazonium chloride, it may be assumed that diazonium salts of the phenolic hydroxyl groups were formed. If the aldehyde has attacked position 6, then all possible positions for the rearrangement of these phenolic salts are blocked and the true coupling reactions cannot proceed beyond this initial step.

It is concluded, therefore, that the aldehyde products may be represented by the general formula previously given.

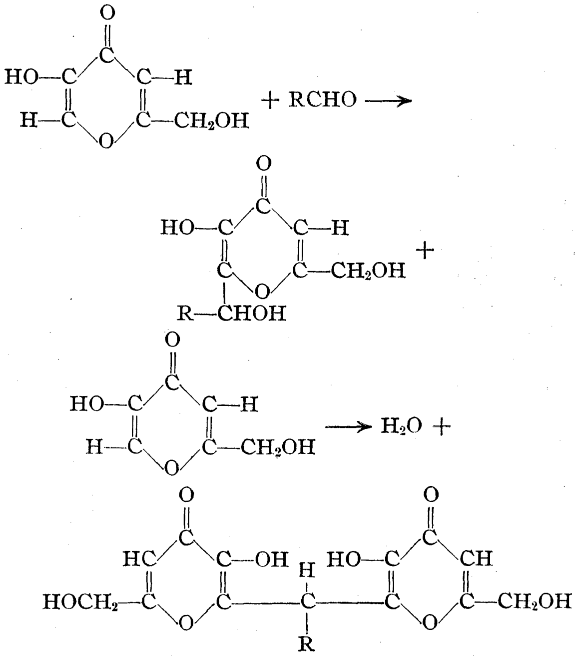
A study of the reaction of aromatic phenols with aldehydes to form resins of the Bakelite type reveals that the mechanism of reaction is probably



and that this reaction continues until a compound is formed which may be represented by



In the case of para substituted phenols, *i. e.*, *p*-cresol, the reaction occurs only at the ortho positions. Assuming that kojic acid reacts as a para substituted phenol, the analogous reaction would be



From this point of view, these aldehyde products may correspond to the compounds which appear in the early stages of phenolic resin formation. The reaction, however, stops at this stage because the ortho and para positions in both rings are blocked. That resins may be formed under certain conditions has already been mentioned under the preparation and purification. We believe that these resinous substances are produced either by molecules of kojic acid condensing from the hydroxymethyl group of one molecule to position 6 of a second molecule and so on, or by the aldehyde products condensing with unchanged kojic acid by a similar mechanism. Further investigation of this field is planned.

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[5] Nevil V. Sidgwick, "Organic Chemistry of Nitrogen," Oxford University Press, Oxford, 1910, p. 287.

[6] Baekeland and Bender, *J. Ind. Eng. Chem.*, **17**, 225–237 (1925).

[7] Morgan, *J. Soc. Chem. Ind. Trans.*, **49**, 245–251 (1930).

[8] Megson and Drummond, *ibid.*, **49**, 251–257 (1930).

[9] Wanscheidt, Itenberg and Andrejewa, *Ber.*, **69**, 1900–1907 (1936).

Conclusions

1. We have shown that kojic acid reacts with aldehydes to form solid derivatives. A series of these products has been prepared using all of the normal, saturated, aliphatic aldehydes up to heptaldehyde, in addition to acrolein, benzaldehyde, hydrocinnamaldehyde, cinnamaldehyde, and α-furfuraldehyde.
2. The probable formula for these products is given.
3. A possible mechanism of reaction is suggested based upon the present theory of resin formation by aromatic phenols and aldehydes.

MANHATTAN, KAN. RECEIVED MARCH 14, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

On the Mechanism of the Catechol–Tyrosinase Reaction

BY HARRY WAGREICH AND J. M. NELSON

Catechol has been used widely as a substrate in the study of oxidases, partly because the aerobic oxidation of this substance is catalyzed by a great many enzymes of this class. Robinson and McCance[1] showed that two atoms of oxygen are consumed in the complete oxidation of catechol, although only one atom is required, stoichiometrically, for the formation of *o*-benzoquinone, the normal product of primary oxidation. The reaction therefore is not a simple one, and a further complication arises from the fact that *o*-benzoquinone is very fugitive in aqueous solutions, especially in the presence of unoxidized catechol, as shown by Dawson and Nelson.[2]

Regarding the mechanism of the oxidation, Onslow,[3] Richter,[4] Platt and Wormall[5] and others favor the idea that hydrogen peroxide is one product of the reaction, which would account for the oxygen consumption

$$C_6H_4(OH)_2 + O_2 \longrightarrow C_6H_4O_2 + H_2O_2$$

On the other hand, Raper[6] suggests that one atom of oxygen converts catechol into *o*-benzoquinone and that this is oxidized further by the second atom consumed. To gain further insight into the problem, it seemed of interest to extend the observations of Dawson and Nelson by following the amount of oxygen consumed.

The apparatus shown in Fig. 1 was used to measure the amount of quinone formed when one atom of oxygen per mole of catechol had been consumed. The vessel was charged with 1250 cc. of 0.02 *M* phosphate–citrate buffer (*p*H 6.2) containing 100 mg. of catechol, and 500 units of tyrosinase preparation[7] (about 15 cc.) was placed in one of the side bulbs (F). The stirrer was started and, when the solutions in the vessel and

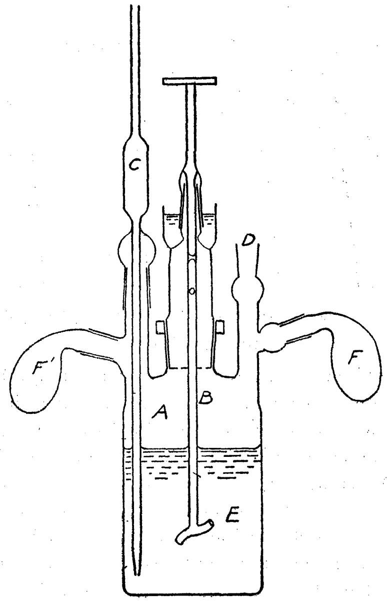

Fig. 1.—A modified form of the apparatus described by Reinders and Vles [*Rec. trav. chim.*, **44**, 1 (1925)]. A represents a heavy 2-liter glass reaction vessel, into which a pump-stirrer B was inserted. At the upper end of the stirrer was a water seal such as described by Rosenthal, Lorch and Hammett [THIS JOURNAL, **59**, 1795 (1937)]. The pipet C permitted the withdrawal of samples from the reaction solution. Tube D was connected to a manometer similar to that described by Reinders and Vles. Bulbs F and F′ were used for introducing the enzyme. The vessel A was fitted into a metal frame so as to be held in position in the thermostat.

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[1] M. E. Robinson and R. A. McCance, *Biochem. J.*, **19**, 251 (1925).

[2] Charles R. Dawson and J. M. Nelson, THIS JOURNAL, **60**, 245 (1938).

[3] M. Wheldale Onslow, "Principles of Plant Biochemistry," University Press, Cambridge, 1931, p. 135.

[4] D. Richter, *Biochem. J.*, **28**, 901 (1934).

[5] B. S. Platt and A. Wormall, *ibid.*, **21**, 29 (1927).

[6] H. S. Raper, *Physiol. Rev.*, **8**, 245 (1928).

[7] Prepared from the common mushroom, *Psalliota campestris*, by the method of Graubard and Nelson, *J. Biol. Chem.*, **112**, 135 (1935).

side bulb had reached the temperature of the thermostat (25°), the bulb F was turned in order to introduce the enzyme into the reaction mixture. After five minutes the oxygen absorbed corresponded to one atom of oxygen per mole of catechol, and at this point 25 cc. of the solution was withdrawn by means of the pipet C and the quinone determined by the method of Dawson and Nelson. The amount of quinone corresponded to 98% of the catechol oxidized. This observation confirms Raper's view that only one atom of oxygen is utilized in the formation of *o*-benzoquinone. The second atom, therefore, must be involved either in the further oxidation of *o*-benzoquinone or in the oxidation of a product of its decomposition.

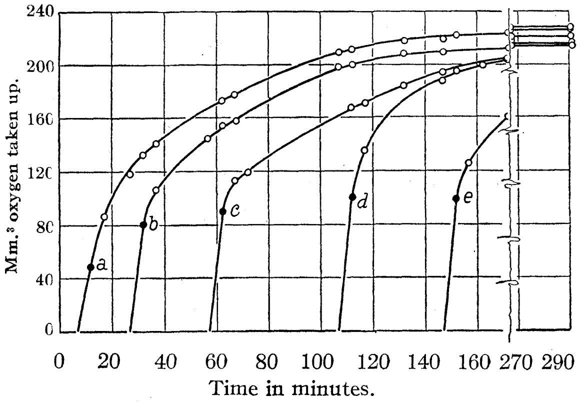

Fig. 2.—Showing the increase in rate of uptake of the second atom of oxygen, with increasing lengths of time elapsing before the enzyme was added to the disappearing *o*-benzoquinone contained in the reaction vessels of the Barcroft–Warburg apparatus. Reaction mixture the same for each curve: 4 cc. of *M* acetate–acetic acid buffer, *p*H 5, 2 cc. catechol solution (2 mg. of catechol); 2 cc. of a solution containing an amount of ceric ammonium sulfate equivalent to oxidizing 2 mg. catechol to *o*-benzoquinone. One cc. of a tyrosinase preparation (3 units) was placed in the side bulb of each reaction vessel, and the enzyme introduced into the reaction mixture at the times indicated on the abscissa axis. Temperature was 25°.

Raper and co-workers[8] found in their excellent study of the enzymatic oxidation of tyrosine to melanin that oxygen was taken up at three different stages in the course of the oxidation, and that the uptake of the last atom of oxygen was independent of the enzyme. To learn whether the uptake of the second atom of oxygen in the oxidation of catechol is catalyzed by tyrosinase the procedure described was followed. To be sure that the first stage was complete, the catechol was first oxidized to *o*-benzoquinone by an equivalent amount of ceric sulfate at *p*H 4.4 (or potassium ferricyanide in the case of more alkaline solutions, *p*H 7.7).[2,9] Since no determination of quinone was necessary, it was more convenient to use the Barcroft–Warburg respirometer method for measuring the amount of oxygen taken up.[10] The results showed that no oxygen uptake occurred in the absence of tyrosinase. When the enzyme was added to the reaction mixture 115 mm.^{3} of oxygen (1.1 atoms) was consumed at *p*H 4.5 in sixty minutes and at *p*H 7.7 in thirty minutes.

That the substance oxidized by the second atom of oxygen is not *o*-benzoquinone, as proposed by Raper, but some compound formed as the quinone disappears (possibly reformed catechol as discussed more fully in the subsequent part of the paper), is suggested by data shown graphically in Figs. 2 and 3. The data shown in Fig. 2 were obtained by placing a series of aqueous solutions containing a given quantity of catechol, freshly oxidized by an equivalent amount of ceric sulfate to *o*-benzoquinone, in the reaction flasks of a Barcroft–Warburg apparatus. After varying periods of time, as indicated on the abscissa scale in the figure, constant amounts of a tyrosinase preparation were added from the side-arms of the respective reaction flasks containing the gradually changing *o*-benzoquinone. The points marked a, b, c, d, and e on the curves correspond to the amount of oxygen taken up during the first five minutes after the addition of the enzyme. It will be observed upon examining the curves that this amount increased with the length of time elapsing before the enzyme was added (to about one hundred minutes). In other words, as the unstable *o*-benzoquinone disappears a new substance seems to be formed which is oxidized by the tyrosinase. The observed increase in the rate of oxygen uptake is due to the gradual increase in the concentration of this new substance with the length of time elapsing before the addition of the enzyme. The lack of further increase in the rate of oxidation occurring when the length of time elapsing before the addition of the enzyme exceeds one hundred minutes suggests an equilibrium being reached between the disappearing *o*-benzoquinone and the new oxidizable substance. This suggestion falls in line with the observation of Dawson and Nel-

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(8) W. C. Evans and H. S. Raper, *Biochem. J.*, **31**, 2162 (1937).

(9) E. G. Ball and T. Chen, *J. Biol. Chem.*, **102**, 691 (1933).

(10) For details of this method, see M. Graubard and J. M. Nelson, *ibid.*, **111**, 757 (1935).

son, who found that *o*-benzoquinone (judging from the liberation of iodine when a portion of the solution was added to acidified potassium iodide solution) did not entirely disappear even after the elapse of considerable time. The same idea is suggested by the curve in Fig. 3 representing the disappearance of *o*-benzoquinone with time, and discussed more fully below.

To obtain, if possible, some idea concerning the quantitative relationship between the amount of *o*-benzoquinone which had disappeared in a given time and the amount of the new oxidizable compound formed, the following experiment was undertaken. A solution consisting of 1030 cc. of water, 200 cc. of *M* sodium acetate–acetic acid buffer (*p*H of final solution 4.8), and 1.1499 g. of ceric ammonium sulfate, was placed in the reaction vessel of the apparatus described in Fig. 1. After the solution had attained the temperature of the thermostat, 100 mg. of catechol dissolved in 25 cc. of water was added, and it was assumed that the catechol was oxidized immediately to *o*-benzoquinone. After thirty-four minutes a 25-cc. portion of the reaction solution was withdrawn and its quinone content was found to have decreased to 10%, based upon the amount of catechol used. To compare this with the amount of the new oxidizable substance formed, 15 cc. of a tyrosinase solution containing 400 units of enzyme was added immediately to the reaction solution after the 25-cc. sample had been withdrawn for determining the amount of quinone remaining at the end of thirty-four minutes. Suspecting the new substance formed as the *o*-benzoquinone disappears to be catechol, which is known to be oxidized rapidly by tyrosinase, 25-cc. portions of the reaction solution were withdrawn one and one-half and three and one-half minutes after the addition of the enzyme. On determining the quinone content it was found to have risen from 10 to 54% at the end of three and one-half minutes. Half of 90%, the loss in quinone at the end of thirty-four minutes, added to the 10% of quinone remaining, is equal to 55%. The experiment was repeated several times, at *p*H 4.5, and similar results were obtained. Thus, interrupting the disappearance of the *o*-benzoquinone, in one instance at 60% and in another at 38% quinone remaining, it was found that on the addition of enzyme the quinone content rose to 80 and 66%, respectively (calcd. 80 and 69%). Another point which should be mentioned is that the newly formed quinone is fugitive just like the original *o*-benzoquinone. The points indicated on the last part of the curve in Fig. 3 represent the quinone content of the reaction solution at the corresponding time intervals.

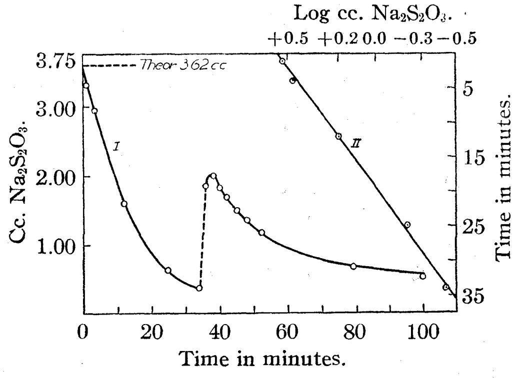
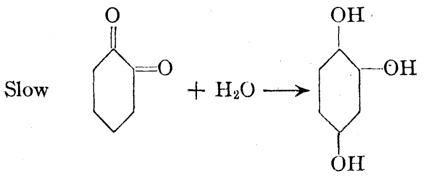
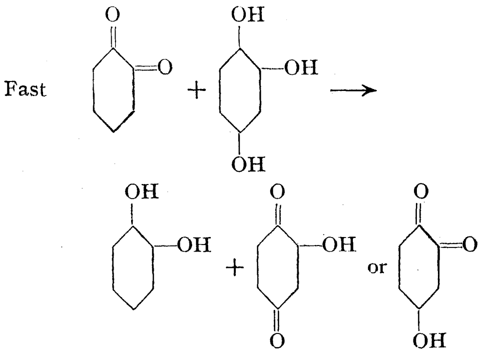


Fig. 3.—Showing the extent of disappearance of *o*-benzoquinone in aqueous solution, and the increase in quinone content, when the product resulting from the disappearing *o*-benzoquinone was oxidized by means of tyrosinase. *p*H = 4.8; temperature 25°; 1 cc. of thiosulfate soln. = 0.539 mg. of *o*-benzoquinone.

In attempting to interpret the data described above, the conclusion reached by Fieser and Peters[11] in their study of β-naphthoquinone is of interest. This quinone also tends to disappear in the presence of water. If the reactions involved in the disappearance of *o*-benzoquinone are similar to those occurring, according to these investigators, in the case of β-naphthoquinone, then they may be expressed in the form of equations (1) and (2)



(1)



(2)

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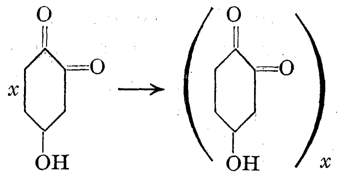
[11] L. F. Fieser and M. A. Peters, THIS JOURNAL, **53**, 793 (1931).


(3)

For every two molecules of *o*-benzoquinone disappearing, one molecule of catechol would be formed, and this in the presence of the enzyme would yield one new molecule of *o*-benzoquinone. Furthermore, if the reaction represented by equation (1) is slower than the reaction indicated in equation (2), then the rate of disappearance of the quinone should tend to be of the first order. The latter seems to be the case, since plotting the logarithms of the cc. of thiosulfate (measure of the quinone remaining) against time gives a straight line, *i. e.*, curve II in Fig. 3. By adding the assumption represented by equation (3) that the hydroxybenzoquinone disappears from the reaction solution, through polymerization, at a rate greater than that of the reaction represented by equation (1), then results such as those described above should be expected. That hydroxybenzoquinone is unstable, at least in alkaline solutions, has been shown by Eller,[12] who found that alkaline oxidation of hydroquinone or catechol results in the formation of humic acid, a dark brown, sparingly soluble polymer of hydroxybenzoquinone. Experiences in this Laboratory also show that aqueous solutions of *o*-benzoquinone, on standing, give rise to the formation of sparingly soluble material resembling humic acid in appearance. In some instances considerable difficulty was encountered in recognizing the disappearance of the starch–iodine blue color, when the quinone contents of solutions were determined by Dawson and Nelson's method.

Szent-Györgyi[13] noticed that the addition of catechol to an aqueous solution of *o*-benzoquinone accelerates the disappearance of the latter. Dawson and Nelson point out that the rate of disappearance of *o*-benzoquinone in dilute aqueous solutions conforms closely to a first order reaction, but deviates from the latter in the presence of higher concentrations of catechol. In the light of these observations, it is possible that the reactions indicated by equations (1) and (2) may only represent the course of the reaction when dilute solutions of catechol are oxidized rapidly by tyrosinase so as to avoid the presence of an appreciable quantity of unoxidized catechol and, under relatively acid conditions, *p*H 4.0–6.0.

Summary

1. Under conditions of low concentration of substrate, high concentration of enzyme, and *p*H 4.5–6.5, catechol is enzymatically oxidized to *o*-benzoquinone with the consumption of one atom of oxygen per mole of catechol.

2. The consumption of the second atom of oxygen per mole of catechol oxidized is also catalyzed by tyrosinase.

3. A substance is formed when *o*-benzoquinone disappears in aqueous solution at *p*H 4.5–6.5, which is aerobically oxidized to a quinone by means of tyrosinase.

4. The quantity of quinone compound formed in the oxidation of the substance mentioned in (3) corresponds to one-half of the *o*-benzoquinone which has disappeared.

5. The substance formed as the *o*-benzoquinone disappears in aqueous solution is oxidized faster by means of the enzyme than the *o*-benzoquinone itself.

NEW YORK, N. Y. RECEIVED MARCH 21, 1938

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[12] W. Eller, *Ber.*, **53**, 1473 (1920).

[13] A. von Szent-Györgyi, *Biochem. Z.*, **162**, 399 (1925).

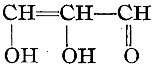
[CONTRIBUTION FROM THE CHEMICAL LABORATORY, HOWARD UNIVERSITY]

The Preparation and Properties of an Ene-diol. α-Phenyl-β-mesitoyl Acetylene Glycol

BY R. P. BARNES AND LEILA S. GREEN[1]

With the proof of the structure of ascorbic acid[2] there came a renewed interest in the chemistry of ene-diols.

Now heretofore, with the exception of reductone[3] (I), it has never been possible to isolate an ene-diol in an open chain compound except in a system with the chain —COCHOHCOCO—.[4]



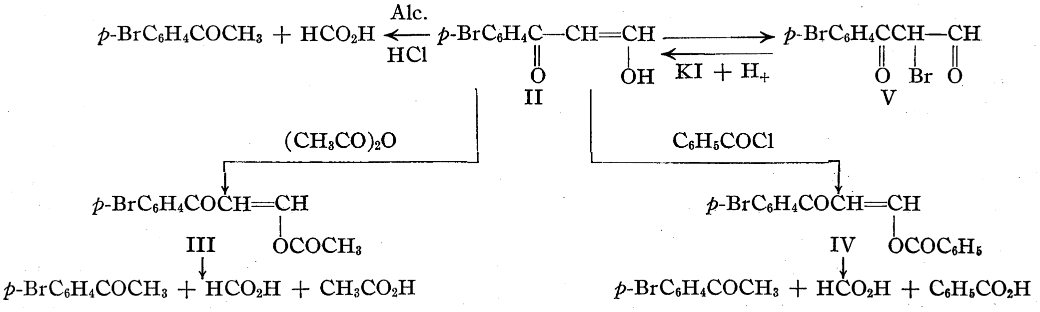
$$\underset{\text{OH}}{\text{CH}}=\underset{\text{OH}}{\text{CH}}-\underset{\text{O}}{\overset{}{\text{CH}}}$$

I

This investigation was undertaken in an attempt to make a new ene-diol with the same open chain carbon skeleton as is present in reductone. The likelihood of accomplishing this end seemed to lie in the possibility of obtaining a system with a chain —COCHOHCO— or —CHOHCOCO— with a hydrogen sufficiently active to shift. It had already been pointed out[5] that dibenzoylcarbinol, which contains the first of these chains, does not exist as an ene-diol. Kohler and Thompson[6] have shown that it is possible to follow, step by step, the isomerization of an hydroxy ketone in solution by way of an intermediate ene-diol, which, however, was too unstable to isolate.

More recently still, substances of an ene-diolic nature have been indicated in solution in connection with the reduction products of dimesitylbutanetrione enol and its methyl ethers.[7]

With a knowledge of the structure of reductone, and knowing that oxymethylene-*p*-bromoacetophenone (II) is enolic because of the presence of the very active aldehydic carbonyl group, we chose this substance as our starting material. The method of preparation of oxymethylene-*p*-bromoacetophenone[8] gives such poor yields that we had to modify the procedure in order to get sufficient material with which to work. This substance is 67% enolic; gives an O-acetate (III); an O-benzoate (IV); and a monobromo derivative (V). When the monobromo derivative, which is 100% enolic, was heated with potassium acetate in glacial acetic acid, decomposition with charring occurred, and no carbinol acetate could be isolated. We had hoped to hydrolyze the carbinol acetate to the carbinol which presumably would have shown some indications of an ene-diolic nature. The parent substance, as well as its acyl derivatives, is hydrolyzed in hydrochloric acid–alcoholic solution to *p*-bromoacetophenone



Kohler and Thompson[6] state that the group —CHCO-Mes promotes enolization and enhances the stability of the enol. Attention also has been called[9] not only to the activating influence of the mesityl nucleus upon an α-hydrogen in mesitylbenzylglyoxal and β-phenylbenzylmesitylglyoxal, but also to its stabilizing influence.

A similar activating effect on an α-halogen atom has also been observed in connection with the coupling reaction of α-bromo-β-phenylbenzyl-

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(1) This report is the summary of a thesis presented in partial fulfilment of the requirements for the Master's Degree.

(2) (a) Hirst, *Chemistry and Industry*, **52**, 221 (1933); (b) Reichstein, Grüssner, and Oppenauer, *Helv. Chim. Acta*, **16**, 561, 1019 (1933); **17**, 510 (1934); (c) Haworth, *et al.*, *J. Chem. Soc.*, 1419 (1933); 62, 1192 (1934); (d) Reichstein and Grüssner, *Helv. Chim. Acta*, **17**, 311 (1934).

(3) Norrish and Griffiths, *J. Chem. Soc.*, 2837 (1928).

(4) (a) Karrer and v. Segesser, *Helv. Chim. Acta*, **18**, 273 (1935); (b) Karrer and Musante, *ibid.*, p. 1140; (c) A. H. Blatt, THIS JOURNAL, **57**, 1103 (1935); **58**, 1894 (1936).

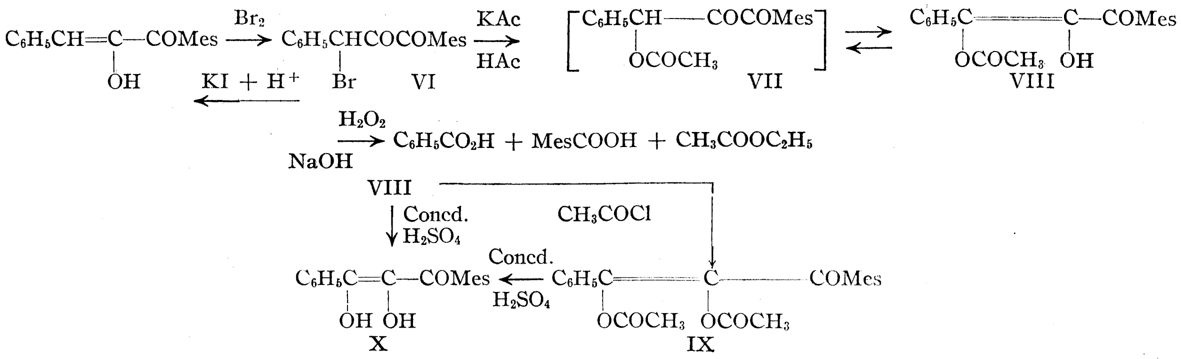
(5) A. H. Blatt and W. Lincoln Hawkins, *ibid.*, **58**, 81 (1936).

(6) E. P. Kohler and R. B. Thompson, *ibid.*, **59**, 887 (1937).

(7) Robert E. Lutz and John L. Wood, *ibid.*, **60**, 705 (1938).

(8) Erich Benary, *Ber.*, **61**, 2252 (1928).

(9) (a) R. P. Barnes, THIS JOURNAL, **57**, 937 (1935), (b) **60**, 1168 (1938).



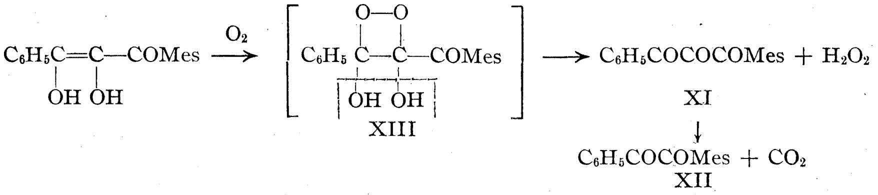
glyoxal[6] and the substitution reaction[9b] whereby it has been possible to obtain an α-oxy-α-diketone and its acetate, in spite of the fact that generally substitution on a methylene group α- to a carbonyl group has a tendency to decrease the activity of remaining substituents. Therefore we set out to test this effect on α-bromobenzylmesitylglyoxal (VI).

The enolic modification of benzylmesitylglyoxal was brominated in cold absolute ethereal solution, producing a golden-yellow oil (VI) which could not be crystallized from any solvent. In acetone solution with hydriodic acid this product is easily reduced to the parent enol. The golden-yellow monobromo compound is 24% enolic. It was dissolved in glacial acetic acid and refluxed with an excess of freshly fused potassium acetate, whereupon potassium bromide separated out. There was no noticeable change in color of the solution. Contrary to the opinion held by Kohler and Brown,[10] and contrary to the mechanism proposed by Blatt,[11] this α-bromo-α-diketone reacts by way of a direct substitution reaction to produce the acetate (VII) of the α-oxy-α-diketone. This substance could not be obtained solid. Its methyl alcoholic solution is of a deep red-wine color. On standing overnight in the cold, this solution deposits a beautiful pale peach-colored solid (VIII), which gives a cherry-red color with alcoholic ferric chloride, and is 100% enolic. This enolic modification of the acetate (VIII) is hydrolyzed simultaneously and cleaved by means of alkaline hydrogen peroxide with the production of benzoic and trimethylbenzoic acids and ethyl acetate.

When the monoacetate (VIII) is refluxed with acetyl chloride it is converted quantitatively into the diacetate (IX). This substance is a pale lemon-yellow solid which produces no color with alcoholic ferric chloride. These acetates are recovered unchanged after refluxing their alcoholic solutions with both hydrochloric and sulfuric acids.

Both the mono- and diacetates dissolve in concd. sulfuric acid with the production of deep orange-colored solutions. When poured over finely crushed ice, an odor of ethyl acetate and a light yellow solid are formed. The yellow solid is the ene-diol (X). It gives a deep greenish-blue color with alcoholic ferric chloride, and is 37% ene-diolic in methyl alcoholic solution as indicated by titration with standard iodine solution.

The ene-diol (X) is not a very stable substance. In the solid state or in solution in peroxide-free ether, it quite readily undergoes autoxidation with production of the tri- and diketones,[12] (XI) and (XII), respectively, and hydrogen peroxide. The course of the reaction is best followed in peroxide-free ether, for thus an acidulated potassium iodide solution rapidly colors up red due to the peroxide oxidation of hydriodic acid to free iodine. The oxidizing substance must be hydrogen peroxide, since oxidation by means of the organic peroxide (XIII) probably would result in a cleavage of the molecule to benzoic and mesitylglyoxylic acids.



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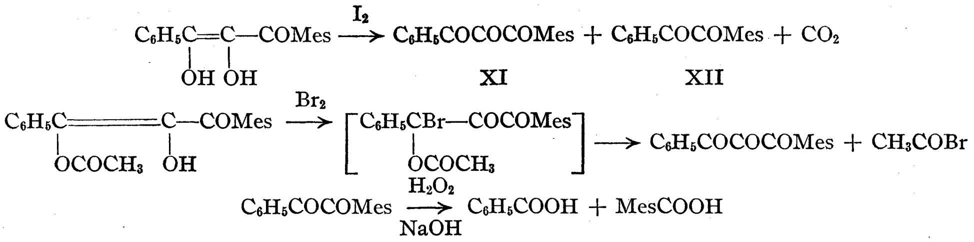
[10] E. P. Kohler and F. W. Brown, THIS JOURNAL, **55**, 4299 (1933).

[11] A. H. Blatt, *J. Wash. Acad. Sci.*, **28**, 1 (1938).

[12] Gray and Fuson, THIS JOURNAL, **56**, 739 (1934); Weinstock and Fuson, *ibid.*, **58**, 1233 (1936).

The ene-diol (X) also suffers oxidation in an acidulated iodine solution. The products of this reaction are the tri- and diketones (XI) and (XII), respectively. The triketone is a deep orange-colored solid, melting at 94°; the diketone is pale yellow and melts at 134°. When the monoacetate (VIII) is brominated in chloroform and heated, the resulting yellow compound is exclusively the diketone. The diketone (XII) is cleaved quantitatively by alkaline hydrogen peroxide to benzoic and trimethylbenzoic acids.



$$\mathrm{C_6H_5\underset{OH}{C}{=}\underset{OH}{C}{-}COMes \xrightarrow{I_2} \underset{XI}{C_6H_5COCOCOMes} + \underset{XII}{C_6H_5COCOMes} + CO_2}$$

$$\mathrm{C_6H_5\underset{OCOCH_3}{C}{=}\underset{OH}{C}{-}COMes \xrightarrow{Br_2} \left[C_6H_5\underset{OCOCH_3}{CBr}{-}COCOMes\right] \longrightarrow C_6H_5COCOCOMes + CH_3COBr}$$

$$\mathrm{C_6H_5COCOMes \xrightarrow[NaOH]{H_2O_2} C_6H_5COOH + MesCOOH}$$

This behavior of the triketone (XI) is consistent with what is known of the chemistry of polyketones, for Gray and Fuson[13] have found that dimesityl tetraketone (XIV) upon heating in alcoholic or glacial acetic acid solution is changed into the corresponding triketone (XV). It seems therefore that dimesityl triketone is far more stable than phenylmesityl triketone, a fact which still further substantiates the stabilizing effect of the mesityl group.

$$\mathrm{\underset{XIV}{MesCOCOCOCOMes} \longrightarrow \underset{XV}{MesCOCOCOMes}}$$

Further investigation of the properties of this ene-diol and its derivatives is in progress.

Experimental

Preparation of Oxymethylene-*p*-bromoacetophenone (II).—A solution of 7.0 g. of metallic sodium in a mixture of 30 cc. of absolute alcohol and 100 cc. of absolute benzene was obtained on long refluxing. It solidified on cooling. To this crystalline mass was added 52 g. of *p*-bromoacetophenone dissolved in 35 g. of pure ethyl formate. The reaction mixture warmed up; the alcoholate dissolved; the solution became brown and a crystal meal was formed. It was allowed to stand overnight at room temperature, and was then filtered and washed with alcohol and finally with ether. The yield was 52 g. of cream colored solid. This sodium compound was dissolved in a large volume of water, filtered and acidified with cold dilute sulfuric acid with rapid stirring. A yield of 45 g. of hard yellow needles, melting at 71°, was obtained. Kurt Myer titrations show that this compound is 67% enolic.

The Acetate of Oxymethylene-*p*-bromoacetophenone (III).—A solution of 5.0 g. of oxymethylene-*p*-bromoacetophenone was made by warming with the smallest possible amount of acetic anhydride. To the solution was added one drop of concd. sulfuric acid. The solution turned red and became hot. The mass solidified. It was dried overnight *in vacuo*, yielding 6.2 g. of crude solid. It was crystallized from methyl alcohol in glistening light yellow scales melting at 125°.

Anal. Calcd. for $C_{11}H_9O_3Br$: C, 48.8; H, 3.4. Found: C, 49.0; H, 3.4.

This substance decolorizes permanganate and bromine solutions. It produces no immediate color with alcoholic ferric chloride, but a cherry-red color slowly develops on standing. It is hydrolyzed completely by alcoholic hydrochloric acid to ethyl acetate and *p*-bromoacetophenone, identified by comparison with an authentic sample.

The Benzoate of Oxymethylene-*p*-bromoacetophenone (IV).—To a solution of 2.27 g. of the oxymethylene-*p*-bromoacetophenone in 50 cc. of ether was added 2 g. of benzoyl chloride. Slowly and with constant shaking, 10% sodium hydroxide was added dropwise to this ethereal solution. With the addition of each drop of alkali an orange-red color was produced. The color disappeared on shaking. The addition of sodium hydroxide was continued until the aqueous layer was permanently alkaline. A yellow solid separated out. The ether was blown off, the solid filtered and washed with sodium hydroxide solution and finally with water. The crude dry material weighed 3.5 g. It was recrystallized from methyl alcohol in bright yellow crystals, melting at 112°.

Anal. Calcd. for $C_{16}H_{11}O_3Br$: C, 58.0; H, 3.4. Found: C, 58.4; H, 3.7.

The benzoate also reduces potassium permanganate, adds bromine and very slowly develops a cherry-red color with alcoholic ferric chloride. It is completely hydrolyzed by alcoholic hydrochloric acid to ethyl benzoate and *p*-bromoacetophenone, identified by comparison with an authentic sample.

α-Bromo-oxymethylene-*p*-bromoacetophenone (V).—To a chilled solution of 16.5 g. of bromine in 150 cc. of chloroform was added slowly and with rapid stirring 20 g. of the sodium derivative of oxymethylene-*p*-bromoacetophenone. The solution finally became colorless. Sodium bromide was formed. The suspension was filtered and the sodium bromide washed thoroughly with chloroform. The chloroform was evaporated and the colorless glassy residue was taken up in hot glacial acetic acid from which it crystallized in shining colorless crystals, melting at 112°.

Anal. Calcd. for $C_9H_6O_2Br_2$: C, 35.3; H, 2.0. Found: C, 35.9; H, 2.5.

The bromo compound gives a beautiful light red color in alcoholic ferric chloride solution. In acetone solution it is reduced quantitatively to oxymethylene-*p*-bromoacetophenone by means of potassium iodide in acid solution.

A differential Kurt Meyer titration indicates that the

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[13] Gray and Fuson, THIS JOURNAL, **56**, 2100 (1934).

bromo compound is 100% enolic, for two atoms of iodine are liberated per mole of bromo compound.

α-Bromobenzylmesitylglyoxal (VI).—An absolute ethereal solution of 15.5 g. of benzylmesitylglyoxal in 100 cc. of absolute ether was chilled and treated dropwise with the calculated quantity of bromine. With the addition of each drop of bromine the red color faded on shaking. Finally copious fumes of hydrogen bromide were given off. The hydrogen bromide and ether were pumped off, leaving 20.2 g. of a golden-yellow oil which could not be crystallized from any solvent.

Anal. Calcd. for $C_{18}H_{17}O_2Br$: C, 62.3; H, 4.9. Found: C, 62.3; H, 5.1.

The bromo compound gives a red color with alcoholic ferric chloride, and is easily reduced by hydriodic acid to the parent α-diketone. Differential titrations show it to be 24% enolic.

The Acetate of α-Oxybenzylmesityl-α-diketone (VII–VIII).—The bromo compound above (20.2 g.) was dissolved in 100 cc. of glacial acetic acid and refluxed for thirty minutes with 40 g. of freshly fused potassium acetate. Potassium bromide crystallized out. The solution was allowed to cool and was poured into a large volume of water. A deep yellow oil separated out. The yield was 15 g. It was dissolved in methyl alcohol, producing a deep red wine-colored solution, which could not be crystallized immediately. On standing overnight in the cold, however, a very pale peach-colored crystalline solid separated out. The yield was 11 g., melting at 71°.

Anal. Calcd. for $C_{20}H_{20}O_4$: C, 74.0; H, 6.2. Found: C, 74.3; H, 6.4.

It gives a red wine-colored solution with alcoholic ferric chloride and is 100% enolic. It is recovered unchanged after refluxing its alcoholic hydrochloric or alcoholic sulfuric acid solution for one hour.

Upon treatment with alkaline hydrogen peroxide an odor of ethyl acetate is observed and the compound is cleaved, yielding benzoic and trimethylbenzoic acids, each of which was identified by comparison with authentic samples.

The Diacetate of α-Phenyl-β-mesitoylacetylene Glycol (IX).—Excess acetyl chloride was added to 3 g. of the acetate of α-oxybenzyl-α-diketone in which it dissolved. It was refluxed for thirty minutes. The acetyl chloride was pumped off over solid sodium hydroxide. A glassy residue was left. It was dissolved in hot methyl alcohol from which it crystallized in pale lemon-yellow crystals, melting at 131°.

Anal. Calcd. for $C_{22}H_{22}O_3$: C, 72.1; H, 6.0. Found: C, 72.1; H, 6.4.

It produces no color with alcoholic ferric chloride, but reduces permanganate and adds bromine. When refluxed in alcoholic hydrochloric or alcoholic sulfuric acid solution, it is recovered unchanged.

α-Phenyl-β-mesitoylacetylene Glycol (X).—To 30 cc. of chilled concd. sulfuric acid was added 2.5 g. of the monoacetate. In three minutes, with stirring, a deep orange-red transparent solution resulted. This solution was poured over finely crushed ice, with the production of a light yellow solid. The suspension was allowed to stand overnight in the cold protected from air. A granular crystalline solid was obtained on filtering and washing with iced water. The yield was 2.2 g., melting at 79–80°.

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.6; H, 6.4. Found: C, 76.4; H, 6.9.

This substance produces a deep green-blue color with alcoholic ferric chloride. The color fades slowly to yellow.

Iodine Titration of Ene-diol.—The following samples of the ene-diol were dissolved in 20 cc. of 95% alcohol each and acidified with 3 cc. of 10% sulfuric acid. Excess of standard iodine solution was then added, and the unused iodine titrated immediately with standard thiosulfate, 1.0 cc. of *N* iodine = 0.142 g. of ene-diol.

No.	Wt. of sample, g.	Vol. of *N* I used as 0.1056 *N* I, cc.	Vol. of *N* thio required as 0.1003 *N* thio, cc.	Vol. of I used up, cc.	% Ene-diol
I	0.0168	1.7334	1.6890	0.0444	37.48
II	.0714	1.8846	1.6990	.1856	36.49
					Mean 36.98

The Tri- and Diketones (XI and XII).—These polyketones are obtained under a variety of conditions.

When the solid ene-diol is exposed to atmospheric oxygen it becomes sticky and finally solidifies. It then produces no color with alcoholic ferric chloride. This solid upon solution in methyl alcohol and chilling gives a deep orange solid, melting at 94°.

Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.14; H, 5.7. Found: C, 77.03; H, 5.8.

The mother liquor from this crystallization on concentrating gives a light yellow solid melting at 134°.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.9; H, 6.4. Found: C, 81.1; H, 6.6.

It is sparingly soluble in methyl alcohol. It is cleaved quantitatively by alkaline hydrogen peroxide to benzoic and trimethylbenzoic acids, identified by comparison with authentic samples.

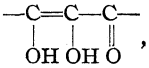
When an ethereal solution of the ene-diol is allowed to stand for a few minutes, it loses its ability to produce color with alcoholic ferric chloride. It liberates iodine very rapidly from an acidulated potassium iodide solution; and on evaporation leaves a residue which upon crystallization from methyl alcohol yields a deep orange solid, melting at 94° and a lighter yellow substance whose melting point is 134°. Mixed melting points with the above analyzed samples are unchanged.

A solution of 2 g. of the ene-diol in 30 cc. of alcohol was acidified with 5 cc. of 10% sulfuric acid. To this solution approximately 0.1 *N* iodine was added slowly. The alcoholic solution decolorized the iodine solution very rapidly. Finally it was allowed to stand overnight in the presence of excess iodine. Deep orange crystals melting at 94° were obtained. The mother liquor from a recrystallization gave the 134° product.

A solution of 1 g. of the ene-diol in 10 cc. of chloroform was treated in the cold with 0.6 g. of bromine in 5 cc. of chloroform. The chloroform solution avidly absorbed each drop of the bromine. Hydrogen bromide was evolved. The chloroform was pumped off and the residue taken up in methyl alcohol. The product of this crystallization was exclusively the light yellow substance, melting point and mixed melting point with the above analyzed sample unchanged.

A solution of the ene-diol in alcoholic ferric chloride produces a deep green-blue color which gradually fades to yellow on standing. Evaporation of this solution yields a light yellow solid, melting point and mixed melting point with the above 134° melting compound unchanged.

Summary

Herein are reported the preparation and properties of a new ene-diol having the open chain  $-\underset{\mathrm{OH}}{\underset{|}{\mathrm{C}}}=\underset{\mathrm{OH}}{\underset{|}{\mathrm{C}}}-\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}-$, and some further evidences of the activating influence of the mesityl nucleus upon α-substituents together with its stabilizing effects on the resulting compound.

WASHINGTON, D. C. RECEIVED MAY 10, 1938

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF ILLINOIS]

Derivatives of 4-Aminobenzenesulfonanilide. I

BY G. L. WEBSTER AND L. D. POWERS

Following the observation made by Trefouel, Trefouel, Nitti and Bovet[1] that 4-aminobenzenesulfonamide was a valuable therapeutic agent in the treatment of infections caused by the β-hemolytic streptococcus, a large number of derivatives and analogs of this compound were tested in the search for other compounds which would be effective against the same and other organisms. Biological tests have shown only a few substances which have comparable action against bacterial organisms of any type.

It has been shown by Buttle, Gray and Stephenson[2] and by Rosenthal, Bauer and Branham[3] that, when given in equal molecular doses, 4-aminobenzenesulfonanilide is just as effective against pneumococcic infections in mice as is 4-aminobenzenesulfonamide. It has also been shown[1,3] that the presence of an amino group para to the sulfonamide group is necessary for therapeutic action.

Only a few derivatives of 4-aminobenzenesulfonanilide, in which an amino or a nitro group has been substituted for a hydrogen atom of the anilide ring, have been reported in the literature. Whitby[4] has published results on the protective action of the tartrates of 4,4′-diaminobenzenesulfonanilide and 4,3′-diaminobenzenesulfonanilide against experimental infections in mice and Bauer and Rosenthal[5] have reported their results with the first of these two diamines and with 4-aminobenzenesulfon-4′-nitroanilide. The authors of these papers presented no syntheses or chemical characterization of these compounds.

We have prepared a series of derivatives of 4-aminobenzenesulfonanilide in which a hydrogen atom of the anilide ring has been substituted with a nitro, amino or hydroxyl group in the hope that biological tests might disclose active chemotherapeutic agents.

Preliminary reports to us have indicated that several of these compounds show some slight protective action against experimental streptococcal infections in mice and one, 4-acetaminobenzenesulfon-4′-aminoanilide, has been described as moderately effective.[6] A more detailed report will be published elsewhere by Dr. Long.

Nitro derivatives of 4-acetaminobenzenesulfonanilide were prepared by the action of 4-acetaminobenzenesulfonchloride on a hot solution of the nitroaniline in dimethylaniline.

The corresponding amino derivatives were prepared by the ferrous hydroxide reduction method of Jacobs and Heidelberger.[7]

The hydroxyl derivatives of 4-acetaminobenzenesulfonanilide were prepared by the action of 4-acetaminobenzenesulfonchloride on a hot aqueous solution of the corresponding aminophenol and also by the method used for preparing the nitro derivatives.

Preparation of derivatives of 4-aminobenzenesulfonanilide was accomplished by boiling the acetamino compounds with an alcoholic solution of hydrochloric acid.

Diazotization of 4-acetaminobenzenesulfon-3′-aminoanilide and heating the resulting solution yielded the corresponding 3′-hydroxy derivative. Diazotization of 4-acetaminobenzenesulfon-4′-aminoanilide and boiling the diazonium solution

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(1) Trefouel, Trefouel, Nitti and Bovet, *Compt. rend. soc. biol.*, **120**, 756 (1935).

(2) Buttle, Gray and Stephenson, *Lancet*, I, 1286 (1936).

(3) Rosenthal, Bauer and Branham, *U. S. Pub. Health Repts.*, **52**, 662 (1937).

(4) Whitby, *Lancet*, I, 1517 (1937).

(5) Bauer and Rosenthal, *U. S. Pub. Health Repts.*, **53**, 40 (1938).

(6) Private communication from Dr. Perrin H. Long, The Johns Hopkins Hospital.

(7) Jacobs and Heidelberger, THIS JOURNAL, **39**, 1435 (1917).

TABLE I

Name 4-Acetaminobenzenesulfon-	M. p., °C.	Formula	Nitrogen, %[a] Calcd.	 Found	Sulfur, %[b] Calcd.	 Found
2′-Nitroanilide	200–201	$C_{14}H_{13}O_5N_3S$	12.53	12.22[c]	9.56	9.50
3′-Nitroanilide	236–237	$C_{14}H_{13}O_5N_3S$	12.53	12.53[c]	9.56	9.55
4′-Nitroanilide	237–238	$C_{14}H_{13}O_5N_3S$	12.53	12.22[d]	9.56	9.65
2′-Aminoanilide	222–223	$C_{14}H_{15}O_3N_3S$	13.77	13.48	10.50	10.47
3′-Aminoanilide	217–218	$C_{14}H_{15}O_3N_3S$	13.77	13.53	10.50	10.28
4′-Aminoanilide	232	$C_{14}H_{15}O_3N_3S$	13.77	13.68	10.50	10.60
2′-Hydroxyanilide	216–217	$C_{14}H_{14}O_4N_2S$	9.15	9.00	10.47	10.43
3′-Hydroxyanilide	217–218	$C_{14}H_{14}O_4N_2S$	9.15	9.07	10.47	10.29
4′-Hydroxyanilide	.....[e]	$C_{14}H_{14}O_4N_2S$	9.15	9.01	10.47	10.43
4′-Acetaminoanilide	.....[e]	$C_{16}H_{17}O_4N_3S$	11.76	11.66	8.97	8.80

[a] Unless otherwise indicated nitrogen was determined by the Kjeldahl method. [b] Sulfur was determined as barium sulfate after oxidation of the compound with a mixture of nitric and perchloric acids. [c] Dumas method. [d] Modified Kjeldahl method, Assoc. Official Agr. Chem., Tentative and Official Methods of Analysis, 1930, p. 11. [e] No m. p. below 260°.

TABLE II*

Name 4-Aminobenzenesulfon-	M. p., °C.	Formula	Nitrogen, %[a] Calcd.	 Found	Sulfur, %[b] Calcd.	 Found
3′-Nitroanilide	171–172	$C_{12}H_{11}O_4N_3S$	14.33	14.11[d]	10.94	10.72
4′-Nitroanilide	165–166	$C_{12}H_{11}O_4N_3S$	14.33	14.11[d]	10.94	10.85
2′-Aminoanilide	201–202	$C_{12}H_{13}O_2N_3S$	15.97	15.72	12.18	12.00
3′-Aminoanilide	176–177	$C_{12}H_{13}O_2N_3S$	15.97	15.85	12.18	12.03
4′-Aminoanilide	155–156	$C_{12}H_{13}O_2N_3S$	15.97	15.78	12.18	12.01
2′-Hydroxyanilide	182–183	$C_{12}H_{12}O_3N_2S$	10.60	10.55	12.14	12.06
3′-Hydroxyanilide	195–196	$C_{12}H_{12}O_3N_2S$	10.60	10.58	12.14	12.04
4′-Hydroxyanilide	196–197	$C_{12}H_{12}O_3N_2S$	10.60	10.58	12.14	12.07

* The significance of the notations in this table is the same as in Table I.

yielded 4-aminobenzenesulfon-4′-hydroxyanilide. When 4-acetaminobenzenesulfon-2′-aminoanilide in dilute sulfuric acid solution was treated with nitrous acid the *o*-diazoimide of 4-acetaminobenzenesulfonanilide was formed.

Experimental Part

4-Acetaminobenzenesulfonnitroanilides.—A solution of 13.8 g. (0.1 mole) of 2-(3- or 4)-nitroaniline in 50 cc. of dry, hot dimethylaniline was treated with 23.3 g. (0.1 mole) of crude 4-acetaminobenzenesulfonchloride[8] added in several portions.[9] The mixture was heated for one hour, on a steam-bath, cooled and the dimethylaniline removed by treating the mixture with cold 1:1 hydrochloric acid. The 2′- and 4′-nitroanilides were obtained first as gums which crystallized after repeated washings with the dilute acid. The 3′-nitroanilide was obtained as a granular mass immediately. The yield of the 2′-nitroanilide was 10 g.; 3′-nitroanilide, 30 g.; 4′-nitroanilide, 15 g.

4-Acetaminobenzenesulfonaminoanilides.—A solution of 200 g. of technical ferrous sulfate in 500 cc. of water was made alkaline with a 10% solution of sodium hydroxide (about 700 cc.). A solution of 33.5 g. (0.1 mole) of the 4-acetaminobenzenenitroanilide in 250 cc. of 10% sodium hydroxide solution was added and the mixture well stirred for fifteen minutes. The mixture was filtered through a large suction filter and the ferric hydroxide residue extracted again with about 300 cc. of water. The combined filtrates were acidified to litmus paper with acetic acid and the precipitated aminoanilide recovered by filtration.

4 - Acetaminobenzenesulfonhydroxyanilides.—These compounds were made (a) by the method described above for the preparation of the nitro derivatives. The yields of hydroxyanilides were smaller than those obtained by the following method. (b) A solution of 21.8 g. (0.2 mole) of 4-aminophenol in 1800 cc. of water at 75° containing 17 g. of anhydrous sodium acetate was treated with 58 g. of partially dried crude 4-acetaminobenzenesulfonchloride, estimated to be 80% pure, with mechanical stirring. Stirring was continued for thirty minutes, the mixture cooled and filtered. The yield of crude, air-dried product was 42 g. The isomeric hydroxyanilides were prepared in like yield.

The derivatives of 4-acetaminobenzenesulfonanilide described above are insoluble in water, ether and benzene; soluble in alcohol, acetone, dioxane and acetic acid. They may be crystallized from alcohol or from diluted alcohol of suitable concentration (50–20%). They dissolve in dilute (10% or less) sodium hydroxide solutions from which the sodium salt is precipitated by the addition of more concentrated alkali. The amino derivatives dissolve in dilute solutions of mineral acids.

4,4′ - Diacetaminobenzenesulfonanilide.—This compound was prepared from 4-acetaminobenzenesulfon-4′-aminoanilide by warming with an excess of acetic anhydride. It is insoluble in water and most of the usual organic solvents. It can be crystallized from a large volume of acetic acid.

Hydrolysis of the Acetyl Group.—A mixture of 10 g. of the 4-acetaminobenzenesulfonanilide in 200 cc. of alcohol and 15 cc. of concd. hydrochloric acid was refluxed on a

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(8) *Org. Syntheses*, **5**, 3 (1925).

(9) Ullmann and Gross, *Ber.*, **43**, 2694 (1910), prepared toluenesulfontoluide by this method using diethylaniline as a solvent.

steam-bath for two hours. The alcohol was distilled off and the residue dissolved or suspended in 75 cc. of water. The aqueous mixture was cooled and made alkaline with ammonium hydroxide and then slightly acid with acetic acid. The desired 4-aminobenzenesulfonanilide was obtained by filtration.

The derivatives of 4-aminobenzenesulfonanilide prepared as described above are insoluble in ether and benzene; slightly soluble in cold water but appreciably soluble in boiling water; soluble in alcohol, acetone, dioxane and acetic acid. They may be crystallized from diluted alcohol (50% for the nitro derivatives, 35–20% for the amino derivatives) or from water (hydroxy derivatives). Amino and hydroxy derivatives were crystallized in an atmosphere of carbon dioxide. All of these compounds are soluble in dilute sodium hydroxide solutions and in dilute mineral acids.

4,4'-Diaminobenzenesulfonanilide Dihydrochloride.—To a solution of 1.2 g. of the pure base in a mixture of 10 cc. of alcohol and 1 cc. of concd. hydrochloric acid an additional 5 cc. of concd. hydrochloric acid was added. The precipitated dihydrochloride was filtered and dried in a desiccator over calcium chloride and sodium hydroxide. The white crystals begin to decompose at 200°. A solution (1:1000) in water has *p*H 2.5. *Anal.*[10] Calcd. for $C_{12}H_{15}O_2N_3Cl_2S$: Cl: 21.10; Found: Cl, 21.27.

Diazotization of 4-Acetaminobenzenesulfon-2'-aminoanilide.—A solution of 3.05 g. (0.1 mole) of 4-acetaminobenzenesulfon-2'-aminoanilide in a mixture of 250 cc. of water and 5 cc. of concentrated sulfuric acid was diazotized with 0.7 g. (0.1 mole) of sodium nitrite, dissolved in 14 cc. of water, at room temperature. The *o*-diazoimide of 4-acetaminobenzenesulfonanilide is precipitated from the reaction mixture immediately.

The product was filtered from the reaction mixture and washed with hot water to remove inorganic compounds and recrystallized from 50% alcohol. The yield was 2.5 g. This compound was stable at the boiling temperature of the mixture but, when recrystallized and dried, it decomposed at 138–140°. The reaction is analogous to that reported by Morgan and Micklethwait[11] in the diazotization of benzenesulfon-2'-aminoanilide. *Anal.* Calcd. for $C_{14}H_{12}O_3N_4S$: N, 17.72; S, 10.14. Found: N (Dumas), 17.82; S, 10.07.

Diazotization of 4-Acetaminobenzenesulfon-3'-aminoanilide.—A solution of 1.5 g. of the 4-acetaminobenzenesulfon-3'-aminoanilide in a mixture of 5 cc. of concd. sulfuric acid and 25 cc. of water was diazotized with 0.35 g. of sodium nitrite in 7 cc. of water without cooling. The solution was heated on a steam-bath for one hour, cooled and filtered. After recrystallization from 20% alcohol, the compound melted at 217–218°. The mixed melting point with the product obtained from coupling 3-aminophenol with 4-acetaminobenzenesulfonchloride was unchanged.

Diazotization of 4-Acetaminobenzenesulfon-4'-aminoanilide.—Three grams of 4-acetaminobenzenesulfon-4'-aminoanilide dissolved in a mixture of 10 cc. of concd. sulfuric acid and 50 cc. of water was diazotized, without cooling, with 0.7 g. of sodium nitrite in 14 cc. of water. A precipitate formed which dissolved when the temperature of the solution was raised to 75°. The solution was heated at 90–95° for three hours and then briefly boiled. After cooling, the solution was made alkaline with ammonium hydroxide and then acid with acetic acid. Recrystallized from water the product melted at 195–196°. The mixed melting point with 4-aminobenzenesulfon-4'-hydroxyanilide was unchanged, indicating that hydrolysis of the acetyl group had taken place.

Summary

The preparation of a number of new nitro, amino and hydroxy derivatives of 4-aminobenzenesulfonanilide and 4-acetaminobenzenesulfonanilide has been described. Work is in progress on other derivatives of these compounds.

CHICAGO, ILLINOIS RECEIVED APRIL 23, 1938

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[10] Method of Thompson and Oakdale, THIS JOURNAL, **52**, 1195 (1930).

[11] Morgan and Micklethwait, *J. Chem. Soc.*, **87**, 73 (1905).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. XXXV. Carbinols from Stallions' Urine

BY RUSSELL E. MARKER, ELMER J. LAWSON, EWALD ROHRMANN AND EUGENE L. WITTLE

Although the presence of oestrone in stallions' urine has been reported by several investigators,[1] apparently no work has been done on the neutral fractions from this source.

As part of an extensive investigation of the steroid substances in various urines, we have made a preliminary study of stallions' urine. After hydrolysis of the urine, and removal of the phenolic and acidic substances with alkali, the neutral extract was treated with Girard's reagent. Only a very small amount of ketonic material, amounting to 100 mg. per 200 gallons (760 liters) was obtained. The non-ketonic fraction was treated with phthalic anhydride and pyridine to separate the carbinols. The carbinol fraction was treated with digitonin to separate the β-sterols. From the digitonide a sterol of m. p. 134° was obtained. This sterol does not decolorize bromine in acetic

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[1] For the literature on this subject, see Fieser, "Chemistry of Natural Products Related to Phenanthrene," 2nd ed., Reinhold Publishing Corp., New York, N. Y., 1936, pp. 198–199.

acid, yields an acetate melting at 124°, and remains largely unepimerized after treatment with sodium in boiling xylene. In view of its source, this sterol has been named β-equistanol. Oxidation of β-equistanol yields the corresponding ketone, equistanone, m. p. 115°. This ketone does not correspond in its solubility behavior or melting point to cholestanone, stigmastanone, ergostanone, or γ-sitostanone. The following table summarizes the properties of these compounds:

	M. p., °C.		M. p., °C.		M. p., °C.
β-Equistanol	134	β-Equistyl acetate	124	Equistanone	115
β-Cholestanol	142	β-Cholestyl acetate	115	Cholestanone	130
Stigmastanol	138.5	Stigmastyl acetate	135	Stigmastanone	160
γ-Sitostanol	144	γ-Sitostyl acetate	143	γ-Sitostanone	...
Ergostanol	151	Ergostyl acetate	144	Ergostanone	164

Evidently this sterol is different from any of the known sterols. Analytical data on β-equistanol, β-equistyl acetate and equistanone are in best agreement with the formula $C_{30}H_{54}O$ or $C_{31}H_{56}O$. We are inclined at present to regard β-equistanol as a phytosterol which is utilized incompletely, or not at all, in the metabolism of the stallion. In view of the herbivorous diet of the animal and of the widespread occurrence of β-sitosterol in plants, it is surprising that no β-sitosterol is present in stallions' urine.

Butenandt[2] has reported the presence of cholesterol in human male urine (4 mg./gal.), while Marker[3] has observed its presence in human pregnancy urine. We have found no evidence of cholesterol either in stallion urine or in mares' pregnancy urine. The occurrence of equistanol in both stallion urine and mares' pregnancy urine[4] indicates that it probably originates from the food and is not a product resulting from the condition of pregnancy.

We cannot overlook the fact that equistanol may be identical with dihydro-α-tritisterol prepared by Karrer, Salomon and Fritzsche.[5] Their compound has 30 carbon atoms with a melting point about the same as ours, but because of a lack of derivatives we are unable to make further comparisons.

The mother liquors from the digitonide were concentrated and the resulting carbinol mixture was epimerized with sodium and boiling xylene to convert any sterols of the *allo* series, originally present in the alpha form at C_3, to the corresponding beta compounds. Digitonin treatment of the epimerized mixture yielded an insoluble digitonide, a somewhat soluble digitonide and a carbinol mixture freed of compounds of the 3(β)-type. The soluble digitonide yielded β-equistanol, showing that the original carbinol mixture from stallions' urine contained, besides β-equistanol, about an equal amount of its epimer, α-equistanol. The latter compound could not, however, be isolated as such from any carbinol fractions.

The insoluble digitonide yielded a mixture of carbinols from which a triol, m. p. 295°, and a tetrol, m. p. 295°, were obtained by crystallization of the less volatile fractions obtained after vacuum sublimation of the mixture. The triol, m. p. 295°, yielded a triacetate, m. p. 140–145°. Analytical data agree best with the formula $C_{21}H_{36}O_3$ for this triol. It is evidently a compound of the *allo* series, and contains a 3(β)-hydroxyl group. As it existed in the urine the 3-OH group was in the epimeric form. We may suppose, by analogy to other carbinols present in urines, that one of the two remaining hydroxyls is at C_{20}, but the position of the third hydroxyl group is completely unknown. It should be noted that this carbinol is not present as such in stallions' urine, but rather is a transformation product of a triol of the *allo* series, having a 3(α)-hydroxyl group, which was originally present in the stallions' urine. These remarks on our knowledge of the triol, m. p. 295°, also apply to the tetrol, $C_{21}H_{36}O_4$, m. p. 295°. This tetrol may be a derivative of the products isolated from cortical extracts by Reichstein,[6] Wintersteiner and Pfiffner,[7] and Kendall.[8] Thus, it is possible that this compound may be a 3(β),11,20,21-*allo*-pregnanetetrol derived from corticosterone.

The epimerized carbinol mixture not precipitable with digitonin was oxidized, and the ketonic fraction distilled. A considerable amount of a mixture of ketones with a fruity odor was collected at 80°. After obtaining smaller fractions at 110–120°, and 120–160°, a fraction distilling at 160–200° was obtained. Crystallization of this

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(2) Butenandt and Dannenbaum, *Z. physiol. Chem.*, **248**, 151 (1937).

(3) Unpublished results.

(4) Marker and Rohrmann, This Journal, **60**, 1565 (1938).

(5) Karrer, Salomon and Fritzsche, *Helv. Chim. Acta*, **20**, 424, 1422 (1937).

(6) Reichstein, *ibid.*, **19**, 29 (1936).

(7) Wintersteiner and Pfiffner, *J. Biol. Chem.*, **111**, 599 (1935).

(8) Mason, Myers and Kendall, *ibid.*, **114**, 613 (1936).

fraction from methanol yielded the known uranetrione, m. p. 247°, as proved by direct comparison with an authentic sample. Since the carbinol fraction which yielded uranetrione contained sterols of the 3(α)-OH type belonging to the normal series in respect to C_5, it is likely that the uranetrione was formed from the same uranetriol which has been found in mares' pregnancy urine.[9] The probable existence of uranetriol in stallions' urine suggests that uranetriol may not be derived from compounds having the function of sex hormones. Rather, it is possible that uranetriol may be derived from the suprarenal cortex or from some hormone of unknown function. The latter view receives some support from the isolation of uranol-11-one-3[10] uranedione,[9] and uranediol-3(β)-11[11] from mares' pregnancy urine.

Experimental Part

Isolation of Carbinol Fraction from Stallions' Urine.—The concentrated extract from 200 gallons (760 liters) of stallions' urine weighed 40 lb. (18.2 kg.). It was steam distilled for twelve hours with 25 lb. (11.4 kg.) of sodium hydroxide in 30% aqueous solution, and then extracted with ether. The ether was evaporated, the residual tar steam distilled with 5 liters of concd. hydrochloric acid and 5 liters of water, and the non-volatile oil extracted with 10 liters of butanol. To the butanol extract was added 15 liters of heptane, causing the precipitation of much tar. The solution was decanted from the tar, treated with boneblack, and the solvents removed *in vacuo*. The sirupy residue was steam distilled with an excess of 30% aqueous sodium hydroxide for three hours, and extracted with ether. The ether was distilled and the residue treated with Girard's reagent to obtain about 100 mg. of ketonic material. The non-ketonic fraction was dried by distillation with benzene, and treated with 125 g. of phthalic anhydride and 150 cc. of pyridine to give 68 g. of carbinols. The carbinol mixture was dissolved in 1 liter of hot alcohol and a solution of digitonin added. The next day the mixture was filtered, and washed with alcohol and ether. There was obtained 8.3 g. of digitonide.

β-Equistanol.—The digitonide obtained as described above was decomposed by warming for fifteen minutes with 90 cc. of pyridine. The solution was poured into 500 cc. of ether and the precipitate collected and washed with ether. The ethereal filtrate was washed with dilute hydrochloric acid and water and evaporated to dryness. The residue was crystallized three times from methanol to give 250 mg. of β-equistanol as needles, m. p. 133°. This sterol is not very soluble in methanol, somewhat more soluble in acetone and readily soluble in ether. It does not decolorize bromine in acetic acid solution.

Anal. Calcd. for $C_{30}H_{54}O$: C, 83.7; H, 12.6. Found: C, 84.0; H, 12.3.

Twenty-five milligrams of β-equistanol was refluxed for twenty minutes with 2 cc. of acetic anhydride. On chilling the solution β-equistanyl acetate crystallized as shining plates, m. p. 124°.

Anal. Calcd. for $C_{32}H_{56}O_2$: C, 81.3; H, 12.0. Found: C, 81.4; H, 11.6. Mol. wt. calcd. for $C_{32}H_{56}O_2$, 472.5; calcd. for $C_{33}H_{58}O_2$, 486.5. Found: 485.

Nine milligrams of β-equistanol in 3 cc. of xylene was refluxed with 80 mg. of sodium for six hours. At the end of this time the sodium was decomposed with alcohol, the solution neutralized with dilute hydrochloric acid, and the organic matter extracted with ether. The ethereal solution was washed with water, and evaporated to dryness. The residue was dissolved in a little hot alcohol and to it was added a solution of 50 mg. of digitonin in 1.5 cc. of hot alcohol. The next day the precipitated digitonide was filtered and washed with alcohol and ether. The dried digitonide weighed 40 mg., corresponding to a recovery of 8 mg. of the sterol. This shows that β-equistanol is a sterol of the *allo* series.

β-Equistanone.—To a solution of 100 mg. of β-equistanol in 10 cc. of acetic acid was added a solution of 30 mg. of chromic acid in 5 cc. of 90% acetic acid. After standing for one hour, the solution was diluted with water, extracted with ether, and the ethereal extract washed with sodium carbonate solution and water. The ether was evaporated and the residue distilled in a high vacuum. The fraction distilling at a bath temperature of 120–150° was crystallized from diluted methanol to obtain β-equistanone, m. p. 115°. β-Equistanone is quite soluble in methanol, differing in this respect from cholestanone, β-sitostanone, and ergostanone.

Anal. Calcd. for $C_{30}H_{52}O$: C, 84.0; H, 12.2. Found: C, 84.2; H, 12.1.

β-Equistanol from α-Equistanol in Stallions' Urine.—The filtrate from the precipitation of β-equistanol digitonide was evaporated and extracted with ether to separate the α-sterols from some β-equistanol digitonide, which is somewhat soluble in alcohol. The ethereal solution was evaporated and the residue refluxed with 600 cc. of xylene and 25 g. of sodium for nine hours. The sodium was destroyed with alcohol, the solution neutralized with dilute hydrochloric acid, and the mixture extracted with ether. The ethereal extract was washed with water, evaporated, and the residue, in hot alcohol, treated with a solution of 25 g. of digitonin in 750 cc. of alcohol. After standing overnight in a refrigerator, the precipitated digitonide was filtered and washed thoroughly with alcohol and ether. The digitonide so obtained was set aside for further investigation. The filtrate was evaporated to dryness, leached with ether, and the soluble digitonide present decomposed by warming with 20 cc. of pyridine for thirty minutes. The resulting solution was poured into ether, the precipitated digitonin filtered, and the ethereal filtrate washed with dilute hydrochloric acid and water. After evaporating the ether, a crystalline residue remained. This residue was crystallized from acetone–methanol, and ethyl acetate, to give a product which proved to be β-equistanol, m. p. 134°.

Anal. Calcd. for $C_{30}H_{54}O$: C, 83.6; H, 12.6. Found: C, 83.8; H, 12.6.

The sterol did not decolorize bromine in acetic acid.

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(9) Marker, Kamm, Oakwood, Wittle and Lawson, THIS JOURNAL, **60**, 1061 (1938).

(10) Marker, Lawson and Crooks, *ibid.*, **60**, 1559 (1938).

(11) Marker, Rohrmann and Wittle, *ibid.*, **60**, 1561 (1938).

When warmed with concentrated sulfuric acid, it gave an orange-red color with a green fluorescence.

Ten mg. of the sterol was refluxed for thirty minutes with 5 cc. of acetic anhydride. On cooling, the acetate separated as shining plates. After recrystallization from methanol, the pure acetate was obtained as needles melting at 124°. This acetate did not depress the melting point of β-equistanyl acetate, but showed a marked depression with β-sitostanyl acetate.

Anal. Calcd. for $C_{32}H_{56}O_2$: C, 81.3; H, 12.0. Found: C, 81.4; H, 11.7. Mol. wt. calcd. for $C_{32}H_{56}O_2$, 472.5; for $C_{33}H_{58}O_2$, 486.5. Found: 485.

allo-Triol and allo-Tetrol from Stallions' Urine.—The insoluble digitonide from the epimerization of the α-sterols in stallions' urine was warmed with 50 cc. of pyridine for thirty minutes and the resulting solution poured into ether. After filtering and washing the precipitated digitonin, the filtrate was washed with dilute hydrochloric acid and water. The ether was evaporated giving 3.1 g. of residue. Crystallization of the residue from 15 cc. of methanol gave 120 mg. of a product melting at 295°. The analysis is that of an *allo*-pregnanetriol.

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 74.9; H, 10.8. Found: C, 74.6; H, 10.9.

This compound gave a triacetate melting at 140–145°.

Anal. Calcd. for $C_{27}H_{42}O_6$: C, 70.1; H, 9.2; mol. wt., 462. Found: C, 70.3; H, 9.3; mol. wt., 457.

This compound originally existed in the urine as the *epi* form at C_3 but due to isomerization with sodium was converted and isolated as the β-form. It is saturated to bromine. The *allo*-configuration at C_5 is established by the isomerization with sodium to a product precipitated by digitonin.

The filtrate from the above triol was sublimed *in vacuo* and the portion that would not sublime below 200° was crystallized from methanol. This yielded 12 mg. of a carbinol melting at 290–295° which gave a depression in melting point when mixed with the first triol. The composition is that of a tetrol.

Anal. Calcd. for $C_{21}H_{36}O_4$: C, 71.6; H, 10.0; mol. wt., 352. Found: C, 71.1; H, 9.85, mol. wt., 362.

Uranetrione from Oxidation of Stallions' Urine Residues.—The ethereal leachings from the soluble digitonide described in the previous experiment contained chiefly α-sterols of the regular series at C_5. This ethereal solution was evaporated to dryness and the residue dissolved in 1 liter of acetic acid, and distilled to remove alcohol and other solvents. The residue was dissolved in 500 cc. of acetic acid and a solution of 20 g. of chromic acid in 90% acetic acid added with cooling over a period of fifteen minutes. The solution was diluted with water and extracted with ether. The ethereal solution was freed of acids by washing with sodium carbonate solution, and then with water. The ether was evaporated and the residue, dissolved in 500 cc. of alcohol, was heated for thirty minutes with 20 g. of Girard's reagent. Ice was added, and the solution diluted with water and extracted with ether. The aqueous layer was heated for thirty minutes on a steam-bath with an excess of hydrochloric acid. The cooled solution was thoroughly extracted with ether, and the ethereal solution evaporated. The residue was distilled in a high vacuum. A fraction, weighing 1.6 g. and distilling at 80°, had a fruity odor. However, it apparently was a mixture. A fraction weighing 500 mg. was collected at 110–120°, and another at 120–160°. A fourth fraction, distilling at 160–200°, was crystallized from methanol and washed with cold ether. The product melted at 247° and gave no depression with uranetrione.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.4; H, 9.1. Found: C, 76.4; H, 9.3.

We wish to thank Dr. Oliver Kamm and Parke, Davis and Company for their generous help and assistance in various phases of this work.

Summary

Stallions' urine yields a carbinol fraction from which a saturated β-sterol of the *allo* series may be obtained. This sterol, β-equistanol, yields β-equistanone on oxidation. The presence of the epimer, α-equistanol, and of two triols is also demonstrated. One of these triols yields uranetrione on oxidation, but the other triol is probably of the *allo* series. It also gave a compound of the composition of an *allo*-pregnanetetrol.

State College, Penna. Received March 16, 1938

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. XXXVI. Ketones from Mares' Pregnancy Urine

BY RUSSELL E. MARKER, ELMER J. LAWSON, EUGENE L. WITTLE AND HARRY M. CROOKS

As part of an extensive investigation of urines from various animal sources, we have been studying during the past two years the steroid content of mares' pregnancy urine. We already have reported the presence of pregnanediol,[1] *allo*-pregnanediol,[1] uranetriol,[2] pregnanetriol,[2] and uranediol[3] in the carbinol fraction from mares' pregnancy urine. The presence of a pregnanetriol which is probably identical with our pregnanetriol, was reported earlier by Haslewood, Marrian and Smith.[4] More recently these authors also have reported[5] the presence of pregnanetriol-3,17,20 in the pregnancy urine of women afflicted with cortical tumors. In the description of our investigation of the carbinol fraction of mares' pregnancy urine we reported the separation of a ketonic fraction from this source. Since Heard[6] has announced the isolation of a number of ketones from mares' pregnancy urine, we feel obliged to report the progress we have made in the course of a similar study. We are able to confirm the presence in mares' urine of the ketone, m. p. 252°, reported by Heard and in addition we have found a number of other steroids present. While a direct comparison of our compound with Heard's ketone has not been made, we believe that the two are identical in view of their apparently similar properties. However, molecular weight determinations of our substance (mol. wt. 672) gave a value twice that of a steroid, indicating that it may be a combination of two sterol molecules through their oxygen atoms. This would account for the inactivity of these atoms. We are not planning further work on this compound since we feel that Dr. Heard is entitled to priority in its discovery.

The accompanying diagram shows the scheme of isolation of our various ketones. The crude semicarbazone mixture from 30,000 gallons (114,000 liters) of mares' pregnancy urine yielded a water solution (A) containing Heard's water-soluble semicarbazone, an ethereal solution (B) containing chiefly non-steroidal semicarbazones, and a solid crude semicarbazone mixture. The latter on systematic fractional crystallization from alcohol yielded solid semicarbazones I, II, III and IV and a mother liquor Z. Each fraction was hydrolyzed with alcoholic sulfuric acid, and further purifications were effected by high-vacuum distillation, half-succinate separation, and fractional crystallization.

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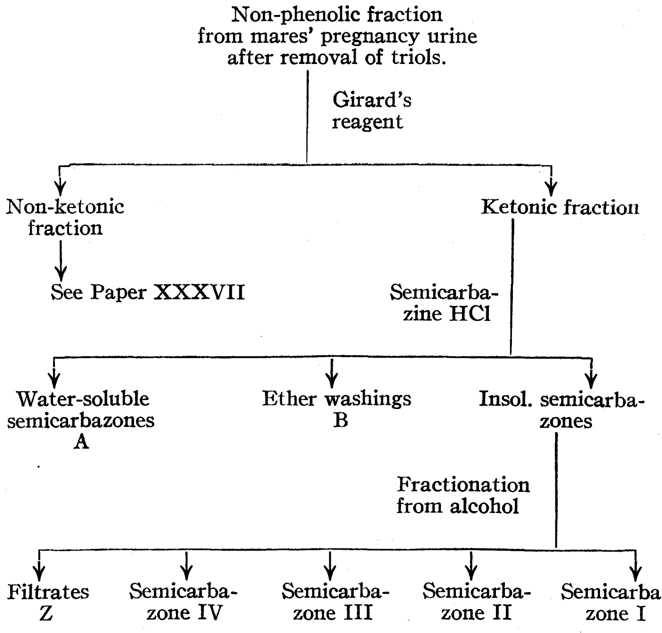

We were surprised to find that all of the semicarbazones yielded both hydroxylated and hydroxyl-free ketones. This occurrence of hydroxyl-free ketones in mares' pregnancy urine is in contrast to the almost complete absence of such ketones in human pregnancy urine.[7] Possibly the course of reduction of progesterone and other hormones in the mare follows a somewhat different path, or else reduction may be more complete in man.

From the most insoluble semicarbazone frac-

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(1) Marker, Kamm, Crooks, Oakwood, Lawson and Wittle, THIS JOURNAL, **59**, 2297 (1937).

(2) Marker, Kamm, Crooks, Oakwood, Wittle and Lawson, *ibid.*, **60**, 210 (1938).

(3) Marker, Rohrmann and Wittle, *ibid.*, **60**, 1561 (1938).

(4) Haslewood, Marrian and Smith, *Biochem. J.*, **28**, 1316 (1934).

(5) Marrian and Butler, *J. Biol. Chem.*, **119**, LXVI (1937).

(6) Heard, THIS JOURNAL, **60**, 493 (1938).

(7) Marker, Kamm and McGrew, *ibid.*, **59**, 616 (1937)

tion (I) we have isolated two substances: a ketone which corresponds in properties to Heard's ketone, $C_{19}H_{26}O_3$, m. p. 252°, but has a molecular weight of 672, and *allo*-pregnanedione. We have also some indication of the presence of at least one other ketone in this hydrolyzed semicarbazone mixture (I). The presence of *allo*-pregnanedione and pregnanedione in mares' pregnancy urine lends further support to the hypothesis that progesterone is the source of most of the steroidal carbinols and ketones, such as pregnanediol, *allo*-pregnanediol, pregnanetriol-3(α),4(β),20(α),[8] *allo*-pregnanol-3(α)-one-20, pregnanol-3-(α)-one-20, pregnanediol-3(β),20(α),[9] pregnenediol-3(β),-20(α),[9] pregnanedione, and *allo*-pregnanol-3(β)-one-20.

Semicarbazones II and III proved to contain the same components. From the hydrolyzed semicarbazones there was obtained a new hydroxyketone, uranol-11-one-3, the known pregnanedione, and *allo*-pregnanol-3(β)-one-20. The structure of uranol-11-one-3 is proved by its composition and oxidation to uranedione. It did not form a half-succinate ester, in agreement with the usual postulated inertness of a hydroxyl group at C_{11}. It gave a Zimmermann test showing the presence of a carbonyl group at C_3. The isolation of this substance lends support to the hypothesis that uranedione and the uranediols (α,α and β,α) may be related to some hormone of as yet unknown function,[10] although it is possible that these substances may be derived from the cortical hormone. The isolation of *allo*-pregnanol-3(β)-one-20 from mares' pregnancy urine is interesting in view of the fact that it was first isolated from corpus luteum extracts.[11-14] The structure of our substance was proved by the composition, melting point, precipitation with digitonin, and oxidation to *allo*-pregnanedione. This is the first 3(β)-hydroxyketone to be isolated from urine, although its occurrence had been foreseen in the light of a proposed course of the reduction of progesterone.

We have not as yet completed our investigation of the ketones from semicarbazones A, B, and Z, since the mixtures have proved to be rather intractable. Semicarbazones B and Z yield a mixture of neutral and hydroxylated ketones. The hydroxyketone mixture from semicarbazone Z does not precipitate digitonin, and therefore no *allo*-pregnenol-3(β)-one-20 is present. Distillation of the neutral and hydroxylated ketones from B gives chiefly ketones subliming below 125°, and possessing characteristic odors. Apparently almost no steroidal ketones are present in fraction B.

Because of the small amounts of ketones present in mares' pregnancy urine, a more extensive investigation of 150,000 gallons (570,000 liters) of urine is now in progress, and the results of this study will be reported shortly.

Experimental Part

Isolation of Ketonic Fractions.—The non-phenolic fraction from 30,000 gallons (114,000 liters) of mares' pregnancy urine from which the uranetriol and pregnanetriol had been removed was dissolved in about 2.5 liters of alcohol and heated for one half hour with 400 g. of Girard's reagent. Ice and water were added and the non-ketonic material extracted thoroughly with ether. The aqueous layer was acidified with an excess of hydrochloric acid and warmed for one hour on a steam-bath. The ketonic matter was extracted with ether and the ether extract washed and concentrated. The residual oil was treated again with Girard's reagent to remove a small amount of inert material which was carried through mechanically. About 30 g. of ketonic material was obtained.

The ketone mixture was dissolved in 300 cc. of alcohol and boiled for one hour with 50 g. of semicarbazide hydrochloride and 60 g. of sodium acetate. The mixture was distilled to remove almost all the alcohol and the resulting paste was stirred with water, filtered, and washed with water and with ether. The water washings were set aside as semicarbazone fraction A, and the ether washings as semicarbazone fraction B. The solid semicarbazone mixture, amounting to about 15–20 g., was fractionated from alcohol. This gave semicarbazone solution Z, and semicarbazones I, II, III, and IV Semicarbazone solutions A and Z were evaporated to dryness to yield semicarbazones A and Z. These six semicarbazone fractions were hydrolyzed separately by boiling for one hour with fifty parts of alcohol and fifteen parts of 1:2 dilute sulfuric acid. Each hydrolysate was diluted with water, extracted with ether, the ether layer washed with water, and then evaporated to dryness. With the exception of the ketones from semicarbazone I, the residues were converted into the acid succinates in order to separate hydroxylated ketones from OH-free ketones.

allo-Pregnanedione and Ketone I from Semicarbazone I.—Hydrolysis of semicarbazone I gave 1.4 g. of solid ketones which could not be separated readily by crystallization. Accordingly, the total ketonic material was distilled in a high vacuum and fractions collected at bath temperature up to 110, 110–140 and 140–180°. The first and third fractions were too small to be investigated fur-

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(8) Marker, Kamm, Wittle, Oakwood and Lawson, This Journal, **60**, 1067 (1938).

(9) Marker and Rohrmann, *ibid.*, **60**, 1565 (1938).

(10) Marker, Lawson, Rohrman and Wittle, *ibid.*, **60**, 1555 (1938).

(11) Wintersteiner and Allen, *J. Biol. Chem.*, **107**, 321 (1934).

(12) Hartmann and Wettstein, *Helv. Chim. Acta*, **17**, 1365 (1934).

(13) Butenandt, Westphal and Hohlweg, *Z. physiol. Chem.*, **227**, 84 (1934).

(14) Slotta, Ruschig and Fels, *Ber.*, **67**, 1270 (1934).

ther. Considerable residue remained in the distillation vessel. The fraction subliming at 110–140° was crystallized repeatedly from dilute acetone and yielded *allo*-pregnanedione, m. p. 196–200°, which gave no depression in melting point when mixed with authentic *allo*-pregnanedione.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2. Found: C, 79.3; H, 10.3.

The non-distillable residue in the sublimation flask was crystallized from benzene–pentane, and yielded a crude ketone (ketone I) which melted at 220°. This ketone approximated the properties of Heard's ketone (m. p. 252°) upon further crystallization.

Anal. Found: C, 76.06; H, 9.85; mol. wt. (several determinations), 672.

The semicarbazone prepared from this ketone melted at 300°.

allo-Pregnanol-3(β)-one-20.—A preliminary investigation of the hydroxyketone from semicarbazones II and III showed that one substance was present in both fractions, which were therefore combined. This hydroxy ketone was sublimed in a high vacuum at a bath temperature of 185°, and the sublimate crystallized from carbon tetrachloride to give a ketone melting at 193°. This ketone depressed the melting point of *allo*-pregnanol-20(β)-one-3 (m. p. 195°), showed no unsaturation to bromine in acetic acid and gave a heavy precipitation with an alcoholic solution of digitonin.

A portion oxidized with chromic acid in the usual manner gave *allo*-pregnanedione, m. p. 197–199°, and showed no depression with an authentic sample of *allo*-pregnanedione, m. p. 200°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2. Found: C, 79.7; H, 10.1.

Uranol-11-one-3, Pregnanedione, and Ketone II from Semicarbazones II and III.—The ketones from semicarbazones II and III were distilled separately and fractions collected at bath temperatures of 135–160°, 160–200°, leaving considerable amounts of glassy residue. The fraction 135–160° was crystallized from diluted acetone to yield a solid melting over the range 100–135°. The material in the mother liquors was then crystallized repeatedly from dilute acetone, sublimed in a high vacuum, and then crystallized from ether–pentane to give pregnanedione, m. p. 118°, which did not depress the melting point of an authentic sample.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2. Found: C, 79.5; H, 10.7.

The fraction subliming at 160–200° was a mixture which could be separated only with difficulty. Repeated crystallization from dilute alcohol and dilute acetone yielded a ketone which melted at 165°, and depressed the melting points of uranedione (m. p. 180°) and *allo*-pregnanedione (m. p. 200°).

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.2; H, 10.8. Found: C, 79.2; H, 10.8.

It gave a gelatinous semicarbazone melting at 250° with decomposition.

Oxidation of a sample with chromic acid in the customary fashion yielded uranedione, m. p. 175–176°, which showed no depression with an authentic sample of uranedione.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2. Found: C, 79.7; H, 10.5.

The glassy residues from sublimation of the neutral ketones up to 200° were combined and crystallized from benzene–pentane to yield about 100 mg. of a ketone melting at 115–120°. It did not precipitate with digitonin.

Anal. Found: C, 74.3; H, 9.65; mol. wt., 462.

We wish to thank Dr. Oliver Kamm and Parke, Davis and Company for their generous help and assistance in various phases of this work.

Summary

The ketonic fraction of mares' pregnancy urine yielded pregnanedione, *allo*-pregnanedione, *allo*-pregnanol-3(β)-one-20, and uranol-11-one-3 in addition to the ketone reported by Heard.

STATE COLLEGE, PENNA. RECEIVED MARCH 16, 1938

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. XXXVII. Uranediol from Mares' Pregnancy Urine

BY RUSSELL E. MARKER, EWALD ROHRMANN AND EUGENE L. WITTLE

In paper XXIX[1] of this series the isolation of uranetriol from mares' pregnancy urine was reported. The urane compounds were shown to differ in structure from pregnane compounds in the configuration at C_9. In the pregnane series the hydrogen at C_9 is *trans* to the methyl group at C_{10}, while in the urane series the hydrogen atom is considered to be *cis* to the methyl group. Clemmensen reduction of uranetrione gave the parent hydrocarbon, urane, which is different from either pregnane or *allo*-pregnane. Evidence was presented to show that the hydroxyl groups in uranetriol are located at the 3-, 11- and 20-positions. The presence of uranediol in mares' pregnancy urine was indicated by the fact that oxidation of a mixture of crude diols gave a diketone which on Clemmensen reduction yielded the hydrocarbon urane.

We have now succeeded in isolating uranediol from the digitonin precipitated fraction of the ketone-free carbinol fraction of mares' pregnancy

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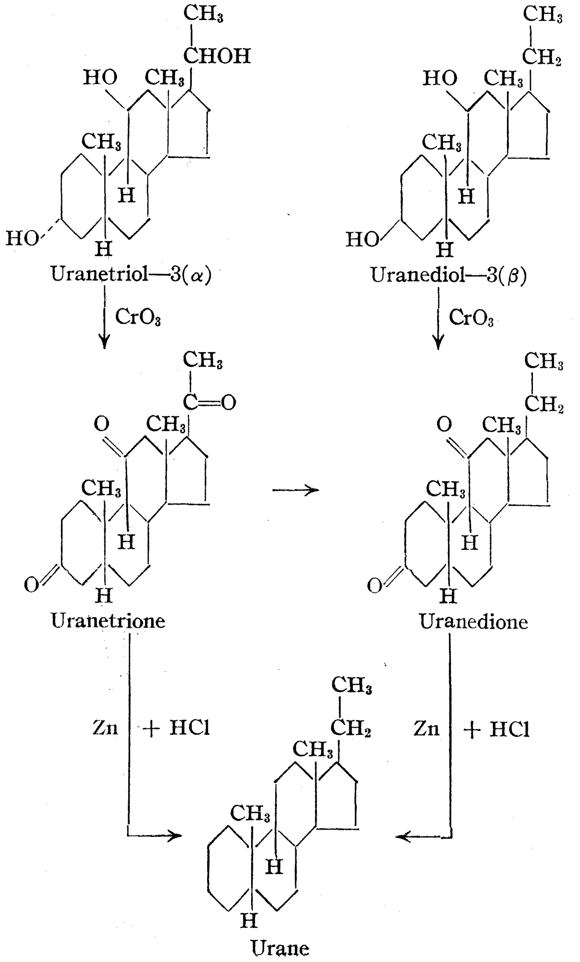
[1] Marker, *et al.*, THIS JOURNAL, **60**, 1061 (1938).

urine. Upon oxidation the diol yields a dione which is identical with that reported in paper XXIX.[1] The fact that the substance is precipitated by digitonin indicates the presence of a β-hydroxyl group in the C_3-position. The dione formed only a monosemicarbazone and a mono-2,4-dinitrophenylhydrazone which indicates that the second hydroxyl group is in the hindered C_{11}-position rather than in the C_{20}-position as in the pregnanediols.

Treatment of uranedione in acetic acid at room temperature with PtO_2 catalyst apparently reduces only the ketonic group at C_3, since epimerization of the resulting reduction products with sodium in xylene results in destruction of the material. Uranediol forms a diacetate.

Isomerization with sodium in xylene yielded material which gave very little precipitation with digitonin, indicating that the substance has the normal configuration at C_5.

The relationship of uranetriol to uranediol is given in the chart.



It is a striking fact that while uranetriol occurs in nature with the *epi* configuration with respect to the hydroxyl at C_3, uranediol possesses the normal or beta configuration at that position. The two compounds are closely related chemically as is shown by the fact that both can be reduced to the hydrocarbon, urane. It is probable, therefore, that they are closely related biologically. If not related to the active principles of the suprarenal cortex they may owe their origin to some as yet uncharacterized hormone.

The separation of uranediol from other digitonin-precipitated substances is greatly facilitated by the fact that it forms a digitonide which is relatively soluble in 95% ethanol. The soluble digitonide is separated by removing most of the alcohol and precipitating with ether. The digitonide so formed on decomposition with pyridine yields uranediol in relatively pure form. Mares' pregnancy urine contains approximately 5 mg. of the substance per gallon.

At present uranediol is the only compound which has been found in urine having the beta configuration at C_3 and the regular configuration at C_5. That other regular compounds with the beta configuration at C_3 are absent is indicated by the fact that when a mixture of digitonin-precipitated compounds was epimerized with sodium and xylene and the resulting $C_3(\alpha)$ compounds oxidized to ketones the only ketone obtained was uranedione.

The steps involved in the experimental work reported in this paper and in the two following articles are outlined in the attached Flow Sheet.

Experimental Part

Precipitation of Mares' Pregnancy Urine Carbinols with Digitonin.—A concentrate of mares' urine carbinols corresponding to 1000 gallons (3700 liters) of urine from which all ketones had been removed previously with Girard's reagent was dissolved in 400 cc. of ether. To this solution was added 2 liters of ligroin and the mixture cooled in a salt–ice bath for one hour, and the upper liquid decanted from the precipitated tar. This gave carbinol fraction I. The supernatant liquid was distilled until approximately two-thirds of the solvent was removed. The resulting mixture was cooled in a salt–ice bath and the supernatant liquid poured from the precipitated tar. This gave carbinol fraction II.

Fraction I was made up to a volume of 2 liters with 95% ethanol. The solution was heated to boiling on the steam-bath and a boiling solution of 30 g. of digitonin in 1 liter of 95% ethanol was added. A precipitate formed at once. The mixture was cooled to 20°, and after three hours was filtered. The solid was washed with 500 cc. of 95% ethanol, resuspended in 500 cc. 95% ethanol and refiltered. This

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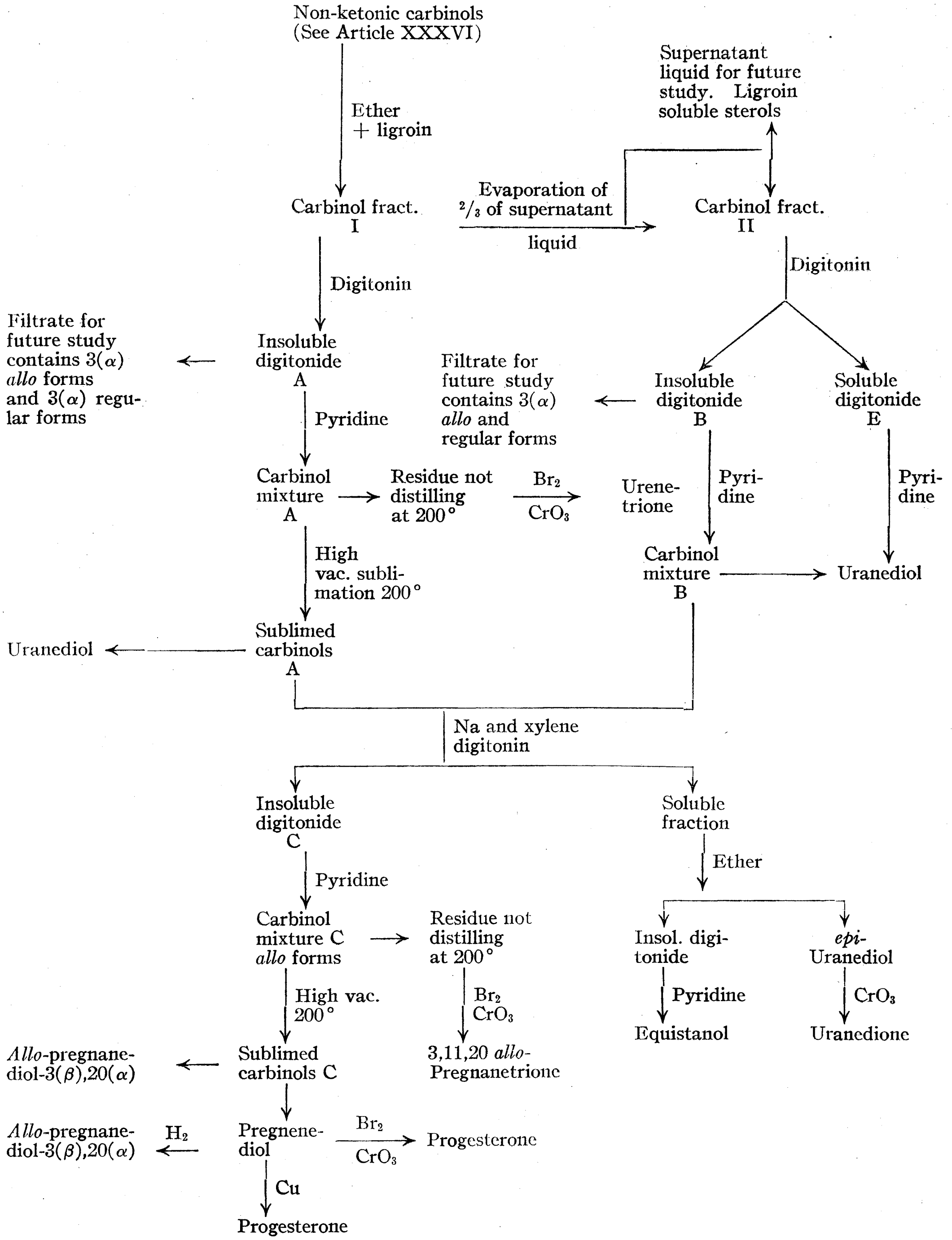

fraction, referred to as digitonide-A, was obtained in a yield of 38 g.

Carbinol fraction II was made up to a volume of 750 cc. with 95% ethanol. It was heated to boiling and a hot solution of 25 g. of digitonin in 1.5 liters of 95% ethanol was added. A precipitate formed after a few minutes. The mixture was cooled to 18°, filtered after two hours and washed with 95% ethanol. This fraction, referred to as digitonide-B, was obtained in a yield of 26 g. The filtrate was evaporated to a volume of about 50 cc. and 1 liter of ether was added. The precipitate was filtered and washed with ether. The residue of soluble digitonide-E weighed 8 g.

Digitonides A and B were reserved for other work. The filtrates likewise were reserved for investigation of the non-digitonin-precipitated substances.

Uranediol from Mares' Urine.—The soluble digitonide-E from carbinol fraction II was dissolved in 50 cc. of hot pyridine and the mixture heated thirty minutes on the steam-bath. The resulting solution was then poured into 1000 cc. of ether and the precipitate filtered and washed with ether. The filtrate was washed first with dilute hydrochloric acid and then with water. The ether was distilled, the crystals which separated were recrystallized from 15 cc. of acetone and washed with cold ether. After two additional recrystallizations from acetone the product was obtained in the form of white needles, m. p. 210°.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.8; H, 11.3. Found: C, 78.8; H, 11.3.

The compound did not discolor bromine and gave a 20° depression in melting point when mixed with 3(β),20(α)-*allo*-pregnanediol.

Preparation of Uranediol Diacetate.—Approximately 75 mg. of uranediol was refluxed with 4 cc. of acetic anhydride for thirty-five minutes. The acetic anhydride was evaporated in vacuum and the crystalline residue recrystallized from methanol to a constant melting point. It crystallized in the form of small white plates, m. p. 160°.

Anal. Calcd. for $C_{25}H_{40}O_4$: C, 74.4; H, 10.0. Found: C, 74.6; H, 10.0.

Oxidation of Uranediol to Uranedione.—Uranediol (100 mg.) was dissolved in 30 cc. of glacial acetic acid. A solution of 150 mg. of chromic anhydride in 10 cc. of 90% acetic acid then was added at room temperature. A precipitate separated at first, but dissolved after the addition of chromic anhydride was completed. The mixture was allowed to stand at room temperature for forty-five minutes. Water was added and the mixture extracted twice with 75-cc. portions of ether. The combined ether extracts were washed with water and then with saturated sodium carbonate solution. The ether was evaporated and the crystalline residue dissolved in 5 cc. of methanol and cooled in a salt–ice bath. One-half cc. of water was added slowly, the precipitate collected and recrystallized from 90% methanol. Recrystallization from acetone gave a product which melted at 177.5° and which gave no depression in melting point when mixed with a sample of uranedione prepared from uranetriol.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2. Found: C, 79.78; H, 10.3.

Uranedione Semicarbazone.—A solution of 20 mg. of uranedione, 30 mg. of semicarbazide hydrochloride and 30 mg. of sodium acetate in 10 cc. of alcohol was refluxed on the steam-bath for one hour, diluted with water and filtered. The product was washed with ether and crystallized from alcohol to yield uranedione monosemicarbazone, m. p. 245°, dec.

Anal. Calcd. for $C_{22}H_{35}O_2N_3$: C, 70.7; H, 9.4. Found: C, 70.4; H, 9.1.

Uranedione Mono-2,4-dinitrophenylhydrazone.—A solution of 30 mg. of uranedione and 40 mg. of 2,4-dinitrophenylhydrazine in 10 cc. of refluxing alcohol was acidified with two drops of concd. sulfuric acid and refluxed for five minutes. The solution was allowed to cool, the crystalline product separated by filtration and crystallized from ethyl acetate to give the mono-2,4-dinitrophenylhydrazone of uranedione, m. p. 200° dec.

Anal. Calcd. for $C_{27}H_{36}O_5N_4$: C, 65.4; H, 7.2. Found: C, 65.0; H, 7.3.

Epimerization of Steroids in the Mother Liquors.—The mother liquors from the crystallization of uranediol were evaporated and the residue dissolved in 200 cc. of xylene. Sodium (5 g.) was added and the mixture refluxed for eight hours. The excess sodium was destroyed with 95% ethanol and the resulting solution washed with dilute hydrochloric acid and water. The xylene was evaporated in vacuo at 40°. The sticky residue obtained was dissolved in 100 cc. of 95% ethanol and a boiling solution of 10 g. of digitonin in 250 cc. of 95% ethanol was added. A flocculent precipitate separated almost at once. The mixture was cooled at 20° for two hours, filtered and washed with 95% ethanol; 10.5 g. of white digitonide was obtained. The ethanol was distilled from the filtrate until a volume of about 50 cc. remained and 250 cc. of ether was added. The precipitate was collected and washed with ether. The ether was evaporated from the filtrate, leaving a sticky residue.

The residue was dissolved in 100 cc. of glacial acetic acid, 2.5 g. of chromic anhydride in 60 cc. of 60% acetic acid was added, and the mixture allowed to stand at room temperature for forty-five minutes. The mixture was then poured into 800 cc. of water and extracted with 800 cc. of ether. The ether extract was washed with water and aqueous sodium carbonate. The residue obtained by evaporation of the ether was sublimed in high vacuum at 130–150°. The sublimed material consisted almost entirely of uranedione, indicating the absence in pregnancy urine of other substances having a beta configuration at C_3 and the coprostane configuration at C_5.

We wish to thank Dr. Oliver Kamm and Parke, Davis and Company for their generous help and assistance in various phases of this work.

Summary

Uranediol, the presence of which in mares' pregnancy urine previously has been demonstrated, now has been isolated. It is shown to have the structure of uranediol-3(β),11. This is the first sterol derivative to be obtained from urine possessing the β-configuration on C_3 and the coprostane configuration on C_5. On oxidation it yields uranedione which, however, forms only a mono-semicarbazone and a mono-2,4-dinitrophenylhydrazone.

STATE COLLEGE, PENNA.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

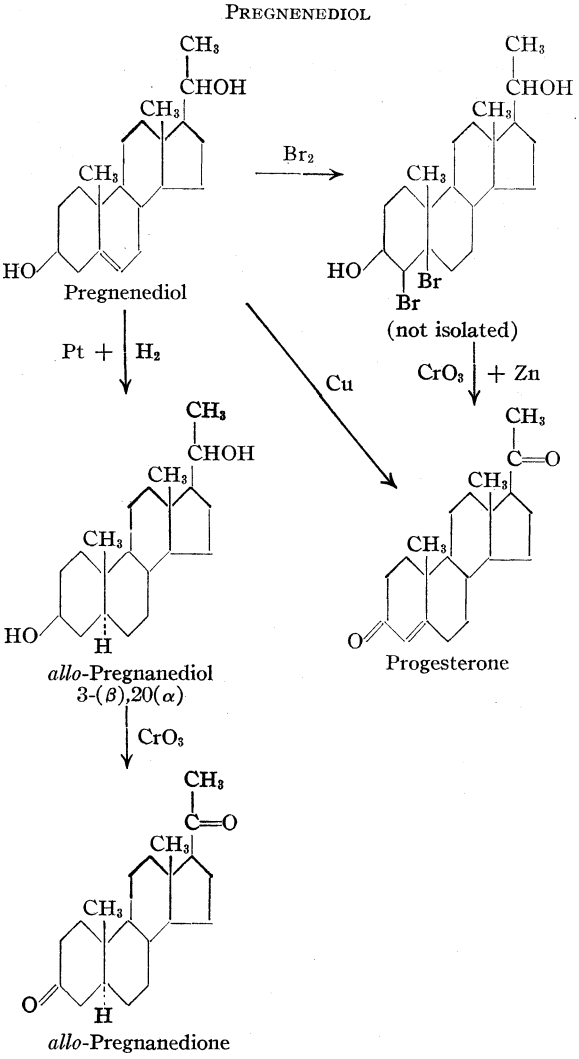
Sterols. XXXVIII. Pregnenediol in Mares' Pregnancy Urine and its Conversion into Progesterone

BY RUSSELL E. MARKER AND EWALD ROHRMANN

It is now fairly well established that pregnanediol and *allo*-pregnanediol are the final *in vivo* reduction products of progesterone. A number of intermediate reduction products, however, also have been isolated from both mares' and human pregnancy urines. *epi*-Pregnanolone[1] and *epi-allo*-pregnanolone[2] represent such partial reduction products which have been isolated from human urine. In addition to these, pregnanedione, *allo*-pregnanedione, and *allo*-pregnanol-3(β)-one-20 have been isolated from the ketonic fraction of mares' pregnancy urine.[3] The presence of these substances in pregnancy urine suggests that other possible reduction products might be present, specifically, compounds derived from $\Delta^{5,6}$-pregnene.

A preliminary study of the digitonin precipitated non-ketonic fraction of mares' pregnancy urine has shown the presence of two other reduction products of progesterone, namely, pregnenediol-3(β),20(α) and *allo*-pregnanediol-3(β),20(α). The fact that these products occur in the digitonin precipitated fraction indicates that the hydroxyl group at C_3 possesses the β-configuration. With the exception of *allo*-pregnanol-3(β)-one-20 all of the previously reported intermediate reduction products of progesterone have been of the *epi*- or (α)-configuration.

Pregnenediol was contaminated with another unsaturated compound, probably urenediol, which rendered complete purification difficult. Reduction of the pregnenediol with platinum catalyst yielded *allo*-pregnanediol-3(β),20(α) which upon oxidation with chromic anhydride gave *allo*-pregnanedione. Sublimation of the pregnenediol with copper yielded progesterone. Bromination followed by oxidation with chromic anhydride likewise yielded progesterone. The reactions involved are illustrated in the chart.



In addition to the reduction products of progesterone referred to above, there was isolated from the carbinol fraction of pregnant mares' urine the sterol β-equistanol, obtained previously from stallion urine.[4] We have found no evidence of the occurrence of cholesterol in mares' pregnancy urine.

Experimental Part

The insoluble digitonides A and B isolated in the work described in the preceding paper were used in this study. They were obtained from the neutral non-ketonic fraction from 1000 gallons (3700 liters) of mares' pregnancy urine. The Flow Sheet presented in Paper XXXVI should be consulted.

Decomposition of Digitonides from Carbinol Fraction I.—The 38 g. of digitonide A from carbinol fraction I was dissolved in 125 cc. of pyridine, the resulting solution was heated on the steam-bath for twenty-five minutes and poured into 1 liter of ether. The precipitate was filtered

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(1) Marker and Kamm, THIS JOURNAL, **59**, 1373 (1937).

(2) Marker, Kamm and McGrew, *ibid.*, **59**, 616 (1937).

(3) Marker, Lawson, Wittle and Crooks, *ibid.*, **60**, 1559 (1938).

(4) Marker, Lawson, Rohrmann and Wittle, *ibid.*, **60**, 1555 (1938).

and washed with ether. The filtrate was then washed first with an excess of dilute hydrochloric acid and then with water. The ether was evaporated on the steam-bath and the residue sublimed in high vacuum at a temperature of 130 to 200°. The sublimed material appeared to be a complex mixture of substances which would not readily crystallize.

The residue from this distillation was reserved for another study.

Decomposition of Insoluble Digitonides from Carbinol Fraction II.—The 26 g. of insoluble digitonide obtained was dissolved in 150 cc. of hot pyridine and the solution heated on the steam-bath for thirty minutes and poured into 1.5 liters of ether. The precipitate was filtered and washed with ether. The filtrate was washed as usual, the ether was distilled off, and the orange colored residue dissolved in methanol and treated with Norite.

This material was combined with the sublimed fraction obtained from digitonide A.

Epimerization of Carbinols from Insoluble Digitonides A and B.—The residues obtained from the decomposition of digitonides A and B were combined and dissolved in 150 cc. of xylene, 7 g. of sodium was added and the mixture refluxed for seven hours. The excess sodium was destroyed with ethanol and the mixture washed with dilute hydrochloric acid and water. The xylene was evaporated *in vacuo* at 40°. The residue was dissolved in 250 cc. of boiling alcohol and to this was added a hot solution of 15 g. of digitonin in 250 cc. of alcohol. The mixture was cooled at 20° for one hour, filtered, and washed with alcohol to give insoluble digitonide C.

The alcohol was evaporated from the filtrate to a volume of about 50 cc., 500 cc. of ether was added and the small amount of precipitate was filtered and washed with ether to give a soluble digitonide D.

Equistanol from Digitonide D.—The 500 mg. of soluble digitonide D was dissolved in 5 cc. of pyridine, heated on the steam-bath for thirty minutes and the solution poured into 100 cc. of ether. The white precipitate was filtered and washed with ether. After washing the filtrate as before, the ether was evaporated from the steam-bath and the residue crystallized from methanol, giving white needles melting at 130°. This material gave no depression in melting point when mixed with a sample of equistanol from stallion urine.

Anal. Calcd. for $C_{30}H_{54}O$: C, 83.6; H, 12.6. Found: C, 84.0; H, 12.3.

Decomposition of Digitonide C.—Digitonide C (18 g.) was decomposed as before, the carbinols sublimed up to a temperature of 200°, and the sublimed material combined. The residue which did not distil at 200° was reserved for further study.

allo-Pregnanediol-3(β),20(α) from Mares' Pregnancy Urine.—The distilled solid from the decomposition of digitonide C containing only *allo* and unsaturated compounds was leached with a small amount of boiling acetone. The mixture was filtered and the insoluble residue was recrystallized from methanol to give small white plates, m. p. 216°, which gave no depression with an authentic sample of 3(β),20(α)-*allo*-pregnanediol.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.8; H, 11.3. Found: C, 78.4; H, 11.3.

Pregnenediol-3(β),20(α) from Mares' Pregnancy Urine.—The filtrate obtained after separation of the *allo*-pregnanediol-3(β),20(α) was evaporated to dryness and the residue fractionally crystallized from acetone. Pure material was difficult to isolate due to contaminating substances of an unsaturated character, possibly urenetriol or urenediol. The material melted poorly at 160–170°. Recrystallized from benzene and then from acetone it melted at 172–176°. It readily took up bromine in acetic acid solution.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.2; H, 10.8. Found: C, 78.9; H, 11.1.

Reduction of Pregnenediol-3(β),20(α).—Pregnenediol (200 mg.) was dissolved in 50 cc. of ether, 0.5 g. of Adams platinum catalyst was added and the material reduced for one hour at room temperature and 45 pounds (3 atm.) pressure. The catalyst was filtered and the ether evaporated from the filtrate. The resulting residue was crystallized from 90% ethanol to give material melting at 217°. This gave no depression in melting point when mixed with an authentic sample of *allo*-pregnanediol-3(β),20(α).

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.8; H, 11.3. Found: C, 78.7; H, 11.2.

allo-Pregnanedione from allo-Pregnanediol-3(β),20 (α).—100 mg. of the *allo*-pregnanediol-3(β),20(α) obtained by reduction of pregnenediol-3(β),20(α) was dissolved in 10 cc. of glacial acetic acid; 200 mg. of chromic anhydride in 10 cc. of 90% acetic acid was added and the mixture allowed to stand at room temperature for thirty minutes. The mixture was then poured into water and extracted with ether. The ether extract was washed with aqueous sodium carbonate and water. The ether was evaporated and the residue crystallized from acetone to give white crystals melting at 199°. This gave no depression in melting point when mixed with an authentic sample of *allo*-pregnanedione.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2. Found: C, 79.6; H, 10.2.

Progesterone from Pregnenediol by Copper Oxidation.—Pregnenediol (100 mg.) was mixed thoroughly with 0.5 g. of Baker precipitated copper. The resulting mixture was heated at 230° at 20 mm. for thirty minutes. The mixture was then sublimed in high vacuum at 125°. The sublimed material was dissolved in 4.5 cc. of alcohol and 1.8 cc. of water was added to the resulting solution. After clarification with Norite the filtrate was cooled in salt–ice and the walls of the container were scratched vigorously. White crystals formed, m. p. 118–119°. This gave no depression in melting point when mixed with a sample of natural progesterone.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.1; H, 9.6. Found: C, 80.0; H, 9.5.

Progesterone from Pregnenediol by Chromium Oxidation.—Pregnenediol (200 mg.) was dissolved in 25 cc. of glacial acetic acid and the theoretical amount of bromine in acetic acid was added. To this solution was added 150 mg. of chromic anhydride dissolved in 20 cc. of 90% acetic acid. The mixture was allowed to stand for thirty minutes at room temperature, 5 cc. of alcohol and 1 g. of zinc dust were added and the mixture heated on the steam-bath for thirty minutes. The mixture was filtered and the filtrate diluted with water and extracted with 250 cc. of ether. The ether extract was washed with sodium carbonate solution and water, the ether evaporated, and the residue sublimed in high vacuum at 125°. After crystallization from 70% ethanol it melted at 118°.

We wish to thank Dr. Oliver Kamm and Parke, Davis and Company for their generous help and assistance in various phases of this work.

Summary

Pregnenediol-3(β),20(α) and *allo*-pregnanediol-3(β),20(α) have been isolated from mares' pregnancy urine. Pregnenediol-3(β),20(α) upon oxidation gave progesterone and upon catalytic reduction gave *allo*-pregnanediol-3(β),20(α). β-Equistanol, previously obtained from stallion urine, has now been detected also in mares' pregnancy urine.

STATE COLLEGE, PENNA. RECEIVED MARCH 16, 1938

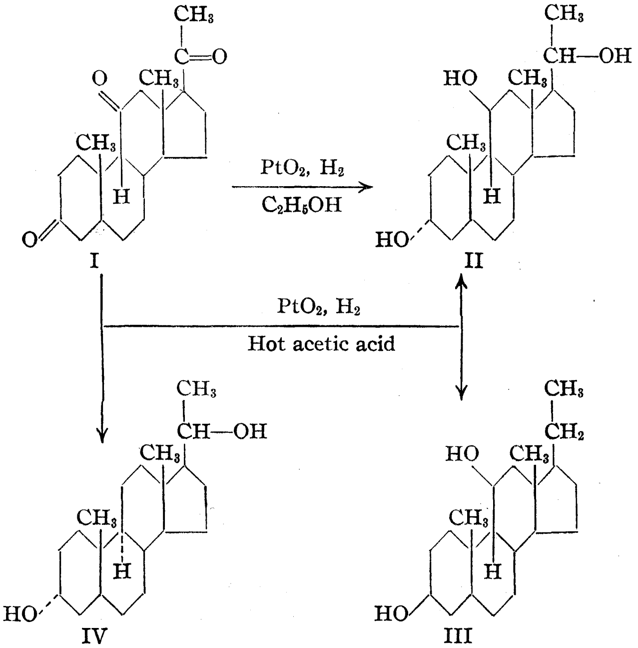
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. XXXIX. The Reduction of Uranetrione

BY RUSSELL E. MARKER, EUGENE L. WITTLE AND THOMAS S. OAKWOOD

Uranetrione (I) is a 3,11,20-triketo-urane which has been found in previous work[1] to give uranedione (3,11-diketo-urane)[2] and pregnanedione when subjected to a series of reactions, the first step being catalytic reduction. In this paper a study of the reduction of uranetrione is presented.

Catalytic reduction of uranetrione (I) with platinum oxide in ethyl alcohol gave a product which on treatment with digitonin yielded a digitonide corresponding to approximately 10% of the product. The major unprecipitated fraction was found to contain a trihydroxy compound (II), as shown by the formation of a triacetate which is unaffected by further vigorous reduction or by chromic acid oxidation. This fraction, which did not precipitate with digitonin, was practically pure triol, showing that reduction of the carbonyl group at C-11 proceeded with the formation of only one of the two possible epimers. This behavior on reduction is therefore similar to that of the carbonyl group at C-20 which also gives only one epimer. The formation from uranetrione of a triol which forms a triacetate is in contrast to the reduction of a cortical steroid studied by Kendall.[3] His acid 1B (3-β-hydroxy-11-keto-aetio-*allo*-cholanic acid) was hydrogenated catalytically, and the resulting dihydroxy-aetio-*allo*-cholanic acid partially oxidized to give acid 1D (3-keto-11-hydroxy-aetio-*allo*-cholanic acid), which was stereoisomeric at C-11 with his dihydro acid 2. Acid 1D does not react with thionyl chloride or with acetylating reagents, and has a configuration at C-11 opposite to that of the natural cortical steroids.



According to our early prediction, uranetriol[1] now can be assigned definite stereochemical configurations. According to the arguments presented in an earlier paper,[1] a C-11α-hydroxyl group in a urane derivative is much more blocked than the epimeric C-11β-hydroxyl group, and, unlike the latter, will not form an acetate. Since triol (II), like uranetriol, forms a triacetate and does not precipitate with digitonin the configurations of the 3- and 11-hydroxyls in both these triols are established to be of the α- and β-configuration, respectively. The two triols, which

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(1) Marker, Kamm, Oakwood, Wittle and Lawson, THIS JOURNAL, **60**, 1061 (1938).

(2) Marker, Rohrmann and Wittle, *ibid.*, **60**, 1561 (1938).

(3) Mason, Hoehn, McKenzie and Kendall, *J. Biol. Chem.*, **120**, 719 (1937).

are not identical, can therefore differ only in regard to the configuration of the hydroxyl group at C-20. By analogy with the pregnanediols, in which only 20α-hydroxyl groups occur naturally and only 20β-hydroxyl groups are formed on catalytic reduction, the configurations of uranetriol-(3α,11β,20α) and triol (II) (3α,11β,20β) are therefore established.

Reduction of uranetrione in hot acetic acid gave a product which was again separated with digitonin. The digitonide, corresponding in this case to approximately 20% of the product, gave on decomposition practically pure uranediol (III) which was identical with uranediol isolated from mares' pregnancy urine.[2] The diacetate prepared from diol (III) was also identical with uranediol diacetate. Thus in this case also the reduction of the carbonyl group at C-11 gave only the β- or natural configuration of the hydroxyl group. The fraction which did not precipitate digitonin was quite impure and could not be crystallized. It was treated with acetic anhydride and the product on crystallization gave the triacetate of triol (II) identical with that obtained from reduction of uranetrione (I) in ethyl alcohol.

The formation of uranediol suggests an alternate mechanism by which in previous work uranedione and pregnanedione were obtained. It now appears that vigorous reduction in hot acetic acid partially removed the carbonyl group at C-20 to form uranediol, and must have partially removed the carbonyl group at C-11, with inversion of the configuration at C-9 from a urane to a pregnane structure, to give pregnanediol (IV). The resulting carbinol mixture on oxidation gave a mixture of uranedione and pregnanedione. The formation of uranediol and pregnanediol could only have taken place in the first step of the transformation of uranetrione to uranedione and pregnanedione[1] as triol II, the other product of reduction, forms a triacetate which in the course of the other reactions to which the mixture was subjected could not give these two products.

It is to be noted that both carbonyl groups which were removed in the above reduction are alpha to a tertiary hydrogen; so the reduction is similar to that of 7-keto-cholesteryl chloride.[4]

Partial reduction of uranetrione in ethyl alcohol gave, besides some unchanged uranetrione, a product which precipitated digitonin (β-hydroxyl group at C-3) and gave an analysis corresponding to a hydroxy diketone $C_{21}H_{32}O_3$. It formed a monoacetate when treated with acetic anhydride. The reduction of uranetrione thus resembles that of the pregnanediones[5] in which the carbonyl group at C-3 is the first to undergo reduction.

In an attempt to isomerize uranediol (III) with sodium in boiling xylene to effect inversion at C-3 the compound was recovered largely in the original form and only a small amount of material not precipitated by digitonin could be obtained. Uranetriol, possessing an α-configuration at C-3, is also changed only slightly by this treatment. It thus appears that the urane compounds are more difficult to isomerize in this manner than those of the pregnane series.

Experimental Part

The Reduction of Uranetrione in Ethyl Alcohol.—A suspension of 50 mg. of platinum oxide in a solution of 500 mg. of uranetrione in 50 cc. of ether and 50 cc. of ethyl alcohol was shaken with hydrogen at 3 atmospheres pressure and 25° for five hours and then filtered to remove the catalyst. The filtrate was distilled until all of the ether was removed and then added to a solution of 300 mg. of digitonin in 50 cc. of ethyl alcohol and allowed to stand for four hours. The digitonide was collected and dried (250 mg.). The filtrate was evaporated to 10 cc. and diluted with 100 cc. of ether. The precipitated digitonin was filtered off and the filtrate after several washings with water was evaporated to dryness leaving a white solid which was very soluble in methyl and ethyl alcohols. It was crystallized from ether–pentane to yield 300 mg. of triol (II), m. p. 255°.

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 74.9; H, 10.8. Found: C, 74.6; H, 10.6.

The triacetate, prepared by refluxing 50 mg. of this compound with 2 cc. of acetic anhydride for one-half an hour, was crystallized from methyl alcohol, m. p. 192°.

Anal. Calcd. for $C_{27}H_{42}O_6$: C, 70.1; H, 9.2. Found: C, 70.2; H, 9.2.

This compound was treated with platinum oxide and hydrogen in acetic acid at 85° but was recovered unchanged. On treatment with an equal weight of chromic anhydride in acetic acid at 25° it was also recovered unchanged.

Reduction of Uranetrione in Hot Acetic Acid.—A suspension of 1 g. of platinum oxide in a solution of 100 cc. of glacial acetic acid containing 0.8 g. of uranetrione was shaken with hydrogen at 3 atmospheres and 85° for eight hours and then filtered from the catalyst while hot. The filtrate was evaporated to dryness in vacuum and the residue was dissolved in ether, washed with a sodium carbonate solution and water, and the solution was evaporated to dryness. The residue was dissolved in 50 cc. of alcohol and to it was added a solution of 1 g. of digitonin in 50 cc. of alcohol. After standing overnight the digitonide

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(4) Marker, Kamm, Fleming, Popkin and Wittle, THIS JOURNAL, **59**, 619 (1937).

(5) Marker, Kamm and Wittle, *ibid.*, **59**, 1841 (1937).

was collected, washed and dried (800 mg.) and heated for one hour on a steam-bath with 10 cc. of pyridine. The solution was diluted with 100 cc. of ether, filtered from digitonin, and the filtrate was washed with dilute hydrochloric acid until acid, and then with water. The ether was evaporated to dryness and the residue was crystallized from methyl alcohol to yield 150 mg. of uranediol, m. p. 215°. It gave no depression in melting point when mixed with uranediol (213°) isolated from mares' pregnancy urine.

The acetate was prepared from this compound in the usual manner, m. p. 160°. It gave no depression in melting point when mixed with uranediol diacetate.

Anal. Calcd. for $C_{26}H_{40}O_4$: C, 74.4; H, 10.0. Found: C, 74.2; H, 10.1.

The filtrate from the digitonide was concentrated to 10 cc. and diluted with 100 cc. of ether to precipitate the excess digitonin. This was filtered off and the filtrate after several washings with water was evaporated to dryness and the remaining oil was found to resist crystallization. The solution was evaporated to dryness and the oily residue was converted to the acetate by refluxing it for one hour with 10 cc. of acetic anhydride and evaporating the solution in vacuum. The residue was crystallized from methyl alcohol to yield the triacetate of triol (II) m. p. 188°. It gave no depression in melting point with the triacetate of triol (II) obtained previously m. p. 192°.

Partial Reduction of Uranetrione in Alcohol.—A suspension of 200 mg. of platinum oxide in a solution of 300 mg. of uranetrione in 200 cc. of ethyl alcohol and 100 cc. of ether was shaken with hydrogen at 3 atmospheres and 25° for one hour and then filtered from the catalyst. The filtrate was distilled to remove the ether and then added to a solution of 2 g. of digitonin and allowed to stand for eight hours. The digitonide (200 mg.) was decomposed as usual, giving 50 mg. of white solid which was purified by crystallization from methyl alcohol, m. p. 225° (fibrous clusters).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.8; H, 9.7. Found: C, 76.0; H, 9.7.

A portion of this compound was converted to the acetate which melted at 250° (from alcohol).

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.7; H, 9.2. Found: C, 73.6; H, 9.2.

Attempted Isomerization of Uranediol.—Uranediol (150 mg.) was dissolved in 50 cc. of xylene, 2 g. of sodium was added and the mixture was refluxed for nine hours. The recovered product was dissolved in 50 cc. of ethyl alcohol and treated with 2 g. of digitonin. The digitonide was filtered off, dried and heated in pyridine for one hour. The solution was diluted with ether and filtered, and the filtrate yielded on evaporation a product which on crystallization from acetone gave 100 mg. of the original uranediol, m. p. 214°. The portion not precipitated by digitonin could not be crystallized to a pure product.

The authors wish to express their thanks to Parke, Davis & Co. of Detroit, Michigan, for a grant of funds supporting this work.

Summary

The reduction products of uranetrione were studied and found to be uranediol, a new triol and uranol-3β-dione-11,20.

STATE COLLEGE, PENNA. RECEIVED APRIL 13, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AT THE OHIO STATE UNIVERSITY]

A New Fluorination Method

BY ALBERT L. HENNE

Principle of the Method.—This paper reports the use of nascent mercuric fluoride as a method for replacing one or several halogen atoms by fluorine in various types of compounds. In practice, the method consists in passing a stream of hydrogen fluoride through a well-stirred mixture of mercuric oxide and the substance to be fluorinated. The reaction between the acid and the oxide occurs instantly, and so also does the one between the mercuric fluoride so generated and the organic material. Since a great deal of heat is evolved, means must be provided to prevent the reaction from escaping control, and also to avoid the loss of volatile or easily destroyed reaction products. These means vary with the substances undergoing fluorination and therefore merely call for some ingenuity.

Dry and Nascent Mercuric Fluoride.—The use of anhydrous mercuric fluoride as a fluorinating agent has been described before.[1] It was pointed out at the time that only the anhydrous salt could be used, and this statement was verified repeatedly. Attempts to manufacture the dry salt by methods more conventional than the action of fluorine upon mercuric chloride forced the conclusion that aqueous reagents invariably would yield a dihydrated salt which could not be converted to the anhydrous salt because it always would lose hydrofluoric acid in preference to water. In an effort to circumvent this, mercuric oxide and hydrogen fluoride were allowed to react in an inert organic liquid. This reaction generates one molecule of mercuric fluoride and only one

(1) Henne and Midgley, THIS JOURNAL, **58**, 884 (1936).

molecule of water, or possibly the monohydrated salt, and it was hoped that this monohydrate in contrast to the dihydrate might be dried to the anhydrous salt. Methylene chloride and chloroform were chosen as reaction media because organic chlorides are not appreciably affected by mercuric fluoride at room temperature, because their low boiling points would automatically maintain the reaction at 40 or 60°, respectively, and because it was hoped that their high densities might cause the water to separate in a top layer. The result of the experiments, however, was quite unexpected, because the white crystalline salt thus obtained was pure mercuric chloride, instead of fluoride, an indication that the nascent mercuric fluoride had reacted instantly with the organic chloride despite the low temperature and the presence of water. An examination of the volatilized reaction products disclosed the presence of methylene fluoride and difluorochloromethane, respectively, two substances described in a preceding paper.[2] This confirmed the interpretation of the reaction course.

Practical Adaptation.—The fluorination of acetylene tetrabromide was studied quantitatively to supply a gage of the practical work of this new fluorination method, and the following simple procedure was found convenient for laboratory operation.

Three gram molecules of acetylene tetrabromide was placed in a tall metal container, preferably made of nickel, and cooled externally with water. One gram molecule of red mercuric oxide was added to the liquid, and immediately stirred to prevent the formation of a heavy paste or cake. Dry hydrogen fluoride from a commercial cylinder was led into the liquid through a metal tube (flexible copper tubing is convenient). The flow of gas was regulated so that the temperature of the reaction mixture never exceeded 40 to 50°. The red color of the mercuric oxide fades progressively to pink, yellow, grayish white and finally to gleaming white; this is the end of the reaction. At this point it was found that about 2.3 gram molecules of hydrogen fluoride had been used, which is an excess of 15% over the theoretical quantity required. The white salt is pure mercuric bromide, with a correct mercury content of 55.6%. It may be noted that an aqueous layer of concentrated hydrofluoric acid floats on the surface. At the end of the reaction the mixture was poured onto cracked ice and washed roughly by decantation to remove the excess of acid. It was then placed in a distilling flask, with twice its volume of water, and heated with a free flame, kept in constant motion to prevent foaming. Steam distillation of the fluorinated material takes place promptly and carries along some acetylene tetrabromide. The distillate was decanted from the water, dried and rectified; it yielded 0.6 gram molecule of CHF_2CHBr_2 and 0.4 gram molecule of $CHFBrCH_2Br$, which is an 80% fluorination yield, based on the mercuric oxide. The material left unsteamed in the distilling flask was cooled overnight, preferably on ice; this causes the mercuric bromide to crystallize out completely and facilitates filtration. The aqueous layer was separated as completely as practical, and the remainder filtered with suction and air dried on the filter. The filtrate separates into a layer of acetylene tetrabromide and a layer of water. The solid material was removed from the filter, placed in a bottle, covered with chloroform, vigorously shaken for twenty minutes, and then filtered by suction. Pure mercuric bromide is left on the filter, while the filtrate is a chloroform solution containing from 75 to 100 cc. of acetylene tetrabromide. Distillation of the chloroform makes it possible to recover the latter material.

Mercury Recovery.—As described so far, this method would be quite costly if the mercury could not be recovered and reoperated. This, however, was performed as follows. The mercury bromide was dropped in small quantities into an aqueous solution of sodium hydroxide. A great deal of heat was evolved, and a black precipitate of mercury oxides was generated, which settled very slowly. The mixture was brought to boiling, then allowed to settle overnight. After decantation of the aqueous layer, water was added and brought to boiling. After again settling overnight the liquid was decanted from the black substance which was then allowed to dry in air, after which it was placed in a steel container (made of pipe fittings), equipped with a screw cap and a delivery tube leading into a pan of water. The steel container was heated with a large gas burner to decompose the mercury oxides and distil the mercury into the water. More mercury was recovered by pouring the distillation residue into water. The recovery of the mercury is quite complete when large enough quantities are used in each batch to avoid mechanical losses.

Temperature and Yields.—The new reaction was then applied to the fluorination of $CH_2BrCHBr_2$, and it was found that $CHFBrCH_2Br$ and CHF_2CH_2Br were generated, as expected, but the fluorination yield of about 30% was at first disconcerting. The mercury bromide was recovered quantitatively, but the tribromoethane was not, and its loss corresponded to the missing fluorinated material. The reaction was tried at different temperatures and it was promptly found that the yield improved as the temperature was lowered. At 0° the yields increased to 50%, and at −20° the yields became about 65 to 70%. This showed that the yield is mostly a matter of adequate temperature control.

Generality of the Reaction.—In order to test the generality of the reaction, the new method was applied to different compounds, at room temperature, with and without saturated hydrocarbons as diluents. Fluorination always occurred instantly and yields were obtained even on small batches and without many precautions, which were always considerably higher than 50%, usually about 70%. More careful handling, tried in only a few cases, always improved the yields markedly. The results were as follows: $AcOCH_2CH_2F$ was obtained from $AcOCH_2CH_2Br$; $AcOCH_2CHF_2$ from $AcOCH_2CHBr_2$; CH_2F_2 from CH_2Cl_2; $CHClF_2$ from $CHCl_3$; CH_3CHF_2 from CH_3CHCl_2; $CH_3(CH_2)_5CHF_2$ from $CH_3(CH_2)_5CHCl_2$; $(C_6H_5)_2CF_2$ from $C_6H_5CCl_3$; $(C_6H_5)_3CF$ from $(C_6H_5)_3CCl$; CF_2ClCF_2Cl from $CFCl_2CFCl_2$, CHF_2CClF_2 from $CHCl_2CClF_2$ and

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[2] Henne, This Journal, **59**, 1400 (1937).

from CHF_2CCl_3. In no case was the fluorination reaction accompanied by loss of hydrogen chloride or hydrogen fluoride and consequently no ethylenic by-product was found. There was usually no tar formation, but a very small quantity was formed in the worst cases, when reagents of "technical" grade were employed.

Summary

A method of fluorination is described which consists in passing a stream of hydrogen fluoride through a mixture of the substance to be fluorinated and mercuric oxide. Practical directions are given for obtaining good yields and for a simple method of recovering the mercury.

THE MIDGLEY FOUNDATION
COLUMBUS, OHIO
RECEIVED APRIL 1, 1938

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF PHYSICS, HARVARD UNIVERSITY]

Variations in the Relative Abundances of the Isotopes of Common Lead from Various Sources

BY ALFRED O. NIER[1]

Because of the apparently constant atomic weight of common or ore lead, the assumption usually has been made that its isotopic composition also is constant. Whereas several isolated isotopic analyses of common lead have been made, there is no record of any systematic study having been undertaken for the purpose of checking the constancy of the relative abundances. In the present work twelve samples were studied with a mass spectrometer and considerable variations were found. The investigation is of particular interest, as the specimens examined vary greatly in both geologic age and geographic origin. Moreover, of the twelve samples, nine have had chemical atomic weight determinations made on them—all in the same laboratory.

Apparatus and Procedure.—The mass spectrometer used for obtaining the results to be presented here already has been described.[2] Positive ions of lead are formed by the collision of electrons with lead iodide vapor. The ions are drawn out of the region where they are formed, are accelerated and sent around a 180° magnetic analyzer where the ion currents are measured with an electrometer tube amplifier.

During an analysis, the portion of the tube containing the semicircular analyzer is kept at room temperature. The part where the ions are formed is held around 400°, and the side-tube from which the lead iodide vapor diffuses into the ionizing region is maintained at approximately 300°, the exact temperature depending on the pressure desired in the ionizing region. In actual practice, this pressure was between 10^{-4} and 10^{-5} mm. The amount of material needed for an analysis is very small. During a typical run, where no attempt was made to economize on material, less than 13 mg. of lead iodide, *i. e.*, less than 6 mg. of lead, was consumed. With reasonable care it should be possible to obtain reliable results on 1 mg. of lead.

The procedure in making an analysis was as follows: the sample to be studied was attached in the evening and the mass spectrometer tube evacuated and baked overnight in order thoroughly to out-gas it. Measurements were taken the next morning and afternoon. The side-tube containing the sample was removed and the mass spectrometer was again baked overnight, this time to remove the lead iodide. The following morning the apparatus was baked for several hours with iodine vapor flowing through it to combine with any metallic lead deposited in the tube from the thermal decomposition of lead iodide. Baking of the tube continued until late in the evening in order to remove the remaining traces of lead iodide. A new sample could then be attached and the procedure repeated. It is seen that an analysis may be performed every two days. Actually, in one case, fifteen samples were examined in thirty-four consecutive days.

Because of the careful treatment of the apparatus between samples, described above, the relative abundances of the isotopes obtained for a given specimen did not depend upon the previous history of the apparatus. That is to say, there was no contamination due to previous samples. In fact, one even could change from a sample of ordinary lead to one of radiogenic lead and then back again to the ordinary lead and reproduce the original results exactly.

The lead iodide was prepared by precipitation

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[1] National Research Fellow.

[2] Nier, *Phys. Rev.*, **52**, 933 (1937).

from a solution of the nitrate (in a few cases from the chloride) with a solution of sodium iodide, washing and drying. Since the groups $I^{127}Br^{79}$ and $I^{127}Br^{81}$ have the same masses as two of the isotopes of lead, the iodine from which the iodide was prepared was carefully freed from bromine, as well as chlorine.

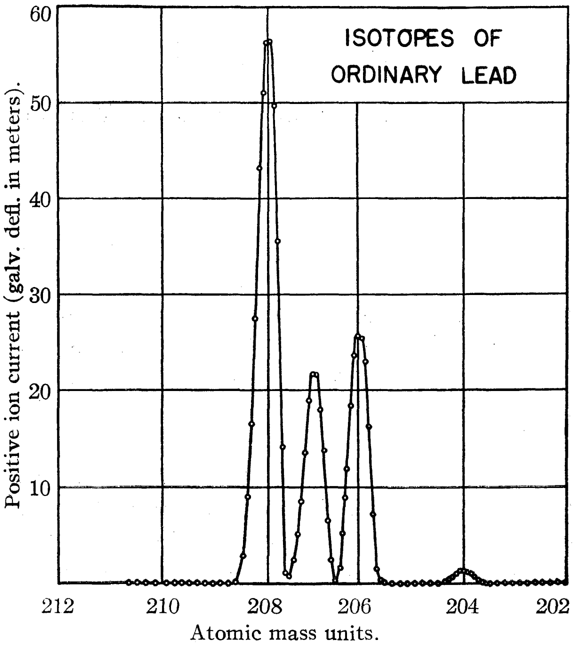

Fig. 1.—Mass spectrum showing the isotopes of common lead. Positive ion current expressed in terms of cm. deflection of galvanometer at its highest sensitivity. One cm. represents about 2.5×10^{-15} ampere.

Results

Preliminary reports on the results to be presented here have already been given.[3] A typical mass spectrum obtained is shown in Fig. 1. The relative abundances of the isotopes are assumed to be proportional to the relative heights of the positive ion current peaks. This assumption is justified in view of the fact that the relative heights as measured were found to be independent of variable conditions in the tube, such as electron current, pressure, etc. As a further check upon any possible discrimination in the apparatus, mercury vapor was admitted occasionally, and the Hg^{198}/Hg^{204} abundance ratio measured under conditions similar to those employed while the lead measurements were being taken. At no time was this ratio found to differ appreciably from that previously given.[2]

Figure 2 gives the lower part of Fig. 1 in greater detail. It can be seen from this that Pb^{204} produces a very definite peak that can be measured with nearly the same accuracy as the other peaks. Inasmuch as the apparatus was thoroughly baked and liquid air used on the traps, the height of the Hg^{204} peak is negligible, since even Hg^{202}, which exists with over four times the abundance of Hg^{204}, cannot be discerned in Fig. 2. In addition, no traces appear of the isotopes Pb^{210}, Pb^{209}, Pb^{205}, and Pb^{203}, at one time reported by Aston[4] with abundances indicated by the horizontal lines above the corresponding mass number position. Later, Aston[5] withdrew these isotopes in view of the fact that in a number of elements his rarer isotopes were found to be of a spurious origin. In particular, Bainbridge and Jordan[6] showed that Pb^{209} could not exist with even one-tenth the abundance originally claimed for it by Aston. That the withdrawal of the other rare lead isotopes was justified is shown by the present work. It is now possible to say that if Pb^{210}, Pb^{209}, Pb^{205}, and Pb^{203} exist, it must be with abundances less than $^1/_{100}$, $^1/_{1000}$, $^1/_3$, and $^1/_{20}$ of those originally given by Aston.

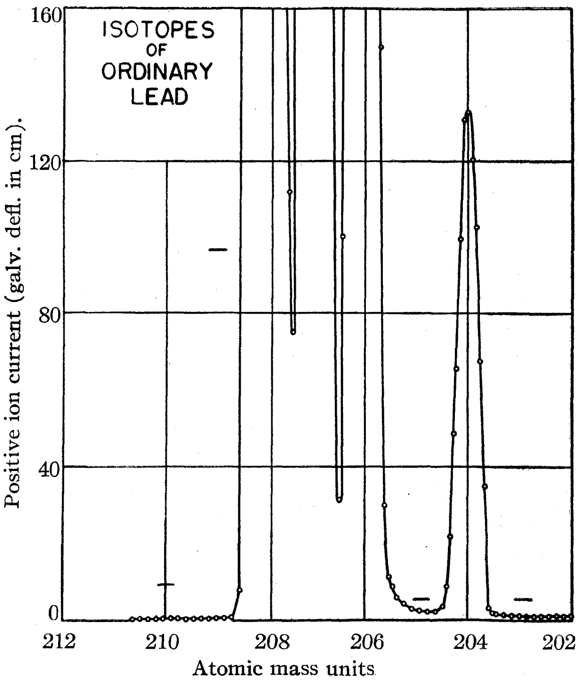

Fig. 2.—Lower portion of Fig. 1, drawn with enlarged ordinate scale.

Columns 4, 5, 6, and 7 of Table I give the relative abundances of the isotopes found for twelve samples of lead varying vastly in both geologic

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(3) Nier, *Phys. Rev.*, **51**, 1007 (1937); **53**, 680 (1938).

(4) Aston, *Proc. Roy. Soc.* (London), **A140**, 535 (1933).

(5) Aston, *Nature*, **137**, 613 (1936).

(6) Bainbridge and Jordan, *Phys. Rev.*, **50**, 282 (1936).

TABLE I

No.	Source of lead, locality	Geological age (in m. y.)	Isotope abundances				Excess			Excess		Mean mass number	Atomic weight	
			204	206	207	208	206	207	208	207/206	208/206		Physical	Chemical
1	Galena Great Bear Lake	Pre-Cambrian 1300	1.000	15.93	15.30	35.3						207.243	207.218[a]	207.206[b]
2	Galena Broken Hill, N. S. W.	Pre-Cambrian 950	1.000	16.07	15.40	35.5						207.242	207.217	
3	Cerussite	Pre-Cambrian	1.000	15.92	15.30	35.3						207.242	207.217	207.21[c]
	Broken Hill, N. S. W.	950	1.000	15.93	15.28	35.2						207.241	207.216	
4	Galena Yancey Co., N. C.	Late Pre-Cambrian 600	1.000	18.43	15.61	38.2	2.50	0.31	2.9	0.12	1.16	207.229	207.204	207.209[d]
5	Galena Nassau, Germany	Carboniferous 240	1.000	18.10	15.57	37.85	2.17	.27	2.55	.12	1.17	207.231	207.206	207.21[c]
6	Cerussite Eifel, Germany	Carboniferous 240	1.000	18.20	15.46	37.7	2.27	.16	2.4	.070	1.06	207.228	207.203	207.20[c]
7	Galena I Joplin, Mo.	Late Carboniferous 230	1.000	21.65	15.88	40.8	5.72	.58	5.5	.10	0.96	207.203	207.178	207.22[c]
8	Galena II	Late Carboniferous	1.000	21.60	15.73	40.3	5.69	.44	5.07	.077	.89	207.200	207.175	
	Joplin, Mo.	230	1.000	21.65	15.75	40.45						207.200	207.175	
9	Galena Metalline Falls, Wash.	Late Cretaceous 80	1.000	19.30	15.73	39.5	3.37	.43	4.2	.127	1.25	207.228	207.203	207.21[c]
10	Cerussite	Late Cretaceous	1.000	15.98	15.08	35.07						207.239	207.214	207.21[c,e]
	Wallace, Idaho	80	1.000	16.10	15.13	35.45						207.242	207.217	
11	Wulfenite & Vanadinite Tucson Mts., Arizona	Miocene 25	1.000	18.40	15.53	38.1	2.47	.23	2.8	.093	1.13	207.229	207.204	207.22[c]
12	Galena[f]		1.000	17.34	15.47	37.45	1.43	.15	2.07	.105	1.45	207.240	207.215	
	Saxony, Germany		1.000	17.38	15.44	37.3						207.238	207.213	
								Average		.10	1.13			

[a] Sample calculation: 207.218 = 207.243 × (1 + 1.55 × 10^{-4})/1.000275. [b] Marble, THIS JOURNAL, **59**, 653 (1937). [c] Baxter and Grover, *ibid.*, **37**, 1027 (1915). [d] Baxter and Alter, *ibid.*, **57**, 467 (1935). [e] Baxter, Faull and Tuemmler, *ibid.*, **59**, 702 (1937). [f] Sample 12 was obtained from Dr. A. V. Grosse, of the University of Chicago, who believed it to be a sample of galena from Saxony, Germany.

age and geographic origin. The abundance of 204 has been chosen arbitrarily as a reference, as it is not produced, as far as is known, by radioactive decay. An examination of the results reveals that variations occur in the relative abundances with different samples. These variations lie outside the possible experimental errors, as is evidenced by the fact that with the four samples where analyses were repeated the agreement was within at least one per cent. The probable error in the measurements is of the order of 0.5%.

In the last two columns of Table I are given the atomic weights as determined by the physical and chemical methods. In computing the atomic weight from the physical data, the mean mass number is first calculated from the relative abundances. The result so obtained is converted to the chemical scale as follows. The conversion factor in going from the physical to the chemical scale is taken as 1.000275.[7] The packing fraction of lead was found by Aston[4] to be between 0 and +1.0, whereas a value of +2.0, or greater, is deduced from Dempster's[8] data. In computing the atomic weight from the physical data, a packing fraction of +1.55 is chosen arbitrarily, as it brings the physical and

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(7) Hahn, *Ber.*, **71**, 1 (1938).

(8) Dempster, *Phys. Rev.*, **53**, 64 (1938).

chemical values into the best possible agreement.

Table II gives the results of previous investigators as well as the results obtained by the writer for his two extreme samples, numbers 1 and 7. All abundances are given in percentages for the sake of comparison. In view of the relatively large variations reported in the present work, no serious discrepancies exist between the work of the various experimenters. It should be mentioned, however, that the measurements on Pb^{204} here reported are the only accurate ones obtained to date.

TABLE II

	208	207	206	204	Mean mass number
Aston[4]	50.1	20.1	28.3	1.5	207.173
Rose and Stranathan[9]	51.5	21.3	26.3	0.8	207.228
Mattauch[10]	52.95	21.35	24.55	1.15	207.25
Nier, Sample 1	52.29	22.64	23.59	1.48	207.243
Nier, Sample 7	51.43	20.00	27.31	1.26	207.203

Discussion

An examination of the variations shows that they are definitely not of a random nature; those samples which contain relatively more Pb^{206} also contain relatively more Pb^{207} and Pb^{208}. Within the experimental errors samples 1, 2, 3, and 10 have the same isotopic constitution and also contain the least amounts of Pb^{206}, Pb^{207}, and Pb^{208}. The fact suggests that one consider the other samples as made up of this kind of lead plus contaminations of uranium lead (Pb^{206} and Pb^{207}) and thorium lead (Pb^{208}). For want of a better name for the lead low in Pb^{206}, Pb^{207}, and Pb^{208}, one may call it "uncontaminated" lead. As the three oldest samples have the isotopic constitution of "uncontaminated" lead there is a strong temptation to identify it tentatively with primeval lead—that is, lead as it existed when the earth's crust formed. The discovery of a sample of common lead containing less Pb^{206}, Pb^{207}, and Pb^{208} might force one to make a quantitative change in the argument to be presented here, but it seems doubtful that one will be found which differs enough to compel one to make a qualitative change.

Samples 1, 2, and 3 will thus be considered tentatively as "uncontaminated" lead. In columns 8, 9, and 10 are then recorded the excess amounts of 206, 207, and 208, *i. e.*, radiogenic contamination, for the other "contaminated" samples. The isotopic constitution of sample 1 is arbitrarily chosen as that for "uncontaminated" lead in making the subtraction. Thus, the amount of excess 206 for sample 4 is obtained by subtracting 15.93 from 18.43, etc. The choice of sample 1 as typical "uncontaminated" lead is a rather unfortunate one in spite of the great age of this sample, as it came from the Great Bear Lake region (a source of uranium ores), and hence might possibly have become contaminated. However, this sample does contain as little 206, 207, and 208 as any of the others, so that the choice is as good a one as can be made at this time.

An examination of the amounts of excess isotopes reveals that the excess 208 is practically equal to the excess 206, whereas the excess 207 is approximately 10% of the excess 206 in each case, the averages for all the contaminated samples being, excess 208/206 = 1.13, excess 207/206 = 0.10. It should be mentioned that the minerals from which the lead was extracted were essentially free of thorium and uranium, and hence, in all probability, the contamination of the "uncontaminated" lead by radiogenic lead took place before the mineral was formed. In the case of the Joplin material, a rough calculation shows that if the excess isotopes were generated by thorium and uranium present as impurities in the galena, the amounts would have to be, respectively, *two and six times as great* as the total amount of lead present!

It is a common belief among many students of ore deposits that ore lead has its ultimate origin in the igneous rocks or the magmas of these rocks. If such is the case, one should expect it to consist of primeval lead contaminated by radiogenic lead, inasmuch as the igneous rocks are known to contain uranium and thorium, and, consequently, radiogenic lead as well as common lead.

The values found for the two ratios for excess isotopes are not at all unreasonable, as far as supporting the contamination hypothesis is concerned, in view of other information at our disposal. If one assumes the age of the earth to be around 2 × 10^9 years, and if one further assumes that the radiogenic lead appearing in the above samples was being formed during the time between the formation of the earth and the formation of the minerals, one may assume the average age of the radiogenic contaminations to be of the order of 1.5 × 10^9 years, the exact value assumed being quite immaterial. As the rate of decay of ura-

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(9) Rose and Stranathan, *Phys. Rev.*, **49**, 916 (1936).

(10) Mattauch, *Naturwissenschaften*, **25**, 763 (1937).

nium is approximately three times that of thorium, the Th/U ratio in the substance in which the radiogenic lead was formed then must have been $3 \times 1.13 = 3.4$. Due to the difference in the rates of decay of thorium and uranium, the Th/U ratio of such a source would be today $3.4/0.85 = 4.0$.

Holmes[11] assumes this ratio to lie between 1.6 and 2.4 for igneous rocks. Evans and Raitt[12] believe the value to be considerably higher, possibly between 5 and 10. Finney and Evans[13] give values between 3.2 and 10.6, with an average of about 7. The Pb^{208}/Pb^{206} ratios found by the writer for the excess lead are thus not inconsistent with the view that ore lead is a concentration from igneous rocks or the magmas of such rocks.

The ratio of excess $Pb^{207}/Pb^{206} = 0.10$ lends further support to this hypothesis, as it is roughly of the right order of magnitude for old uranium lead. An actual calculation using new data available for the relative abundances of the uranium isotopes[14] indicates that for the uranium lead formed during the period between 2×10^9 and 5×10^8 years ago the Pb^{207}/Pb^{206} ratio would be approximately 0.14. In view of the fact that the numbers given in the column of excess Pb^{207} are obtained by subtracting two numbers very nearly equal, one can hardly expect better agreement. Moreover, this ratio depends in a somewhat critical way on what one assumes the isotopic constitution of primeval lead to be. The disagreement might well indicate that "uncontaminated" lead differs slightly from primeval lead.

In a recent paper, Holmes[11] makes use of the constancy of the atomic weight of common lead (and the alleged isotopic constancy) in an attempt to prove that it cannot be a concentration from granitic or basaltic rocks, or their respective magmas, but must have its origin in some deeper source in the earth. The present work shows definitely that the relative abundances of the isotopes of common lead do vary, but that the manner of variation is such as to have little effect upon the atomic weight. Moreover, the data are not inconsistent with the view that ore lead is related to ordinary igneous rocks, provided that one assumes the Th/U ratio in such rocks to be around 4.0, rather than 1.6 to 2.4 as is assumed by Holmes. Nine of the twelve samples studied by the writer were the *identical* samples which appear among those listed in Holmes' Table IV.

On a simple igneous rock derivation picture one should expect the oldest samples to contain a minimum of radiogenic lead contamination and the youngest a maximum. In this respect the data have some deficiencies which may or may not be of a serious nature. Except for the fact that the three oldest samples contain a minimum of apparent contamination there is no direct correlation between the age of the deposit and the amount of contamination. In fact, sample 10, a young mineral, has essentially the same isotopic constitution as the assumed "uncontaminated" lead. Such apparent difficulties may be only a manifestation of the fact that the total amounts of uranium and thorium in rocks vary greatly from specimen to specimen, and hence the proportion of radiogenic lead to ordinary lead in such specimens also varies quite independently of any variation with time.

In conclusion, the writer wishes to emphasize the fact that the explanation for the variations advanced in this paper is to be taken as tentative only. The accumulation of more data may lead the way to a better theory. However, with the information now available, the interpretation does seem to be reasonable and not in serious disagreement with any well established fact. An objection may be raised that the variations might be present in primeval lead itself. In answer to this, one can only say that the variations are much larger than any that have been reported for other elements (with the possible exception of hydrogen and a few other isolated cases, where the variations can be explained very easily by isotopic separation taking place in nature). It does not seem likely that the variations reported here can be due to isotopic separation, as one would expect them to be a monotonic function of the mass. The view entertained by some that common lead may be only a mixture of thorium and uranium leads generated since the earth's beginning certainly is not correct for at least two reasons, namely, (1) common lead contains Pb^{204} which apparently is not produced by the disintegration of uranium or thorium, and (2) the Pb^{207}/Pb^{206} ratio in common lead is far too high to be consistent with our knowledge of the relative rates of decay of the actinium and uranium series,

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(11) Holmes, *Economic Geol.*, **32**, 763 (1937).

(12) Evans and Raitt, *Phys. Rev.*, **48**, 171 (1935).

(13) Finney and Evans, *ibid.*, **48**, 503 (1935).

(14) Nier, Bulletin American Phys. Soc., Washington Meeting, 1938.

provided one assumes the age of the earth to be of the order of 2×10^9 years.

The writer wishes to express his appreciation to Professor G. P. Baxter of the Department of Chemistry, Harvard University, who very kindly prepared and furnished eleven of the twelve samples used. It was only through his interest and coöperation that this work was possible.

Summary

1. A mass spectrographic study of the isotopes of twelve samples of common lead shows that the relative abundances vary considerably in spite of a nearly constant atomic weight.

2. A tentative explanation for the variations is found if one arbitrarily considers some of the samples to be "uncontaminated" lead and the others "uncontaminated" lead to which has been added approximately equal quantities of uranium and thorium leads. As the minerals from which the lead was obtained are essentially free of thorium and uranium, such contamination probably took place before the mineral was formed.

3. A search for the isotopes Pb^{210}, Pb^{209}, Pb^{205}, and Pb^{203} indicated that if such isotopes exist at all they must exist with much lower abundances than was at one time supposed.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE INSTITUTE OF TECHNOLOGY OF THE UNIVERSITY OF MINNESOTA]

Studies on Aging and Properties of Precipitates. XXII. The Induced Precipitation of Mercuric Sulfide from Sodium Mercuric Sulfide Solutions by Zinc Sulfide. A New Case of Postprecipitation

BY I. M. KOLTHOFF, FRANK S. GRIFFITH AND D. ROMUND MOLTZAU

It was found by Feigl[1] that when a solution of a zinc salt is added to a solution of sodium mercuric sulfide under such conditions that the resulting liquid phase is not supersaturated with regard to mercuric sulfide, the precipitate which separates contains mercury and its color varies from white to yellow, orange or brown, depending upon the amount of mercury in the precipitate. The mercury is not removed readily from the precipitate by extracting with sodium sulfide solutions. Moreover, Feigl found that the sulfides of cadmium, lead and manganese acted in a manner similar to zinc sulfide whereas the sulfides of silver, cupric and cuprous copper, ferrous and ferric iron, thallium, bismuth and cobalt did not induce the precipitation of mercuric sulfide from a sodium mercuric sulfide solution. In the present paper it is shown that the induced precipitation of mercuric sulfide by zinc sulfide is a phenomenon of postprecipitation. This case of postprecipitation is different from others[2] previously investigated in this Laboratory, in that the mercuric sulfide is taken up by the zinc sulfide from a solution which is *not supersaturated* with regard to the former. Such a postprecipitation will occur only when the following two conditions are fulfilled: (1) the postprecipitated substance is soluble in the primary precipitate or forms a compound with it; (2) the speed of separation of the primary precipitate is greater than that of the postprecipitated substance. If the former condition is not fulfilled no postprecipitation can occur from solutions which are not supersaturated with regard to the second precipitate. If the first condition is fulfilled but not the second a coprecipitation and not a postprecipitation will take place.

Materials Used

Zinc sulfate solutions were made from recrystallized C. P. chemicals. They were standardized against potassium ferrocyanide.[3]

Mercuric perchlorate solutions were made from reagent quality mercuric oxide and perchloric acid. A 0.05 *M* perchloric acid solution in equilibrium with mercuric oxide was found to be 0.004 *N* in free acid.

Sodium Sulfide.—The commercial products available were not suitable for the present work because of large amounts of impurities (thiosulfate). Therefore, the sodium sulfide solutions were made by passing washed hydrogen sulfide through a measured quantity of 5.30 *N* sodium hydroxide. A slight excess of hydrogen sulfide as measured by the increase in weight of the solution, was absorbed and the concentrated solution diluted with oxygen-free water. The solution was then analyzed for sulfide and total basicity and the appropriate amounts of

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[1] F. Feigl, *Z. anorg. allgem. Chem.*, **157**, 269 (1926).

[2] For a review see I. M. Kolthoff and D. R. Moltzau, *Chem. Rev.*, **17**, 293 (1935).

[3] I. M. Kolthoff and E. A. Pearson, *Ind. Eng. Chem., Anal. Ed.*, **4**, 147 (1932).

sodium hydroxide solution and water needed to give the desired composition were calculated and added. In order to guard against air oxidation the air above the liquid was swept out with nitrogen.

Air Oxidation of Sodium Sulfide Solutions.—Most of the work was first carried out without taking precautions against air oxidation of the sulfide. The results were not well reproducible and were sometimes confusing due to air oxidation of sulfide. This oxidation can be considerable after a relatively short time of exposure to air as is evident from the following experiments. Two hundred milliliters of a freshly prepared sodium sulfide solution which was 0.1 N in excess of sodium hydroxide was distributed between four 250-ml. flasks, the latter were partially stoppered with one-hole rubber stoppers and shaken gently with a rotary motion for twenty-four hours. The contents of the flasks were mixed and analyzed for sulfide, polysulfide, thiosulfate and total basicity (see below). The freshly prepared solution was 0.189 M in sulfide, the total alkalinity being 0.472 N. After exposure for twenty-four hours the sulfide concentration was 0.110 M, that of polysulfide less than 0.001 M, the thiosulfate concentration 0.035 M and the total alkalinity 0.402 N. Hence about 37% of the sulfide was oxidized after twenty-four hours of exposure to air. This air oxidation is prevented by taking precautions to exclude air. A large number of experiments were run in which the flasks containing the sulfide solutions were swept out with nitrogen both before the solutions (kept under nitrogen) were added and before the flasks were stoppered. Under such conditions only 0.53% of the sulfide was found to be oxidized after twenty-four hours.

Methods of Analysis.—The sum of sulfide, polysulfide and thiosulfate was determined by oxidation with bromine (bromate–bromide and acid) to sulfate.[4] The thiosulfate was determined by the method recommended by the Committee on Analytical Reagents of the American Chemical Society[5] for testing the purity of sodium sulfide. The sulfide and polysulfide are precipitated by adding an excess (enough to remove excess of alkali) of oxygen-free zinc sulfate solution. After standing for half an hour the solution is filtered and an aliquot portion of the filtrate titrated with standard iodine. The polysulfide was usually determined by Schulek's[6] method in which it is transformed into thiocyanate. The latter is oxidized to bromocyanide and determined iodometrically.

The total alkalinity was determined by titrating with standard acid. Just before the end-point most of the hydrogen sulfide was removed by aspiration of air and the titration finished with methyl orange as indicator.

Mercury.—In the study of the postprecipitation of mercuric sulfide with zinc sulfide from sodium mercuric sulfide solutions the remaining mercury in solution was determined volumetrically.

After investigating various procedures the following method was found to be suitable for routine analyses. An excess of hydrochloric acid was added to the sodium mercuric sulfide solutions to precipitate the mercuric sulfide, the solution boiled for a few minutes to remove hydrogen sulfide and then 2 ml. of concentrated nitric acid added. Oxidation was complete within a few seconds but boiling was continued for a few minutes to remove oxides of nitrogen and to gather the finely divided sulfur into larger particles. After removing the flask from the hotplate 5 ml. of 6 N sodium hydroxide was added, the solution cooled, indicator added and the solution exactly neutralized. If the indicator is added to the strongly acid solution it is sometimes oxidized. A mixture of equal volumes of brom cresol green (0.1%) and methyl red (0.1%) was found to be a very suitable indicator, the color change being from red (acid) to blue (alkaline). After neutralization, the mercury is determined by the cyanide method[3] (p. 198) by adding an excess of standard potassium cyanide solution and titrating back with standard hydrochloric acid.

$$\mathrm{HgCl_2 + 2KCN \longrightarrow Hg(CN)_2 + 2KCl}$$
$$\mathrm{KCN + HCl \longrightarrow HCN + KCl}$$

Degree of Saturation of Sodium Mercuric Sulfide with Mercuric Sulfide.—Although the air oxidation of sulfide was prevented by carrying out the experiments in an atmosphere of nitrogen, it was desirable, especially in long period experiments, to have a quick method available to test for an accidental change of the sulfide concentration solution. This can be done roughly by titrating with a standard mercuric chloride solution until the turbidity does not disappear on further shaking.

$$\mathrm{2S^{=} + HgCl_2 \longrightarrow HgS_2{}^{=} + 2Cl^-}$$
$$\mathrm{HgS_2{}^{=} + HgCl_2 \longrightarrow 2HgS + 2Cl^-}$$

As the solubility of mercuric sulfide in sodium sulfide is dependent upon the concentration of sodium hydroxide,[7] the method cannot be used to determine accurately the sulfide content of solutions. It is suitable, however—with an accuracy to 1 to 2%—to determine the amount of mercuric salt needed to saturate a sodium sulfide (or sodium mercuric sulfide) solution with mercuric sulfide.

Experimental Results

Rate of Postprecipitation of Mercuric Sulfide from Sodium Mercuric Sulfide Solutions in the Presence of Freshly Precipitated Zinc Sulfide.—In the following experiments zinc sulfate solution was added to the sodium mercuric sulfide solution which contained an excess of sulfide. Ten ml. of 0.05 M zinc sulfate was added to a mixture of 25 ml. of 0.189 M sodium sulfide which was 0.094 N in sodium hydroxide and 10 ml. of 0.044 M mercuric perchlorate which was 0.004 N in free acid. If no co- or postprecipitation occurred the supernatant liquid after precipitation of 0.5 mmol. of zinc sulfide would be 0.051 N in sodium hydroxide, 0.075 M in sodium sulfide and 0.0098 M in sodium mercuric sulfide. About 8 ml. of the 0.044 M mercuric perchlorate solution could be added before the solution became saturated with mercuric sulfide. Before mixing the solutions in screw-cap bottles the air was swept out with nitrogen, and this gas was passed over again before screwing the caps on. The bottles were shaken for a given length of time, centrifuged and 25 ml. was taken for analysis for mercury. The color of the freshly formed zinc sulfide was white, indicating that *no coprecipitation of mercuric* sulfide had occurred, after two

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[4] I. M. Kolthoff and H. Menzel, "Die Maszanalyse," 2d edition, Verlag von Julius Springer, Berlin, 1931, p. 514.

[5] *J. Ind. Eng. Chem.*, **19**, 1372 (1927).

[6] E. Schulek, *Z. anal. Chem.*, **65**, 352 (1925).

[7] J. Knox, *Trans. Faraday Soc.*, **4**, 29 (1908).

minutes of shaking a yellow tinge of the precipitate was noticeable and after one hour the precipitate was of a cadmium sulfide yellow. The results on the rate of postprecipitation of mercury are given in Table I. A similar set of experiments was run in the presence of a larger excess of sodium sulfide. After precipitation of 0.5 mmol. of zinc sulfide the supernatant liquid was 0.062 N in sodium hydroxide, 0.19 M in sodium sulfide and 0.011 M in sodium mercuric sulfide. The results are given in Table II.

TABLE I

RATE OF POSTPRECIPITATION OF MERCURIC SULFIDE WITH ZINC SULFIDE

Time of shaking	6 min.	52 min.	7.5 hrs.	24 hrs.	7 days
Mercury pptd., %	14.0	27.9	32.1	34.0	34.2, 35.5

TABLE II

RATE OF POSTPRECIPITATION OF MERCURIC SULFIDE IN THE PRESENCE OF LARGER EXCESS OF SULFIDE

Time of shaking	5 min.	35 min.	2.5 hrs.	45 hrs.	7 days
Mercury pptd., %	8.4	12.8	14.0	16.4	15.5

A comparison of Tables I and II (see also Fig. 1) reveals that the amount of postprecipitation mercury decreases to about one-half when the excess of sulfide in solution is doubled. Moreover, it is evident that after about one to two days of shaking with freshly precipitated zinc sulfide a state of equilibrium in the distribution of mercury between solution and the solid state is attained.

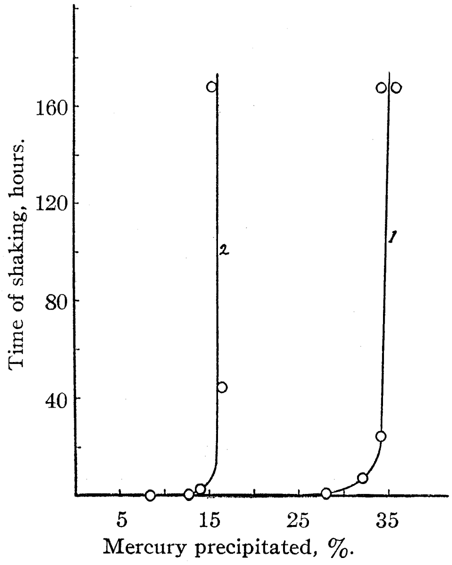

Fig. 1.—1, Small excess of sulfide; 2, larger excess of sulfide.

Rate of Postprecipitation of Mercuric Sulfide with Zinc Sulfide of Varying Degree of Perfection and Age.—The results of the following experiments in which sodium mercuric sulfide solution was added to a zinc sulfide suspension show conclusively that the induced precipitation of mercuric sulfide by zinc sulfide is a phenomenon of postprecipitation. The rate of this postprecipitation decreases with increasing degree of perfection and decreasing surface development of the zinc sulfide. Zinc sulfide samples of various degree of perfection and age were prepared.

1. Precipitation from and Aging in Alkaline Solution.—Ten ml. of 0.05 M zinc sulfate was added to 2.8 ml. of a solution which was 0.19 M in sodium sulfide and 0.116 N in sodium hydroxide. The bottles were swept out with nitrogen and the zinc sulfide aged for the indicated periods of time.

2. Precipitation from and Aging in Slightly Acid Medium (*p*H about 5).—Ten ml. of 0.05 M zinc sulfate containing 0.25 g. of sodium acetate trihydrate was saturated with hydrogen sulfide. After aging for the given period of time most of the excess of hydrogen sulfide was removed by evacuating the bottle while swirling well (blanks showed that only about 0.004 mmol. of hydrogen sulfide stayed in solution after this treatment). After evacuation 0.17 ml. of 0.19 M sodium sulfide, 0.25 ml. of 5.3 N sodium hydroxide and 2.4 ml. of water were added, thus making the volume, amount of sulfide and hydroxide the same as in the suspensions of product 1.

3. Precipitation from and Aging in More Acid Solution (final *p*H about 1.15).—Ten ml. of 0.05 M zinc sulfate was saturated with hydrogen sulfide. After aging the samples were subjected to the same treatment as products 2. If the samples were aged for less than one hour a small amount of the zinc might have remained unprecipitated. For complete precipitation of zinc sulfide Jeffries and Swift[8] recommend a *p*H of 1.6.

Procedure of Postprecipitation Experiments

The 100-ml. bottles containing the zinc sulfide suspensions which had been aged for the indicated periods of time were swept out again with nitrogen whereupon 35 ml. of sodium mercuric sulfide solution of about the same composition as that used in Table I was added. Immediately after mixing, the liquid phase was 0.058 N in sodium hydroxide, 0.0845 M in sodium sulfide and 0.0105 M in sodium mercuric sulfide. The bottles were stoppered and shaken vigorously, some for two hours and some for two days, centrifuged and 25 ml. of the supernatant liquid was analyzed for mercury by the procedure outlined previously. The mercuric sulfide separating from mixtures containing acetate (products 2) was filtered off, washed, and treated with aqua regia. The fibers of filter paper were filtered off before titrating the mercury. The filtration of mercuric sulfide was necessary as the acetate interferes with the mercury titration. The results are given in Table III and reproduced graphically in Fig. 2.

When a range of time is given in the table the shorter time refers to zinc sulfide products 1, and the longer time to products 2 and 3. The experiments referring to an age of zinc sulfide of zero (in parentheses in Table III) were carried out in a way similar to those in Tables I and II; the zinc sulfate solution was added to a solution containing sodium mercury sulfide, sodium sulfide and sodium hydroxide of appropriate concentrations so that after precipitation of the zinc sulfide the solution had the same composition as prevailed in the other experiments. It is seen that zinc sulfide precipitated in the absence of mercury and which was only seven minutes old (product 1) is

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[8] C. E. P. Jeffries and E. H. Swift, THIS JOURNAL, **54**, 3219 (1932).

TABLE III

RATE OF POSTPRECIPITATION OF MERCURIC SULFIDE WITH ZINC SULFIDE OF VARYING DEGREE OF PERFECTION AND AGE

	% Hg in ppt. after 2 hours of shaking with Na_2HgS_2 soln.			% Hg in ppt. after 2 days of shaking with Na_2HgS_2 soln.		
Age of ZnS	Products 1	2	3	Products 1	2	3
(0)	(25.5)	..	...	(28.4)	..	..
3–7 min.	24.0	15.4	7.5	28.4	18.0	13.1
1 hour	14.2	11.5	...	19.0	11.6	10.0
12–16 hours	12.0	6.8	3.4	14.1	8.5	2.5
7 days	10.9	3.9	0.6	11.8	5.5	0.6
7 days hot[a]	0.9	0	−1	8.0	0.7	−1

[a] Aged on gravel at a temperature of about 80–90°.

about as effective as fresh zinc sulfide precipitated in the presence of mercury.

Products 3 are much coarser and more perfect than samples 2 and the latter more so than products 1. The rate of postprecipitation of mercuric sulfide (see 3–7 minutes old zinc sulfide) decreases in the order of products 1, 2, 3. It is also evident that product 3 ages much more rapidly at a *p*H of 1.15 than product 2 at a *p*H of 5 and the latter more than product 3 in alkaline medium. After aging for seven days at room temperature product 3 hardly takes up any mercury even after shaking for two days with the sodium mercuric sulfide solution. Product 1 ages very slowly at room temperature but the perfection becomes pronounced when aged at 80–90°. Apparently the speed of postprecipitation of mercuric sulfide with zinc sulfide is a good indicator of the degree of perfection of the latter.

Effect of Varying Amounts of Zinc Sulfide and of Mercury and Sulfide Concentrations.—During the postprecipitation of mercuric sulfide the sodium sulfide concentration in the solution increases: $Na_2HgS_2 \longrightarrow [HgS] + Na_2S$. When the initial sulfide composition of the solutions is identical, but the amount of postprecipitation after attainment or approximate attainment of equilibrium different, a quantitative comparison of the results is not simple. A series of experiments was run adding different amounts of zinc sulfate and mercuric perchlorate to sodium sulfide solutions of such concentrations that the sulfide concentrations after the formation of the zinc sulfide and mercuric sulfide complex were identical. The amount of postprecipitation was determined after four days of shaking at room temperature. For the sake of brevity the experimental details are omitted and the results given in a condensed form in Table IV.

TABLE IV

EFFECT OF VARYING AMOUNTS OF ZINC SULFIDE AND OF MERCURY AND SULFIDE CONCENTRATIONS; 4 DAYS OF SHAKING, TEMP. 25°

ZnS, mmol.	Hg originally in soln., mmol.	Na_2S *final* amount, mmol.	Hg *final* amount in soln., mmol.	Hg in ppt., mmol.	Hg pptd., %
0.5	0.5	3.41	0.341	0.159	31.8
1.0	.5	3.44	.222	.278	55.6
0.5	1.0	3.41	.696	.304	30.4
1.0	1.0	3.52	.502	.498	49.8
0.5	0.5	7.08	.416	.084	16.8
1.0	.5	7.02	.329	.171	34.2
0.5	1.0	7.00	.854	.146	14.6
1.0	1.0	7.01	.727	.273	27.3

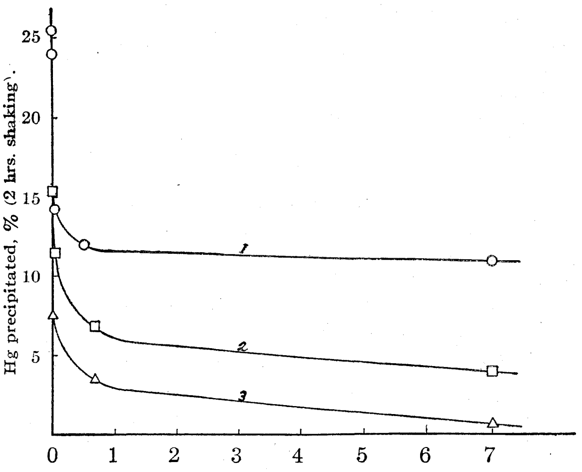

Fig. 2.—1, Zinc sulfide, aged in basic solution; 2, aged at *p*H of 5; 3, aged at *p*H of 2.

Postprecipitation at 80°.—In the following experiments the state of equilibrium of the distribution of mercuric sulfide between solution and the solid was approached at 80°. After running some preliminary series the sulfide concentration in each set was adjusted in such a way as to give identical sulfide concentrations in the solutions after attainment of distribution equilibrium. The bottles containing the sodium mercuric sulfide solution were placed in a beaker of hot water until the temperature of the contents was 90° and then zinc sulfate solution (25°) was added from a pipet. After thorough mixing the bottles were capped and kept for two days at a temperature of 80° in the beaker of hot water, the contents of the bottle being shaken by hand several times during the course of an experiment. After the heating period the bottles were allowed to cool to room temperature, centrifuged and an aliquot part of the supernatant liquid analyzed for mercury. In several cases a thin film of black mercuric sulfide separated at the gas–liquid interface during the heating process which after cooling did not dissolve easily in the solution although the latter was far from saturated with mercuric sulfide. The amount of mercuric sulfide formed at the interface was less than 1% of the total amount of mercury present and was not considered in the calculation of the results which are reported in an abbreviated form in Table V.

TABLE V

POSTPRECIPITATION OF MERCURIC SULFIDE AT 80° AFTER SHAKING FOR 2 DAYS

ZnS, mmol.	Hg originally in solution, mmol.	Na_2S final amount, mmol.	Hg finally in soln., mmol.	Hg in ppt., mmol.	Hg pptd., %	Color of ppt. after 2 days
0.5	0.5	3.57	0.286	0.214	42.8	Orange-brown
1.0	.5	3.55	.180	.320	64.0	Orange
0.5	1.0	3.60	.444	.556	55.6	Dark brown
1.0	1.0	3.51	.368	.632	63.2	Brown
0.5	0.5	7.01	.398	.102	20.4	Yellow
1.0	.5	7.10	.315	.185	37.0	Yellow
0.5	1.0	7.03	.817	.183	18.3	Orange-brown
1.0	1.0	7.02	.673	.327	32.7	Orange

Extractability of Mercuric Sulfide from the Mixed Zinc-Mercuric Sulfide.—A mixed precipitate containing 0.125 mmol. of mercuric sulfide and 0.5 mmol. of zinc sulfide which had been aged for two weeks was extracted several times with 0.2 *M* sodium sulfide solutions. In the first extraction the precipitate was shaken for ten hours with the sulfide solution; only 0.043 mmol. of mercury was found in the solution. After removing the supernatant liquid the precipitate was shaken with a fresh 50-ml. portion of sodium sulfide solution for two days after which time only 0.018 mmol. of mercury had been further removed from the precipitate. A further extraction for a day with a new portion removed only 0.007 mmol. of mercury.

The resulting precipitate was washed once with water and then extracted once with 0.5 *N* hydrochloric acid saturated with hydrogen sulfide; this treatment removed 95% of the zinc. After adding the acid the orange precipitate darkened slowly, within three minutes it was orange-brown and within ten minutes it was black. The acid was removed after seventy minutes of shaking, the precipitate washed with water and extracted for three hours with 50 ml. of sodium sulfide solution. The remainder of the mercury (0.059 mmol.) was thereby extracted. Feigl[1] also found that mercury was difficultly extractable from the mixed precipitate by sodium sulfide, but our interpretation is quite different from his.

Discussion

All the results reported so far tend to show that the postprecipitation of mercuric sulfide from solutions which are far from saturated with this compound is to be attributed to a solid solution formation with zinc sulfide. If such a solution of mercuric sulfide in zinc sulfide is considered ideal, it is possible to calculate the distribution coefficient of mercury between liquid and solid phases.

If the solution is in thermodynamic equilibrium with the solid, the thermodynamic potential of the mercuric sulfide in both phases is identical. Taking the activity of the mercuric sulfide in the pure solid as the standard state, we find that in case the solid solution behaves as an ideal solution

$$(a\text{HgS})_1 = S_{\text{HgS}} \cdot N_{\text{HgS}} \qquad (1)$$

in which $(a\text{HgS})_1$ denotes the activity of the mercuric sulfide in the liquid phase, S_{HgS} the solubility product of mercuric sulfide and N_{HgS} the mole fraction of mercuric sulfide in the solid.

In the presence of an excess of sulfide practically all of the mercury in the liquid phase is present in the form of $\text{HgS}_2^=$ ions; from practical viewpoint we are interested in the distribution of total mercury between solution and solid.

$$\text{HgS}_2^= \rightleftarrows (\text{HgS})_1 + \text{S}^=$$

or

$$(a\text{HgS})_1 = K_{\text{HgS}_2^=} \frac{a\text{HgS}_2^=}{a\text{S}^=} \qquad (2)$$

Since both HgS_2 and S ions are divalent their activity coefficients at various ionic strengths may be expected to be of the same order of magnitude and equation (2) may be approximated to

$$(a\text{HgS})_1 = K_{\text{HgS}_2^=} \frac{[\text{HgS}_2^=]}{[\text{S}^=]} \qquad (3)$$

in which the symbols between brackets denote the molar concentrations in solution. Combining (1) and (3) gives

$$\frac{[\text{HgS}_2^=]}{[\text{S}^=]} = \frac{S_{\text{HgS}}}{K_{\text{HgS}_2^=}} N_{\text{HgS}} = KN_{\text{HgS}} \qquad (4)$$

According to Knox[7] S_{HgS} at 25° is equal to 2.8×10^{-54}, and K_{HgS^-} to 1.96×10^{-55}. Hence, when equilibrium distribution is established and if the solution is ideal

$$[\text{HgS}_2^=] = KN_{\text{HgS}}[\text{S}^=] = 14.3\ N_{\text{HgS}}[\text{S}^=]\ (25°) \qquad (5)$$

From the results given in Table IV it is possible to calculate the value of *K* at 25°. In these experiments the volume of the solutions was 45 ml., the excess of sulfide in the first four experiments being 3.45 mmols. (average), and in the last four 7.04, corresponding to sodium sulfide concentrations of 0.0766 *M* and of 0.156 *M*, respectively. The concentrations of excess of sodium hydroxide corresponded to 0.064 *N* in the first four experiments and to 0.062 *N* in the last four experiments. Taking the second ionization constant of hydrogen sulfide equal to 10^{-15} and the ionic product of water equal to 10^{-14}, we find from the hydrolysis equation of the sulfide ion

$$\frac{[\text{OH}^-][\text{SH}^-]}{[\text{S}^=]} = \frac{K_{\text{w}}}{K_{2(\text{H}_2\text{S})}} = 10 \quad (25°) \qquad (6)$$

If the HS^- ion concentration is designated by *X*, then $[\text{OH}^-] = C_{\text{NaOH}} + X$ and $[\text{S}^=] = C_{\text{Na}_2\text{S}} - X$. Introducing these expressions into equation (6) yields a quadratic equation which can be solved for *X*.

The values of *K* calculated in this way from the results of experiments in Table IV are given in Table VI and plotted in Fig. 3.

An attempt was made to calculate the values of *K* at 80° from the results reported in Table V. According to Jellinek and Czerivinski[9] the degree of hydrolysis of sodium sulfide solutions does not change between 0 and 25°. On the basis of this result we have assumed in our calculations that the hydrolysis constant of the sulfide at 80° is equal to that at 25°. This is probably incorrect as is also evidenced by the fact that the values of *K* calculated from experiments in

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(9) K. Jellinek and J. Czerivinski, *Z. physik. Chem.*, **102**, 476 (1922).

TABLE VI

DISTRIBUTION COEFFICIENT *K* OF MERCURIC SULFIDE BETWEEN SODIUM MERCURIC SULFIDE AND ZINC SULFIDE AT 25 AND AT 80°

Temp., °C.	N_{HgS}	$[HgS_2^{=}]$ molar	$[S^{=}] \times 10^3$	*K*
25	0.242	0.341	1.06	29.6
25	.218	.222	1.06	21.4
25	.378	.696	1.06	38.6
25	.332	.502	1.06	31.6
25	.214	.727	3.28	23.0
25	.226	.854	3.28	25.6
25	.146	.329	3.28	15.3
25	.144	.416	3.28	19.6
80	.300	.286	1.06	20.0
80	.242	.180	1.06	15.6
80	.527	.444	1.06	17.7
80	.387	.368	1.06	19.9
80	.246	.673	3.28	18.6
80	.268	.817	3.28	20.7
80	.156	.315	3.28	13.7
80	.169	.398	3.28	16.0

which the sodium sulfide concentration was 0.0766 *M* fall on a different line than those in which the sodium sulfide concentration was 0.156 *M* (see Fig. 3). On the other hand, the values of *K* calculated from the results of experiments at room temperature at different sulfide concentrations fall approximately on one straight line. It is seen from the results and particularly from Fig. 3 that the value of *K* is not constant, but increases as a linear function of the mole fraction of mercury in the solid solution. A similar result was found by Yutzy and Kolthoff[10] for the change of the distribution coefficient of bromide between aqueous solutions and mixed crystals of silver chloride and bromide at different mole fractions of bromide in the solid.

The change of *K* with the mole fraction of mercury in the solid shows that the solid solutions do not behave as ideal solutions, and that activities cannot be taken equal to mole fractions. It is gratifying that the values of *K* are of the order of magnitude of the calculated value of 14.3 based on the assumption of ideal solutions and equilibrium constants of Knox.

From the graph it is seen that at 80° the values of *K* increase less with increasing mole fraction of mercury than at 25°. Hence, at higher temperatures the system approaches that of an ideal system. Qualitatively, a similar result was found again by Yutzy and Kolthoff,[10] who at 100° found in the system silver chloride–bromide a value of the distribution coefficient which was independent of the composition of the solid.

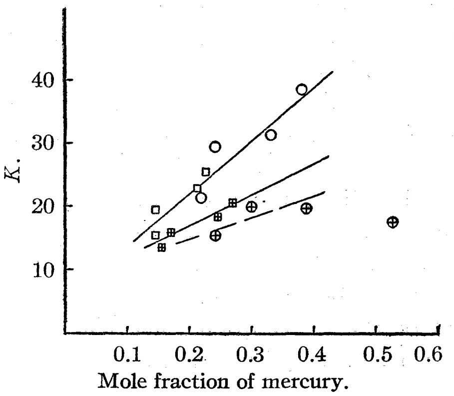

Fig. 3.—○, in 0.0766 *M* Na_2S at 25°; □, in 0.156 *M* Na_2S at 25°; ⊕, in 0.0766 *M* Na_2S at 80°; ⊠, in 0.156 *M* Na_2S at 80°.

Figure 3 shows that at high mole fractions of mercuric sulfide with solid (at $N_{HgS} > 0.5$) the value of *K* does not increase further with increasing N_{HgS} at 80°. This might indicate that the solid consists of two phases, the second phase being mercuric sulfide or, more likely, a solution of zinc sulfide in mercuric sulfide.

It is of interest to note that according to equation (5) the distribution coefficient of the mercuric sulfide between solution and precipitate is independent of the chemical nature of the solid as long as the latter can form ideal solid solutions with mercuric sulfide. Hence, it may be expected that under comparable conditions the distribution of mercuric sulfide between sodium mercuric sulfide solution and zinc, lead or manganese sulfides will be of the same order of magnitude.

Direct evidence from X-ray measurements of mixed crystal formation between mercuric and zinc sulfide was given by Moltzau and Kolthoff.[11] They found that zinc sulfide dissolved in mercuric sulfide to a limited extent. The present study shows that mercuric sulfide is soluble—at least to a certain extent—in zinc sulfide.

An X-ray examination of an orange colored precipitate, kindly made for us by Mr. M. L. Fuller of the New Jersey Zinc Co., showed that it had a zinc sulfide cubic lattice expanded about 1%. The broadness of the lines on the film prevented an exact measurement.

Summary

1. Mercuric sulfide is postprecipitated with

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[10] H. C. Yutzy and I. M. Kolthoff, THIS JOURNAL, **59**, 916 (1937).

[11] D. R. Moltzau and I. M. Kolthoff, *J. Phys. Chem.*, **40**, 637 (1936).

zinc sulfide from sodium mercuric sulfide solutions which are undersaturated with mercuric sulfide. Such a postprecipitation occurs only when the mercuric sulfide is soluble in the primary precipitate, and the speed of separation of the latter from solution is greater than the speed of dissociation of the $HgS_2^=$ ion into HgS and $S^=$.

2. The distribution coefficient of mercuric sulfide between aqueous solution and solid has been determined at 25 and 80°. The solid solution does not behave as an ideal solution, but the values of the distribution coefficient are of the same order of magnitude as the value calculated upon the basis of formation of ideal solutions. This calculated value is independent of the nature of the solid, as long as the latter acts as a solvent for mercuric sulfide.

3. The speed of attainment of distribution equilibrium between sodium mercuric sulfide solution and zinc sulfide is a good indicator of the degree of perfection and the progress of aging of the latter. It is shown that zinc sulfide precipitated at a *p*H of 1.15 is more perfect and ages more rapidly at this *p*H than the sulfide formed and aged at a *p*H of 5 and the latter more so than the sulfide formed and aged in alkaline medium.

Minneapolis, Minn. Received April 14, 1938

[Contribution from the Department of Research in Pure Chemistry, Mellon Institute of Industrial Research]

Hydroxyalkyl Ethers of Basic Phenols. The Antipneumococcic Activity of Some 8-Quinolyl Ethers

By C. L. Butler and Alice G. Renfrew

It appeared to be of considerable general interest to extend the application of the hydroxyalkylation method used in the cinchona alkaloid field[1] to other types of basic phenolic substances. More specifically, it was hoped that studies carried out on simpler basic phenols would give a partial explanation, at least, of the low yields obtained in attempts to hydroxyethylate phenolic cinchona alkaloids with ethylene chlorohydrin.[2] Further, the preparation of simpler substances, related structurally to these alkaloids, was of interest in the chemotherapeutic study of pneumonia. Experiments undertaken with these considerations in view are described in the present report.

Phenol, aniline, *p*-aminophenol, *p*-acetaminophenol, *m*-diethylaminophenol and 8-hydroxyquinoline were chosen as suitable starting materials for the investigations. The compounds were alkylated in the usual way with benzyloxyalkyl *p*-toluenesulfonates[3] and the resulting aminoaryl benzyloxyalkyl ethers were hydrolyzed in dilute hydrochloric acid to hydroxyalkyl derivatives.[1] Yields were high in nearly all cases. The reaction with *p*-aminophenol was complicated by nitrogen alkylation. *p*-Acetaminophenol, however, gave with benzyloxyethyl *p*-toluenesulfonate, a high yield of the benzyloxyalkyl ether, which was readily converted to β-hydroxyphenetidine. Hydroxyalkylation of *m*-diethylaminophenol and 8-hydroxyquinoline was accomplished without difficulty.

It seemed possible that the failure of ethylene chlorohydrin to hydroxyethylate phenolic cinchona alkaloids[2] might be due to the presence in the cinchona structure of basic groups, with which this substance reacted with greater ease than with the phenolic group; or by which it was destroyed before it could react. Several alkylations with ethylene chlorohydrin were carried out in attempts to get further information on this point. According to Rindfusz[4] a 50% yield of hydroxyethyl phenyl ether is obtained on alkylation of sodium phenolate with this reagent. In the present work the reaction was carried out in the presence of one molecular equivalent of triethylamine. Only 13% of the theoretical quantity of hydroxyethyl phenyl ether was obtained in this experiment. The presence of triethylamine, however, did not decrease the yield of alkylation product when benzyloxyethyl *p*-toluenesulfonate was used as alkylating reagent. 8-Hydroxyquinoline, on alkylation with ethylene chlorohydrin, gave only 19% of the theoretical amount of

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[1] Butler and Renfrew, This Journal, **60**, 1473 (1938).

[2] Butler, Renfrew, Cretcher and Souther, *ibid.*, **59**, 227 (1937).

[3] Butler, Renfrew and Clapp, *ibid.*, **60**, 1472 (1938).

[4] Rindfusz, *ibid.*, **41**, 669 (1919); see also Bentley, Haworth and Perkin, *J. Chem. Soc.*, **69**, 164 (1896).

TABLE I

ANTIPNEUMONIC ACTIVITY AND TOXICITY OF 8-QUINOLYL ETHERS

	Bactericidal power *in vitro*[a]		Toxicity[a] 20 g. mice; deaths at dosages of					
Substance	Growth	Dilution	1 mg.	2 mg.	3 mg.	7 mg.	8 mg.	10 mg.
8-Hydroxyquinoline sulfate	Complete inhibition	1:400000	8/30	30/30	30/30			
8-Quinolyl Ether Hydrochlorides								
Ethyl	Slight inhibition	1:50000					2/10	13/30
β-Hydroxyethyl	Slight inhibition	1:100000			0/30	0/10	0/30	
γ-Hydroxypropyl	No inhibition	1:50000					0/10	
α-Methyl β-hydroxyethyl	No inhibition	1:50000			0/30	0/10	0/10	2/30

[a] Detailed results will be published by the medical staff associated with the Mellon Institute in the chemotherapeutic study of pneumonia.

hydroxyethyl 8-quinolyl ether, as compared with the 50% yield obtained by Rindfusz[4] in the hydroxyethylation of phenol, where there could be no question of complication with basic nitrogen groups. Hydroxyethyl 8-quinolyl ether was obtained in 67% yield, using benzyloxyethyl *p*-toluenesulfonate. *m*-Diethylaminophenol gave practically identical quantities of hydroxyethyl ether with the two reagents. It is believed that these results confirm the opinion that the unfavorable yields reported in the earlier work on hydroxyalkylation of cinchona alkaloids with ethylene chlorohydrin[2] were due to complications involving the two nitrogen atoms of the alkaloids. The difficulty can be avoided to a very large extent by the use of the benzyloxyalkyl aromatic sulfonates for alkylations of this type.

The preparation of the quinoline derivatives had an added interest because of the structural relationship of these compounds to the cinchona alkaloids, and because of the marked germicidal activity of many substances of this type.[5] Hirschfelder and co-workers[6] found that 8-hydroxyquinoline sulfate was highly active *in vitro* against the pneumococcus. In spite of this observation the possibility of the usefulness of simpler quinoline derivatives as antipneumococcic agents has received very little attention. More recently, a series of eighteen quinoline derivatives was investigated by Bührmann[7] and several substances derived from 2-phenyl-4-amino- and 4-amino-6-hydroxyquinolines, were found which inhibited the growth of pneumococci. In view of Hirschfelder's results,[6] it seemed advisable to have further tests run on 8-hydroxyquinoline and the 8-quinolyl ethers prepared in the course of this work. Interest in these compounds was enhanced by the suggestion that 8-hydroxyquinoline may stimulate the defense mechanism of the body[5] (p. 33). In Table I, both the mouse toxicity and the pneumococcicidal activity are seen to be reduced sharply by alkylation of the phenolic hydroxyl group. Some pneumococcicidal activity is maintained in the ethyl and hydroxyethyl derivatives. Further biological examination of these substances would appear to be desirable, especially in view of their very low toxicities.

Experimental

Half molecular quantities of the compounds to be alkylated were converted to potassium salts with the calculated amount of potassium hydroxide in about 300 cc. of absolute alcoholic solution. The alkylating reagent was then added and the mixture was refluxed for two to two and one-half hours on a water-bath. When ethylene chlorohydrin was used as alkylating reagent, the reaction mixtures were worked up directly in the usual way for hydroxyethyl ether. The crude reaction products from the benzyloxyalkyl *p*-toluenesulfonate alkylations were isolated by evaporating the solvent from the filtered alcoholic solution and separating from alkali-soluble material. The benzyl derivatives were hydrolyzed in dilute hydrochloric acid to hydroxyalkyl ethers as previously described[1] and the products were worked up and purified by the usual methods.

Phenoxyethyl Benzyl Ether.—The ether was obtained as an oil on alkylation of phenol with benzyloxyethyl *p*-toluenesulfonate. The product was purified by fractional distillation; yield 67%; b. p. 175° at 3 mm.

In a second experiment, conditions were altered by adding to the alkylation mixture one equivalent of triethylamine. The presence of this base did not interfere with the desired reaction, as was evidenced by the high yield (78% of the theoretical) of ether obtained.

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.9; H, 7.1. Found: C, 79.05; H, 6.9.

β-Hydroxyethyl Phenyl Ether.[4]—The alkylation of phenol with ethylene chlorohydrin was carried out in the usual way except that one equivalent of triethylamine was added to the reaction mixture. The yield of β-hydroxyethyl phenyl ether was only 12.5%, as compared with the 50% yield obtained by Rindfusz.[4]

β-Hydroxyethylaniline.—Aniline was alkylated with benzyloxyethyl *p*-toluenesulfonate and the crude benzyl-

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(5) Von Oettingen, "Therapeutic Agents of the Quinoline Group," The Chemical Catalog Company, Inc., New York, 1933.

(6) Hirschfelder, Jensen and Swanson, *Proc. Soc. Exptl. Biol. Med.*, **20**, 402 (1923).

(7) Bührmann, *Z. Immunitätsforschung*, **84**, 300 (1935).

oxyethylaniline was hydrolyzed in 11% hydrochloric acid[1] to β-hydroxyethylaniline; yield 50%; b. p. 157–158° at 13 mm.

A portion of the hydroxyethylaniline was converted to N-benzoxyethyl benzanilide with benzoyl chloride, in 80% yield. The melting point was 91–92°, which agrees with the figure found by Schorigin and Below.[8]

Alkylation of *p*-Aminophenol with Benzyloxyethyl *p*-Toluenesulfonate.—The only product which could be isolated in this experiment was a crude trialkylated substance of probable structure $C_6H_5CH_2OCH_2CH_2OC_6H_4N(CH_2CH_2OCH_2C_6H_5)_2$. A small amount of this material was converted to a crystalline sulfate and analyzed.

Anal. Calcd. for $C_{33}H_{37}O_4N \cdot 0.5\,H_2SO_4$: SO_4, 8.5. Found: SO_4, 7.7.

The main portion of the reaction product was hydrolyzed in dilute hydrochloric acid to remove benzyl groups. The yield of hydrolysis product was very low. Since the crude substance formed only mono-acyl derivatives with *p*-toluenesulfonyl chloride and acetyl chloride, it consisted probably of phenylmorpholine *p*-hydroxyethyl ether.

Anal. Amorphous *p*-toluenesulfonyl derivative. Calcd. for $C_7H_7SO_3CH_2CH_2OC_6H_4N(CH_2CH_2)_2O$: $C_7H_7SO_3K$, 55.7. Found: $C_7H_7SO_3K$, 55.4.

Crystalline acetyl derivative from alcohol; m. p. 118–119°. Calcd. for $CH_3CO_2CH_2CH_2OC_6H_4N(CH_2CH_2)_2O$: CH_3CO, 16.2. Found: CH_3CO, 16.4, 16.7.

Benzyloxyethyl *p*-Acetaminophenyl Ether.—*p*-Acetaminophenol was readily alkylated with benzyloxyethyl *p*-toluenesulfonate. The solid ether was purified by crystallization from absolute alcohol; yield 88%; m. p. 88°.

Anal. Calcd. for $C_{17}H_{19}O_3N$: C, 71.6; H, 6.7. Found: C, 71.3; H, 7.0.

β-Hydroxyphenetidine.—Benzyloxyethyl *p*-acetaminophenyl ether was hydrolyzed in 11% hydrochloric acid in the usual way[1] to β-hydroxyphenetidine; yield 80%. A sample recrystallized from alcohol melted at 73°.

Anal. Calcd. for $C_8H_{11}O_2N$: N, 9.15. Found: N, 9.2.

A small sample was converted to a crystalline diacetyl derivative with acetyl chloride. The melting point was 128°, which was in fair agreement with the figure found by Katrak.[9]

β-Hydroxyethyl *m*-Diethylaminophenyl Ether.—*m*-Diethylaminophenol, on alkylation with ethylene chlorohydrin, gave a 62% yield of β-hydroxyethyl *m*-diethylaminophenyl ether. An identical over-all yield was obtained when the hydroxyalkylation was carried out through the intermediate benzyloxyethyl derivative. There is, therefore, no advantage in the use of benzyloxyethyl *p*-toluenesulfonate in this case; b. p. 148° at 3 mm., m. p. 41°.

Anal. Calcd. for $C_{12}H_{19}O_2N$: N, 6.7; C, 68.9; H, 9.1. Found: N, 7.9; C, 69.3; H, 9.6.

An acetyl derivative was obtained as a viscous liquid with acetic anhydride and sodium acetate.

Anal. Calcd. for $C_{14}H_{21}O_3N$: CH_3CO, 17.1. Found: CH_3CO, 16.9, 17.4.

β-Hydroxyethyl 8-Quinolyl Ether.—8-Hydroxyquinoline was alkylated with benzyloxyethyl *p*-toluenesulfonate, and the crude benzyloxyethyl 8-quinolyl ether was hydrolyzed to β-hydroxyethyl 8-quinolyl ether in dilute hydrochloric acid. The substance was purified by crystallization of its hydrochloride from absolute alcohol; yield 70%; m. p. 199–200°.

Anal. Calcd. for $C_{11}H_{11}O_2N \cdot HCl$: Cl, 15.7. Found: Cl, 15.8.

The base was recovered from the hydrochloride and crystallized from alcohol; m. p. 83–84°.

Anal. Calcd. for $C_{11}H_{11}O_2N$: C, 69.8; H, 5.9; N, 7.4. Found: C, 69.5; H, 6.1; N, 7.3.

β-Acetoxyethyl 8-quinolyl ether was obtained by acetylation of the hydroxyethyl ether with acetyl chloride. It was purified by crystallization of its hydrochloride from alcohol; m. p. 153°.

Anal. Calcd. for $C_{13}H_{13}O_3N \cdot HCl$: CH_3CO, 16.1; Cl, 13.25. Found: CH_3CO, 16.8; Cl, 13.1.

A more direct preparation of β-hydroxyethyl 8-quinolyl ether was accomplished by alkylation of 8-hydroxyquinoline with ethylene chlorohydrin. The yield, however, was only 19% using this method.

α-Methyl-β-hydroxyethyl and γ-Hydroxy-*n*-propyl 8-Quinolyl Ethers.—The compounds were prepared by alkylation of 8-hydroxyquinoline with the appropriate benzyloxyalkyl *p*-toluenesulfonates and hydrolyzing the intermediate benzyloxyalkyl ethers to the desired hydroxyalkyl derivatives.

α-Methyl-β-hydroxyethyl 8-quinolyl ether was purified by crystallization of its hydrochloride from alcohol; yield 40%.

Anal. Calcd. for $C_{12}H_{13}O_2N \cdot HCl$: Cl, 14.8; N, 5.8. Found: Cl, 14.6; N, 6.3.

The base was liberated from the hydrochloride and crystallized from ether; m. p. 65°. With acetyl chloride it gave a solid acetyl derivative, which was crystallized from acetone; m. p. 99°.

Anal. Calcd. for $C_{14}H_{15}O_3N$: CH_3CO, 17.5. Found: CH_3CO, 17.0, 18.1.

γ-Hydroxy-*n*-propyl 8-quinolyl ether was similarly purified; yield 59%; m. p. 129°.

Anal. Hydrochloride. Calcd. for $C_{12}H_{13}O_2N \cdot HCl$: Cl, 14.8. Found: Cl, 14.5. Base. Calcd. for $C_{12}H_{13}O_2N$: N, 6.9. Found: N, 7.1.

γ-Acetoxy-*n*-propyl 8-quinolyl ether was obtained as a reddish oil on acetylation with acetic anhydride and sodium acetate.

Anal. Calcd. for $C_{14}H_{15}O_3N$: CH_3CO, 17.5. Found: CH_3CO, 17.5, 17.6.

8-Ethoxyquinoline.—8-Hydroxyquinoline was alkylated in the usual way with ethyl *p*-toluenesulfonate; b. p. 178° at 28 mm.[10] The base was converted to hydrochloride, which was crystallized from alcohol.

Anal. Calcd. for $C_{11}H_{11}ON \cdot HCl$: Cl, 16.9. Found: Cl, 16.9.

Summary

The preparation of several hydroxyalkyl ethers of basic phenols has been described. Some

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[8] Schorigin and Below, *Ber.*, **68**, 833 (1935).

[9] Katrak, *J. Indian Chem. Soc.*, **13**, 334 (1936).

[10] Fischer and Renouf, *Ber.*, **17**, 759 (1884).

physiological properties of hydroxyalkyl 8-quinolyl ethers having a bearing on the chemotherapy of pneumonia have been presented briefly.

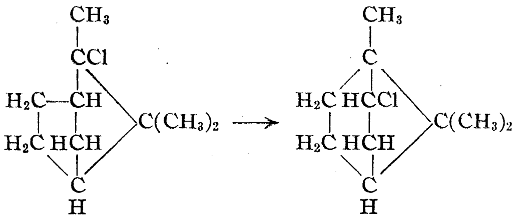
PITTSBURGH, PENNA. RECEIVED MAY 19, 1938

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

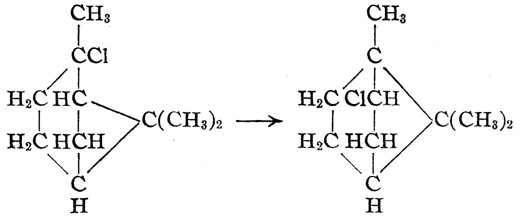
The Wagner–Meerwein Rearrangement. A Kinetic Reinvestigation of the Isomerization of Camphene Hydrochloride[1]

BY PAUL D. BARTLETT AND IRVING PÖCKEL

About a year ago we reviewed the evidence[2] that the rearrangement of camphene hydrochloride (I) into isobornyl chloride (II), and of pinene hydrochloride (III) into bornyl chloride (IV) involves complete Walden inversion at carbon atom no. 2 of the camphane ring system (the point of attachment of the chlorine in bornyl and isobornyl chlorides). Analogy with well-known cases of Walden inversion led us to propose that this rearrangement was a collision process, involving donors or acceptors of chloride ions, or both. Such a potential donor and acceptor is always present in solutions of camphene hydrochloride, since this compound dissociates rapidly and reversibly into camphene and hydrogen chloride, and this equilibrium is attained more rapidly than the rearrangement occurs.



I II



III IV

If hydrogen chloride played an essential part in the rearrangement, the reaction could not be a spontaneous, monomolecular one as reported by Meerwein and van Emster.[3] Since these authors had not considered higher orders of reaction, we recalculated their data in terms of first, second and three-halves order equations and found that in six of the nine solvents studied the data were best fitted by the formulation of the second order with respect to camphene hydrochloride, while in the remaining three solvents the three-halves order formulation was best. This left it quite uncertain in what manner hydrogen chloride entered into the rearrangement process.

We have now carried out a number of kinetic experiments designed to provide clear evidence of the order of the reaction. Nitrobenzene was chosen as a solvent because it allows the rearrangement to proceed at the most convenient rate for measurement. The results show clearly that the rearrangement involves one molecule of camphene hydrochloride and one of hydrogen chloride, and they provide a complete explanation for the apparent variation of the order of the reaction with change of solvent under the conditions of measurement used by Meerwein and van Emster and, initially, by ourselves. The dissociation equilibrium

$$\text{Camphene hydrochloride} \rightleftarrows \text{Camphene} + \text{HCl} \quad (1)$$

lies, in the case of most of our solutions, more than 94% to the left. With pure camphene hydrochloride, the hydrogen chloride concentration in the solution will be proportional to the square root of the camphene hydrochloride concentration, and hence the rate of reaction is proportional to the $^3/_2$ power of the camphene hydrochloride concentration. However, when a large excess of camphene is present, the amount of hydrogen chloride at equilibrium is diminished and its concentration becomes proportional to that of the camphene hydrochloride. The reaction under these conditions is slowed down and becomes apparently bimolecular with respect to camphene hydrochloride. The explanation of the fact that the rearrangement seems to be sometimes second and sometimes $^3/_2$ order is that it is almost im-

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(1) Most of this material was included in a paper presented at the Organic Symposium at Richmond, Va., on December 30, 1937.

(2) Bartlett and Pöckel, THIS JOURNAL, **59**, 820 (1937).

(3) Meerwein and van Emster, *Ber.*, **55B**, 2500 (1922).

possible to prepare camphene hydrochloride free from camphene. If the amount of camphene present in a particular sample is small enough, the reaction will approximate the $^3/_2$ order, but it easily may be great enough to make the second order a better approximation.

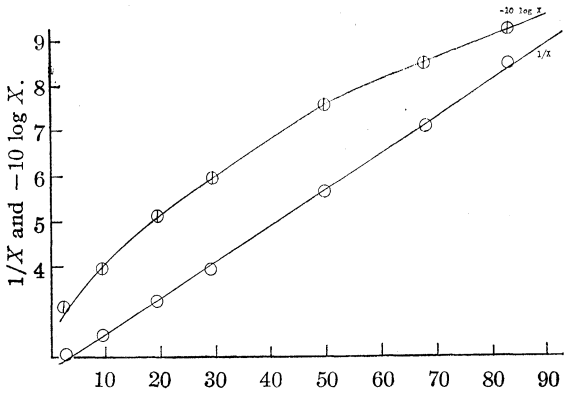

Fig. 1.—Rate of rearrangement of camphene hydrochloride to isobornyl chloride in nitrobenzene solution at 20° in the presence of excess free camphene: ○, $1/X$; ⦶, $-10 \log X$.

There are several quantitative tests, described in full below, which show that this description of the kinetics of the rearrangement is correct. First, with our purest samples of camphene hydrochloride, we were able to duplicate Meerwein's kinetic data which fit the equation of the $^3/_2$ order. Second, by the addition of excess camphene the reaction is made strictly bimolecular (Fig. 1). Third, such additions of camphene diminish the rate of the reaction to the extent predicted from the assumption that there is no spontaneous rearrangement not involving hydrogen chloride (Fig. 2). Fourth, the velocity constant for the reaction between camphene hydrochloride and hydrogen chloride is the same for the rapid reaction in which excess hydrogen chloride is present as for the slow reaction with excess camphene. Fifth, a general equation, derived on the assumption here set forth, fits the kinetic data under these conditions and in those intermediate cases where neither of the limiting formulations holds.

The supposed spontaneous rearrangement of camphene hydrochloride is therefore a process catalyzed by hydrogen chloride. Nevertheless, the balance of the evidence does not seem to be in favor of the donor hypothesis which led us to undertake this investigation. The free chloride ion, which should be the best possible donor, is without effect on the rate of the rearrangement in acetone solution, as shown by kinetic runs with and without lithium chloride. Although all the catalysts for the rearrangement reported as such by Meerwein and van Emster contain chlorine and hence are potential donors of chloride ions, we find that *o*-cresol is not only a good solvent for the rearrangement, as reported by these authors, but a specific catalyst when dissolved in nitrobenzene. Its catalytic efficiency is about one-third that of hydrogen chloride, and it takes the place of hydrogen chloride kinetically. No cresol is consumed in this reaction. Since lithium chloride, which can be a donor, is not a catalyst, and cresol, a good catalyst, cannot be a donor, this way of explaining the Walden inversion attending the rearrangement is untenable.

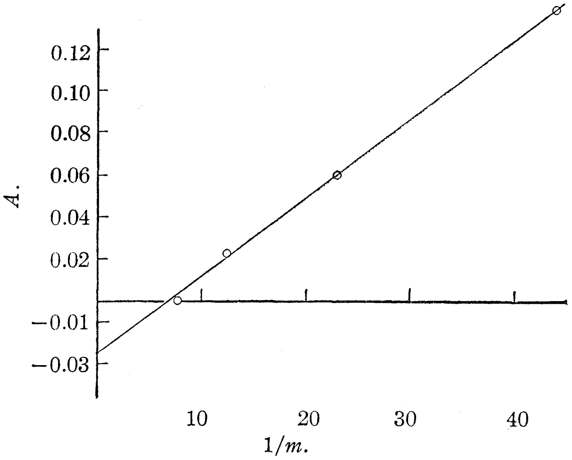

Fig. 2.—Plot of A against $1/m$: A is free camphene added; m is bimolecular rate constant.

Nevertheless, from the occurrence of the Walden inversion in the rearrangement, it seems clear to us that either the carbonium ion has spatial properties quite different from those that have been currently attributed to it, or else the mechanism of Meerwein requires important modification. We are continuing our work and hope to be able to choose between these alternatives. Further discussion of the mechanism is therefore postponed to a later paper.

The fact that hydrogen chloride is necessary to the otherwise uncatalyzed rearrangement explains the anomalous position of ether among the solvents of Meerwein and van Emster. Ether, though not possessing the lowest dielectric constant of the series of solvents which these authors studied, was unique for the slowness with which the rearrangement proceeded in it. A glance at their list of solvents shows that ether is the only one with definitely basic properties. Hydrogen chloride in this solvent must exist largely as diethyloxonium chloride, in which form it is incapable of assisting the removal of chloride ion from the camphene hydrochloride molecule. In harmony with this conclusion, we have found that acetone, which also possesses a basic oxygen atom, also allows the rearrangement to proceed much more slowly than corresponds to its position in the dielectric constant series. Meerwein and van Emster[3] (p. 2511) correlated the effect of ether with its basicity, although the connection could not be clear when the rearrangement was regarded as largely uncatalyzed.

Derivation of the Kinetic Equations

Wynne-Jones has shown[4] that hydrogen chloride behaves as a normal, undissociated and unassociated solute in nitrobenzene. Let x, y, and z denote the concentrations of camphene hydrochloride, hydrogen chloride, and isobornyl chloride, respectively. During any run there is a constant difference between the concentrations of hydrogen chloride and camphene, and the latter accordingly can be designated by $y + c$. By the conditions of equilibrium 1

$$K = \frac{y(y + c)}{x} \tag{2}$$

so that

$$y = \sqrt{Kx + \frac{c^2}{4}} - \frac{c}{2}$$

The general rate equation is

$$\frac{dz}{dt} = -\frac{dx}{dt} - \frac{dy}{dt} = kx\left(\sqrt{Kx + \frac{c^2}{4}} - \frac{c}{2}\right)$$

For the purpose of integration we make the substitution

$$v = \sqrt{Kx + \frac{c^2}{4}}$$

Then

$$-dv - \frac{2v dv}{K} = \frac{k}{K}\left(v^2 - \frac{c^2}{4}\right)\left(v - \frac{c}{2}\right) dt$$

The integrated form is

$$\frac{c - K}{c^2} \ln \frac{v + c/2}{v - c/2} + \left(1 + \frac{K}{c}\right)\frac{1}{v - c/2} = kt + \text{Constant} \tag{3}$$

This integral is a linear function of time for all our runs, whether c be large or small, positive or negative. The use of this equation requires a knowledge of the values of c and K. When c is small its value is uncertain by reason of the great difficulty of obtaining samples of camphene hydrochloride which contain an excess of neither camphene nor hydrogen chloride. We have not found any titration method for camphene suitable in the presence of camphene hydrochloride, and hence to obtain the best estimate of K we have made use of the following considerations.

When c is large compared to y, we may replace $(y + c)$ in Equation (2) with c. This leads to the expression

$$y = Kx/c$$

whence, if K is small enough so that x is much greater than y

$$\frac{dz}{dt} = -\frac{dx}{dt} = k\frac{K}{c}x^2$$

and

$$\frac{1}{x} = \frac{kK}{c}t + \text{Constant} \tag{4}$$

The reaction under these conditions is therefore of the second order with respect to camphene hydrochloride, and the second order rate constant is equal to kK/c.

We now make up a series of runs by adding different known amounts A of camphene to portions of a stock solution of a single sample of camphene hydrochloride containing an unknown excess c_0 of camphene. In these runs

$$c = c_0 + A$$

Denoting the observed bimolecular rate constants for these runs by m, we get the relationship

$$m = kK/(c_0 + A)$$

which can be transformed to

$$A = (kK/m) - c_0 \tag{5}$$

According to this, if the known values of A be plotted as ordinates against the observed $1/m$ values as abscissas, the plot should be a straight line of slope kK and of intercept $-c_0$ on the axis of ordinates. Figure 2 shows this plot for a series of runs made on the stock solution without added camphene and with three known concentrations of camphene added. The bimolecular formulation is not valid for the run without added camphene, since the value of c in this case is not high enough to make the assumptions valid. This point has nevertheless been put on the graph for comparison. It can be seen that the three points for which Equation (4) is valid fall on a good straight line and allow an extrapolation to be made which gives a value of 0.0253 for c_0 and of 3.72×10^{-3} for kK. Knowing the true values of c for all the runs, we can now calculate a value of K for each point of the kinetic run where we

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[4] Wynne-Jones, *J. Chem. Soc.*, 1064 (1930).

have values of both x and y. Among all the determined quantities, y is the least certain, since hydrogen chloride has a great tendency to escape during the sealing and opening of the ampoules. However, the average values of K for the several runs are in good agreement, and we take the general average of 1.8×10^{-3} as the most probable value. This K is used wherever Equation (3) has been applied. The use of Equation (3) on the run of the present series to which no camphene was added yields a k of 2.45 in as good agreement with the value 2.07 determined from the slope of the line in Fig. 2 as the uncertainty of K would lead us to expect.

When c becomes zero, Equation (2) becomes

$$K = y^2/x$$

and the kinetic equations are

$$\frac{dz}{dt} = -\frac{dx}{dt} - \frac{\sqrt{K}}{2\sqrt{x}}\frac{dx}{dt} = k\sqrt{K}\,x^{3/2}$$

and

$$\frac{2}{\sqrt{Kx}} + \frac{1}{2x} = kt + \text{Constant} \qquad (6)$$

In the concentration range actually used, only the first term of the integral is of importance, and the reaction should therefore be of the $^3/_2$ order. In only a few of our runs, and of Meerwein's, was the camphene hydrochloride pure enough to approach this behavior; for even the small amount of camphene present in the run of Fig. 1 causes the run to be more nearly second than $^3/_2$ order.

In the presence of a large excess of hydrogen chloride, y is practically equal to $-c$, and only then will the reaction be kinetically of the first order with respect to camphene hydrochloride.

Equation (3) can be shown, by the usual methods of evaluating limits, to approach these special cases under appropriate conditions.

Materials and Experimental Procedure

The nitrobenzene used as solvent was purified by distillation through a nine-foot (2.75-meter) column. It boiled at 98° at 19 mm. and melted at 5.3°.

The camphene was prepared by the methods of Ullmann and Schmid[5] and Bertram and Walbaum.[6] All samples of camphene melted above 49°.

Camphene hydrochloride was prepared at first by the method of Meerwein and van Emster. This method of preparation involves keeping for some time in a vacuum desiccator over alkali, which in our experience always results in a preparation containing excess camphene. Our samples of the hydrochloride most free from camphene were obtained by keeping the product, after drying, in an atmosphere of hydrogen chloride for one hour. This resulted in preparations containing as much as 20% of isobornyl chloride. Run 3.5, which shows $^3/_2$ order kinetics, was carried out with a sample prepared in this manner. In the run with acetone as a solvent, it was found necessary to allow the samples to stand with sodium methoxide for two hours instead of one, to ensure complete decomposition of the camphene hydrochloride.

The technique of Meerwein and van Emster was used in the kinetic runs, except for the substitution of methyl red for iodoeosin as indicator. For comparison with the results of Meerwein, the temperature of 20° was chosen and used throughout. The temperature was controlled by a thermostat within less than 0.1°.

Most of the runs were carried beyond 70% completion, to make possible a clear differentiation between orders of reaction.

Kinetic Results

Our conditions were so chosen that the order of reaction in most cases can be seen clearly from a plot of the function of concentration of camphene hydrochloride which should vary linearly with time. Figure 1 shows such a plot for one of the runs with excess camphene. In this case the reaction should be second order if hydrogen chloride is essentially involved in it, and first order if it is a spontaneous reaction of the camphene hydrochloride. The figure shows that it is second order.

The problem of calculating the rate constant from a given run is essentially that of finding the slope of the best straight line through the experimental points. One can determine this quantity by the method of least squares, but for runs with relatively few points there is no better way than plotting the points and drawing the line by inspection, determining its slope graphically. This is the method which we have employed. It has the further advantage of providing a visible check for each run that the kinetic formulation employed is that which actually gives a straight line without trend.

The most stringent test of the correctness of our formulation of the reaction is provided by the comparison, in Table I, of the values of the rate constant, referred to camphene hydrochloride and hydrogen chloride concentrations, obtained from runs with excess camphene, excess hydrogen chloride, and the purest available camphene hydrochloride, using in each case the suitable equation for the interpretation of the data.

In spite of the benefit which we have gained from the publication in full of the original data of Meerwein and van Emster, we are reporting here only sample data for each type of run, in ac-

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[5] Ullmann and Schmid, *Ber.*, **43**, 3206 (1910).

[6] Bertram and Walbaum, *J. prakt. Chem.*, **49**, 8 (1894).

TABLE I

VELOCITY CONSTANTS IN NITROBENZENE AT 20°, CALCULATED FOR REACTION BETWEEN CAMPHENE HYDROCHLORIDE AND HYDROGEN CHLORIDE

Run	Initial x	Excess camphene	Excess HCl	k (moles/l., hrs.)	Equation used
3.9	0.432	—	0.0438	2.69	-
M	.396	Small	—	2.28	6
3.5	.189	Small	—	2.19	6
3.6	.144	0.548	—	2.50	4
3.8	.480	.109	—	2.07	3
4.2	.550	.033 (cal.)	—	2.00	3
4.5	.577	.055 (cal.)	—	2.01	3
5.3	.472	.0253	—	2.45	3
5.5	.489	.0479	—	2.10	4
5.6	.514	.0856	—	2.08	4
5.7	.525	.1642	—	2.07	4

Run M is the one by Meerwein and van Emster.

cordance with the usual policy of THIS JOURNAL. The variation in the determined concentrations of hydrogen chloride is due not to any lack of sharpness of the titration method, but to the ease with which hydrogen chloride escapes from solution during the sealing and opening of the ampoules.

TABLE II

RATE OF CONVERSION OF CAMPHENE HYDROCHLORIDE INTO ISOBORNYL CHLORIDE IN NITROBENZENE SOLUTION AT 20° IN THE PRESENCE OF 0.0479 MOLE/LITER EXCESS CAMPHENE (See Fig. 1)

Sample run: Experiment 5.5. A = 0.0226 Mole/Liter

Time, hours	Cc. 0.1 N methylate consumed by the free HCl	Cc. 0.1 N methylate consumed by the camphene hydrochloride	X camphene hydrochloride moles/liter	Y free HCl moles/liter
2.33	—	24.21	0.489	—
9.47	0.56	19.90	.402	0.0119
19.28	.47	15.30	.309	.0095
29.17	.41	12.64	.255	.0083
49.78	.29	8.60	.174	.0059
67.88	.27	6.97	.141	.0055
82.90	.23	5.80	.117	.0046

TABLE III

RATE OF CONVERSION OF CAMPHENE HYDROCHLORIDE INTO ISOBORNYL CHLORIDE IN NITROBENZENE SOLUTION AT 20° IN THE PRESENCE OF EXCESS HYDROGEN CHLORIDE

Experiment 3.9

Time, hours	Cc. 0.1 N methylate consumed by the free HCl	Cc. 0.1 N methylate consumed by the camphene hydrochloride	Camphene hydrochloride moles/liter	Free HCl moles/liter
0.5	2.35	21.34	0.4324	0.0476
1.0	2.83	20.02	.4057	.0574
3.0	2.48	16.07	.3256	.0503
5.5	2.34	10.65	.2158	.0474
7.0	2.11	9.57	.1939	.0428
8.5	2.19	7.79	.1579	.0444
10.5	1.75	6.73	.1364	.0355
12.5	1.63	5.62	.1139	.0330
15.0	1.77	4.45	.0902	.0359
			Average	.0438

TABLE IV

RATE OF CONVERSION OF CAMPHENE HYDROCHLORIDE INTO ISOBORNYL CHLORIDE IN NITROBENZENE SOLUTION AT 20° IN THE PRESENCE OF A SMALL EXCESS OF CAMPHENE

Experiment 5.3. Excess camphene 0.0253 mole/liter

Time, hours	Cc. 0.1 N methylate consumed by the free HCl	Cc. 0.1 N methylate consumed by the camphene hydrochloride	Camphene hydrochloride moles/liter	Free HCl moles/liter	Value of left-hand member of Eq. 3
2.05	—	23.38	0.472	—	85.5
9.18	0.70	17.50	.353	0.0141	102.2
19.00	.53	12.95	.261	.0107	124.1
28.92	.47	9.66	.195	.0095	149.9
49.5	.39	6.33	.128	.0079	199.3
67.67	.35	4.61	.093	.0071	249.2
82.67	.31	3.96	.080	.0063	278.8
93.83	.23	3.70	.075	.0047	294.0

TABLE V

RATE OF REARRANGEMENT OF OUR PUREST SAMPLE OF CAMPHENE HYDROCHLORIDE INTO ISOBORNYL CHLORIDE IN NITROBENZENE SOLUTION AT 20°

(The low value of K_e indicates a small excess of camphene.)

Time, hours	Cc. 0.1 N methylate consumed by the free HCl	Cc. 0.1 N methylate consumed by the camphene hydrochloride	Free HCl Y moles/liter	Camphene HCl X moles/liter	$K_e \times 10^3$ Y^2/X
0.5	0.78	9.38	0.0158	0.1893	1.3
7.0	.79	8.69	.0159	.1755	1.4
26	.63	5.63	.0128	.1136	1.4
48	.45	3.77	.0091	.0760	1.1
77.5	.49	2.53	.0098	.0511	1.9
				Average	1.4

In all experiments the samples analyzed were 4.954 cc. each.

For a test of the effect of chloride ion on the rate of the rearrangement we were obliged to go to acetone as a solvent, since this solvent dissolves lithium chloride in amount sufficient for the test. Figure 3 shows the rates of reaction with and without 0.02 M lithium chloride. Although these runs are plotted according to Equation (4), the reaction appears to be of higher order than this. This may be due to the fact that over the long period of duration of the run, acetone is condensing with itself under the influence of the hydrogen chloride, and the nature of the solvent is thus undergoing change. There is also the possibility, which we have not investigated, that the equilibrium between isobornyl chloride and camphene hydrochloride may be more in favor of the latter in this solvent, so that the reaction cannot so well be treated as irreversible. The coincidence of the two curves in this case is good evidence that lithium chloride has no appreciable catalytic influence upon the reaction.

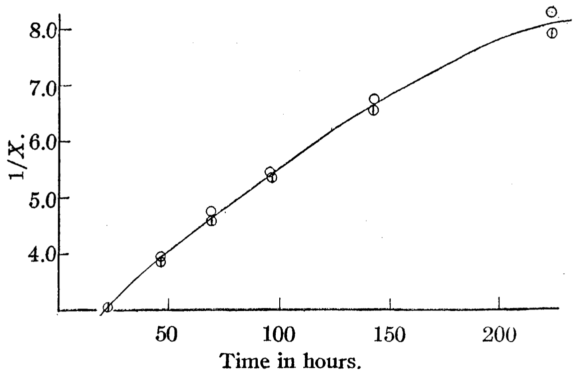

Fig. 3.—Rate of rearrangement of camphene hydrochloride into isobornyl chloride in acetone solution at 20° both in the presence of 0.02 mole/liter of LiCl and without the presence of LiCl: X = concn. camphene hydrochloride in moles/liter: ⦶, lithium chloride present; ○, lithium chloride not present.

For investigating the catalytic effect of *o*-cresol on the rearrangement, we chose to use an excess of camphene, in order that the hydrogen chloride-catalyzed reaction might be repressed to a minimum. Under these conditions the reaction in the absence of cresol would be strictly second order with respect to camphene hydrochloride, in accordance with Equation (4). The reaction actually observed in the presence of *o*-cresol is faster than this, and is first order over 70% of the total reaction, as shown in Fig. 4. From the known values of the rate constants we calculate that the reaction due to hydrogen chloride is less than 5% of the total reaction observed under these conditions. The order of the reaction shows (1) that hydrogen chloride is not involved in the cresol-catalyzed rearrangement, and (2) that cresol is not consumed and is thus a true catalyst. The velocity constant for reaction between camphene hydrochloride and cresol is 0.88. Cresol is thus about one-third as effective a catalyst for the reaction as hydrogen chloride.

A similar experiment using acetic acid instead of cresol showed that this compound too has a feeble catalytic activity in the Wagner–Meerwein rearrangement. The velocity constant here is 0.063. This constant, however, is not directly comparable to that for cresol, since acetic acid in nitrobenzene solution exists in the form of double molecules[7] in which the acid hydrogen is probably bound up in the formation of a chelate ring. The small catalytic activity observed may be that of the small fraction present as monomeric acetic acid. This uncertainty does not apply to the case of cresol.

Summary

1. The rearrangement of pure camphene hydrochloride into isobornyl chloride in solution requires the participation of hydrogen chloride. Since this hydrogen chloride is in equilibrium with camphene and camphene hydrochloride, the reaction rate varies with the camphene hydrochloride concentration in a manner which depends upon whether hydrogen chloride, or camphene, or neither, is present in excess.

2. A number of kinetic experiments under these various conditions support the quantitative implications of the essentially catalytic nature of the reaction.

3. The chloride ion is not a catalyst for the reaction. *o*-Cresol is a strong catalyst and acetic acid is a weak one.

4. The importance of hydrogen chloride in the reaction explains the slowness of the reaction in the basic solvents, ether and acetone.

5. Further work is being done on the mechanism of the rearrangement.

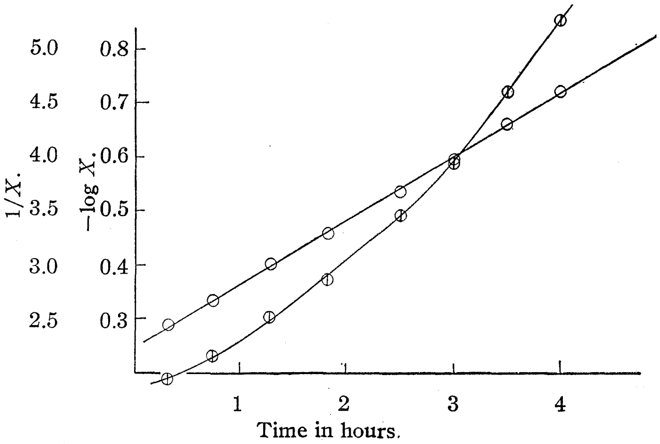

Fig. 4.—The rate of rearrangement of camphene hydrochloride to isobornyl chloride in nitrobenzene solution at 20° in the presence of 0.300 mole/liter of excess camphene and 0.311 mole/liter of *o*-cresol: ○, $-\log X$; ⦶, $1/X$.

CAMBRIDGE, MASS. RECEIVED APRIL 11, 1938

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[7] Waentig and Pescheck, *Z. physik. Chem.*, **93**, 541 (1919).

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Amino Alcohols Derived from Carbazole[1]

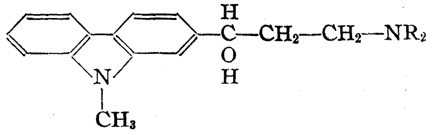
BY LEONE RUBERG AND LYNDON SMALL

In previous reports from this Laboratory the synthesis of numerous derivatives of the phenanthrene and dibenzofuran series has been described.[2] Many of these compounds bear a superficial resemblance to morphine in containing a portion of the morphine nucleus, to which is attached one or more of the peripheral groups that appear to be important for the analgesic action and other physiological effects of morphine. Those derivatives carrying an amino group and an alcoholic hydroxyl group, attached directly to the nucleus or in a side chain, have proved to be particularly active.[3] Diethylaminomethyl-3-phenanthrylcarbinol, for example, produces in the cat marked analgesia and a physiological picture very like that of morphine.[4]

Certain substitution products derived from dibenzofuran show analgesic action even stronger than the analogous derivatives of phenanthrene,[3b] and, as a working hypothesis, the assumption seems justified that various carbocyclic or heterocyclic nuclei, in themselves indifferent, may be activated by, or serve to carry, groups conferring the desired type of physiological effect.

We were therefore led to extend our investigations to the simple amino and amino-9-methylcarbazoles, which were found to possess definite and prolonged analgesic action, combined with relatively low toxicity.[5] Systematic studies on a series of alkylamino and alkyldiamino carbazoles will be presented in a later paper. The present communication deals with the preparation of carbazole amino alcohols resembling the phenanthrene amino alcohols that have been found to possess the most desirable physiological action.

The two types of amino alcohols that have been synthesized are represented by formulas I and II.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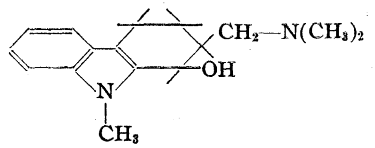
II

In formula I, —NR_2 represents the dimethylamino, diethylamino, or tetrahydroisoquinolino group. These compounds were prepared by application of the Mannich reaction to 2-acetyl-9-methylcarbazole, using the modification of van de Kamp and Mosettig,[6] *i. e.*, by treatment of the ketone with paraformaldehyde and the hydrochlorides of the respective secondary amines. The amino ketones were then reduced catalytically to the corresponding amino alcohols. The compound of formula II was prepared by analogous reactions, starting with 1-keto-9-methyl-1,2,3,4-tetrahydrocarbazole.

Whereas 2-(3-dimethylamino-1-hydroxy-*n*-propyl)-9-methylcarbazole (I, R = CH_3) yielded a well crystallized hydrochloride, for reasons which are not obvious the diethylamino and tetrahydroisoquinolino analogs were decomposed by alcoholic hydrogen chloride. The cyclic alcohol II apparently suffered loss of water in the presence of alcoholic hydrogen chloride to yield a compound that we believe to be 2-dimethylaminomethyl-9-methyl-3,4-dihydrocarbazole hydrochloride. The tendency of similar amino alcohols in the tetrahydrophenanthrene series to split out water has been pointed out by Burger and Mosettig.[7]

The experimental work in this series will be extended to the resolution of the diethylamino alcohol of type I, and to the preparation of similar compounds in the benzocarbazole series.

The most active of the substances here described is 2-(3-diethylamino-1-hydroxy-*n*-propyl)-9-methylcarbazole (I, R = C_2H_5). This approaches codeine in analgesic action, but has a

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[1] The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, the University of Virginia, and the University of Michigan.

[2] Mosettig, Burger, van de Kamp and co-workers, THIS JOURNAL, 1930–1938.

[3] (a) Eddy, *J. Pharmacol.*, **55**, 419 (1935); (b) **58**, 159 (1936).

[4] Eddy, *ibid.*, (Proc.), **54**, 140 (1935).

[5] Eddy, *ibid.*, **60**, 105 (1937).

[6] Van de Kamp and Mosettig, THIS JOURNAL, **58**, 1568 (1936).

[7] Burger and Mosettig, *ibid.*, **58**, 1570 (1936).

disadvantageous convulsant effect. In experiments on mice, it may be remarked that some of the animals showed the Straub reaction (erection of the tail in S form) that is so typical of morphine derivatives.

Experimental

Amino Ketones.—The method of Plant and Williams[8] for the preparation of 2-acetyl-9-methylcarbazole proved to be so laborious for making the ketone on a large scale that the following procedure was used. A suspension of 2,9-diacetylcarbazole (once recrystallized) in acetone, mechanically stirred, was treated dropwise with dimethyl sulfate and excess concentrated potassium hydroxide solution. Hydrolysis and methylation took place in a single step, and the product was easily purified by recrystallization from dilute acetic acid (70% by volume). The yield averaged 77% of the calculated amount. The amino ketones were all prepared in the same general way, by treating under reflux for fifteen or twenty minutes a mixture of 2-acetyl-9-methylcarbazole or 1-keto-9-methyl-1,2,3,4-tetrahydrocarbazole (1 mole), the amine hydrochloride (1.2 moles), and paraformaldehyde (2.5 moles) in isoamyl alcohol. The quantity of ketone was usually 10 to 15 g., in 100 to 150 cc. of isoamyl alcohol. In some experiments the amino ketone hydrochloride precipitated from the reaction mixture when it was cooled, or diluted with ether. In these instances the precipitate was filtered out and washed with ether or acetone. In other reactions, dilution with ether caused the hydrochloride to separate as an oil, which was then extracted into water. The free bases were obtained by treating the aqueous solution of the hydrochloride with dilute ammonia, and filtering or extracting with ether, according to the consistency of the precipitate.

2-(3-Dimethylamino-1-oxopropyl)-9-methylcarbazole.—The yield of pure ketone obtained was 18% of the calculated amount. A large amount of starting material was recovered, but was very difficult to purify. The amino ketone crystallized from ethyl acetate in transparent, colorless plates of m. p. 111.5–113.5°.

Anal. Calcd. for $C_{18}H_{20}ON_2$: N, 10.00. Found: N, 10.00.

The hydrochloride precipitated as fine silky needles, m. p. 191.5–193°, when alcoholic hydrogen chloride was added to a solution of the base in absolute alcohol.

Anal. Calcd. for $C_{18}H_{21}ON_2Cl$: C, 68.22; H, 6.68. Found: C, 68.17; H, 6.61.

2-(3-Diethylamino-1-oxopropyl) - 9 - methylcarbazole.—The yield of purified amino ketone was from 20 to 25% of the calculated amount; it is rather unstable. It crystallized from ligroin (b. p. 70–90°) in creamy-white irregular crystals that sintered at 69° and melted at 70.5–72.5°.

Anal. Calcd. for $C_{20}H_{24}ON_2$: C, 77.87; H, 7.85. Found: C, 77.72, 77.49; H, 7.41, 7.93.

The hydrochloride crystallized from absolute alcohol in glistening leaflets that softened at about 160° and melted at 163.5–166°.

Anal. Calcd. for $C_{20}H_{25}ON_2Cl$: Cl, 10.29. Found: Cl, 10.11.

2-(3-Tetrahydroisoquinolino-1-oxopropyl)-9-methylcarbazole.—The hydrochloride of this amino ketone precipitated after the reaction mixture had been boiled for two to three minutes, and heating was then discontinued. The salt was only slightly soluble in water, and was converted to the base by trituration with dilute ammonia. The base crystallized from ethyl acetate in glistening leaflets of m. p. 123–125°; yield 37% of the theoretical amount.

Anal. Calcd. for $C_{25}H_{24}ON_2$: C, 81.48; H, 6.56. Found: C, 81.62; H, 6.77.

The hydrochloride crystallized from absolute alcohol–acetone mixture in short colorless rods that sintered at 209° and melted at 211–213°.

Anal. Calcd. for $C_{25}H_{25}ON_2Cl$: Cl, 8.76. Found: Cl, 8.89.

2-Dimethylaminomethyl-1-keto-9-methyl-1,2,3,4-tetrahydrocarbazole.—The starting material for this synthesis was obtained by methylation of 1-keto-1,2,3,4-tetrahydrocarbazole according to the method of Smith and Tucker;[9] yield nearly quantitative. 1-Keto-9-methyl-1,2,3,4-tetrahydrocarbazole crystallized from methanol in long colorless prisms, m. p. 101.5–103.5°.

Anal. Calcd. for $C_{13}H_{13}ON$: C, 78.35; H, 6.58. Found: C. 78.16; H, 6.21.

By the Mannich reaction with dimethylamine hydrochloride the above ketone was transformed in 10–15% yields to (crude) 2-dimethylaminomethyl-1-keto-9-methyl-1,2,3,4-tetrahydrocarbazole. This compound crystallized from petroleum ether in almost colorless transparent plates that sintered at 72.5° and melted at 74–75°.

Anal. Calcd. for $C_{16}H_{20}ON_2$: C, 74.95; H, 7.87. Found: C, 74.90; H, 8.12.

The hydrochloride of the amino ketone crystallized from a mixture of absolute alcohol and acetone in short, colorless rods, which sintered at about 180°, and melted with decomposition at about 190°. Both the base and the hydrochloride were unstable and became colored after a few weeks.

Anal. Calcd. for $C_{16}H_{21}ON_2Cl$: C, 65.61; H, 7.23; N, 9.58. Found: C, 65.74; H, 7.44; N, 9.47.

Amino Alcohols.—The hydrochlorides of the amino ketones were hydrogenated in solution in 60% alcohol, using platinum oxide catalyst. It was found to be essential for the success of the hydrogenation that the salts be of a high degree of purity. In most instances reduction stopped after slightly more than one mole of hydrogen had been absorbed.

2-(3-Dimethylamino-1-hydroxy-*n*-propyl)-9-methylcarbazole.—The reduction of 5.3 g. of the amino ketone in the presence of 0.25 g. of platinum oxide required about three hours. The catalyst was removed, and the solvent was distilled off under diminished pressure, leaving a residue which was taken up in water, treated with ammonia, and extracted with ether. The residue from distillation of the ether crystallized from ligroin (b. p. 90–120°) in colorless rosets, of m. p. 96.5–99°; yield of purified amino alcohol, 80% of the calculated amount.

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[8] Plant and Williams, *J. Chem. Soc.*, 1142 (1934).

[9] Smith and Tucker, *ibid.*, **123**, 2140 (1923).

Anal. Calcd. for $C_{18}H_{22}ON_2$: C, 76.55; H, 7.86. Found: C, 76.37; H, 7.71.

The hydrochloride was prepared in absolute alcohol with alcoholic hydrogen chloride; it crystallized as fine colorless needles of m. p. 195–196.2°. It is very soluble in water.

Anal. Calcd. for $C_{18}H_{23}ON_2Cl$: Cl, 11.13. Found: Cl, 11.24.

The *p*-nitrobenzoate hydrochloride was prepared by combining equivalent amounts of the amino alcohol and *p*-nitrobenzoyl chloride in dry benzene. The yellow amorphous compound was washed with absolute ether and was recrystallized from a mixture of absolute alcohol and ether. It formed short yellow rods that softened at 164° and melted at 165–166.5°.

Anal. Calcd. for $C_{25}H_{26}O_4N_3Cl$: N, 8.99; Cl, 7.58. Found: N, 8.93; Cl, 7.24.

2-(3-Diethylamino-1-hydroxy-*n*-propyl)-9-methylcarbazole.—Reduction of the diethylamino ketone (11 g.) with platinum oxide (0.55 g.) proceeded like that of the dimethylamino derivative, and the product was isolated in the same way. The amino alcohol was purified by fractional crystallization from petroleum ether, from which it separated as soft, glistening irregular crystals that sintered at 73° and melted at 75.2–76°; yield 80% of the calculated amount.

Anal. Calcd. for $C_{20}H_{26}ON_2$: C, 77.36; H, 8.45. Found: C, 77.14; H, 8.47.

It is particularly important in this reduction that the amino ketone salt be pure. In one reduction, apparently with less pure material, absorption of hydrogen proceeded slowly and a precipitate formed. This was warmed into solution, the catalyst removed, and the solution was permitted to crystallize. Long yellow needles were deposited, which were purified from alcohol and melted at 133–135°. The new compound was not basic, and formed an oxime, colorless prisms from alcohol, m. p. 172–173°; its nature has not been determined. From the mother liquors, the amino alcohol could be obtained, but was very difficult to purify.

The amino alcohol did not form a crystalline hydrochloride, but was extensively decomposed by alcoholic hydrogen chloride.

The picrate crystallized from alcohol in golden-yellow needles of m. p. 136–138.5°.

Anal. Calcd. for $C_{26}H_{29}O_8N_5$: C, 57.86; H, 5.42. Found: C, 57.98; H, 5.63.

The *p*-nitrobenzoate hydrochloride crystallized from a mixture of absolute alcohol and ether in short yellow rods, which sintered at 177° and melted at 179–180.5°.

Anal. Calcd. for $C_{27}H_{30}O_4N_3Cl$: C, 65.36; H, 6.10; N, 8.48. Found: C, 65.57; H, 6.03; N, 8.25.

2-(3-Tetrahydroisoquinolino-1-hydroxy-*n*-propyl)-9-methylcarbazole.—After reduction of the amino ketone hydrochloride, the reaction mixture was warmed with additional solvent until the separated material redissolved, and the catalyst was removed. A small amount of amino alcohol base crystallized from the cooled solution. The solution was concentrated under diminished pressure and made alkaline with ammonia. The yield of crude product (m. p. 148–152°) was 90% of the calculated amount. It crystallized from alcohol in long colorless prisms of m. p. 151.5–153°. Repeated recrystallization and sublimation did not effect further purification. The following analyses were made on different samples.

Anal. Calcd. for $C_{25}H_{26}ON_2$: C, 81.03; H, 7.08. Found: C, 81.23, 81.52, 81.64, 81.43, 81.37, 81.73; H, 6.64, 7.29, 7.22, 7.03, 6.96, 7.07.

The amino alcohol was insoluble in dilute hydrochloric acid, and was decomposed by alcoholic hydrogen chloride.

The styphnate crystallized from alcohol in small orange clusters that sintered above 135° and melted with decomposition at 171–175°.

Anal. Calcd. for $C_{31}H_{29}O_9N_5$: C, 60.46; H, 4.75. Found: C, 60.21; H, 4.75.

The *p*-nitrobenzoate hydrochloride crystallized from absolute alcohol in small yellow prisms that sintered at 153° and melted at 159.5–161°.

Anal. Calcd. for $C_{32}H_{30}O_4N_3Cl$: C, 69.10; H, 5.44. Found: C, 69.13; H, 5.73.

2-Dimethylaminomethyl-1-hydroxy-9-methyl-1,2,3,4-tetrahydrocarbazole.—After reduction of the amino ketone hydrochloride and removal of the catalyst and solvent as described above, the residue was dissolved in water, and the solution was extracted with ether. The base was liberated from the aqueous layer with ammonia, and extracted into ether. The product was recrystallized successively from dilute alcohol and from ethyl acetate–petroleum ether mixture (1:15), and consisted of colorless six-sided plates of m. p. 123.5–125°. The yield of pure amino alcohol was 46% of the calculated amount.

Anal. Calcd. for $C_{16}H_{22}ON_2$: C, 74.36; H, 8.59; N, 10.85. Found: C, 74.36, 74.50; H, 8.38, 8.63; N, 10.89.

Attempts to prepare the hydrochloride of this amino alcohol resulted in the formation of a hydrochloride which analysis showed to lack the elements of water from the expected formula. The compound, tentatively designated as 2-dimethylaminomethyl-9-methyl-3,4-dihydrocarbazole hydrochloride, crystallized from absolute alcohol on addition of ether as colorless irregular crystals that sintered at about 180° and melted with decomposition at 192–194°. It was somewhat unstable, and showed a lower melting point after a few weeks.

Anal. Calcd. for $C_{16}H_{23}ON_2Cl$: C, 65.16; H, 7.87; N, 9.51. Calcd. for $C_{16}H_{21}N_2Cl$: C, 69.41; H, 7.65; N, 10.13. Found: C, 69.71; H, 7.67; N, 10.21.

Summary

The preparation of amino alcohols derived from 9-methylcarbazole and from 1-keto-9-methyltetrahydrocarbazole is described. Several of these amino alcohols show marked analgesic action, the most effective being 2-(3-diethylamino-1-hydroxy-*n*-propyl)-9-methylcarbazole.

UNIVERSITY, VIRGINIA

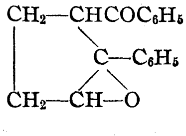
RECEIVED MAY 19, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

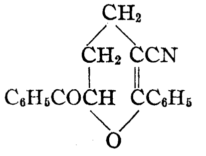
A Synthesis of 3-Benzoyl-2-phenylcyclopentanone

BY REYNOLD C. FUSON, ROBERT JOHNSON AND WAYNE COLE

3-Benzoyl-2-phenylcyclopentanone (III) has been obtained by rearrangement of 1-phenyl-5-benzoylcyclopentene oxide (I),[1] and by the action of hot phosphoric acid on 2-phenyl-3-cyano-6-benzoyl-5,6-dihydro-1,4-pyran (II).[2]



I



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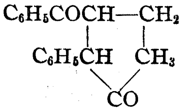
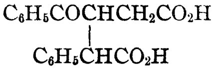


III

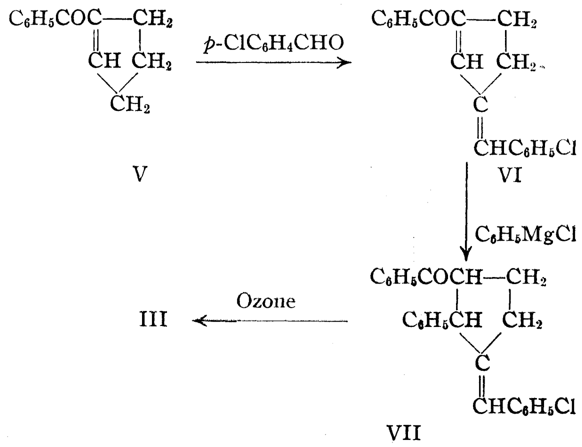


IV

The structure of the cyclopentanone (III) could hardly be deduced from the manner in which it originates, for the transformations which lead to its formation might be expected to yield a variety of products. It was necessary, therefore, to establish the structure of III in some other way. The first attempt consisted in oxidizing the cyclopentanone to the open-chain dibasic acid, β-benzoyl-α-phenylglutaric acid (IV). This compound was isolated in the two forms required by theory,[3] but since these had not been synthesized hitherto the proof of structure was inconclusive.

We have now established the structure of the cyclopentanone (III) by a synthesis based on the principle of vinylogy.[4] From this principle it was to be expected that 1-benzoylcyclopentene (V) like 1-benzoylcyclohexene and similar α,β-unsaturated ketones would have active hydrogen atoms in the γ-position,[5] and may condense with aldehydes.

This expectation was realized. 1-Benzoylcyclopentene reacted with p-chlorobenzaldehyde to give the normal p-chlorobenzal derivative (VI). The next step in the synthesis was the addition of phenylmagnesium bromide to the benzal derivative. It was foreseen that 1,2-, 1,4- and 1,6-addition are possible, but because of the phenyl groups in positions 1 and 6 the addition was expected to be primarily of the 1,4-type. This proved to be the case. 1-Benzoyl-2-phenyl-3-(p-chlorobenzal)-cyclopentane (VII) was obtained in two forms which were evidently stereoisomers since they yielded the same ozonization products. These were p-chlorobenzaldehyde and the desired cyclopentanone (III). The latter proved to be identical with the compound derived from the oxide (I) and the cyanopyran (II).



Experimental

1-Benzoylcyclopentene (V).—This material was prepared by the Friedel–Crafts reaction. Forty-four grams of aluminum chloride was added slowly to a mixture of 20 g. of cyclopentene, 43 g. of benzoyl chloride and 180 g. of carbon disulfide, which was kept at −5° during the addition. Decomposition with ice gave a crude addition product which, after three hours of heating with 28 g. of diethylaniline at 180°, yielded 16 g. (32% of the theoretical) of 1-benzoylcyclopentene, boiling at 119–122° (3 mm.); $n^{20}\text{D}$ 1.5668.

Anal. Calcd. for $C_{12}H_{12}O$: C, 83.72; H, 7.00. Found: C, 83.41; H, 7.15.

1-Benzoyl-3-(p-chlorobenzal)-cyclopentene (VI).—A sodium methylate solution prepared from 2.5 g. of sodium and 25 cc. of methanol was added to a methanol solution of 10 g. of benzoylcyclopentene and 14 g. of p-chlorobenzaldehyde. After standing at room temperature for twelve hours, the solution was acidified with glacial acetic acid and cooled; the product separated as crystals. These were recrystallized from methanol; the yield of the condensation product, melting at 118°, was 8.2 g. (48% of the theoretical).

Anal. Calcd. for $C_{19}H_{15}OCl$: C, 77.43; H, 5.09; Cl, 12.05. Found: C, 77.26; H, 4.92; Cl, 12.30.

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(1) Fuson and Farlow, THIS JOURNAL, **56**, 1593 (1934).

(2) Fuson, Kuykendall and Wilhelm, *ibid.*, **53**, 4187 (1931).

(3) Babcock and Fuson, *ibid.*, **58**, 2325 (1936).

(4) Fuson, *Chem. Rev.*, **16**, 1 (1935).

(5) Christ and Fuson, THIS JOURNAL, **59**, 893 (1937).

1-Benzoyl-2-phenyl-3-(*p*-chlorobenzal)-cyclopentane (VII).—A Grignard reagent containing 0.0046 mole of phenylmagnesium bromide was added to a solution of 1 g. of 1-benzoyl-3-(*p*-chlorobenzal)-cyclopentene in anhydrous ether. The mixture was refluxed for one hour, then hydrolyzed by shaking with 5% hydrochloric acid. The product was recrystallized from ethanol, yielding 1 g. (79% of the theoretical) of the addition compound, melting at 171° (corr.). Larger runs were made with equivalent yields.

Anal. Calcd. for $C_{25}H_{21}OCl$: C, 80.56; H, 5.64; Cl, 9.52. Found: C, 80.76; H, 5.74; Cl, 9.53.

A solution of 0.7 g. of the addition product in 400 cc. of ethanol was refluxed with excess hydroxylamine. Concentration of the solution gave a small quantity of an oxime, melting at 115–120°.

Anal. Calcd. for $C_{25}H_{22}ONCl$: N, 3.62. Found: N, 3.69.

A solution of 1 g. of the addition compound (m. p. 171°) in 20 cc. of methanol was refluxed with 0.25 cc. of 10% sodium hydroxide solution for twenty minutes. An isomer melting at 178° (corr.) crystallized when the solution was cooled.

Anal. Calcd. for $C_{25}H_{21}OCl$: C, 80.56, H, 5.64. Found: C, 80.55; H, 5.91.

This isomerization seemed to be hastened by the presence of a small quantity of *p*-chlorobenzaldehyde, for in the presence of this aldehyde the compound underwent rearrangement in ten minutes. A mixture of these two isomers melted at 158–161°.

Ozonization of 1-Benzoyl-2-phenyl-3-(*p*-chlorobenzal)-cyclopentane.—One-half gram of the addition product (either form) was suspended and partly dissolved in 200 cc. of glacial acetic acid. This suspension was treated with ozone for four hours at 10°; during this time the material dissolved completely. The ozonide was decomposed with a mixture of 100 cc. of water, 3 g. of zinc dust and 1 cc. of 5% silver nitrate solution. This mixture was then filtered to remove zinc, steam distilled to remove the aldehyde and most of the acetic acid, and neutralized with sodium bicarbonate. Concentration of the ether extract of neutral material yielded crystals of 3-benzoyl-2-phenylcyclopentanone (III) which, after recrystallization from methanol and from ethyl acetate–petroleum ether, melted at 158°. A mixture of this material with a sample (m. p. 159°) prepared by Babcock and Fuson[3] also melted at 158°.

When the lower-melting isomer of 1-benzoyl-2-phenyl-3-(*p*-chlorobenzal)-cyclopentane was used in the ozonization, the yield of 3-benzoyl-2-phenylcyclopentanone was 0.08 g. (22% of the theoretical amount); when the higher-melting isomer was used, the yield was 0.2 g. (56% of the theoretical amount).

Oxidation of the crude aldehyde with hydrogen peroxide gave 0.1 g. of *p*-chlorobenzoic acid, melting at 239–240°. This acid was also precipitated by acidification of the sodium bicarbonate washings.

3-Benzoyl-2-phenylcyclopentanone formed an *oxime* which after recrystallization from ethyl alcohol melted at 222–224°.

Anal. Calcd. for $C_{18}H_{17}O_2N$: C, 77.4; H, 6.1; N, 5.02. Found: C, 77.1; H, 6.2; N, 5.08.

3-Benzoyl-2-phenyl-5-(*p*-chlorobenzal)-cyclopentanone.—A solution of 0.2 g. of 3-benzoyl-2-phenylcyclopentanone and 0.2 g. of *p*-chlorobenzaldehyde in 7 cc. of methanol containing one drop of 10% sodium hydroxide solution was refluxed for eight minutes. When the solution was cooled, crystals of 3-benzoyl-2-phenyl-5-(*p*-chlorobenzal)-cyclopentanone separated. These melted at 207° and gave no depression in melting point when mixed with the compound prepared by the method of Babcock and Fuson.[3]

Summary

1-Benzoylcyclopentene has an active methylene group, in accordance with the prediction based on the principle of vinylogy, and condenses with *p*-chlorobenzaldehyde.

This condensation product gives 1,4-addition of phenylmagnesium bromide as shown by ozonization of the addition compound to give *p*-chlorobenzaldehyde and 3-benzoyl-2-phenylcyclopentanone.

This synthesis of the cyclopentanone constitutes a proof of structure.

URBANA, ILLINOIS RECEIVED MAY 2, 1938

[CONTRIBUTION FROM THE CARNEGIE INSTITUTE OF TECHNOLOGY]

Fermentation of Cellulose and Cellulose Humic Acid and Lignin and Lignin Humic Acid

BY E. BERL AND W. KOERBER

Those scientists who believe that lignin is the parent material of bituminous coal, as well as of lignites, base their belief on the assumption that cellulose, and other carbohydrates which form the bulk of plants, are decomposed by bacteria much more quickly and more completely than lignin. This assumption has found friends and opponents. Olson and Peterson[1] found that very small amounts of lignin (1%) inhibit the fermentation of pulp by cellulose fermenting bacteria. One of us has expressed the opinion that lignin and its derivatives are not the exclusive parent material for bituminous coals. It has been shown that under conditions which may have existed geochemically (high temperature and pressure) and with *p*H values above 7, bituminous coals could be obtained by artificial incoalification of carbohydrates. Those artificial carbohydrate coals show exactly the same properties as natural bituminous coals. This result never could be obtained with lignin and its derivatives, like lignin humic acid.

During the first stage of their conversion, with the *p*H above 7, cellulose and other carbohydrates form partly saccharinic acids which, upon further incoalification (with the formation of carbon dioxide, water, and lower hydrocarbons), give carbohydrate (cellulose) humic acids.

Until now all those alkali-soluble materials present in peat and lignites resulting from the decomposition of plants have been considered as lignin humic acids, and not as mixtures of cellulose humic acids and lignin humic acids. As yet no method of determining the amount of cellulose humic acids in these mixed acids has been found. We know that cellulose humic acids, in their chemical composition and in their behavior toward further incoalification, are fundamentally different from lignin humic acids. Furthermore, as may be shown in another publication, their heat stability is completely different from the heat stability of carbohydrates and of lignin, and lignin humic acids.

It was of great interest to find out how certain anaerobic and aerobic bacteria which decompose cellulose[2,3] would behave toward cellulose (carbohydrate) humic acid, lignin humic acid, and lignin. These experiments, which are described below, have been carried out and show a remarkable result. Anaerobic and aerobic bacteria which decompose cellulose do not attack cellulose humic acids, lignin, and lignin humic acids at all. They do not attack natural humic acids isolated from peat.

It has been shown that rather little cellulose, as such, may be present in peat and lignites and that under certain conditions the carbohydrate content of peat and lignites decreases with age. This does not lead to the conclusion that cellulose and lower carbohydrates are completely converted into gases and water-soluble compounds. They are very likely transformed into carbohydrate humic acids which resist the action of bacteria because of their phenolic structure. That cellulose humic acids may be present in those alkali-soluble materials obtained from peat can be seen by the fact that the peat humic acid used in our experiments contains only a few per cent. of methoxyl compared with 10.6% of methoxyl found in the lignin humic acid produced under very drastic conditions at 250° in a rotating closed vessel. A certain amount of methoxyl may be split off by the action of bacteria (see Waksman[4]).

Experimental Part

Cellulose, cellulose humic acid, lignin humic acid, and humic acid from peat were used for the fermentation experiments. The preparation of these materials was carried out in the following way.

(a) **Cellulose** was used in the form of wadding.

(b) **Cellulose Humic Acids.**—Linters were heated at 250° for ten hours with *N*/sodium hydroxide in a revolving bomb. The product was filtered and the dark brown filtrate obtained was acidified with hydrochloric acid, the precipitated humic acids filtered and dried. The finely pulverized material was washed with water until the chloride reaction disappeared and then dried over calcium chloride. The dark brown humic acids were dissolved in acetone, the solvents evaporated, and the residue dried *in*

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[1] Olson and Peterson, *Ind. Eng. Chem.*, **29**, 9, 1026 (1937).

[2] W. Omeliansky, *Zentr. Bakt.*, II, **36**, 472 (1913); II, **12**, 33 (1904); II, **11**, 369 (1904); II, **8**, 193 (1902).

[3] Van Tieghem, *Bull. soc. botan. France*, **1**, 24, 128 (1877).

[4] S. A. Waksman and H. W. Smith, THIS JOURNAL, **56**, 1225 (1934).

TABLE I

AEROBIC FERMENTATION OF CELLULOSE, *p*H 7.4, FIVE DAYS, 55°

Flask	Cell. G./200 cc.	Fermented cellulose Cell. dec. G.	%	Total acid G.	% of cell. dec.	Volatile acid Calcd. as acetic G.	% of cell. dec.	Non-vol. acid G.	% of cell. dec.	Alcohol G.	% of cell. dec.	Gas % of cell. dec.	Culture
30	2.92	2.00	67.4	1.11	55.8	0.97	48.3	0.14	7.5	0.050	2.5	9.1	A
31	2.80	2.24	80.1	1.46	65.3	1.26	56.2	.22	9.1	.067	3.0	11.8	A
32	3.10	2.19	70.6	1.30	59.1	1.11	50.6	.18	8.5	.044	2.0	9.5	C
33	3.00	2.34	78.2	1.45	61.8	1.32	56.5	.12	5.3	.051	2.2	14.2	C
34	2.98	1.81	60.7	0.82	45.2	0.73	40.2	.09	5.0	.029	1.6	13.9	F
Av.	2.96	2.12	71.4	1.23	57.4	1.08	50.3	.15	7.1	.048	2.2	11.8	

TABLE II

AEROBIC FERMENTATION OF CELLULOSE *p*H 6.0, FIVE DAYS, 55°

Flask	Cell. g./200 cc.	Fermented cellulose Cell. dec. G.	%	Total acid G.	% of cell. dec.	Volatile acid Calcd. as acetic G.	% of cell. dec.	Non-vol. acid G.	% of cell. dec.	Alcohol G.	% of cell. dec.	Gas % of cell. dec.	Culture
35	2.83	0.62	22.0	0.12	19.8	0.12	19.8	None		None		2.2	A
36	3.10	.56	18.1	.08	15.2	.08	15.2	None		None		2.9	A
37	3.00	.71	23.8	.14	20.3	.14	20.3	None		None		3.5	C
38	2.95	.74	25.2	.17	23.4	.17	23.4	None		None		1.8	C
39	2.98	.50	16.9	.06	12.7	.06	12.7	None		None		4.2	F
Av.	2.97	.63	20.9	.11	18.1	.11	18.1	None		None		2.8	

vacuo over phosphorus pentoxide: C, 68.2; H, 6.1; O, 25.7; CH_3O, 0.

(c) **Lignin.**—Lignin was prepared from sawdust according to the hydrochloric acid method of Willstätter. The product obtained was refluxed with 5% sulfuric acid for five hours, filtered, and washed. A treatment with copper ammonium hydroxide at room temperature for twenty-four hours was added. The residue was thoroughly washed with hot acidified water and dried over phosphorus pentoxide: C, 62.4; H, 5.8; O, 27.8; CH_3O, 14.6.

(d) **Lignin Humic Acids.**—The lignin as described under **c** was treated with *N* sodium hydroxide at 250° for three hours in a revolving bomb. The further preparation was carried out as described under b: C, 63.8; H, 6.7; O, 29.5; CH_3O, 10.5.

(e) **Humic Acids from Peat.**—Peat from Wisconsin was finely pulverized and extracted with *N* sodium hydroxide on a shaking machine for twenty-four hours. The alkali-soluble part was separated by filtration, acidified, and the humic acids isolated as described under **b**: C, 63.4; H, 4.8; O, 31.8; CH_3O, 1.9.

Isolation of Aerobic Cellulose Fermenting Bacteria.—A cellulose fermenting bacillus was isolated from horsedung according to the method described by Snieszko.[5] Control experiments were carried out with cellulose in salt media of *p*H 7.4 and 6.

Conical flasks of 300 cc. were each charged with 200 cc. of a salt medium containing 0.1% KNO_3, 0.1% $MgSO_4$, 0.1% K_2HPO_4, 0.5% peptone, exactly 2 g. of calcium carbonate and 3 g. of cellulose (latter dried over phosphorus pentoxide), *p*H 7.4. After sterilization the flasks were inoculated with the above-mentioned cellulose fermenting culture and incubated for five days at 55°. After this time the flasks were removed from the incubator and each of them titrated with *N* hydrochloric acid. From the titrated calcium carbonate the total acid formed was calculated. More acid was added and the contents of the flasks filtered and washed. The residue was unattacked cellulose; 25 cc. of 80% H_3PO_4 was added to the filtrate, which was then steam distilled. The distillate was titrated with *N* sodium hydroxide (volatile acids expressed as acetic acid). In order to determine the alcohol, the neutral distillate was ether-extracted three times, the ether evaporated, and the extract refluxed with acetyl chloride for two hours. After neutralization the solution was ether-extracted again, hydrolyzed with 10 ml. of 0.5 *N* sodium hydroxide, and back-titrated with 0.5 *N* hydrochloric acid (Tables I, II).

Aerobic Fermentation Experiments on Cellulose Humic Acids, Lignin, Lignin Humic Acids, and Humic Acids from Peat.—The above materials were exposed to the action of the cellulose-fermenting bacteria under the same conditions as were used in the control experiments on cellulose. None of these products could be fermented by those cultures which were active on cellulose. Even after four weeks no fermentation could be obtained with *p*H 7.4 and 6.

Isolation of Anaerobic Cellulose Fermenting Bacteria.—*Amylobacter navicula* was isolated from human feces under anaerobic conditions as described by Clausen.[6] Control experiments were performed with cellulose in a salt medium with *p*H 7.4 and 6.

Tubes were each charged with 150 ml. of a salt medium containing 0.1% $(NH_4)_2SO_4$, 0.1% $MgHPO_4$, 0.05% NaCl, and 1 g. of calcium carbonate; 1.5 g. of cellulose (dried over phosphorus pentoxide) accurately weighed, was added, *p*H 7.4. After sterilization the tubes were inoculated with an active cellulose fermenting culture of *amylobacter navicula* and incubated at 37° for five days under anaerobic conditions. After this time the tubes were removed from the incubator, their contents filtered, the residue washed and dried over calcium chloride *in vacuo*. The only fermentation products being gases, no other determinations were carried out than the weighing of the undecomposed cellulose.

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[5] S. Snieszko, *Zentr. Bakt.*, II, **88**, S., 403 (1933).

[6] P. Clausen, *ibid.*, II, **84**, A., 20–60 (1931).

TABLE III

ANAEROBIC FERMENTATION OF CELLULOSE, *p*H 7.4, FIVE DAYS, 37°

Expt.	Cellulose in medium g./150 cc.	Fermented g./150 cc.	% cellulose decomposed
1	1.52	0.95	62.5
2	1.40	.96	68.5
3	1.55	1.01	65.3
4	1.45	1.01	70.0
5	1.43	0.92	64.5
Av.	1.47	.97	66.1

TABLE IV

ANAEROBIC FERMENTATION OF CELLULOSE, *p*H 6, FIVE DAYS, 37°

Expt.	Cellulose in medium g./150 cc.	Fermented g./150 cc.	% cellulose decomposed
6	1.50	0.21	14.1
7	1.48	.28	19.0
8	1.47	.24	16.3
9	1.49	.27	18.1
10	1.46	.22	15.2
Av.	1.48	.24	16.5

Anaerobic Fermentation Experiments on Cellulose Humic Acids, Lignin, Lignin Humic Acids, and Humic Acids from Peat.—The above materials were exposed to the action of the anaerobic cellulose-fermenting bacteria under the same conditions as were used in the control experiments on cellulose. None of these products could be fermented by those cultures which were active on cellulose. Even after four weeks no fermentation could be obtained with *p*H 7.4 and 6.

We thank Professor Harold L. Lang for his kind support of this investigation.

Summary

1. (a) A cellulose fermenting bacillus isolated from horse-dung showed in agreement with Sineszko a decomposition of approximately 70% of the cellulose used. Fermentation products are volatile acids, non-volatile acids, and alcohol in medium of *p*H 7.4. (b) The fermentation in medium of *p*H 6 by the same bacteria showed a decomposition of about 20% of the original cellulose.

2. Fermentation experiments carried out with the same culture on cellulose humic acids, lignin, lignin humic acids, and humic acids from peat showed that none of those products can be fermented, neither in medium of *p*H 7.4 or *p*H 6, even after four weeks of incubation.

3. (a) The anaerobic cellulose fermenting *amylobacter navicula* isolated from human feces as described by Clausen showed a fermentation of 63% of cellulose in salt medium of *p*H 7.4 under anaerobic conditions. (b) The same culture in medium of *p*H 6 fermented cellulose in an amount of approximately 15%.

4. Fermentation experiments carried out with the same culture on cellulose humic acids, lignin, lignin humic acids, and humic acids from peat showed that none of those products can be fermented, neither in medium of *p*H 7.4, nor *p*H 6, even after four weeks of incubation.

These experiments prove that derivatives of carbohydrates, like cellulose humic acids, which are formed from carbohydrates of plants are resistant toward the action of bacteria used in these experiments. These cellulose humic acids probably form bituminous coals and crude oil without further activity of bacteria.

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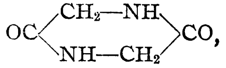
[CONTRIBUTION FROM GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 649]

The Crystal Structure of Diketopiperazine

BY ROBERT B. COREY

Introduction

For many years 2,5-diketopiperazine, "glycine anhydride,"  $\mathrm{OC}\left\langle\begin{matrix}\mathrm{CH_2{-}NH}\\ \mathrm{NH{-}CH_2}\end{matrix}\right\rangle\mathrm{CO}$, has been of considerable interest to those concerned with the constitution of proteins. Substituted diketopiperazines have been shown to be present among the products of protein hydrolysis[1] and much experimental evidence has suggested that these compounds might play a major role in the elucidation of the structure of protein molecules.[2] Although this importance of diketopiperazine as a basic unit in protein chemistry is not now generally conceded, its relation to the amino acids and dipeptides renders a determination of its structure of fundamental value to further knowledge of these compounds. The present investigation was therefore

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(1) E. Abderhalden and W. Stix, *Z. physiol. Chem.*, **132**, 238 (1924).

(2) E. Klarmann, *Chem. Rev.*, **4**, 51 (1927).

undertaken as a part of a program of research on the structure of proteins now being carried on in this Laboratory.

Bernal, in an extensive survey,[3] tabulated the results of a preliminary study of fifteen amino acids and related compounds, including diketopiperazine, by means of X-rays. Diketopiperazine is there described as having a monoclinic unit with $a_0 = 5.19$ Å., $b_0 = 11.5$ Å., $c_0 = 3.96$ Å., $\beta = 83°$, containing two molecules. The space group is $C_{2h}^5 - P2_1/a$. Cleavage is along (010) and (101). The crystals possess negative birefringence with α nearly perpendicular to (101), indicating approximately flat molecules lying in or near this plane. From these data he inferred that "diketopiperazine is built from centro-symmetrical, almost flat, hexagonal molecules linked together in ribbons by their residual electrical forces." No attempt was made, however, to determine from X-ray intensity data the positions of the atoms in this compound or in any other of the compounds studied.

Experimental

The crystals used in this study were prepared by G. A. Albrecht. They consisted of monoclinic prisms, varying in shape from thin needles, elongated in the direction of the *c*-axis, to tiny tabular specimens, less than a half-millimeter in greatest dimension.

Goniometric measurements of the crystals, oscillation and rotation photographs and Weissenberg photographs taken about the *b*- and *c*-axes, using Cu–K radiation, showed diketopiperazine to be built upon a monoclinic unit cell having the dimensions $a_0 = 5.19_2$ Å., $b_0 = 11.50_5$ Å., and $c_0 = 3.96_4$ Å. The angle β is $83 \pm 1°$. The general absence of all ($h0l$) reflections having h odd and of odd orders of ($0k0$) established the space group as $C_{2h}^5 - P2_1/a$. These observations thus confirmed the unit cell and space group previously assigned by Bernal.

Data from ($hk0$) Reflections.—The relative intensities of ($hk0$) reflections were obtained from a series of equatorial Weissenberg photographs made with exposure times varying from one hour to thirty-six hours. The specimen used was a needle-shaped crystal about 1 mm. long and less than 0.1 mm. in diameter. It gave sharp, well-defined spots, the intensities of which readily could be estimated by superposition of the films. The data thus obtained are listed in Table I.

The presence of two molecules in the unit cell requires the placing of four atoms each of O, C, methylene C, and N in the four general positions xyz, $\bar{x}\bar{y}\bar{z}$; $^1/_2 - x, y + {}^1/_2, \bar{z}$; and $x + {}^1/_2, {}^1/_2 - y, z$. This results in a grouping of the atoms in pairs about two centers of symmetry which are connected by the operation of the glide-plane at $y = {}^1/_4$ with glide parallel to the a-axis. For convenience, the atoms were arranged about the center of symmetry at ($^1/_2\ ^1/_2\ ^1/_2$) and its equivalent ($00^1/_2$), each of which thus became the center of symmetry of a molecule.

As a first tentative model, the bonds between C, CH_2, and NH were assumed to form tetrahedral angles with each other to give a "puckered" ring similar to that found for such saturated, six-membered ring structures as benzene hexabromide and hexachloride,[4] dioxane,[5] cyclohexane,[6] and paraldehyde.[7] The C–O bond was oriented so as to be coplanar with the adjacent C–C and C–N bonds and to form equal angles with them. The interatomic distances within the molecule were assumed to be C–O, 1.25 Å., C–N, 1.47 Å., and C–C, 1.54 Å. Packing radii for determining contacts between atoms, or groups, in different molecules were taken as O, 1.35 Å., C, 0.77 Å., CH_2, 1.86–2.00 Å., and NH, 1.5–1.8 Å. Space-filling considerations alone soon made it apparent that CH_2 and NH groups could not lie far from the (101) plane, and investigations were thus limited to rotations near this plane about the center of symmetry.

In all calculations the scattering power of oxygen was assumed to be that determined in single crystals of urea.[8] For carbon and nitrogen the values used were those found in urea and hexamethylenetetramine.[9]

Although some regions were found in which approximate packing was attained, no agreement could be reached between observed and calculated intensities for even the simplest planes. Planes (200), (110), (020), (040), (210), and (120) were most useful since, if the contribution of oxygen were disregarded, the values for their scattering powers were practically unaffected by the angular position of the C–N–C ring. By their use it could be shown that no parameters whatsoever

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[3] J. D. Bernal, *Z. Krist.*, **78**, 363 (1931).

[4] R. G. Dickinson and C. Bilicke, THIS JOURNAL, **50**, 764 (1928).

[5] L. E. Sutton and L. O. Brockway, *ibid.*, **57**, 473 (1935).

[6] L. Pauling and L. O. Brockway, *ibid.*, **59**, 1223 (1937).

[7] D. C. Carpenter and L. O. Brockway, *ibid.*, **58**, 1270 (1936).

[8] R. W. G. Wyckoff, *Z. Krist.*, **81**, 102 (1932).

[9] (a) R. W. G. Wyckoff, *ibid.*, **75**, 529 (1930); (b) R. W. G. Wyckoff and R. B. Corey, *ibid.*, **89**, 462 (1934).

could be assigned to the oxygen atom which would bring agreement between observed and calculated intensities. This model therefore had to be abandoned.

A completely coplanar molecule was next assumed, with interatomic distances the same as in the preceding one except that the distance between the keto carbon and the nitrogen atom was shortened to 1.32 Å. The bond angles were taken to be C–N–C, 110°; N–C–CH_2, 125°; C–CH_2–N, 125° and N–C–O, 117°. This molecule was rotated about the center of symmetry with all atoms in the (101) plane. Excellent agreement for all sixty (*hk*0) reflections was obtained when a line joining the oxygen atoms made an angle of 35° with the XZ-plane, corresponding to the parameters.

O : $x = 0.15$, $y = 0.37$
C : $x = 0.32$, $y = 0.43$
CH_2 : $x = 0.545$, $y = 0.37$
NH : $x = 0.29$, $y = 0.545$

Inspection of the structure factors showed that no change was to be expected in the signs (except in the case of "absent" reflections) without major alterations in atomic positions. A two-dimensional Fourier analysis of the distribution of scattering power in the crystal unit projected on the (001) plane was made according to the equation

$$\rho(x,y) = \text{constant}\ \Sigma_h\Sigma_k\ F_{(hk0)} \cos 2\pi(hx + ky)$$

using the observed *F*'s for all planes with signs obtained from the structure factors as listed in Table I. The plot of $\rho(x,y)$ over half of the unit cell is shown in Fig. 1. The positions of the peaks as shown by contour lines indicate small but definite changes in the positions of all atoms except carbon. The corresponding parameters then become

O : $x = 0.160$, $y = 0.368$
C : $x = 0.320$, $y = 0.430$
CH_2 : $x = 0.545$, $y = 0.380$
NH : $x = 0.280$, $y = 0.544$.

In Table I structure factors calculated from these parameters are compared with those obtained from the estimated intensities.

TABLE I

INTENSITIES AND STRUCTURE FACTORS FOR (*hk*0) REFLECTIONS

Indices	Intensities Obsd.	Intensities Corr.	Obsd. *F*	Calcd. *F*
020	4200	7250	31.5	33.8
110	700	753	11.2	15.9
120	665	713	11.9	19.9
130	0	0	0	5.4
040	2800	3890	33.9	−34.4
200	1120	1260	20.7	−25.7
210	560	593	14.4	−18.1
140	182	185	8.0	− 9.0
220	560	593	15.0	−18.6
230	175	178	8.8	−12.0
150	26	26	3.4	− 4.9
240	63	63	5.6	− 5.4
060	70	70	5.9	− 6.5
160	525	554	17.5	−21.0
250	280	288	13.0	13.9
310	0	0	0	0.7
320	30	30	4.3	.8
330	280	288	14.2	−13.5
170	26	26	4.2	− 6.5
260	7	7	2.2	1.8
340	28	28	4.5	5.4
080	28	28	4.6	5.9
270	21	21	4.1	4.2
180	56	56	6.7	− 4.9
350	54	54	6.6	− 6.7
400	0	0	0	0.3
360	91	92	9.1	7.9
410	0	0	0	2.6
280	70	70	8.0	8.9
420	23	23	4.6	4.7
190	0	0	0	− 0.7
430	0	0	0	1.1
370	210	214	14.2	14.0
440	26	26	5.0	5.7
0, 10, 0	91	92	9.5	− 9.0
290	161	164	12.7	−10.6
450	0	0	0	− 1.6
1, 10, 0	0	0	0	− 0.6
380	28	28	5.3	5.1
2, 10, 0	53	53	7.3	7.5
460	0	0	0	− 1.2
1, 11, 0	0	0	0	1.2
390	77	78	8.7	8.0
510	35	35	5.8	5.0
520	98	99	9.7	−11.3
470	26	26	5.0	2.9
530	26	26	5.0	4.2
540	14	14	3.5	1.4
2, 11, 0	53	53	6.8	4.9
480	0	0	0	− 3.4
0, 12, 0	98	99	9.3	−10.1
3, 10, 0	0	0	0	0.8
550	0	0	0	.2
1, 12, 0	28	28	5.0	3.8
490	56	56	6.5	5.9
560	7	7	2.3	4.3
2, 12, 0	0	0	0	2.9
3, 11, 0	19	19	3.6	− 3.9
570	56	56	6.0	− 3.6
600	21	21	3.5	4.7

Data from (*h*0*l*) Reflections.—Considerable difficulty was experienced in obtaining a crystal which would yield good photographs when rotated about the *b*-axis. Although most of the thin, needle-like crystals were comparatively perfect and gave excellent reflections, their elongation in the c-direction made them of little value for the collection of data about [010]. Attempts were made to mount such specimens rigidly on the b-axis and then reduce them to cylindrical form by dissolving away the end portions, but the excessive softness and fragility of the crystals rendered such efforts fruitless. It was therefore necessary to select tiny tabular specimens having dimensions as nearly equal in all directions as possible. Such crystals were generally very imperfect as the result of twinning and internal strains and distortion. Two specimens were finally selected which gave good equatorial reflections with the Weissenberg camera, the first about 0.7 mm. and the second less than 0.3 mm. in greatest dimension. Even with these samples, the slight differences in shape of reflections from planes of widely different position made the estimation of relative intensities less exact than in the case of ($hk0$) reflections. Added to this was the fact that the scattering powers of most planes were structurally weak, so that long exposures, in one case seventy-two hours, were necessary. The estimated intensities and scattering powers calculated from them for all ($h0l$) planes capable of reflection are listed in Table II.

As a start in determining the z-parameters, the molecule was still assumed to be completely coplanar with all atoms lying in the (101) plane and having the x-parameters already accurately determined from ($hk0$) reflection data. Structure factors calculated from these parameters

O : $x = 0.160, y = 0.84$
C : $x = 0.320, y = 0.68$
CH_2 : $x = 0.545, y = 0.455$
NH : $x = 0.280, y = 0.72$

showed general agreement with observed values although some planes, notably (002), ($40\bar{1}$), ($20\bar{3}$), and (204), indicated the necessity for further refinement. Since simultaneous displacement of all atoms was probable, recourse was had to a second Fourier analysis, using only those planes whose signs were considered certain. Values of the function

$$\rho(x,z) = \text{constant}\ \Sigma_h\Sigma_l\, F_{(h0l)} \cos 2\pi(hx + lz)$$

were plotted along lines of constant x corresponding to this parameter for each atom. Definite changes in all z-parameters were indicated from which structure factors were calculated, to determine the signs of planes previously in doubt. All planes were then introduced into the Fourier summation and the positions of the resulting peaks used to complete the determination

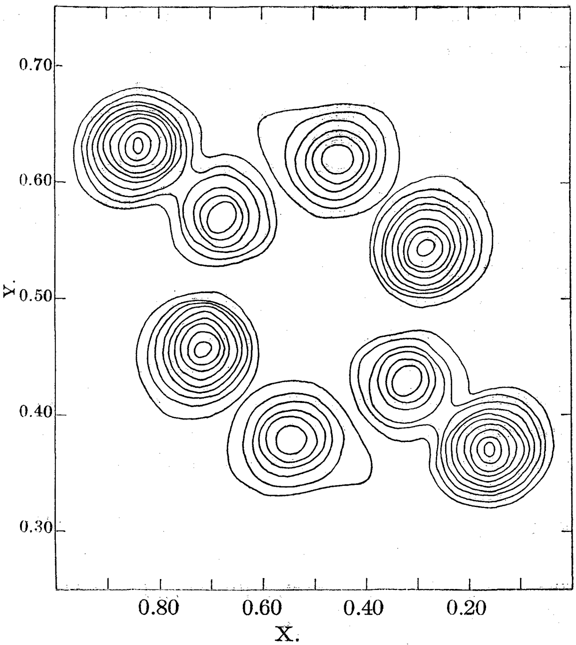


Fig. 1.—Distribution of scattering power, $\rho(x, y)$, for diketopiperazine projected upon the (001) face. Contour lines represent values of $\rho(x, y)$ from 2 to 11.

TABLE II

INTENSITIES AND STRUCTURE FACTORS FOR ($h0l$) REFLECTIONS

	Intensities				Obsd. F		
	Cryst. 1		Cryst. 2				
Indices	Obsd.	Corr.	Obsd.	Corr.	Cryst. 1	Cryst. 2	Calcd. F
001	290	339	425	546	8.4	10.6	−11.3
200	670	1032	500	676	18.7	15.1	−25.7
201	260	299	170	186	10.9	8.6	−12.2
$20\bar{1}$	125	133	160	175	7.8	9.0	− 5.8
002	30	30	54	55	3.8	5.2	− 8.2
202	1000	2075	960	1917	35.6	34.2	36.4
$20\bar{2}$	4	4	5	5	1.7	1.9	− 1.8
003	8	8	8	8	2.6	2.6	− 0.1
400	4	4	5	5	1.8	2.1	.3
401	0	0	0	0	0	0	− 4.3
203	0	0	0	0	0	0	1.1
$40\bar{1}$	125	133	150	163	11.3	12.5	−10.5
402	60	60	80	83	7.6	9.0	−12.1
$20\bar{3}$	250	287	320	384	16.8	19.5	−15.3
$40\bar{2}$	60	60	70	73	7.6	8.4	6.7
004	10	10	10	10	3.0	3.1	− 1.2
403	10	10	20	20	3.0	4.3	− 3.8
204	0	0	0	0	0	0	1.3
$20\bar{4}$	12	12	19	19	2.8	3.5	3.3
$40\bar{3}$	120	129	80	83	8.7	7.0	9.3
601	1	1	5	5	0.7	1.7	− 0.5
600	17	17	25	25	3.2	3.8	4.6
404	6	6	10	10	1.6	2.2	6.0
602	0	0	0	0	0	0	1.1
$60\bar{1}$	125	133	85	89	7.4	6.0	6.7

of the atomic arrangement. The final parameters were found to be

O	: $x = 0.160$,	$y = 0.368$,	$z = 0.885$
C	: $x = 0.320$,	$y = 0.430$,	$z = 0.705$
CH_2	: $x = 0.545$,	$y = 0.380$,	$z = 0.495$
NH	: $x = 0.280$,	$y = 0.544$,	$z = 0.695$

A comparison of the observed scattering powers of all ($h0l$) planes with those calculated for these positions is shown in Table II. Although careful study of both the Fourier plot and structure factor calculations failed to give justification for any departures from these parameters, certain discrepancies in the agreement between observed and calculated values are to be noted. Most conspicuous is (404), for which the calculated scattering is about equal to that of ($60\bar{1}$) but which gave faint reflections on all films. The reason for this is doubtless to be found in the fact that this plane is practically parallel with the plane of the molecule, a position for which thermal agitation would have greatest effect in reducing the atomic scattering factors with increased sin θ. Thus it is seen that for planes (201), (002), (401), and (402) the intensity observed is less than that calculated, whereas the reverse is true for planes ($20\bar{1}$), ($40\bar{1}$), and ($20\bar{3}$). The positions of these planes relative to the plane of the molecule are shown in Fig. 2. It is seen that those having positive index l are more nearly parallel to the molecular plane than are those of negative index. Discrepancies in these cases are thus doubtless to be attributed in part to the predictable effect of orientation upon atomic scattering factors in crystals of this and similar structure.

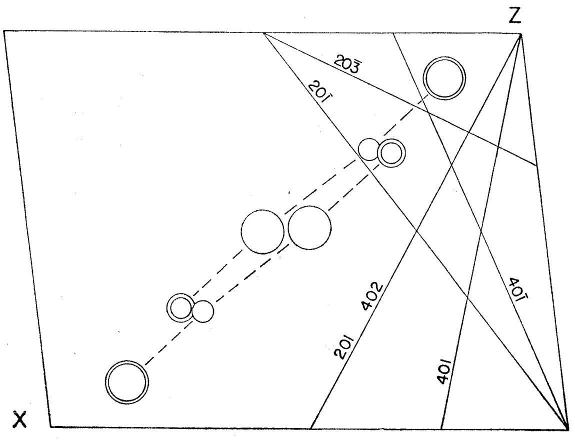


Fig. 2.—The relative positions of some planes (having positive and negative values of l) with respect to the plane of the molecule.

Discussion of the Structure

The positions of the atoms in an elementary unit cell and in three adjacent cells are shown in Fig. 3a. The molecule of diketopiperazine is found to be a nearly plane hexagon inclined at about 5.5° to (101). Interatomic distances within the molecule are C–O, 1.25 Å.; C–N, 1.33 Å.; C–C, 1.47 Å.; and N–CH_2, 1.41 Å., all accurate to about ± 0.03 Å.

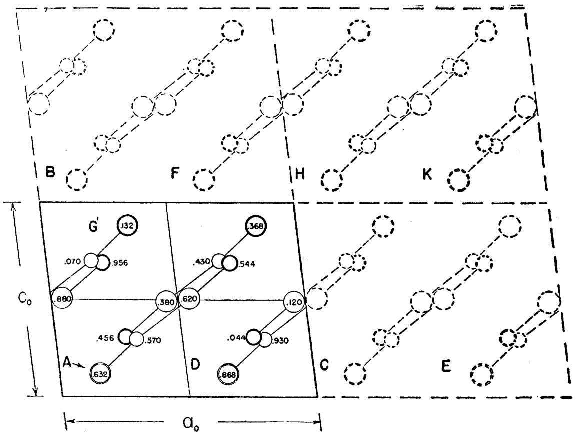


Fig. 3a.—Arrangement of diketopiperazine molecules in the unit cell. Numerals show the y-parameters of the atoms. Letters refer to subsequent packing drawing.

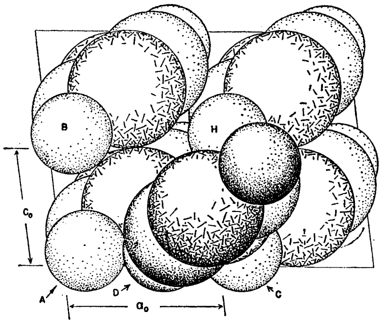
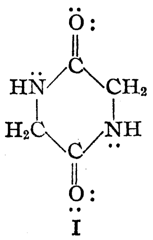
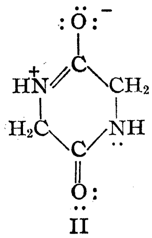
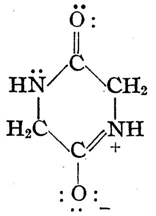


Fig. 3b.—A packing drawing of diketopiperazine viewed along the b-axis showing four molecules in the same layer at the centers of adjacent unit cells and one in the layer immediately above.

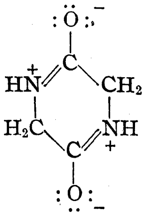
The molecule may be expected to resonate among the structures


I


II



III



IV

The bond distances for C–O and C–N should then have the values characteristic of resonance of this type, which are about 1.25 and 1.33 Å., respectively, as observed. Similar values are also found for other resonating molecules of like type.[6] In urea[9b] the interatomic distances within the molecules were found to be C–O, 1.24 Å. and C–NH_2, 1.37 Å., and in thiourea[10] C–NH_2 is 1.35 Å. The shortening of the CH_2–N and CH_2–C distances below the single bond values 1.47 and 1.54 Å., respectively, is surprising. It is possible that it is to be attributed, in part at least, to the effect of electric charge,[11] and perhaps to a resonance of a new type, involving double bonds with the methylene group. It is of interest that in hexamethylenetetramine[9b] the separation CH_2–N is 1.42 Å., almost exactly that found in the present structure (1.41 Å.).

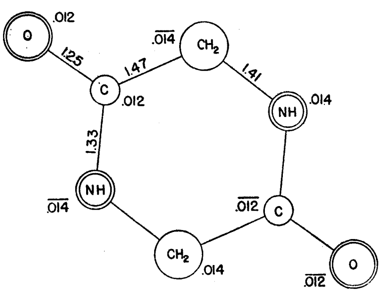


Fig. 4.—The diketopiperazine molecule as viewed perpendicular to a median plane. Dimensions are in Ångström units.

The angles between all bonds are 120 ± 3°. The extent to which the molecule, indicated by the parameter values, departs from true planarity is most readily shown by passing a median plane between the atoms and observing the distance of each atom from this plane. Figure 4 is a view perpendicular to such a plane in which numerals, positive and negative, show the distances in Ångström units of each atomic position above and below it. It is seen that none deviates from the plane by as much as 0.015 Å., which is within the limit of error of the determination of the atomic positions themselves. The completely coplanar configuration is, of course, expected for resonance among the structures I to IV, in consequence of the stereochemical properties of the C–N double bonds in the ring. Thus the observed coplanarity provides strong evidence for resonance, inasmuch as all known six-membered rings, involving only single bonds, are puckered.[4–7]

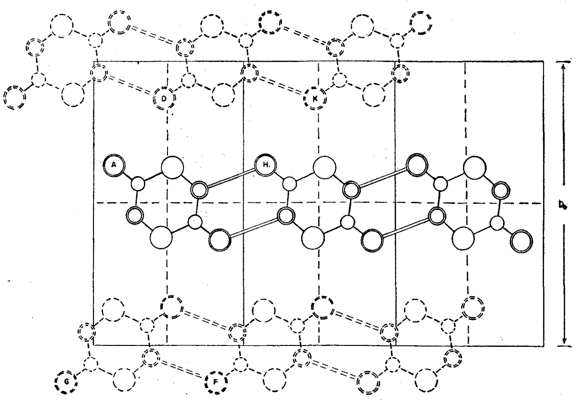


Fig. 5a.—A view perpendicular to (101) showing chains of molecules held together by hydrogen bonds.

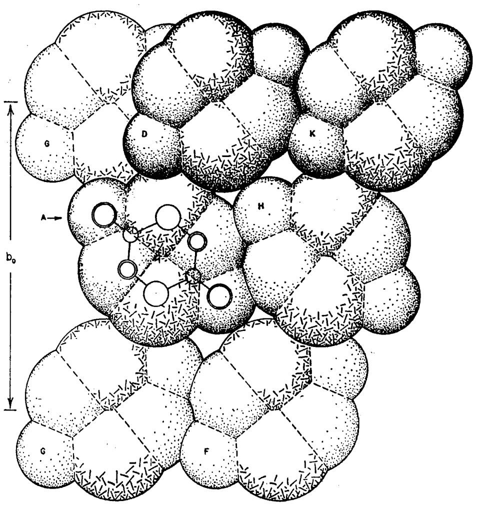


Fig. 5b.—A packing drawing of some of the molecules of Fig. 5a. The radius of the carbon atom is too small to permit its appearance in this and other packing figures.

The packing of the molecule is shown in Figs. 3b, 5b, and 6. In these drawings CH_2 is given a radius of 1.98 Å.; NH, 1.8 Å. and O, 1.35 Å. The radius of carbon (0.77 Å.) is too small to permit its appearance. Each CH_2 group is at a distance of 3.96 Å. from four other CH_2 groups, two in the same layer with it and two others above or below.

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(10) R. W. G. Wyckoff and R. B. Corey, *Z. Krist.*, **81**, 386 (1932).

(11) N. Elliott, THIS JOURNAL, **59**, 1380 (1937).

Figure 3b shows the packing of adjacent CH_2 groups in the same layer, contacts between those in different layers being indicated in Figs. 5b and 6. Each oxygen is in contact with two CH_2 groups, one at 3.32 Å. in the same layer (B in Fig. 3b) and one at 3.33 Å. in the layer above or below (C in Figs. 3b and 6). Each nitrogen is distant 3.55 Å. from a CH_2 group (molecules A and B, Fig. 6) and 3.69 Å. from another nitrogen (Fig. 5b). The very pronounced cleavage along (010) and that along (101) are clearly brought out in Fig. 6.

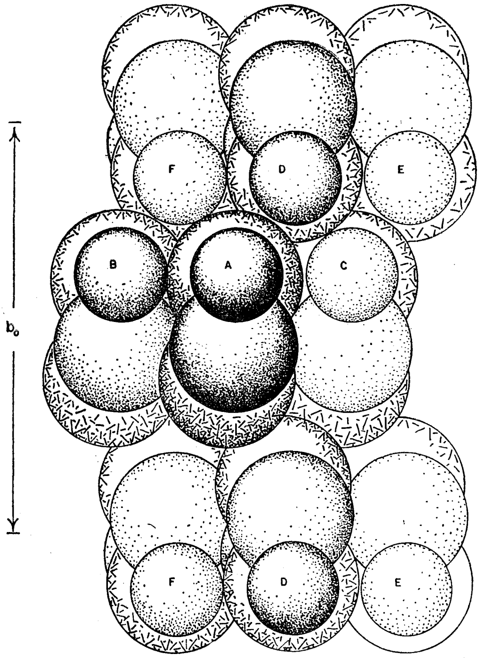

Fig. 6.—A packing drawing of the molecules of diketopiperazine viewed in the direction of the molecular chains.

Assuming tetrahedral bond angles and a C–H distance 1.08 Å., parameters could be assigned to the two methylene hydrogen atoms as follows

H_1: $x = 0.658, y = 0.334, z = 0.664$
H_2: $x = 0.472, y = 0.319, z = 0.322$

The distances between hydrogen atoms in adjacent methylene groups then become 2.68 Å. in the same layer, and 2.66 Å. in the next layer. These separations correspond to an atomic domain for hydrogen of radius 1.33–1.34 Å., which is slightly greater than the value 1.29 Å. suggested by Mack[12] from consideration of the packing of organic molecules in which there is no free rotation. Distances between oxygen and hydrogen are 2.57 Å. in the same layer and 2.48 Å. in the next layer, which are slightly less than analogous distances (2.68–2.70 Å.) observed in metaldehyde.[13]

Acknowledgments.—This investigation has been made possible by the financial support of the Rockefeller Institute for Medical Research and the courtesy of the California Institute of Technology in providing the facilities of its laboratories. The author is indebted to Professor Linus Pauling for proposing the subject of this research and for his many suggestions and criticisms throughout the progress of the work, to Dr. J. H. Sturdivant for assistance with experimental details, and to W. R. Newton for the construction of special equipment.

Summary

X-Ray examination of crystals of 2,5-diketopiperazine shows them to be built upon a simple monoclinic unit having $a_0 = 5.19$ Å., $b_0 = 11.50$ Å., $c_0 = 3.96$ Å., and $\beta = 83°$, containing two molecules. All atoms are in the general positions of the space group $C_{2h}^5 - P2_1/a$ with the following parameters: oxygen, $x = 0.160$, $y = 0.368$, $z = 0.885$; carbon, $x = 0.320$, $y = 0.430$, $z = 0.705$; methylene carbon, $x = 0.545$, $y = 0.380$, $z = 0.495$; nitrogen, $x = 0.280$, $y = 0.544$, $z = 0.695$. The molecule is a nearly flat hexagonal ring possessing a center of symmetry, the angles between all bonds being 120 ± 3°. The interatomic distances within the molecule are: carbon–oxygen 1.25 Å., carbon–carbon 1.47 Å.; carbon–nitrogen 1.33 Å. and nitrogen–methylene carbon 1.41 Å., each ± 0.03 Å. All molecules are held together by hydrogen bonds to form long, parallel chains throughout the crystal. Packing of the molecules is discussed.

PASADENA, CALIFORNIA RECEIVED MAY 9, 1938

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[12] E. Mack, THIS JOURNAL, **54**, 2141 (1932).

[13] L. Pauling and D. C. Carpenter, *ibid.*, **58**, 1274 (1936).

[CONTRIBUTION NO. 639 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, AND FROM THE GEORGE FISHER BAKER LABORATORY OF CHEMISTRY OF CORNELL UNIVERSITY]

The Electron Diffraction Study of Digermane and Trigermane

BY LINUS PAULING, A. W. LAUBENGAYER AND J. L. HOARD

In order to obtain information about the covalent radius and bond angle of germanium we have prepared and analyzed electron diffraction photographs of digermane and trigermane, with the results described below.

Preparation and Purification of Substances.—A mixture of the hydrides of germanium was prepared by the action of dilute hydrochloric acid on magnesium germanide which had been made from very pure germanium and magnesium.[1] This mixture of hydrides was then subjected to fractionation in a vacuum apparatus.[2] The sample was cooled with liquid air and all of the free hydrogen contaminating the hydrides was pumped off. The monogermane, GeH_4, was removed by holding the hydrides at $-130°$ and distilling off all of the material which was volatile at that temperature. The residue was warmed to $-70°$ and the digermane, Ge_2H_6, was distilled off. This fraction was found to possess the characteristic constants reported for digermane. The remaining material was freed of the last traces of digermane by distillation at $-60°$ for several hours. The temperature was then raised to $-20°$ and a fraction was collected. This fraction possessed the properties of pure trigermane, Ge_3H_8.

Preparation of the Photographs.—The electron diffraction photographs were prepared in the usual manner.[3] The sample of trigermane was allowed to vaporize into the evacuated apparatus for a minute or two at 0° to remove any residuum of digermane, and was then heated to about 20° for exposure of the photographs. The stopcock was held open for a few seconds before each exposure at this temperature. The entire sample of the substance was evaporated in the preparation of the series of photographs. About ten photographs were prepared and measured for each substance.

Analysis of the Photographs.—The photographs obtained for the two substances are closely similar in appearance. They show eight well-defined rings, with the measured s_0 values and estimated intensity values given in Table I. The appearance of the rings does not differ greatly from that corresponding to a single sin ls/ls curve; the intensity drop between the third ring and the fourth ring seems larger than for the other steps.

The radial distribution curve[4] calculated for digermane with use of the c values given in the table, obtained from the estimated intensity values by multiplication by the factor $s^3e^{-As^2}$ as recommended by Schomaker and Degard,[5] is given in Fig. 1. The curve shows a peak at 2.41 Å., representing the Ge–Ge distance. The other interatomic distances in the molecule are of less importance in the intensity function and are not apparent in the radial distribution curve.

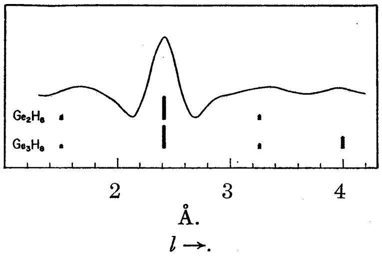

Fig. 1.

The simplified intensity curve corresponding to the model with Ge–Ge = 2.44 Å. and Ge–H = 1.52 Å. (the sum of single-bond covalent radii) and with all angles 109°28′, shown in Fig. 2, agrees well with the photographs in appearance. The quantitative comparison given in Table I leads to the average value 2.40 Å. for the Ge–Ge distance, the first three s_0 values being ignored as unreliable.

The radial distribution curve for trigermane, for which the same I values were estimated as for digermane, is not appreciably different from that for the latter substance shown in Fig. 1, except that the Ge–Ge peak occurs at 2.42 Å. It is surprising that there is no definite indication of a Ge–Ge peak at 4.0 Å., corresponding to the distance between the two end germanium atoms. It

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(1) L. M. Dennis, R. B. Corey and R. W. Moore, THIS JOURNAL, **46**, 658 (1924).

(2) A. W. Laubengayer and R. B. Corey, *J. Phys. Chem.*, **30**, 1043 (1926).

(3) See L. O. Brockway, *Rev. Modern Phys.*, **8**, 231 (1936).

(4) L. Pauling and L. O. Brockway, THIS JOURNAL, **57**, 2684 (1935).

(5) V. Schomaker and C. Degard, *ibid.*, to be published.

TABLE I

ELECTRON DIFFRACTION DATA FOR DIGERMANE AND TRIGERMANE

Max.	Min.	I	c	Digermane s_0	Digermane s^a	Digermane Ge–Ge	Trigermane s_0	Trigermane s^b	Trigermane Ge–Ge
1		10	1	3.29	3.17	(2.35 Å.)	3.44	3.34	(2.37 Å.)
	2			4.59	4.43	(2.35)	4.52	4.31	(2.33)
2		9	5	5.97	5.80	(2.37)	5.91	5.68	(2.35)
	3			7.19	7.08	2.40	7.28	7.16	2.40
3		8	10	8.52	8.38	2.40	8.43	8.30	2.40
	4			9.83	9.60	2.38	9.80	9.41	2.34
4		6	10	11.13	10.84	2.38	11.11	11.03	2.42
	5			12.47	12.21	2.39	12.40	12.13	2.39
5		5	9	13.73	13.56	2.41	13.64	13.47	2.41
	6			15.00	14.88	2.42	14.93	14.94	2.44
6		4	6	16.29	16.10	2.41	16.20	16.03	2.42
	7			17.62	17.29	2.40	17.53	17.10	2.38
7		3	3	18.92	18.56	2.39	18.78	18.80	2.44
	8			20.24	20.00	2.41	20.11	19.97	2.42
8		2	1	21.56	21.34	2.42	21.25	21.24	2.44
Average						2.40 Å.			2.41 Å.
Radial distribution value						2.41 Å.			2.42 Å.

[a] Calculated for the model with Ge–Ge = 2.44 Å., Ge–H = 1.52 Å., and all angles 109°28′. [b] Calculated for the model with Ge–Ge = 2.44 Å., Ge–H = 1.52 Å., angle Ge–Ge–Ge = 112°, angles H–Ge–Ge = 109°28′.

is possible that the bending frequency of the Ge–Ge–Ge chain is very low, and that in consequence the longer Ge–Ge separation varies widely at room temperature, causing the peak to be flattened out.[6] The possibility that the photographs obtained from the trigermane sample are really due to digermane has occurred to us. We believe, however, that the procedure followed was such as to make this unlikely.

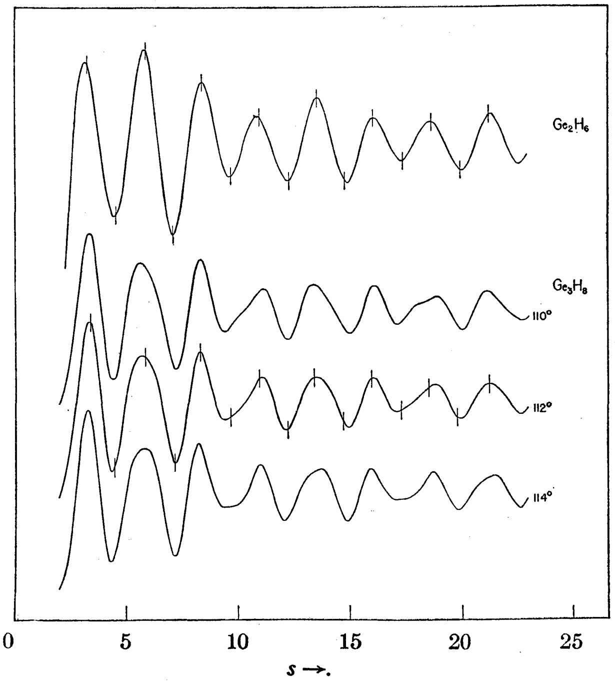

Fig. 2.

The radial distribution curve shows that the photographs cannot be used to evaluate the Ge–Ge–Ge bond angle reliably. Of the three simplified intensity curves shown in Fig. 2, calculated for the distances Ge–Ge = 2.44 Å. and Ge–H = 1.52 Å. and the angles H–Ge–Ge = 109°28′ and Ge–Ge–Ge = 110, 112 and 114°, respectively, the 112° curve seems to resemble the photographs somewhat more closely than the others. The quantitative comparison with this curve leads to the value 2.41 Å. for the Ge–Ge distance.

Discussion of Results.—The investigation shows that the Ge–Ge bond distance in both digermane and trigermane is about 2.41 (± 0.02 Å.). There is some small evidence that the value for trigermane is 0.01 Å. larger than that for digermane; this difference is, however, less than the estimated probable errors of the values.

The Ge–Ge distance in elementary germanium, which crystallizes with the diamond structure, is 2.44 Å. This is the basis for the value 1.22 Å. assigned as the single-bond covalent radius of germanium.[7] The decrease of about 0.03 Å. in interatomic distance observed for digermane and trigermane is probably real, and suggests that the covalent radius of germanium for use in compounds may be as low as 1.21 or 1.20 Å. The decrease may be due either to some

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(6) Temperature effects of this kind will be discussed by Dr. V. Schomaker in a paper to be published soon.

(7) L. Pauling and M. L. Huggins, *Z. Krist.*, **87**, 205 (1934).

interaction with the Ge–H bonds in the germanes or to partial metallic character (incomplete covalent character) of the element; in the former case the value 1.22 Å. for the radius would be the more generally applicable and in the latter case a smaller value. The uncertainty of 0.01 or 0.02 Å. in the radius is not of great significance.

The Ge–H bond distance in the substances is probably about 1.50 Å., and the bond angles are probably close to the tetrahedral value 109°28′; these values are, however, not derived from the experimental data.

Acknowledgment.—We wish to thank Dr. K. S. Palmer and Dr. V. Schomaker for assistance in the preparation and measurement of the photographs.

Summary

The Ge–Ge bond distance in both digermane and trigermane is found by the electron diffraction method to be about 2.41 ± 0.02 Å.

PASADENA, CALIFORNIA
ITHACA, NEW YORK RECEIVED APRIL 5, 1938

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF NORTH CAROLINA]

The Activity Coefficients of Lead Chloride in Aqueous Solutions of Mannitol at 25°[1]

BY H. D. CROCKFORD AND J. C. LOFTIN

An extensive study of the activity of lead chloride in aqueous solutions at 25° has been made by Carmody.[2] For this study he employed the following chemical cell

$$\text{Pb–Hg (2 phase)} \mid PbCl_2(m_1) \mid \text{AgCl–Ag}$$

By the use of their extended Debye–Hückel equation La Mer, Gronwall and Greiff[3] employed the data of Carmody to calculate the mean distance of closest approach of the ions of lead chloride. Crockford and Thomas[4] and Crockford and Farr[5] employed the same cell to determine the activity coefficients of lead chloride in aqueous solutions of cadmium nitrate and barium nitrate at 25°. The purpose of the work was to test the relationship proposed by Crockford and Thomas[4] for the calculation of the $\bar{a}$ parameter in solutions containing two electrolytes. In this paper are given the results of a series of studies designed to determine the effect of mannitol on the activity of lead chloride in aqueous solutions at 25°. From the data obtained has been calculated the mean distance of closest approach of the ions.

The chemical cell given above was used in the work. Four series of data were obtained: (I) constant molality of mannitol and varying concentrations of lead chloride; (II) constant ratio of lead chloride and barium nitrate and varying concentrations of mannitol; (III, IV) constant molalities of lead chloride and varying concentrations of mannitol.

The mannitol used was the Pfanstiehl C. P. grade; it was dried and kept in a vacuum desiccator until used. For the purification of other materials, preparation of solutions, preparation of electrodes, and general experimental technique the same procedures as employed by Crockford and Farr[5] were followed. Except for the very dilute solutions the e. m. f. values given are reproducible to 0.05 mv.

Results and Calculations

Tables I–IV give a summary of the experimental data and the calculated values for the activity coefficients and the a values.

The activity coefficients were calculated from the equation

$$E(\text{mv.}) + 88.7308\,(0.200687 + \log m) = E_0(\text{mv.}) - 88.7308 \log f$$

this being the equation for a chemical cell without transference after the proper constants for a 1–2 salt at 25° have been introduced. The value $E_0 = 0.34320$ v. calculated by La Mer, Gronwall and Greiff[3] from the data of Carmody[2] was used in the calculations.

TABLE I

Series I. Constant Molality of Mannitol 0.1000

	m_1, $PbCl_2$	E, v.	f	a, Å.
1	0.02109	0.50132	0.493	1.70
2	.01580	.50956	.532	1.62
3	.01056	.51970	.587	1.80
4	.00528	.54194	.688	1.58
5	.00262	.56592	.742	1.40

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[1] From a thesis presented by Mr. Loftin to the faculty of the University of North Carolina as partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] Carmody, THIS JOURNAL, **51**, 2905 (1929).

[3] La Mer, Gronwall and Greiff, *ibid.*, **53**, 2245 (1931).

[4] Crockford and Thomas, *ibid.*, **55**, 568 (1933).

[5] Crockford and Farr, *ibid.*, **58**, 87 (1936).

TABLE II

Series II. m_1/m_2 Constant

	m_1 $PbCl_2$	m_2 $Ba(NO_3)_2$	m_3 Mannitol	E, v.	f	$\bar{a}$, Å.
1	0.01090	0.02339	0.20698	0.52694	0.419	2.19
2	.01083	.02324	.15708	.52658	.498	2.26
3	.01076	.02308	.10002	.52606	.509	2.39
4	.01069	.02294	.05009	.52582	.515	2.46
5	.01063	.02281	.00000	.52558	.522	2.57

TABLE III

Series III. Constant Molality of $PbCl_2$ 0.01055

	m_3 Mannitol	E, v.	f	a, Å.
1	0.0000	0.51995	0.608	1.76
2	.1012	.52047	.600	1.60
3	.2897	.52166	.582	1.40
4	.5609	.52540	.528	1.44
5	.7313	.52702	.506	1.25

TABLE IV

Series IV. Constant Molality of $PbCl_2$ 0.023455

	m_3 Mannitol	E, v.	f	a, Å.
1	0.0000	0.49724	0.493	1.80
2	.0990	.49827	.480	1.71
3	.2899	.50000	.459	1.50
4	.5604	.50224	.433	1.30
5	.7304	.50470	.406	1.29

The ion size parameter values were calculated graphically according to the procedure outlined by La Mer, Gronwall and Greiff.[3] It is to be noted that the value for the dielectric constant varied with the concentration of mannitol. The values for the various solutions used can be calculated from the data of Åkerlöf,[6] who has made a thorough study of the dielectric constant of aqueous mannitol solutions. However, in the construction of the family of curves necessary for the determination of the a parameter the dielectric constant of pure water was used. The error so introduced is very small. But in the evaluation of the $10^{-8}K$ function for the various solutions the value for the dielectric constant obtained from the data of Åkerlöf was employed.

Discussion of Results

An inspection of the data in Series III and IV shows that the activity coefficient of the lead chloride decreases with increasing concentration of mannitol. Series I illustrates the same point when compared with the results of Carmody.[2] Series III and IV show that the a value decreases with increasing concentration of mannitol. In the solutions with zero concentration of mannitol the a values are close to the value of 1.75 Å. as calculated by La Mer, Gronwall and Greiff.[3] According to the equation of Crockford and Thomas[4] the $\bar{a}$ values in Series II should remain constant. Based on data given by Crockford and Farr[5] the value should be 2.53 Å., a value very close to that obtained in solution 6 which contains no mannitol. However, as in Series III and IV this value decreases with increasing concentration of mannitol.

We wish to acknowledge our indebtedness to the Rockefeller Foundation for financial aid in the original purchase of part of the equipment used.

Summary

The activity coefficients of lead chloride in aqueous solutions of mannitol at 25° have been determined. In Series I the molality of mannitol was kept constant. In Series II the ratio of lead chloride to barium nitrate was kept constant but the molality of the mannitol was varied. In Series III and IV the molality of lead was kept constant but the molality of mannitol was varied.

From the activity coefficients in Series I, III and IV the a parameter values for lead chloride were calculated. From Series II the mean $\bar{a}$ values for mixtures of lead chloride and mannitol were calculated.

The data obtained show that the activity coefficients and the a parameter values decrease with increasing concentrations of mannitol.

CHAPEL HILL, N. C.

RECEIVED APRIL 23, 1938

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[6] G. Åkerlöf, THIS JOURNAL, **54**, 4125 (1932).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BROWN UNIVERSITY]

Unilateral Triple Ion Formation in Aqueous Hydrofluoric Acid

BY CHARLES BUSHNELL WOOSTER

The phrase "unilateral triple ion formation" has been coined[1] to describe the situation in which a single ionic equilibrium of the type, $B^- + AB \rightleftarrows AB_2^-$, is superposed on the customary binary ionization of the electrolyte, AB, and to distinguish this situation from that in which the corresponding equilibrium $A^+ + AB \rightleftarrows A_2B^+$, is also involved.[2] In a previous paper[1] it has been shown that with suitable approximations the conductance function for unilateral triple ion formation may be obtained in the linear form[3]

$$\left(\frac{f\Lambda}{m}\right)^2 \frac{C}{(1 - \Lambda/\Lambda_0)} = \Lambda_0^2K + \frac{(2\Lambda_0\lambda_0 - \Lambda_0^2)K}{k}\left(1 - \frac{\Lambda}{\Lambda_0}\right) C \quad (1)$$

and this equation was applied successfully to the conductivity of dilute solutions of the metal ketyl, sodium benzophenone, in liquid ammonia. Because of the unusual character of this electrolyte and also due to the fact that additional equilibria must be considered in the analysis of this conductance curve in the more concentrated regions, it is very desirable to test equation 1 independently by applying it to another electrolyte. However, instances of unilateral triple ion formation are relatively rare since they may generally be expected to occur only when some specific interaction (formation of a chemical bond) between a simple ion and an ion pair is possible.[4] The only well established instance seems to be in aqueous hydrofluoric acid solutions where the equilibrium, $F^- + HF \rightleftarrows HF_2^-$, was first suggested by Pick,[5] who carried out an analysis of the conductance data by assuming arbitrary values for the limiting conductivity of the triple ion. His conclusions were substantially verified by Davies and Huddleston[6] through a study of the anionic transference numbers.[7]

It is the purpose of this paper to present the results of applying equation 1 to the analysis of the conductance curves for aqueous hydrofluoric acid solutions and to compare them with the results which may be obtained by a substantially independent method from the transference data of Davies and Huddleston. The use of equation 1 involves the assumption that only the solute species H^+, F^-, HF and HF_2^- and the equilibria $HF \rightleftarrows H^+ + F^-$ and $HF_2^- \rightleftarrows HF + F^-$ need be considered and that the species F_2^{--} and H_2F_2 are present only in negligible proportions, if at all. Since it is probable that the hydrofluoride ion owes its existence to hydrogen bridge formation,[8] it is evident that there is no corresponding justification for assuming the existence of F_2^{--}. The existence in the gaseous state[9] of H_6F_6 suggests the possible presence of H_2F_2 (or higher polymers) in solution, but the results of the present analysis decisively exclude this possibility in aqueous solutions of hydrofluoric acid at concentrations 1 *N* and less. This result may be interpreted as indicating that H_2F_2 is a very strong acid or that the addition of a second proton to the hydrofluoride ion greatly weakens the hydrogen bridge, or both. In Section III the results obtained from the data on hydrofluoric acid are applied to the interpretation of the conductivity of potassium hydrofluoride.

I. Analysis of the Conductance Curve

The conductance data of Deussen[10] were chosen as the most reliable of those available and two series one at 25° and one of probably lesser accuracy at 0° were employed in the calculations. In order to apply equation 1 it is also necessary to have independent values of the limiting equivalent conductance, the dielectric constant and the

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[1] Wooster, THIS JOURNAL, **59**, 377 (1937).

[2] Fuoss and Kraus, *ibid.*, **55**, 2387 (1933).

[3] C is the total concentration in equivalents (as AB) per liter, Λ is the equivalent conductance, $K = [A^+][B^-]/[AB]$, the constant for binary dissociation, $k = [B^-][AB]/[AB^-_2]$, the dissociation constant for the triple ion equilibrium, Λ_0 the limiting value of Λ, λ_0 the sum of the limiting values of the mobility of the triple ion and of the single ion with opposite charge, f the activity coefficient defined by $-\log f = \beta\Lambda_0^{-1/2}\sqrt{C\Lambda}$ and m a mobility coefficient defined as $1 - \alpha\Lambda_0^{-3/2}\sqrt{C\Lambda}$. The constants α and β have the same significance as in the paper of Fuoss and Kraus [THIS JOURNAL, **55**, 476 (1933)]. In water at 25° $\alpha = 0.228\Lambda_0 + 59.7$ and $\beta = 0.504$; at 0°, $\alpha = 0.220\Lambda_0 + 29.0$ and $\beta = 0.486$.

[4] It is also conceivable, of course, that coulomb forces alone occasionally may give rise to a situation which closely simulates unilateral triple ion formation in media of appropriate dielectric constant, if one of the simple ions is much larger than the other and particularly if the larger ion is unsymmetrical.

[5] Pick, *Nernst's Festschrift*, 360 (1912).

[6] Davies and Huddleston, *J. Chem. Soc.*, **125**, 260 (1924).

[7] The only other attempt at analysis of these conductance data is that of Kendall [THIS JOURNAL, **39**, 7 (1917)] on the basis of a more or less empirical equation for "transition electrolytes."

[8] Huggins, *J. Org. Chem.*, **1**, 409 (1936).

[9] Simons and Hildebrand, THIS JOURNAL, **46**, 2183 (1924).

[10] Deussen, *Z. anorg. Chem.*, **44**, 312 (1905).

viscosity. The values which were used, $\Lambda_0 = 404$, $D = 78.57$, $\eta = 0.00895$ at 25° and $\Lambda_0 = 255$, $D = 88$, $\eta = 0.01794$ at 0°, were obtained from a variety of sources but do not differ in any important respect from the values given in the "International Critical Tables."

Plots of $f^2C\Lambda^2/m^2(1-\Lambda/\Lambda_0)$ against $C(1-\Lambda/\Lambda_0)$ appear in Fig. 1 where curve I represents values based on the measurements at 25° and curve II at 0°. It is evident that, in accordance with the requirements of equation 1, the points fall very nearly on a straight line. By applying the method of least squares to the ten points covering the dilution range 1–512 liters at 25° the values 351.5 for the slope and 112.4 for the intercept were obtained and in a similar way a slope of 201.1 and intercept of 71.2 were obtained from nine points at 0° over the dilution range 1–256 liters. The lines in Fig. 1 are drawn in accordance with these values from which the equilibrium constants are found to be $K = 6.89 \times 10^{-4}$ at 25° and 10.95×10^{-4} at 0°, $k = 0.320(2\,\lambda_0/\Lambda_0 - 1)$ at 25° and $0.354\ (2\lambda_0/\Lambda_0 - 1)$ at 0°. The ionization constant obtained at 25° differs very little from that (6.9×10^{-4}) obtained by other investigators[11] but the value at 0° is somewhat higher than that in the literature[11] (9×10^{-4}).

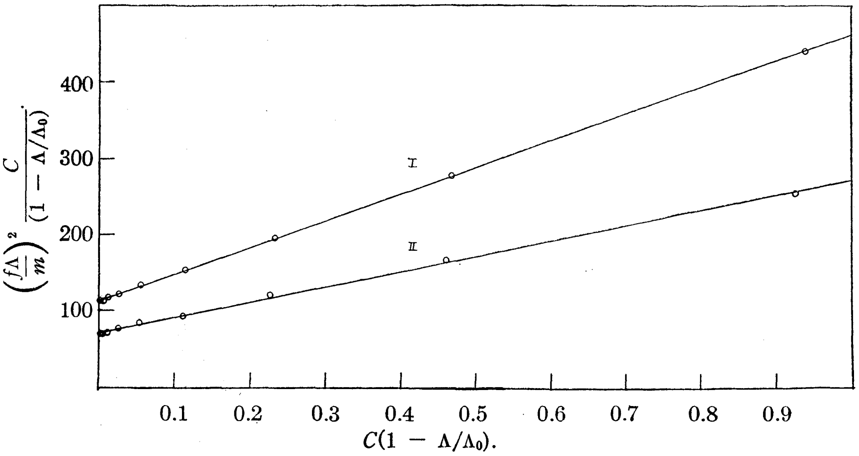

Fig. 1.—Unilateral triple ion formation in aqueous hydrofluoric acid.

The excellent agreement with equation 1 at such high total concentrations requires some explanation which is afforded by the facts that due to the low value of the ionization constants and the high values of the triple ion dissociation constants[12] the dielectric constant of the medium reduces the interionic (coulomb) forces so much that the approximate forms of the Debye–Hückel–Onsager equations employed serve adequately to calculate the effective values of the activity and mobility coefficients.

The applicability of equation 1 to unilateral triple ion equilibria is also determined by the degree to which the ratio λ_0/Λ_0 approximates unity, since this approximation was used to dispose of a second order term in the derivation of the equation. In general, this ratio may not be obtained directly from the conductance data and the sole available test of the validity of this approximation may often be the extent to which the linear form of equation 1 is satisfied by the data. In the present instance, however, additional information is available from two sources. First, the difference between λ_0 and Λ_0 is determined entirely by the difference in the limiting mobilities of the simple anion (F^-) and the triple anion (HF_2^-) which is doubtless so small in comparison with the high mobility of the hydrogen ion (351 at 25° and 229 at 0°) that the ratio λ_0/Λ_0 cannot differ widely from unity. Second, the value for the limiting mobility of the triple anion which may be obtained from the transference data (see Section II) yields the value $\lambda_0 = 437$ at 25° so that at this temperature $\lambda_0/\Lambda_0 = 1.08$. The maximum alteration in the slope of the plot due to neglect of the second order term in deriving equation 1 is given in percentage by $100(1 - \lambda_0/\Lambda_0)^2/[(2\lambda_0/\Lambda_0 - 1) + (1 - \lambda_0/\Lambda_0)^2]$ which on substituting 1.08 for λ_0/Λ_0 becomes 0.55% and is well within the limits of the experimental errors involved in Deussen's measurements.

It may also be noted at this point that evaluation of the ratio λ_0/Λ_0 permits the calculation of $k = 0.371$ at 25° and (assuming λ_0/Λ_0 independent of temperature as it would be if Walden's rule applies) 0.411 at 0°.

Using the slopes and intercepts given above the conductance curve (Λ against log V) has been calculated as previously described[1] and the re-

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[11] "International Critical Tables," McGraw-Hill Book Co., Inc., New York, N. Y., 1929, Vol. VI, p. 260.

[12] The order of magnitude of k is given by 0.320 at 25° and 0.354 at 0° since the coefficient $(2\lambda_0/\Lambda_0 - 1)$ does not differ widely from unity.

sults appear in Fig. 2 where the smooth curves represent the calculated values and the circles represent the experimental points. The arrows indicate the limits beyond which the smooth curve represents an extrapolation, the experimental points in these regions not having been used in determining the slopes and intercepts given. The experimental points lie very close to the calculated curve except in the most dilute region. Due to experimental difficulties in maintaining a constant temperature at 0° under the conditions of Deussen's measurements, the data at this temperature, particularly in the more dilute region, are less reliable than that at 25°.

II. Analysis of Transference Data

By combining values for the anionic transference numbers with those for the equivalent conductances at various concentrations, Davies and Huddleston[6] have calculated the values for the triple ion dissociation constant and the mobility, U, of the triple ion which appear in the second and third rows of Table I.

TABLE I

CONSTANTS FROM TRANSFERENCE DATA AT 25°

V	1	2	4	8	16	32
k	0.212	0.215	0.210	0.199	0.165	0.137
U	73.0	68.3	64.9	61.0	53.4	47.3
k corr.	0.338	0.338	0.324	0.356	0.340	0.288
U_0	85.6	83.6	83.5	89.0	89.3	84.3

It may be observed that Davies and Huddleston's values of k show an average deviation of 13.7% from the mean 0.190 which, itself, is much lower than the figure 0.371 obtained in the previous section. The two values are not strictly comparable, however, since these authors introduced no corrections for the effect of interionic forces on the activities and mobilities of the ions. The effect of this omission is particularly evident in their values for the mobility of the triple ion, which show a 12.1% average deviation from the mean and a pronounced trend toward decreasing values of U with decreasing concentration, whereas the true mobilities of ions should increase with decreasing concentration.

In the fourth and fifth rows of the table are given values of k and of the *limiting* mobility of the triple ion, U_0, which have been obtained from the same data by introducing activity and mobility coefficients.

This method of calculation uses Davies and Huddleston's equations[13] with the following substitutions: K/f^2 for K_1[14]; 351 m_a for a, and 53 m_b for b. The figures 351 and 53 represent the limiting mobilities of the hydrogen and the fluoride ions and the m's are mobility coefficients calculated by the use of the following form of Onsager's equation for the mobility of an ion of the type j.

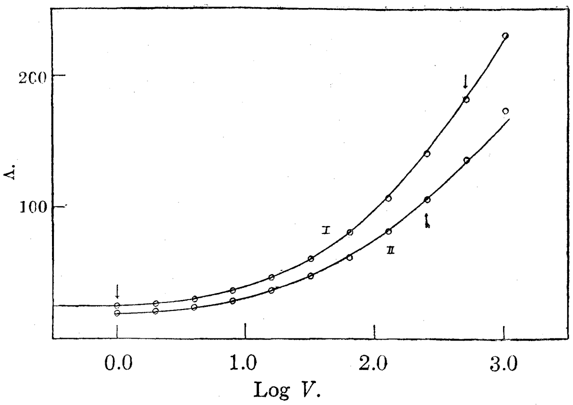

Fig. 2.—Conductance curves for aqueous hydrofluoric acid.

$$\Lambda_j = \Lambda_j{}^0 \left\{ 1 - \left[\frac{8.15 \times 10^5}{(DT)^{3/2}\,\Lambda_0{}^{1/2}} + \frac{41}{\Lambda_j{}^0 (DT)^{1/2} \eta \Lambda_0{}^{1/2}} \right] \sqrt{C\Lambda} \right\} \quad (2)$$

In the present instance this reduced to the following values for the mobility coefficients, $m_a = 1 - 0.0156\sqrt{C\Lambda}$ and $m_b = 1 - 0.0395\sqrt{C\Lambda}$. The values for the limiting mobility of the triple ion were obtained from the values, U, of the mobility at various concentrations also by the use of equation 2 in the reduced form

$$U_0 = \frac{U + 1.49\sqrt{C\Lambda}}{1 - 0.0113\sqrt{C\Lambda}} \quad (3)$$

It is evident on inspection of Table I that the "corrected" calculations give more consistent values of k (0.331 ± 4.9%) and of U_0 (85.9 ± 2.6%) which, unlike U, should be independent of concentration. It is further noteworthy that the value of k from transference data now agrees reasonably well with that obtained substantially independently[15] from conductance data. Al-

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(13) Equation 9 of Davies and Huddleston[6] (p. 267) is in error due to a misprint and should read

$$[\mathrm{F}'] = \frac{p - r}{2b} - \frac{\sqrt{(p - r)^2 - 8bK_1(aC - p)}}{2b}$$

(14) For the sake of consistency the value 6.89×10^{-4} was used for K instead of the figure 7.4×10^{-4} employed by Davies and Huddleston. It may also be noted that their $K_2 = 1/k$.

(15) It is true that U_0 from transference data was used to obtain $k = 0.371$ from conductance data, but this apparent dependence could be avoided easily by comparing $k = 0.320\ (2\lambda_0/\Lambda_0 - 1)$ from conductance data alone with $k = 0.286\ (2\lambda_0/\Lambda_0 - 1)$ from transference data by the "corrected" method of Davies and Huddleston; the direct comparison of the k values is more convenient, however.

though the difference of 11.4% between these values is greater than the average deviation of the transference k values from the mean, it must be noted that the error in U_0 is also involved in making the comparison. Furthermore, it is doubtful that the precision of the transference data is sufficient to render the mean value 0.331 reliable to within less than 12% as an *absolute* value of k.[16]

III. The Conductivity of Potassium Hydrofluoride

Data for the conductivity of potassium hydrofluoride over the dilution range 50–1000 liters based on the measurements of Walden[17] are given in the "International Critical Tables"[11] (p. 251).

Since the conductivity of this electrolyte exceeds that of potassium fluoride at corresponding concentrations, Walden concluded that the salt decomposed into potassium fluoride and hydrofluoric acid. Although his conclusion appears to be substantially correct at low concentrations, it was based partly on the erroneous assumption that the mobility of the hydrofluoride ion could not exceed that of the fluoride ion.

In view of the results obtained with hydrofluoric acid in Sections I and II and the fact that potassium fluoride is a strong electrolyte, it is likely that only the following solute species: K^+, H^+, F^-, HF_2^-, HF and equilibria: $HF \rightleftarrows H^+ + F^-$, $HF_2^- \rightleftarrows HF + F^-$ need be considered in interpreting the conductivity of potassium hydrofluoride, but this restriction is insufficient to permit direct analysis of the data. It is possible, however, to use the equilibrium constants and mobilities which have been obtained for independent calculations of the equivalent conductance at various concentrations.

The equivalent conductance is related to the total concentration and the concentrations of the several ionic species (indicated by the terms in parentheses) by equation 4

$$C\Lambda = 74m_{K^+}(K^+) + 83m_{HF_2^-}(HF_2^-) + 53m_b(F^-) + 351m_a(H^+) \quad (4)$$

where the numerals are the values of the limiting mobilities and the m's represent the Onsager mobility coefficients. The mobility and activity coefficients may be approximated with sufficient accuracy for the present calculations by setting the total ion concentration equal to $2C$ so that

$$-\log f = 0.504\sqrt{C} \text{ and } Mj = 1-(0.228 + 29.9/\Lambda j^0)\sqrt{C}$$

The concentration (K^+) is given directly by $(K^+) = C$, and the concentrations of the other four species are related by the following four independent equations.

$$(H^+)(F^-)/HF = K/f^2 \quad (5)$$

$$(HF)(F^-)/(HF_2) = k \quad (6)$$

$$C = (HF_2^-) + (HF) + (H^+) \quad (7)$$

$$2C = 2(HF_2^-) + (HF) + (F^-) \quad (8)$$

On solving these simultaneously it is possible to obtain the concentration of the fluoride ion from the cubic equation

$$(F^-)^3 + k(F^-)^2 + k[K/f^2 - C](F^-) - 2CkK/f^2 = 0 \quad (9)$$

by the usual methods, and the other two ionic concentrations by successive substitution in equations 10 and 11

$$(HF_2^-) = (F^-)[2C - (F^-)]/[k + 2(F^-)] \quad (10)$$

$$(H^+) = (F^-) + (HF_2^-) - C \quad (11)$$

Using the values $K = 6.89 \times 10^{-4}$, $k = 0.368$, the following results were obtained at $C = 0.0200$: $(F^-) = 0.02007$, $(HF_2^-) = 0.00098$, $(H^+) = 0.00105$, $(HF) = 0.01797$ and $\Lambda = 136.0$; the observed value of Λ is 138.

At lower concentrations decomposition of the hydrofluoride ion is so great that the solution of the cubic equation becomes too sensitive to the value of k to be useful. A better approximate calculation of Λ is then obtained by setting $(HF_2^-) = 0$, so that the other ion concentrations are given by equations 12 and 13.

$$2(H^+) = -[C + K/f^2] + \sqrt{[C + K/f^2]^2 + 4KC/f^2} \quad (12)$$

$$(F^-) = C + (H^+) \quad (13)$$

The complete results are given in Table II.

It is unfortunate that data are not available at higher concentrations where the triple ion equilibrium plays a more important part, although it is true that at much higher ion concentrations the interionic coulomb forces will

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(16) In fact, it is probable that a part of the self-consistency of the results from transference data is due to the fact that Davies and Huddleston used values interpolated from a smoothed curve and not the direct experimental measurements. The same values were used in the above calculations in order to obtain results comparable with those of Davies and Huddleston. Since the conductance data are much more precise than the transference data, and since a satisfactory equation for the conductance curve is now available, it would seem a more advisable procedure to use the experimentally determined transference data in combination with interpolated (and, where necessary in the concentrated region, extrapolated) conductance data. This method applied to the ten transference measurements in the concentration range 2.33 to 0.327 moles per liter yielded $k = 0.327 \pm 5.8\%$, $U_0 = 83.0 \pm 6.1\%$, from which it is evident that the results are less self consistent, although the agreement of the mean with the results from the conductance equation is substantially unchanged: k from conductance equation using $U_0 = 83.0$ to calculate λ_0 is 0.368. The difference from 0.327 is 11.8% of the mean.

(17) Walden, *Z. physik. Chem.*, **2**, 49 (1888).

complicate the analysis. The relatively large deviation at $C = 0.006$ is, of course, due to the error introduced by neglecting the concentration of the hydrofluoride ion; at lower concentrations this error becomes of less importance.

TABLE II

THE CONDUCTIVITY OF AQUEOUS POTASSIUM HYDROFLUORIDE AT 25°

C	0.020	0.006	0.005	0.002	0.001
Λ exptl.	138	150	167	217	270
Λ calcd.	136.0	163.3	169.6	217.7	265.5
% Dev.	1.45	8.87	1.56	0.32	1.67

Summary

It has been shown that the conductance function for unilateral triple ion formation applies satisfactorily to the conductance data for aqueous hydrofluoric acid at 25 and at 0°. The constants determined in this way are consistent with the substantially independent values which may be obtained from transference measurements and they may be employed successfully to calculate the conductivity of potassium hydrofluoride solutions.

PROVIDENCE, R. I. RECEIVED APRIL 20, 1938

[JOINT CONTRIBUTION FROM THE CHEMISTRY LABORATORIES OF CANISIUS COLLEGE AND OF THE UNIVERSITY OF MARYLAND]

The Critical Increment of Ionic Reactions. III. The Influence of Dielectric Constant and Ionic Strength

BY JAMES LANDER[1] AND W. J. SVIRBELY

Recently,[2] equations were derived which predicted the influence of dielectric constant and ionic strength upon the critical increments of ionic reactions. The critical increments obtained by means of the theoretical equations were then compared with the experimental critical increments obtained for the reaction between ammonium and cyanate ions in methanol–water mixtures of constant dielectric constants. In the present investigation, the same reaction was studied over a temperature range of 30 to 60° in mixtures of water with ethylene glycol at the fixed dielectric constants of 63.5, 60, 55, 50, 45 and 40 in order to observe if there would be any specific medium effects due to the use of a different solvent. The experimental critical increments were then compared with the values obtained by means of the theoretical equations.[2]

Experimental

The ethylene glycol used was Eastman Best Grade (Highest Purity). The glycol was distilled and the fraction boiling sharply at 197° (uncorr.) was used. All other materials were prepared or purified as described in previous papers[3] which also describe the procedure used in this investigation. All temperatures were checked against a thermometer calibrated by the Bureau of Standards. Thermostat temperatures were maintained constant within ±0.01°. Dielectric constants for glycol–water mixtures were taken from the work of Åkerlöf.[4]

Average values of the limiting velocity constants were determined by means of the equation[3b,2]

$$k_0t = \left\{\frac{1 + 4A\sqrt{C}}{C}\right\} - \left\{\frac{1 + 4A\sqrt{C^0}}{C^0}\right\} \qquad (1)$$

and are listed in Table I. Deviations (δ) of the experimental value of $C/(1 + 4A\sqrt{C})$ from the value calculated from the average k_0 are plotted[3b] against the experimental values of this function in Figs. 1 and 2. The filled circles represent values of $C^0/(1 + 4A\sqrt{C^0})$. In Table II, we give velocity constants (k_1) at $\sqrt{\mu} = 0.194$ obtained from k_0 by the relation[3b]

$$k_1 = k_0/(1 + 2A\sqrt{\mu}) \qquad (2)$$

In Fig. 3, log k_0 is plotted against $1/T$ for the various media. These lines, as well as those obtained by plotting log k_1 against $1/T$, can be expressed by the general equation

$$\log k = \log K - (E/4.58T) \qquad (3)$$

Values of $\log K_0$ and E_0 and of $\log K_1$ and E_1 obtained by means of equation (3) are listed in Tables I and II, respectively. The tables also contain values of k_0 and k_1 calculated by equation (3) using the tabulated values of log K and E.

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[1] From the thesis presented to the Graduate Committee of Canisius College by James Lander in partial fulfilment of the requirements for the degree of Master of Science, June, 1938.

[2] (a) Svirbely and Warner, THIS JOURNAL, **57**, 1883 (1935); (b) Svirbely and Schramm, *ibid.*, **60**, 330 (1938).

[3] (a) Warner and Stitt, *ibid.*, **55**, 4807 (1933); (b) Warner and Warrick, *ibid.*, **57**, 1491 (1935).

[4] Åkerlöf, *ibid.*, **54**, 4125 (1932).

TABLE I

SUMMARY OF DATA AT ZERO IONIC STRENGTH IN GLYCOL–WATER MEDIA

Constant dielectric constant media

Temp., °C.	63.5			60			55			50			45			40		
	Wt. % of gly.	k_0 Eq. 1	k_0 Eq. 3	Wt. % of gly.	k_0 Eq. 1	k_0 Eq. 3	Wt. % of gly.	k_0 Eq. 1	k_0 Eq. 3	Wt. % of gly.	k_0 Eq. 1	k_0 Eq. 3	Wt. % of gly.	k_0 Eq. 1	k_0 Eq. 3	Wt. % of gly.	k_0 Eq. 1	k_0 Eq. 3
30	44.25	0.0113	0.0113	54.20	0.0141	0.0139	68.0	0.0191	0.0191	76.15	0.0265	0.0264	85.75	0.0384	0.0372	94.10	0.0509	0.0508
40	33.56	.0321	.0329	44.90	.039	.040	58.8	.0533	.0548	70.35	.0756	.0746	82.18	.106	.106	90.8	.141	.146
50	22.70	.0910	.089	34.90	.1096	.108	50.6	.148	.148	64.0	.202	.203	75.64	.280	.287	86.65	.380	.393
60	11.55	.230	.227	24.20	.279	.275	41.6	.387	.376	56.6	.528	.515	69.95	.730	.727	81.70	.996	.995
log K_0 (eq. 3)		12.51			12.54			12.67			12.76			12.91			13.06	
E (eq. 3)		20,060			19,980			19,970			19,900			19,900			19,920	

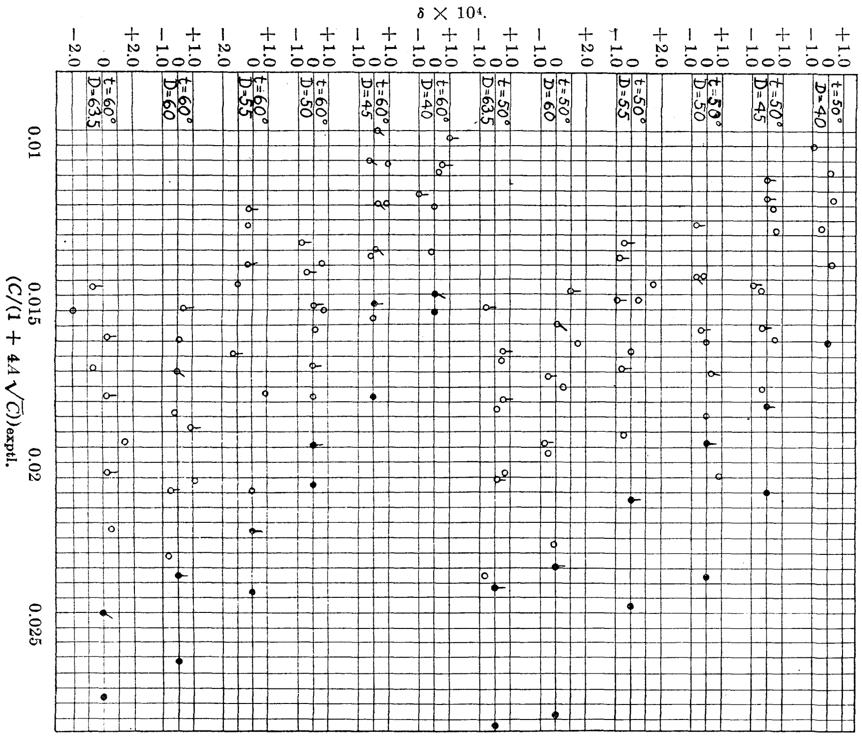

Fig. 2.—Glycol-water mixtures.

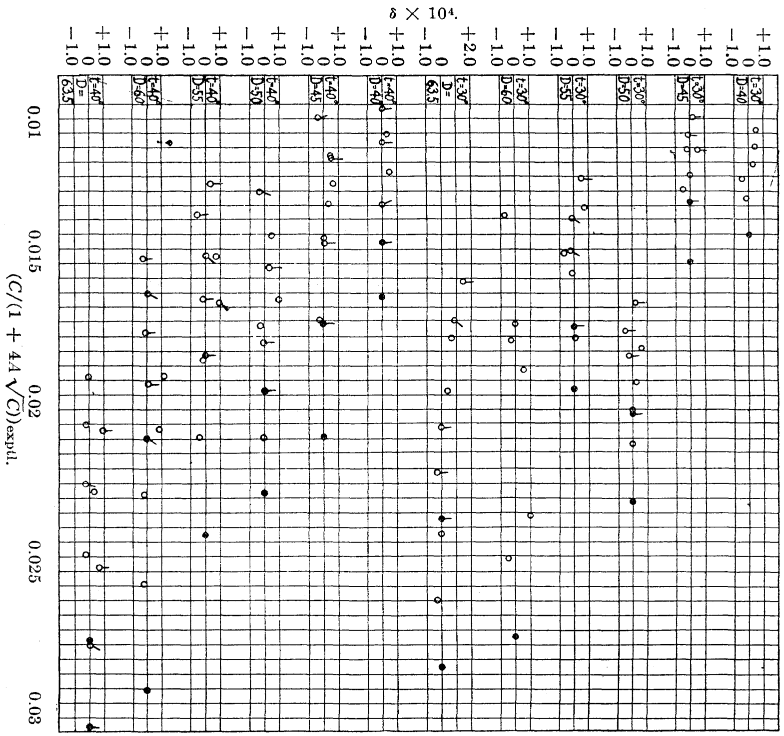

Fig. 1.—Glycol-water mixtures.

TABLE II

SUMMARY OF DATA AT $\sqrt{\mu} = 0.194$

Constant dielectric constant media

Temp., °C.	63.5 k_1 Eq. 2	63.5 k_1 Eq. 3	60 k_1 Eq. 2	60 k_1 Eq. 3	55 k_1 Eq. 2	55 k_1 Eq. 3	50 k_1 Eq. 2	50 k_1 Eq. 3	45 k_1 Eq. 2	45 k_1 Eq. 3	40 k_1 Eq. 2	40 k_1 Eq. 3
30	0.00703	0.00703	0.00847	0.00829	0.0109	0.0107	0.0142	0.0142	0.0190	0.0183	0.0230	0.0228
40	.0203	.0211	.0239	.0245	.0311	.0319	.0413	.0418	.0538	.0539	.0655	.0667
50	.0586	.0586	.0684	.0680	.0878	.0882	.113	.115	.145	.148	.180	.183
60	.151	.153	.177	.177	.234	.230	.301	.297	.387	.383	.486	.469
log K (eq. 3)	12.68		12.69		12.79		12.80		12.91		12.95	
E(eq. 3)	20,580		20,500		20,480		20,330		20,320		20,250	
E(eq. 6 at 50°)	20,400		20,330		20,360		20,330		20,360		20,310	

From the equation[2a]

$$(E^0)_{\text{fixed comp.}} = (E_D^{0*}) + 2.3RT^2\left(\frac{\partial \log k_0}{\partial D}\right)_T \frac{dD}{dT} \qquad (4)$$

one obtains in this case using water as the solvent of fixed composition

$$(E^0)_{H_2O} - (E_D^{0*}) = 605\,\frac{T}{D} \qquad (5)$$

Using equation (5) one calculates the difference between the critical increments in water and in glycol–water media of fixed dielectric constant to be 2800 cal. at 50°. Using the experimental values of the E_0s given in Table I and taking E_0 in water[2] to be 23,580 cal. one observes that the difference between the critical increments in water and in glycol–water media of fixed dielectric constant has an average value of 3620 cal. Thus E_D^{0*} is here apparently independent of dielectric constant.

By taking logarithms and differentiating equation (2) one obtains a relationship between E_0 and E at a fixed ionic strength, namely

$$E = E^0 + \frac{(12.5 \times 10^6\ \sqrt{\mu}\ RT)}{(TD)^{3/2} + 8.36 \times 10^6\ \sqrt{\mu}}\left(1 + \frac{d \ln D}{d \ln T}\right) \qquad (6)$$

Using equation (6) we have calculated E at $\sqrt{\mu} = 0.194$ from E_0 of the various media. The results are listed in Table II and are in fair agreement with the Es obtained by equation (3).

An equation for ionic reactions has been developed by Scatchard[5] from consideration of the dielectric effect of the medium, namely

$$\log k - \log k_0{}^* = \frac{e^2 Z_A Z_B}{2.3KTr}\left(\frac{1}{D^0} - \frac{1}{D}\right) \qquad (7)$$

where $k_0{}^*$ is the rate constant at zero ionic strength in a standard solvent of dielectric constant D^0 and k_0 is the corresponding rate constant at zero ionic strength in a solvent of dielectric constant D. Using water as the standard solvent we have plotted in Fig. 4 the values of ($\log k_0 - \log k_0{}^*$) against the corresponding differences in the reciprocals of D^0 and D at the different temperatures. The plots, according to equation (7), should be linear and have slopes varying from -108 at 60° to -119 at 30° (assuming $r = 2 \times 10^{-8}$ cm.). The curves depart from the predicted linearity. The limiting slopes of the curves are in fair agreement with the predicted values, increasing from ~ -88 at 60° to ~ -96 at 30°.

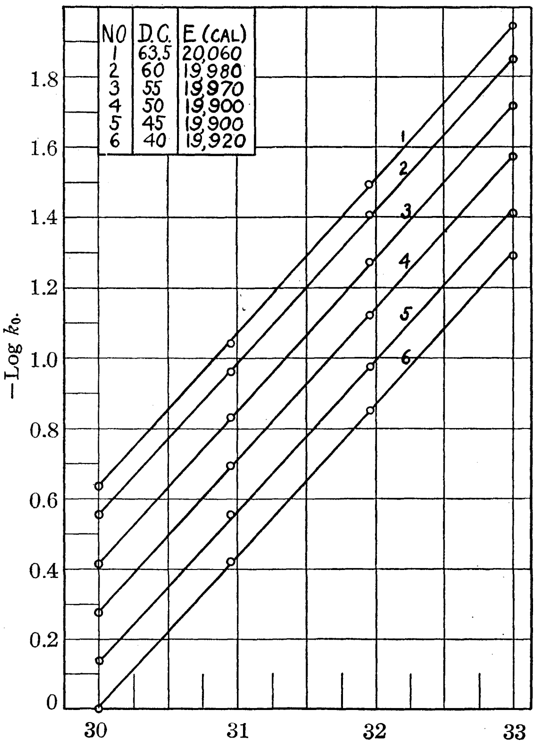

Fig. 3.—Influence of temperature on the rate of conversion of ammonium cyanate to urea in ethylene glycol–water media at zero ionic strength.

By reference to Table I, one observes that an empirical relation can be obtained between the dielectric effect and the temperature effect on the value of the limiting velocity constant for this reaction in glycol–water mixtures of constant dielectric constant, namely

$$\left(\frac{\Delta k_0}{\Delta D}\right)_T = -0.70\left(\frac{\Delta k_0}{\Delta T}\right)_D \qquad (8)$$

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(5) Scatchard, *Chem. Rev.*, **10**, 229 (1932).

In the case of the methanol–water media, the constant on the right side of the equation was equal to unity.[2b]

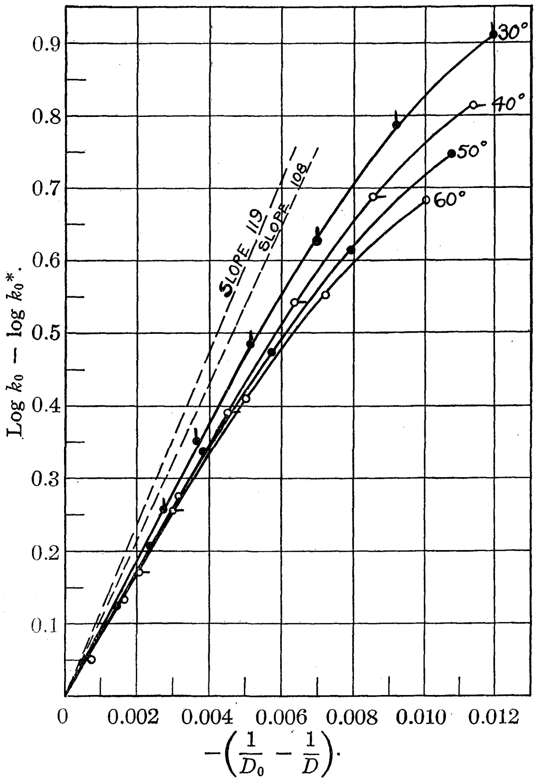

Fig. 4.

Discussion

It will be recalled that the equations previously derived[2] and used in this investigation were based on the assumption that the rate of reaction between ions depends only upon the temperature, the dielectric constant of the medium and the ionic strength. From previous investigations,[3b] and from the comparison of rates of the ammonium cyanate reaction in methanol–water media[2b] and in glycol–water media, we know that this assumption is only approximately true. However, considering these limitations the experimental data presented for this reaction in methanol–water media and in glycol–water media are in satisfactory agreement with those calculated by means of the equations and thus they very definitely show the influence of the dielectric constant and of the ionic strength upon critical increments.

We have summed up all of our observations in the two different solvent–water mixtures including some specific solvent influences:

(a) In methanol–water mixtures the log Ks for the constant dielectric constant media were constant, the average value being 11.77. In glycol–water media, however, the log Ks for the constant dielectric constant mixtures increase with decreasing dielectric constant.

(b) In methanol–water mixtures E_{D}^{0*} decreased with decreasing dielectric constant. In glycol–water media, however, E_{D}^{0*} is apparently independent of dielectric constant.

(c) In agreement with equation (6) the critical increments increased with ionic strength in both solvent–water mixtures of constant dielectric constant. In both cases calculated and experimental critical increments are in good agreement.

(d) The limiting slopes of the plots of (log k_0 − log k_0*) against ($1/D^0 - 1/D$) are in fair agreement with the predicted values in both cases.

(e) At 50° the rate constants in glycol–water mixtures are very nearly the same as those in isopropyl alcohol–water media and in dioxane–water media[3b] for the same constant dielectric constant mixtures.

As a result of the constancy of E_{D}^{0*} in glycol–water media, the suggestion previously made[2b] that possibly some of the decrease in E_{D}^{0*} with decreasing dielectric constant in methanol–water media was due to the method of calculating the k_0s, must either be dismissed or we must assume compensating medium effects operating in the glycol–water media. Unfortunately we cannot satisfactorily decide this question at present.

Summary

1. The rate of conversion of ammonium cyanate to urea has been studied over the temperature range 30 to 60° in glycol–water mixtures at the constant dielectric constants of 63.5, 60, 55, 50, 45 and 40.

2. The influence of ionic strength upon the observed critical increments at zero ionic strength is in good agreement with equations previously derived. It is observed that the critical increment is apparently independent of the dielectric constant in glycol–water media of constant dielectric constant.

3. Empirically it is shown that for this reaction in glycol–water mixtures of constant dielectric constant the following relation holds

$$\left(\frac{\Delta k_0}{\Delta D}\right)_T = -0.70\left(\frac{\Delta k_0}{\Delta T}\right)_D$$

4. The influence of the dielectric constant

of the solvent upon the rate constants is in fair agreement with the Scatchard–Christiansen theory.

5. The experimental results for this reaction are compared in methanol–water and in glycol–water mixtures.

BUFFALO, N. Y.
COLLEGE PARK, MD. RECEIVED APRIL 22, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

On the Mechanism of the Catechol–Tyrosinase Reaction. II. The Hydrogen Peroxide Question

BY CHARLES R. DAWSON AND BERNARD J. LUDWIG

The dihydric phenol catechol has been used widely as an experimental substrate in the study of phenolic–oxidase action. These studies, and the widespread occurrence of catechol derivatives in nature, have motivated the suggestion that the utilization of molecular oxygen during the respiration of certain types of plants probably is largely dependent on this type of enzymatic action.[1] Robinson and McCance[2] in 1925 were among the first to show that the enzymatic oxidation of catechol results in the absorption of two atoms of oxygen per molecule of the dihydric phenol. Although it has been established definitely that *o*-benzoquinone is one of the initial products formed during the action of a phenolic oxidase such as tyrosinase on catechol,[3–5] the nature of the enzymatic action and the chemical mechanisms involved have not yet been explained satisfactorily.

The conversion of catechol to *o*-benzoquinone is an oxidation requiring theoretically only one atom of oxygen, and thus much of the controversy during the past decade has been in reference to the fate of the second oxygen atom. Since aerobic oxidations are attended frequently by the initial formation of hydrogen peroxide, it is not surprising that one of the first mechanisms, as suggested by Onslow and Robinson,[6] accounted for the second atom of oxygen by the formation of hydrogen peroxide, *i. e.*

$$C_6H_4(OH)_2 + O_2 \longrightarrow C_6H_4O_2 + H_2O_2$$

These investigators, and others,[7] have claimed to have detected traces of hydrogen peroxide in the reaction mixture resulting from the enzymatic oxidation of catechol, and they attributed the difficulty in detecting this substance to the presence of peroxidase and catalase in their tyrosinase or oxidase preparations. Others have attributed the difficulty of detecting hydrogen peroxide in many catalytic oxidations to the presence of small amounts of certain metals.[8,9]

The reliability of the methods used by Onslow and Robinson, and others,[7] for the detection of hydrogen peroxide has been questioned, and several workers have expressed doubt concerning the formation of hydrogen peroxide during the enzymatic oxidation of catechol. Pugh and Raper[4] studied the oxidation of catechol using tyrosinase preparations that possessed appreciable catalase activity, and observed that the total oxygen uptake did not deviate from two atoms per molecule of substrate. They pointed out that the presence of catalase would tend to decompose any hydrogen peroxide formed during the enzymatic oxidation and would thereby return the second atom of oxygen to the reaction mixture. These workers suggested that the second oxygen atom is consumed during further oxidation of *o*-benzoquinone. Furthermore, Nobutani[10] found that catalase has no effect on the oxygen consumption during the enzymatic oxidation of *p*-cresol, and therefore concluded that hydrogen peroxide is not formed during this reaction.

A study of the reports of Pugh and Raper and of Nobutani, however, reveals that their conclusions have been based on evidence that is not entirely convincing. These investigators did not indicate the strengths of the catalase preparations used nor did they demonstrate that the catalase remains active throughout the oxidation process.

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(1) A. von. Szent-Györgyi, *Science*, **72**, 125 (1930).

(2) M. E. Robinson and R. A. McCance, *Biochem. J.*, **19**, 251 (1925).

(3) A. von Szent-Györgyi, *Biochem. Z.*, **162**, 399 (1925).

(4) C. E. M. Pugh and H. S. Raper, *Biochem. J.*, **21**, 1370 (1927).

(5) H. Wagreich and J. M. Nelson, *J. Biol. Chem.*, **115**, 459 (1936).

(6) M. W. Onslow and M. E. Robinson, *Biochem. J.*, **20**, 1138 (1926).

(7) B. S. Platt and A. Wormall, *ibid.*, **21**, 26 (1927).

(8) H. Wieland, "On the Mechanism of Oxidation," Yale University Press, New Haven, Conn., 1932.

(9) H. Wieland and W. Franke, *Ann.*, **457**, 1 (1927).

(10) F. Nobutani, *J. Biochem.* (Japan), **23**, 472 (1936).

Furthermore, it appears from some recent studies of Keilin and Hartree[11] that under certain conditions catalase may promote a secondary oxidation involving the hydrogen peroxide produced during an enzymatic oxidation. These authors have shown that when catalase functions in this capacity, the decomposition of the hydrogen peroxide does not result in the liberation of oxygen, *i. e.*, it does not return molecular oxygen to the reaction system. If, during the enzymatic oxidation of catechol, the introduction of catalase should promote such a secondary oxidation between hydrogen peroxide and some suitable intermediate, it is possible that the total oxygen uptake might not deviate from two atoms per molecule of substrate. Under such conditions, therefore, the formation of hydrogen peroxide would not be detected by oxygen uptake measurements.

In 1930 Pugh[12] reported that the activating action of traces of catechol and other dihydric phenols on the tyrosinase-monohydric phenol reaction could be attributed to the formation of either hydrogen peroxide or both hydrogen peroxide and *o*-quinone. More recently, Evans and Raper[13] have reported that the addition of purified peroxidase to the mealworm tyrosinase–tyrosine reaction causes a considerable decrease in the accumulation of dopa (3,4-dihydroxyphenylalanine). Since peroxidase itself has no action on mono- or dihydric phenols, they presented this as evidence that either hydrogen peroxide or an organic peroxide, which is capable of being activated by peroxidase, is produced in the tyrosinase–tyrosine reaction.

It has been found recently in these Laboratories[14] that the quinone produced during the enzymatic aerobic oxidation of catechol can be followed by iodimetric titration. When produced under certain conditions, *i. e.*, with an optimum amount of enzyme in very dilute solutions of catechol buffered in the *p*H range 4.2 to 6.6, the stability of the quinone is such that the stoichiometric relationship between it and catechol can be demonstrated. Since both quinone and hydrogen peroxide liberate iodine from hydriodic acid, it was apparent at an early stage in these studies that the indefinite status of the hydrogen peroxide controversy tended to cloud all interpretations. For this reason it became essential that more conclusive experimental evidence be obtained concerning the questionable role of hydrogen peroxide in this enzymatic oxidation.

In order to avoid the questionable reliability of the oxygen absorption methods which have been applied previously to this problem, the reaction course was followed by means of the iodimetric titration method previously described.[14] The study reported in this communication deals with the effect of hydrogen peroxide and the effect of catalase on the production and stability of the oxidation products formed during the catechol–tyrosinase reaction.

The Tyrosinase Preparations.—The tyrosinase preparations used in the present study were obtained from common mushrooms (common or field mushroom "*Psalliota campestris*"). The detailed procedure used for obtaining tyrosinase preparations from mushrooms will be published later. In brief, the mushrooms were frozen, ground, treated with cold acetone, and extracted with water. After an acetone precipitation and one or two ammonium sulfate precipitations, the enzyme was adsorbed on kaolin, eluted, and then adsorbed on alumina. The last step was followed by elution and dialysis, and the activity of the resulting preparation was measured according to the method proposed by Graubard and Nelson.[15]

The preparations were found to be free of peroxidase activity and to have negligible catalase activity. Typical data in support of this statement are compiled in Table I. These data were obtained using the procedure of Balls and Hale[16,17] for the determination of peroxidase activity.

The negligible magnitude of the catalase activity in the tyrosinase preparations can be judged by an inspection of the values of $(a - x)/t$ in column 1 of this table. The very small values of $(a - x)/t$ indicate a very low rate of decomposition of hydrogen peroxide by 5 cc. of the tyrosinase solution in the absence of pyrogallol. The absence of peroxidase activity in the tyrosinase solutions is shown by a comparison of the values of $(a - x)/t$ in columns 2 and 3 with those in column 1. The introduction of pyrogallol at

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[11] D. Keilin and E. F. Hartree, *Proc. Roy. Soc.* (London), **B119**, 141 (1935).

[12] C. E. M. Pugh, *Biochem. J.*, **24**, 1442 (1930).

[13] W. C. Evans and H. S. Raper, *ibid.*, **31**, 2155 (1937).

[14] C. R. Dawson and J. M. Nelson, THIS JOURNAL, **60**, 250 (1938).

[15] M. Graubard and J. M. Nelson, *J. Biol. Chem.*, **112**, 135 (1935).

[16] A. K. Balls and W. S. Hale, *J. Assoc. Off. Agr. Chem.*, **16**, 445 (1933).

[17] A. K. Balls and W. S. Hale *J. Biol. Chem.*, **107**, 767 (1934).

TABLE I

250 cc. of 0.02 *M* phosphate buffer contained 4.0 cc. of 0.1 *N* H_2O_2 with enzyme and pyrogallol as shown. The solution was covered with oil to prevent access of air and was stirred with nitrogen. Titrations were made on 25-cc. portions with thiosulfate solution (approximately 0.01 *N*). The value of $(a - x)/t$ gives a measure of the rate of decomposition of the hydrogen peroxide.

	*p*H 6.6 5 cc. tyrosinase soln. 56.5 units No pyrogallol		*p*H 6.6 5 cc. tyrosinase soln. 56.5 units 0.6 g. pyrogallol		*p*H 7.8 5 cc. tyrosinase soln. 56.5 units 0.6 g. pyrogallol		*p*H 7.8 5 cc. peroxidase diluted (1:20) 0.6 g. pyrogallol		*p*H 7.8 5 cc. peroxidase diluted (1:20) 0.6 pyrogallol 5 cc. tyrosinase 56.5 units	
Time, min.	Thio., cc.	$\frac{a-x}{t}$	Thio., cc.	$\frac{a-x}{t}$	Thio., cc.	$\frac{a-x}{t}$	Thio., cc.	$\frac{a-x}{t}$	Thio., cc.	$\frac{a-x}{t}$
0	4.07		4.10		4.42		4.06		3.91	
2	4.03	0.02	4.05	0.02	4.40	0.01	3.70	0.18	3.56	0.18
5	4.00	.01	4.00	.02	4.39	.01	3.19	.17	3.06	.17
8	3.93	.02	3.92	.02	4.37	.01	2.71	.17	2.60	.16
10	3.86	.02	3.85	.02	4.33	.01	2.43	.16	2.32	.16

*p*H 6.6 did not increase the rate of decomposition of hydrogen peroxide, and at *p*H 7.8 caused a slightly lower rate of decomposition. Furthermore, as shown in columns 4 and 5, a mixture of 5 cc. of the tyrosinase solution with 5 cc. of a diluted horse radish peroxidase preparation had the same peroxidase activity as the peroxidase preparation alone.

The Effect of Hydrogen Peroxide on the Stability of the Oxidation Product Formed During the Enzymatic Oxidation of Catechol.—In dilute solutions buffered within the *p*H range 4.2 to 6.6 and in the presence of sufficient tyrosinase, catechol is rapidly and completely converted by air to an oxidized state that is equivalent to two atoms of iodine per molecule of catechol.[14] This iodine equivalency naturally suggests the oxidation product to be a benzoquinone, but does not preclude the possibility that the titration values may correspond to a mixture of a benzoquinone and hydrogen peroxide. Within this *p*H range the decrease in stability of the oxidation product with increase in *p*H is small, as can be seen in curves 1, 2 and 3 of Fig. 1, but at higher *p*H values the product is too unstable to be determined effectively. Since the tyrosinase preparations used in these experiments possess negligible catalase and peroxidase activity, hydrogen peroxide, if formed during the oxidation of catechol under these conditions, should be detectable, provided that the hydrogen peroxide does not undergo a secondary reaction with the benzoquinone.

To determine the conditions favoring such a secondary reaction between the benzoquinone and hydrogen peroxide, the enzymatic oxidation of catechol in the presence of given amounts of hydrogen peroxide at different hydrogen ion concentrations were studied. The results obtained are shown graphically in curves 5, 6 and 7 of Fig. 1. The experimental conditions and other points of information are given in the legend of this figure. As explained in this legend, 1.91 cc. of the thiosulfate solution is the titration value that represents complete conversion of 10 mg. of catechol to the quinone state, *i. e.*, to an oxidized state that is equivalent to two atoms of iodine per molecule of catechol. Thus, in the presence of an amount of hydrogen peroxide equivalent to 3.30 cc. of the thiosulfate solution per titration sample (see curve 4, Fig. 1), the complete enzymatic conversion of 10 mg. of catechol to this quinone state should be represented by a titration value of 5.21 cc. of thiosulfate solution, provided the hydrogen peroxide and quinone are perfectly compatible. Curves 6 and 7 of this figure show the quinone and hydrogen peroxide to be incompatible in solutions buffered to *p*H values of 5.5 and 6.7, respectively. However, at *p*H 4.1 hydrogen peroxide appears to have very little effect on the stability of the quinone produced in this enzymatic oxidation, as can be judged from a comparison of curve 5 with curve 1 in this figure. Since hydrogen peroxide and the quinone appear to be compatible at *p*H 4.1, it is evident that experiments designed for the detection of hydrogen peroxide as a reaction product in this enzymatic oxidation should be conducted in solutions buffered to approximately this *p*H value.

The Effect of Catalase on the Reaction Course as Determined by the Iodimetric Titration Method.—By the use of a sufficient amount of the enzyme catalase, the decomposition of hydrogen peroxide can be effected at a rate so rapid as to be practically immeasurable. For this reason, the presence of a relatively large amount of catalase in the reaction system, during the enzymatic oxidation of catechol at *p*H 4.1, should alter materially the reaction course, as determined by the iodimetric titration method, if hydrogen peroxide is responsible for any part of the titration values.

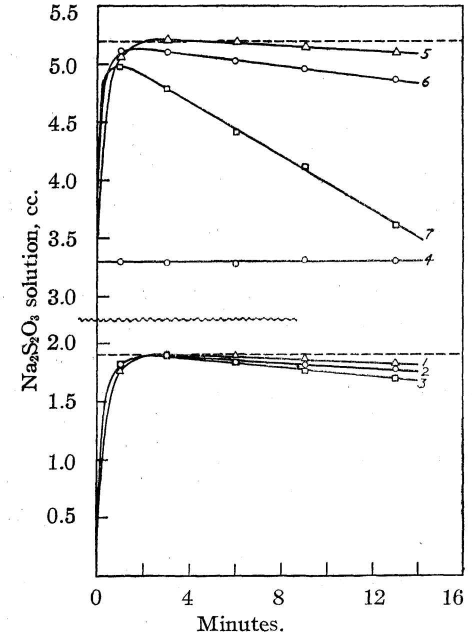

Fig. 1.—Curves showing the effect of *p*H and of hydrogen peroxide on the production and stability of the oxidation product formed in the catechol–tyrosinase reaction. 3.5 units of tyrosinase per mg. of catechol was used in solutions buffered to the following *p*H values: Curve 1, *p*H 4.1; 2, *p*H 5.3; 3, *p*H 6.7; 5, *p*H 4.1; 6, *p*H 5.5; 7, *p*H 6.7. The enzymatic oxidations represented by curves 1, 2 and 3 were run at 25° in a total reaction volume of 250 cc., of which 25 cc. was 0.2 *M* phosphate buffer; 5 cc. was 0.2% freshly prepared catechol solution (10 mg.), and 5 cc. was enzyme solution. The enzyme was added at zero time. With air bubbling through the reaction solution, 25-cc. samples were removed at the time intervals noted and added to 25 cc. of 2 *N* sulfuric acid. After adding 10 cc. of 10% potassium iodide they were allowed to remain in the dark for fifteen minutes before titrating the liberated iodine with standard thiosulfate solution. Thus the plotted volumes of thiosulfate solution required to take care of the iodine liberated in each sample are a measure of the amounts of oxidation product causing this iodine liberation. 1 Mg. of catechol per 25 cc. (0.1 reaction volume) when completely oxidized is equivalent to 9.10×10^{-6} mole of iodine which in turn is equivalent to 1.91 cc. of 0.00950 *N* sodium thiosulfate solution. The runs represented graphically by curves 5, 6 and 7 differ from those of curves 1, 2 and 3 in that the reaction system corresponding to the upper curves contained in addition to 10 mg. of catechol and 35 units of enzyme 2.0 cc. of approximately 0.15 *N* hydrogen peroxide. The titration values plotted in curve 4 (3.30 ± 0.01 cc.) are those obtained when the system contained only this amount of hydrogen peroxide. The upper dotted line (at 5.21 on the ordinate axis) is the sum of the hydrogen peroxide equivalent (3.30) and the catechol equivalent (1.91) in cc. of 0.00950 *N* sodium thiosulfate solution.

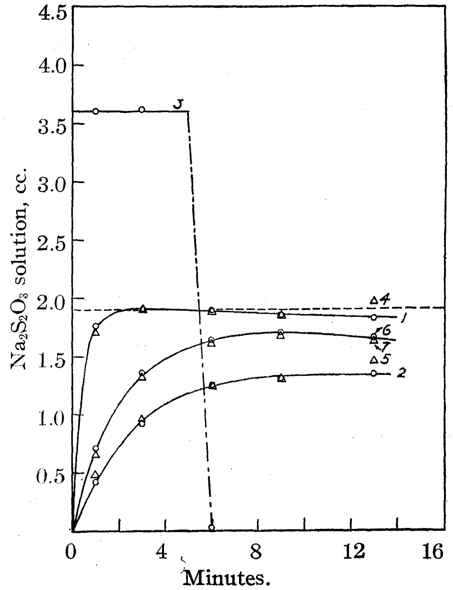

Fig. 2.—Curves showing the absence of hydrogen peroxide in the products resulting from the enzymatic oxidation of catechol. The data represented in curves 1, 2, 4 and 5 were obtained using 10 mg. of catechol per 250 cc. reaction volume (buffered to *p*H 4.1) according to the procedure described in the legend of Fig. 1. The data represented in curves 6 and 7 were obtained with similar solutions buffered to *p*H 5.6. Tyrosinase used per mg. of catechol: curves 1 and 4, 3.5 units; curves 6 and 7, 1.0 unit; curves 2 and 5, 0.5 unit. The systems represented by curves 4 and 5 differ from those of curves 1 and 2 only in that the initial reaction volume (250 cc.) of the former systems contained, in addition to catechol and tyrosinase, 2.0 cc. of a diluted catalase preparation. The data represented in curve 3, which has been included to give an indication of the catalase activity possessed by this amount of the catalase preparation, were obtained by use of the same titration procedure. The system contained initially only 2.0 cc. of approximately 0.17 *N* hydrogen peroxide in 250 cc. This amount of hydrogen peroxide is nearly twice that theoretically producible in the enzymatic oxidation of catechol under these conditions. As can be seen in this curve, one minute after the addition of 2.0 cc. of the diluted catalase preparation, only a negligible quantity of hydrogen peroxide remained. To demonstrate that the catalase remained active throughout the oxidation process, a similar amount of hydrogen peroxide (2.0 cc. of 0.17 *N* hydrogen peroxide) was added after the expiration of twelve minutes to the systems represented by curves 4 and 5. Had the catalase been inactivated completely the last titration value in each of these curves would have been greater by about 5.8 cc. of the thiosulfate solution. The system represented by curve 7 differs from that of curve 6 only in that the former contained initially 5 cc. of a diluted (1:20) peroxidase preparation in addition to the catechol and tyrosinase. The activity of this amount of peroxidase can be judged from an inspection of the data in column 4 of Table I. The titrations in the experiments represented by curves 6 and 7 were made with 0.00964 *N* sodium thiosulfate.

Curves 1 and 2 in Fig. 2 show the reaction course, as determined by this method, when 10 mg. of catechol in 250 cc. of solution buffered to *p*H 4.1 was oxidized rapidly with 35 units of tyrosinase and more slowly oxidized with 5 units of the enzyme. Curves 4 and 5 show the results obtained when the experiments were repeated in the presence of a relatively large amount of catalase. This negative effect of catalase on the reaction course was observed also at other *p*H values within the *p*H range 4.1 to 6.7. Experiments of this type were also conducted at several *p*H values using peroxidase rather than catalase for the purpose of detecting hydrogen peroxide. In no case did the presence of peroxidase alter the reaction course. A typical example is presented in the form of curves 6 and 7 of Fig. 2 (see legend). As explained in the legend and shown in curve 3 of this figure, the amount of catalase used in these studies was sufficient to decompose in about one minute nearly twice the amount of hydrogen peroxide that theoretically could be produced during this enzymatic oxidation. Since the catalase remained active throughout the enzymatic oxidation (see legend of Fig. 2) and caused no change in the course of the reaction as followed by this method, it can be concluded definitely that the titration values are in no part due to hydrogen peroxide.

Discussion

It is quite apparent that the uptake of the extra atom of oxygen over and above that which is required for the formation of *o*-benzoquinone from catechol cannot be accounted for in this enzymatic oxidation simply by the formation of hydrogen peroxide as suggested by Onslow and Robinson,[6] *i. e.*

$$C_6H_4(OH)_2 + O_2 \longrightarrow C_6H_4O_2 + H_2O_2$$

This statement, based largely on the evidence that has been presented above, has recently received further substantiation during the course of other investigations in these Laboratories. By simultaneously following the enzymatic oxidation of catechol with both oxygen uptake measurements and iodimetric titration measurements, Wagreich and Nelson[18] have found that the complete conversion of catechol to the quinone state, as indicated by iodimetric titration, requires the absorption of only one atom of oxygen. It appears quite probable that the second oxygen atom is used in oxidation of a product resulting from the action of water on *o*-benzoquinone.

The question of whether or not hydrogen peroxide has an intermediary function during the formation of the initial quinone may be considered to be still open to debate. For such to be the case, the hydrogen peroxide must perform this function at a rate greater than the rate of its own decomposition by relatively large amounts of catalase, and its concentration therefore at any given time must be extremely low. If the tyrosinase preparations had possessed appreciable peroxidase activity, such an intermediary function of hydrogen peroxide would be more readily conceivable. Considering the facts that have been presented above, there appears to be little reason at present for supporting such a view of the enzymatic oxidation of catechol.

Summary

1. The enzymatic oxidation of catechol has been studied using tyrosinase preparations having no peroxidase activity and negligible catalase activity.

2. In dilute solutions buffered within the *p*H range 4.1 to 6.7 the oxidation product formed in the initial stages of the catechol–tyrosinase reaction is equivalent to two atoms of iodine per molecule of catechol. This iodine equivalency corresponds to a benzoquinone.

3. This quinone and hydrogen peroxide are incompatible in solutions buffered to *p*H values above 4.1.

4. In the *p*H range 4.1 to 6.7, the course of the catechol–tyrosinase reaction, as followed by iodimetric titration, is unaltered by large amounts of catalase or peroxidase.

5. It is concluded that hydrogen peroxide is not responsible for any part of the titration values, and that the consumption of two atoms of oxygen per molecule of catechol during the enzymatic oxidation cannot be directly attributed to the formation of hydrogen peroxide.

NEW YORK, N. Y.

RECEIVED MAY 4, 1938

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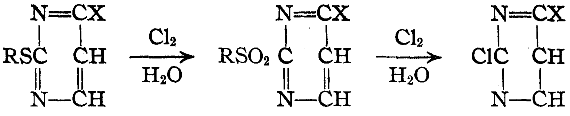
(18) H. Wagreich and J. M. Nelson, THIS JOURNAL, **60**, 1545 (1938).

[CONTRIBUTIONS FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

Researches on Pyrimidines. CLVIII. The Oxidation of Mercaptopyrimidines with Chlorine Water

BY TREAT B. JOHNSON AND JAMES M. SPRAGUE[1]

In a recent publication from this Laboratory by the authors[2] it was shown that chlorine gas and certain 2-mercaptopyrimidines interact smoothly in aqueous solution at low temperature with production of the corresponding 2-alkylsulfonyl derivatives. This reaction is applicable to 2-mercaptopyrimidines conforming in constitution to Formula I. By raising the reaction temperature, however, the chlorination process proceeds further with replacement of the sulfonyl grouping of the pyrimidine II by chlorine. These changes are expressed by Formulas I, II and III.

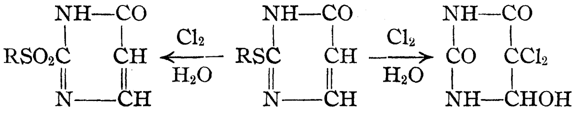


$$\begin{array}{c}N{=}CX\\ RSC\quad CH\\ N{-}CH\end{array} \xrightarrow[H_2O]{Cl_2} \begin{array}{c}N{=}CX\\ RSO_2C\quad CH\\ N{-}CH\end{array} \xrightarrow[H_2O]{Cl_2} \begin{array}{c}N{=}CX\\ ClC\quad CH\\ N{-}CH\end{array}$$

I II III

(X = halogen, OCH_3 or OC_2H_5, SC_2H_5 and NH_2).

During study of this chlorination reaction in 1935 we experimented also with several 2-mercapto-4-oxypyrimidine compounds but were unable to prepare the 2-alkylsulfonyl pyrimidines corresponding to Formula IV. The products of reaction were always sulfur free and they were identified as 2,4-diketohexahydropyrimidines as is represented by Formula VI.



$$\begin{array}{c}NH{-}CO\\ RSO_2C\quad CH\\ N{-}CH\end{array} \xleftarrow[H_2O]{Cl_2} \begin{array}{c}NH{-}CO\\ RSC\quad CH\\ N{-}CH\end{array} \xrightarrow[H_2O]{Cl_2} \begin{array}{c}NH{-}CO\\ CO\quad CCl_2\\ NH{-}CHOH\end{array}$$

IV V VI

In other words, the chlorination reaction in aqueous solution proved to be specific, and serves to differentiate between 2-mercaptopyrimidines represented by structures expressed in Formulas I and V, respectively. In pyrimidines of type I the unsaturation of the pyrimidine cycle is not changed by chlorination, and the mercapto grouping is oxidized, giving a stable sulfonyl pyrimidine II. In the case of pyrimidines of type V the chlorination process is more complicated. Here we are dealing with three different reaction changes: (1) oxidation of the 2-mercapto grouping, (2) saturation of the double bond in positions 5 and 6 of the pyrimidine cycle and (3) hydrolysis in position-2 with formation of an alkyl sulfonic acid and a 2,4-diketohexahydropyrimidine derivative.

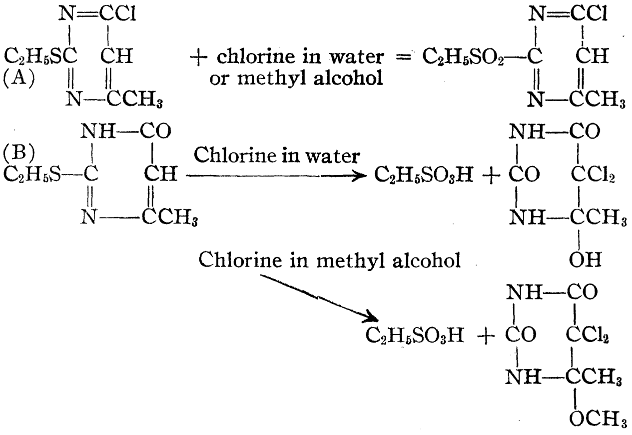
This specificity of reaction is also exhibited by chlorination of mercaptopyrimidines in alcohol solutions. The mercaptopyrimidines of type V behave as the corresponding 2,4-diketotetrahydropyrimidines, giving the same products, the 2,4-diketohexahydropyrimidines.[3] This characteristic difference in chemical behavior is illustrated in the equations expressed under sections A and B below.

Several mercaptopyrimidines of type V have been utilized in different research programs in progress in this Laboratory, and in every case thus far examined the respective mercaptopyrimidine has undergone the characteristic transformations expressed under section B. These 2,4-diketohexahydropyrimidines are converted quantitatively into 2,4-diketotetrahydropyrimidine derivatives by digestion with reducing agents.

Experimental Part

I. The Oxidation of the Mercaptopyrimidines to their Corresponding Sulfonyl Derivatives

$C_2H_5SO_2\overline{C{=}NCH{=}C(CH_3)C(NHCl){=}N}$, **2-Ethylsulfonyl-4-chloroamino-5-methylpyrimidine.**—Two grams of 2-ethylmercapto-4-amino-5-methylpyrimidine[4] was dissolved in 3 cc. of cold methyl alcohol and the solution acidified with 1 cc. of concentrated hydrochloric acid.



$$(A)\ \begin{array}{c}N{=}CCl\\ C_2H_5SC\quad CH\\ N{-}CCH_3\end{array} + \text{chlorine in water or methyl alcohol} = \begin{array}{c}N{=}CCl\\ C_2H_5SO_2{-}C\quad CH\\ N{-}CCH_3\end{array}$$

$$(B)\ \begin{array}{c}NH{-}CO\\ C_2H_5S{-}C\quad CH\\ N{-}CCH_3\end{array} \xrightarrow{\text{Chlorine in water}} C_2H_5SO_3H + \begin{array}{c}NH{-}CO\\ CO\quad CCl_2\\ NH{-}CCH_3\\ OH\end{array}$$

$$\xrightarrow{\text{Chlorine in methyl alcohol}} C_2H_5SO_3H + \begin{array}{c}NH{-}CO\\ CO\quad CCl_2\\ NH{-}CCH_3\\ OCH_3\end{array}$$

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[1] Sterling Professorship of Chemistry Research Assistant 1936–1937.

[2] Sprague and Johnson, THIS JOURNAL, 57, 2252 (1935).

[3] Johnson and Sprague, *ibid.*, 59, 2436 (1937).

[4] Wheeler and Johnson, *Am. Chem. J.*, 31, 597 (1904).

After diluting to 20 cc. with ice water chlorine gas was then bubbled slowly into the cold solution until the precipitation of a crystalline solid was complete. This reaction product (2 g.) was dried over phosphorus pentoxide and purified by crystallization from ethyl acetate. It melted at 125–126° and responded to qualitative tests for sulfur and chlorine.

Anal. Calcd. for $C_7H_{10}O_2N_3SCl$: N, 17.83; S, 13.61; Cl, 15.15. Found: N, 17.88; S, 13.77; Cl, 15.25; (active Cl, 15.05).

$C_2H_5SO_2\overline{C{=}NCH{=}C(CH_3)C(NH_2){=}N}$, **Formation of 2-Ethylsulfonyl-4-amino-5-methylpyrimidine.**—The above chloroaminopyrimidine was suspended in dilute sodium bisulfite solution and the mixture agitated vigorously for several minutes. The insoluble material was then filtered off, dried in vacuum and purified by crystallization from ethyl acetate. It melted at 136–137° and proved to be identical with the pyrimidine obtained by the action of ammonia on 2-ethylsulfonyl-5-chloro-5-methylpyrimidine.[5]

Anal. Calcd. for $C_7H_{11}O_2N_3S$: N, 20.88; S, 15.94. Found: N, 21.03; S, 16.06.

On exposure of this pyrimidine to the action of chlorine in dilute hydrochloric acid the chloroamino compound (above) was formed and melted at 125–126°.

$C_2H_5SO_2\overline{C{=}NC(CH_3){=}CHC(Cl){=}N}$, **2-Ethylsulfonyl-4-chloro-6-methylpyrimidine.**—This was prepared by suspending 10 g. of 2-ethylmercapto-4-chloro-6-methylpyrimidine[6] in 75 cc. of ice water and then saturating the cold solution with chlorine gas. This pyrimidine chloride separated as an oil. After extraction with ether and drying over calcium chloride the oil was purified by distillation. It boiled at 189–191° at 3.5 mm.; n^{25}_{D} 1.5422.

Anal. Calcd. for $C_7H_9O_2N_2Cl$: N, 12.70. Found: N, 12.60.

$NH_2C{=}N{-}\overline{C(CH_3){=}CHC(Cl){=}N}$, **Formation of 2-Amino-4-chloro-6-methylpyrimidine.**[7]—This is formed smoothly by interaction of 2-ethylsulfonyl-4-chloro-6-methylpyrimidine with cold saturated alcoholic ammonia solution. It is also formed by heating the chloropyrimidine with strong aqueous ammonia at 100° for one hour. The yield is 80% of the theoretical. After purification by crystallization from hot alcohol it melted at 182–183°.

Anal. Calcd. for $C_5H_6N_3Cl$: N, 29.27; Cl, 24.74. Found: N, 29.40; Cl, 24.65.

$C_2H_5SO_2\overline{C{=}NC(CH_3){=}CHC(NHCl){=}N}$, **2-Ethylsulfonyl-4-chloroamino-6-methylpyrimidine.**—Four grams of 2-ethylmercapto-4-amino-6-methylpyrimidine was dissolved in 5 cc. of dilute hydrochloric acid and the solution diluted with 35 cc. of ice water. The above pyrimidine was formed on saturating the cold aqueous solution with chlorine gas. The pyrimidine crystallizes from benzene and melts at 133–134°. Analysis of the compound after drying *in vacuo* at 100°: Calcd. for $C_7H_{10}O_2N_3SCl$: N, 17.83. Found: N, 17.86.

II. The Conversion of 2-Mercapto-4-oxypyrimidines into 2,4-Diketohexahydropyrimidines

$\overline{CONHCH(OCH_3)C(CH_3)ClCONH}$, **2,4-Diketohexahydro-5-methyl-5-chloro-6-methoxypyrimidine.**—Four grams of 2-ethylmercapto-4-oxy-5-methylpyrimidine[8] was dissolved in 50 cc. of methyl alcohol and the ice-cooled solution saturated with chlorine gas. The excess of alcohol was then removed below a temperature of 30° under diminished pressure. During this operation there was a distinct odor and lachrymator effect of ethyl sulfonyl chloride. The crystalline reaction product which separated (3 g.) was washed with cold water and petroleum ether, and then purified by crystallization from boiling water. The compound obtained was free from sulfur and crystallized from water in the form of needles melting at 220–221°.

Anal. Calcd. for $C_6H_9O_3N_2Cl$: N, 14.54; Cl, 18.42; methoxyl (OCH_3), 16.12. Found: N, 14.43; Cl, 18.60; methoxyl (OCH_3), 16.14.

This pyrimidine is very soluble in acetone, ethyl acetate, ethyl alcohol, ether and hot water. It is also soluble in dilute alkali solution from which it is precipitated by neutralization of the alkali with acids. On digesting the hexahydropyrimidine with hydriodic acid,[9] it is converted quantitatively into "thymine."

$\overline{CONHC(CH_3)(OCH_3)CClCONH}$, **2,4 - Diketotetrahydro-5,5-dichloro-6-methyl-6-methoxypyrimidine.**—Four grams of 2-ethylmercapto-4-oxy-6-methylpyrimidine[10] was chlorinated according to the experimental technique described in the preceding experiment. Five grams of the hexahydropyrimidine was obtained. This was purified by crystallization from methyl alcohol and melted at 274–275°, with effervescence. The compound failed to give a test for sulfur.

Anal. Calcd. for $C_6H_8O_3N_2Cl_2$: N, 12.33, methoxyl (OCH_3), 13.67. Found: N, 12.33; methoxyl (OCH_3), 13.60.

On digesting this pyrimidine with tin and hydrochloric acid,[11] it is converted quantitatively into 5-chloro-6-methyluracil, $CONHC(CH_3){=}CClCONH$. This crystallized from hot water in the form of needles.

Anal. Calcd. for $C_5H_5O_2N_2Cl$: N, 17.45. Found: N, 17.40.

$\overline{CONHCH(OCH_3)CCl_2CONH}$, **2,4-Diketotetrahydro-5,5-dichloro-6-methoxypyrimidine.**—This is formed quantitatively by chlorination in methyl alcohol solution of 2-ethyl or 2-methylmercapto-6-oxypyrimidine.[12] The pyrimidine melts at 225–226°[3] and is converted into 5-chlorouracil by digestion with tin and hydrochloric acid.

Summary

1. 2-Mercaptopyrimidines of types I and II, respectively, can be differentiated by their char-

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(5) Sprague and Johnson, THIS JOURNAL, **58**, 426 (1936).

(6) Johns, *Am. Chem. J.*, **40**, 350 (1908).

(7) Gabriel and Colman, *Ber.*, **32**, 2922 (1899).

(8) Wheeler and Merriam, *Am. Chem. J.*, **29**, 487 (1903); Wheeler and Johnson, *ibid.*, **31**, 595 (1904).

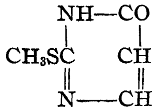
(9) Baudisch and Davidson, *J. Biol. Chem.*, **64**, 234 (1925).

(10) List, *Ann.*, **236**, 12 (1886); Wheeler and Merriam, *Am. Chem. J.*, **29**, 478 (1903).

(11) Johnson, *ibid.*, **40**, 27 (1908).

(12) Wheeler and Johnson, *Am. Chem. J.*, **29**, 483 (1903).

acteristic behavior toward chlorine gas in water and alcohol solutions.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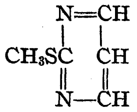
II

2. Pyrimidines of type I are desulfurized completely with formation of 2,4-diketohexahydropyrimidine compounds.

3. Pyrimidines of type II are oxidized to the corresponding 2-alkyl sulfonyl pyrimidine compounds. The double bond in positions 5 and 6 of the pyrimidine cycle is not altered.

NEW HAVEN, CONN.

RECEIVED APRIL 4, 1938

[CONTRIBUTION FROM THE FLEISCHMANN LABORATORIES, STANDARD BRANDS INCORPORATED]

The Volatile Constituents of Roasted Coffee

BY WILLIAM R. JOHNSTON AND CHARLES N. FREY

Our interest in the staling of roasted coffee led us to attempt to isolate and identify some of the aroma and flavor constituents. It is evident that any effort to prevent or retard the staling of roasted coffee can be undertaken with better prospects of success if the identity and nature of the substances responsible for its flavor and aroma can be more completely ascertained.

When we started our investigation the best information on the subject was contained in the patents issued to Staudinger and Reichstein.[1] They outlined a method of isolating coffee volatiles by vacuum distillation and listed a number of compounds supposedly present in roasted coffee. Some of the compounds reported were: hydrogen sulfide, methyl mercaptan, furfuryl mercaptan, dimethyl sulfide, acetaldehyde, furfuraldehyde, diacetyl, acetyl-propionyl, furfuryl alcohol, acetic acid, guaiacol, vinyl guaiacol, pyridine, pyrazine and N-methylpyrrole. However, in British Patent 260,960, the statement is made that the compounds reported were not actually found in coffee but were split products obtained by analysis—the real products being unstable and difficult to isolate. This statement is somewhat confusing since some of the substances mentioned have been reported previously by earlier investigators as being present in coffee. For example, pyridine, furfuraldehyde, furfuryl alcohol and acetic acid actually have been isolated from roasted coffee. The older literature on this subject has been surveyed critically by Prescott and his co-workers.[2] With this contradiction in mind, we decided to use the work of Staudinger and Reichstein as a guide and attempt to isolate the volatile coffee components as nearly unchanged as possible. Their procedure includes distillation at 2–5 mm. pressure at 100–110° and the use of steam or liquid water to assist in removal of volatile substances from roasted coffee. We believed that this treatment was not ideal because previous work on staling had convinced us that very small amounts of oxygen were sufficient to cause appreciable deterioration of the coffee and in addition that moisture had a distinct accelerating effect on this deterioration. Consequently, we decided to utilize a high vacuum apparatus and to avoid the use of water during the distillation. By distilling at low pressures and working in the practical absence of oxygen we have been able to isolate as actual constituents of coffee several of the substances reported by Staudinger and Reichstein. We also have detected methylacetylcarbinol as a new constituent of roasted coffee.

Shortly after we had completed our investigation, two excellent papers by Prescott and his associates[2,3] supplied valuable new information on the constituents of roasted coffee. Prescott and his collaborators relied on solvent extraction of coffee brew and dry roasted coffee to isolate several new substances which were identified in the usual manner. The following substances were reported: furfuryl alcohol, furfuraldehyde, acetic acid, formic acid, diacetyl, diethyl ketone, kahweol, vanillone, *p*-vinylguaiacol, guaiacol, *n*-heptacosane, *p*-vinylcatechol, sylvestrene, eugenol, and a hydrocarbon melting at 116–117°. Of these substances, formic acid, diethyl ketone, vanillone, *n*-heptacosane, *p*-vinylcatechol, sylves-

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(1) Staudinger and Reichstein, British Patents 246,454 and 260,960.

(2) Prescott, Emerson and Peakes, *Food Research*, **2**, 1–20 (1937).

(3) Prescott, Emerson, Woodward and Heggie, *ibid.*, **2**, 165–173 (1937).

trene, eugenol, and the hydrocarbon (m. p. 116–117°) have not been mentioned specifically by previous workers.

Judging from this work and from our own it is likely that the substances reported by Staudinger and Reichstein were not split products but actual coffee constituents.

Although not directly concerned with coffee, the paper by Reichstein and Beitter[4] on the aroma constituents of roasted chicory is well worth the study of anyone interested in the chemistry of coffee. The methods of isolation and identification described by Reichstein and Beitter are very probably quite similar to those used previously by Staudinger and Reichstein.

Apparatus and Procedure

Dry Distillation of Roasted Coffee (Santos).—The high vacuum distillation equipment included a heavy copper flask of about 15-liters capacity which was suitable for holding a charge of 15 kg. of finely ground coffee; a Pyrex glass manifold carrying 3 receivers of 200-cc. and 3 of 100-cc. capacity, a trap for mercury vapor, a mercury vapor pump, and a Cenco Hy-vac pump as a backing pump.

After charging the copper distillation flask with coffee it was fitted with a rubber stopper carrying a glass tube which was sealed to the receiver manifold. The joints between the rubber stopper, copper and glass were sealed vacuum tight with hard deKhotinsky cement.

The larger receivers were cooled with solid carbon dioxide and the smaller ones with liquid air. Each was fitted with a ground joint which permitted the removal of the lower portion holding the condensate.

In carrying out the distillation, after all leaks had been eliminated, the pumps were operated for several hours to remove all of the oxygen in the system. During this time the distillation flask was at room temperature but even at this temperature appreciable amounts of carbon dioxide, water vapor, and volatile aroma and flavor constituents condensed in the receivers. Only traces of substances condensed in the final liquid air trap and only small amounts of gas, presumably carbon monoxide, passed this receiver, since the pressure at that point was usually about 0.005 mm. The pressure in the copper flask could not be measured at any time but since the bore of the manifold and receiver tubes was of the order of 1 cm. at all points, it is probable that no considerable drop in pressure existed between the distillation flask and the last receiver.

When oxygen had been eliminated completely from the system, the distillation flask was heated gradually to 100° on the water-bath and maintained at that temperature throughout the distillation. Condensate accumulated rapidly after the coffee was heated, most of the water condensing in the receivers cooled with solid carbon dioxide, while carbon dioxide, traces of water, and a small amount of a pale yellow liquid having a strong coffee aroma condensed in the liquid air receivers.

When it became necessary to remove a receiver, oxidation of the condensate was avoided by filling the manifold with pure nitrogen. After removal from the apparatus the receiver was sealed and stored in a packing of solid carbon dioxide until analysis of the condensate was undertaken. The distillation was continued until practically no more liquid condensed in the solid carbon dioxide receivers. This usually required about forty hours. After one charge of coffee had been distilled, the copper flask was removed, a fresh charge introduced, and the distillation continued, following the procedure just outlined. In a typical experiment in which 100 lb. (45 kg.) of coffee was distilled, about 850 cc. of condensate in the solid carbon dioxide receivers and approximately 50 cc. of condensate in the liquid air receivers were obtained. The amount of liquid air condensate (50 cc.) is exclusive of the condensed carbon dioxide which was not retained.

Examination of Condensates.—The condensate from the receivers cooled with liquid air was allowed to volatilize at atmospheric pressure, the effluent gas, chiefly carbon dioxide, being passed through receivers cooled with solid carbon dioxide. The gas finally escaping smelled strongly of hydrogen sulfide and of mercaptans or organic sulfides. Testing with lead acetate identified the hydrogen sulfide beyond question. The residual condensate (50 cc.) was a dilute aqueous solution supporting a thin layer of a pale yellow liquid. This mixture was distilled at atmospheric pressure on the water-bath at 75° in a slow stream of nitrogen until about 2 cc. of a pale yellow liquid condensed in a receiver cooled with solid carbon dioxide. The residual aqueous solution was combined with the primary condensate obtained in the three receivers cooled with solid carbon dioxide.

The pale yellow liquid was redistilled on a water-bath in an atmosphere of pure nitrogen, using receivers cooled with solid carbon dioxide. Three fractions were taken distilling at 25–35, 35–50 and 50–85°, only a trace of brownish residue remaining in the distilling flask. The first fraction (0.4 cc.) was mostly soluble in water and had an odor of acetaldehyde. This substance was identified by formation of its 2,4-dinitrophenylhydrazone, m. p. 162–164°. A mixed melting point with an authentic sample confirmed the identification. Judging by the amounts of hydrazone formed, acetaldehyde was the chief ingredient of this fraction. A trace of furan seemed to be present since a pine splinter gave a green reaction and a brown precipitate was obtained on treatment with concentrated hydrochloric acid.

The second fraction (0.8 cc.) also contained acetaldehyde and, in addition, a mixture of perhaps several aldehydes and ketones, for a mixture of 2,4-dinitrophenylhydrazones was obtained. An attempted separation was not successful because of the small amount of material available.

The third fraction (0.4 cc.) was found to contain a small amount of diacetyl which was isolated as a *bis*-semicarbazone, m. p. 281–282°. A mixed melting point of 281–282° confirmed the identification. The third fraction had a good coffee-like aroma and also a mercaptan-like odor. Sulfur was detected but mercaptans or sulfides could not be isolated or identified. A ketone was isolated in the form of a red 2,4-dinitrophenylhydrazone, m. p. 258–259°, but its identification was not completed, again because of the minute amounts of material available.

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[4] Reichstein and Beitter, *Ber.*, **63B**, 816–826 (1930).

The primary condensate from the receivers cooled with solid carbon dioxide contained droplets of oil. Immediately on exposure to air the oil droplets turned reddish-brown and the solution gradually darkened and deposited a brownish resin or tar. This also took place when the condensate was heated to 100–110° in pure nitrogen. The oxidized oil droplets had an odor very similar to that of very stale coffee.

From a portion of the condensate diacetyl was precipitated as its characteristic osazone, *m. p.* 243–245°, the identification being confirmed by a mixed melting point with the osazone obtained from an authentic sample of diacetyl.

The bulk of the condensate was separated from the oil droplets and acids and then roughly fractionated. It was first distilled at about 50–60 mm. pressure in a slow stream of pure nitrogen to remove the water. After practically all the water had distilled over, the distillation was stopped and the oily residue sealed in nitrogen to be saved for further work. The aqueous distillate was saturated with potassium carbonate and extracted with pure ethyl ether. The ether extract was concentrated to yield a viscous brown oil (3–4 cc.) which was distilled at 20–30 mm. in a stream of nitrogen. Two fractions were taken: A (1 cc.) distilling at 20–35°; and B (1 cc.) 35–65°; and a residue of about 2 cc. was set aside. Fraction A was found to be mainly a mixture of aldehydes and ketones and was not investigated further. Fraction B had an odor of pyridine and yielded a picrate melting at 167–168°. A mixed melting point with an authentic sample of pyridine picrate confirmed the identification.

Fraction B was fractionated at atmospheric pressure in pure nitrogen to yield a main fraction of 0.5 cc. boiling at 145–165°. This distillate gave a phenylhydrazone melting at 97° which proved to be the phenylhydrazone of furfuraldehyde. A mixed melting point clinched the identification. The aniline acetate test was also positive.

A few drops of a higher boiling liquid were also obtained from fraction B which seemed to be furfuryl alcohol but the identification was not confirmed by preparation of a derivative.

The distillate from fraction B coming over at 145–165° also yielded a phenylhydrazone melting at 237–240° which on purification melted at 244–245°. A mixed melting point with diacetyl osazone was 244–245°, so it was evident that either diacetyl or methylacetylcarbinol must have been present in fraction B. But diacetyl is excluded by its boiling point so the compound was identified as methylacetylcarbinol which boils at 148° and yields diacetyl on oxidation. Its isolation may be ascribed to the care with which oxygen was excluded during manipulations. Its oxidation to diacetyl occurred during the preparation of the osazone in the presence of air.

Tests on the higher boiling fractions obtained from the aqueous condensate and on the small amount of water insoluble oils, indicated that phenols, nitrogenous compounds other than pyridine and high boiling aldehydes and ketones were present. The phenolic fractions had a coffee-like odor and were very sensitive to heat and oxygen.

Discussion

In the main, our work has been an extension, a general confirmation, and an elucidation of the patent disclosures of Staudinger and Reichstein. We have found high vacuum distillation to be very suitable for isolating the volatile coffee constituents and have isolated several coffee constituents which have been reported by Staudinger and Reichstein to be split products and not actual constituents. As mentioned previously, the indications are that most if not all of the substances listed by Staudinger and Reichstein are actually present in coffee.

The identification of diacetyl, furfuraldehyde, pyridine, and furfuryl alcohol further confirms previously published reports. The detection of acetaldehyde, furan and hydrogen sulfide confirms the work of Staudinger and Reichstein, but the isolation of methylacetylcarbinol is new. Separation of fractions containing phenols, nitrogenous compounds other than pyridine, and mixtures of aldehydes and ketones again confirms several previous investigations, but the detection of sulfur in a volatile fraction is the first confirmation in this respect of Staudinger and Reichstein's work. We are inclined to agree with their belief that the compounds containing sulfur are of major importance with respect to the distinctive character of coffee aroma. The fraction containing sulfur had a very intense odor which seemed to embody the unusual aroma and taste sensations imparted by roasted coffee.

The work of Prescott and his associates, mainly on the less volatile constituents of coffee, also confirms certain aspects of the researches of Staudinger and Reichstein and is of great importance in understanding the changes which take place on staling. We are in complete agreement with Prescott with respect to the probable changes occurring during the staling process Staling probably involves volatilization, oxidation, hydrolysis, and polymerization of the various flavor and aroma constituents, and has little if anything to do with the fat of coffee.

At the present time we have an imposing list of coffee aroma and flavor constituents which should be of great assistance in studying the staling of coffee and various other problems of the coffee industry.

Summary

The utilization of high vacuum distillation to isolate the volatile aroma and flavor components of roasted coffee is described. The identification

of diacetyl, methylacetylcarbinol, furan, furfuraldehyde, furfuryl alcohol, acetaldehyde, pyridine, and hydrogen sulfide is reported. The contributions of Staudinger and Reichstein and of Prescott and his associates are discussed and the relation of the volatile constituents to the staling of coffee is considered briefly. Coffee staling is probably concerned with changes in the volatile aroma and flavor substances and does not involve fat rancidity.

810 GRAND CONCOURSE
NEW YORK, N. Y.

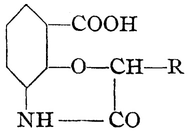
RECEIVED APRIL 12, 1938

[CONTRIBUTION FROM THE MELLON INSTITUTE OF INDUSTRIAL RESEARCH AND E. R. SQUIBB AND SONS]

The Preparation of 2-Methyl-8-carboxy-3-keto-3,4-dihydro-1,4-benzoxazine

BY HAROLD W. COLES[1] AND WALTER G. CHRISTIANSEN[2]

In the search for new analgesics without the chemical structures said to cause agranulocytosis[3] we have been interested in the possibilities of the benzoxazine ring system, and particularly in the 8-carboxy-3-keto-3,4-dihydro-1,4-benzoxazines (I) since it is seen that these compounds



I

may be considered as derivatives of salicylic acid, and they also contain the skeleton of acetanilide. The carboxyl group not only acts in a detoxifying capacity, but also permits the preparation of a soluble sodium salt.

A number of carboxylated benzoxazines have been reported in the literature[4] but, so far as we know, were not tested pharmacologically. Therefore, 2-methyl-8-carboxy-3-keto-3,4-dihydro-1,4-benzoxazine (I, R = CH_3) was synthesized and, being physiologically inactive, no further members of this series were prepared.

The authors wish to record their appreciation for the interest and advice of Dr. George D. Beal, Assistant Director of Mellon Institute, during the progress of this work.

Experimental Part

3-(α-Bromopropionylamino)-salicylic Acid.—The procedure, here described, is adapted from directions given by Sanna[5] for the non-carboxylated aminophenols. One mole equivalent (4.25 g.) of 3-aminosalicylic acid and slightly more than one mole equivalent (6.25 g.) of α-bromopropionyl bromide was added to 50 g. of dry benzene. The aminosalicylic acid remained suspended in the benzene since it is quite insoluble. The Erlenmeyer flask contents were refluxed on a water-bath for twelve to fourteen hours with the evolution of acid fumes. The flask contents were chilled and the grayish crystalline material was removed to a Büchner funnel and washed repeatedly with cold benzene. The crystals, after drying in the air, weighed 8 g. representing a practically theoretical yield. It was recrystallized from a minimum of boiling 50% alcohol, washing repeatedly on the filter with distilled water. It was dried in an 80° oven. The white solid has an irritating odor, and in a melting point tube it softened quite sharply at 178°, but the column did not break until 188° (U. S. P. corr.).

Anal. (Kjeldahl). Calcd. for $C_{10}H_{10}O_4BrN$: N, 4.86. Found: N, 4.64.

The crystals are easily soluble in acetone, alcohol and alkalies, but sparingly soluble in water and benzene.

2-Methyl-8-carboxy-3-keto-3,4-dihydro-1,4-benzoxazine (I, R = CH_3).—3-(α-Bromopropionylamino)-salicylic acid (3.3 g.) was dissolved in 25 cc. of 10% sodium hydroxide solution and warmed on the water-bath at 60° for one hour. The color darkened considerably. The solution was cooled, filtered and dilute (1:1) hydrochloric acid added until the dark solution was acid to congo red. A dark precipitate came out on standing, and was washed repeatedly with distilled water. Recrystallized from a minimum of boiling absolute alcohol, the product was secured as colorless crystals (yield 60%). The substance is sparingly soluble in the usual solvents. It is readily soluble in alkalies; m. p. 285° (U. S. P. corr.).

Anal. Calcd. for $C_{10}H_9O_4N$: N, 6.61. Found: N, 6.76.

Pharmacological Tests.[6]—6-Carboxy-3-keto-3,4-dihydro-1,4-benzoxazine[4a] and 2-methyl-8-carboxy-3-keto-3,4-dihydro-1,4-benzoxazine, administered intravenously to mice, rats and rabbits, exhibited no antipyretic or hypnotic action in doses up to 2000 mg. per kg. The first compound shows some toxic effects above 500 mg. per kg., while the second is non-toxic at least up to a dosage of 1500 mg. per kg. The compounds were not tested as to possible local anesthetic properties. The effect of the introduction of the carboxyl group into the benzene ring is very marked

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(1) Senior Industrial Fellow, E. R. Squibb and Sons Industrial Fellowship, Mellon Institute.

(2) E. R. Squibb and Sons, Brooklyn, N. Y.

(3) Council on Pharmacy and Chemistry, A. M. A., *J. Am. Med. Assoc.*, **102**, 2183 (1934).

(4) (a) Christiansen, THIS JOURNAL, **47**, 1158 (1925); **48**, 460 (1926); (b) Einhorn and Oppenheimer, *Ann.*, **311**, 154 (1900).

(5) Sanna and Vacca, *Gazz. chim. ital.*, **62**, 555 (1932); Puxeddu and Sanna, *ibid.*, **61**, 158 (1931).

(6) The authors are greatly indebted to the Biological Laboratories, E. R. Squibb & Sons, New Brunswick, N. J., for these tests.

in this series, as benzoxazines without the carboxyl group, or with other groups such as the methyl group, have been reported as being of considerable medicinal value.[7]

Summary

3-(α-Bromopropionylamino)-salicylic acid was synthesized and, from this by treatment with alkali, 2-methyl-8-carboxy-3-keto-3,4-dihydro-1,4-benzoxazine. Both of these substances are new compounds.

Neither 2-methyl-8-carboxy-3-keto-3,4-dihydro-1,4-benzoxazine nor 6-carboxy-3-keto-3,4-dihydro-1,4-benzoxazine exerts either antipyretic or analgesic action in various test animals.

PITTSBURGH, PENNA.
BROOKLYN, N. Y.

RECEIVED FEBRUARY 28, 1938

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[7] F. Hoffman, La Roche & Co. A.-G., British patent 370,375 (Apr. 17, 1931); German patent, 557,111 (Apr. 18, 1931); Preiswerk and Mayer, U. S. patent 1,951,807 (Mar. 20, 1934).

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF MARYLAND]

A New Method for the Purification of the Alcoholate of the Trimer of Hydroxypyruvic Aldehyde

BY WILLIAM E. EVANS, JR., C. JELLEFF CARR AND JOHN C. KRANTZ, JR.

Hydroxypyruvic aldehyde is of interest owing to its relationship to the intermediate metabolites of glucose. This compound has been prepared by the oxidation of dihydroxyacetone[1-4] and by the photochemical decomposition of glyoxal.[5] Evans and Waring[1] treated dihydroxyacetone with an excess of cupric acetate and removed the excess of copper by precipitation as sulfide. Friedemann[2] employed the same method but did not separate the compound from solution. This process was objectionable on account of the formation of sulfur derivatives of hydroxymethyl glyoxal which are toxic. Küchlin and Böeseken[3] decomposed the sulfur compounds with an excess of silver acetate at 30° and subsequently removed the excess of silver as chloride. Hynd[4] found that the use of silver acetate caused the formation of a highly polymerized product. He avoided the use of hydrogen sulfide by precipitating the excess copper with barium hydroxide. The barium was then removed as sulfate. Norrish and Griffiths[5] prepared small amounts of glycerosone by the photochemical decomposition of glyoxal and isolated it as the trimer combined with one molecule of alcohol.

Experimental

Preparation of Hydroxypyruvic Aldehyde.—One mol of dihydroxyacetone was dissolved in 10 mols of water and treated at room temperature with 2.25 mols of finely divided crystallized cupric acetate. The mixture was shaken frequently in order to keep the solution saturated with copper acetate. The reaction was allowed to proceed until the calculated amount of cuprous oxide was precipitated. The usual period of time necessary was five to seven days. At this time a grayish-colored precipitate of cupric oxalate began to appear. The excess of Cu^{++} was then precipitated carefully by the addition of a calculated amount of a 10% solution of oxalic acid. After filtering the solution was reduced to a small volume by distilling at 17 mm. at 35°. Successive portions of alcohol were added and the product was reduced to dryness at 17 mm. The residue was then dissolved repeatedly in small amounts of absolute alcohol and precipitated by the addition of ether. The ether–alcohol solutions were worked up later, using the same procedure, to recover some of the product. Substances which were insoluble in water and in absolute alcohol were removed and the product was dried *in vacuo* at 70°. The yield of the product was 87%. After purification for biological use the yield was 64%. The product gave a negative test for Cu^{++} or oxalate. It was obtained as a pale yellow amorphous solid which melted between 155 and 160°. A 1% aqueous solution exhibited a *p*H of 3.12 at 25°. It reduced Fehling's solution and mercuric chloride solution rapidly in the cold. No immediate reaction was obtained when Schiff's reagent was added to the freshly prepared solution but the characteristic color appeared within several minutes.

Anal. Calcd. for $(C_3H_4O_3)_3 \cdot C_2H_5OH$: C, 42.47; H, 5.85; mol. wt., 310. Found: C, 42.57; H, 5.42; mol. wt., 306.

This is in agreement with the results obtained by Norrish and Griffiths.[5]

On account of the ease of depolymerization, molecular weight determinations had to be made with the greatest possible rapidity.

The aqueous solution was depolymerized by long standing or by heating for ten minutes in a water-bath at 60–70°.

Mol. wt. Calcd. for $3C_3H_4O_3 + 1C_2H_5OH$: 77.6. Calcd. for $2C_3H_4O_3 + C_3H_4O_3 \cdot C_2H_5OH$: 103. Found 99.3. These mol. wts. confirm those of Norrish and Griffiths.[5]

Quinoxaline derivative: m. p. 250–251°; reported[5] m. p. 165°.

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[1] W. L. Evans and C. E. Waring, THIS JOURNAL, **48**, 2678 (1926).

[2] T. E. Friedemann, *J. Biol. Chem.*, **73**, 331 (1927).

[3] A. T. Küchlin and J. Böeseken, *Rec. trav. chim.*, **47**, 1011 (1928).

[4] A. Hynd, *Biochem. J.*, **25**, 11 (1931).

[5] R. G. W. Norrish and J. G. A. Griffiths, *J. Chem. Soc.*, 2829 (1928).

Phenylglycerosazone: m. p. 132°; reported[1,5] m. p. 132°. Hydroxymethylglyoxime: m. p. 134–135°. Reported[5] m. p. 168°.

Anal. Calcd. for $C_3H_6O_3N_2$: N, 23.7. Found: N, 23.4.

An aqueous solution of the dioxime gave a red color with cobalt acetate in the presence of sodium acetate. On careful addition of dilute sodium hydroxide to this solution a green base was precipitated.

Summary

1. The alcoholate of the trimer of hydroxypyruvic aldehyde was prepared free from sulfur derivatives.

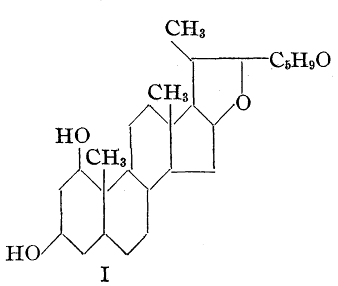
2. The quinoxaline derivative, phenylosazone, and dioxime were prepared.

BALTIMORE, MD. RECEIVED FEBRUARY 28, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY]

Saponins and Sapogenins. VI. Surface Films of Chlorogenin and Derivatives

BY C. R. NOLLER



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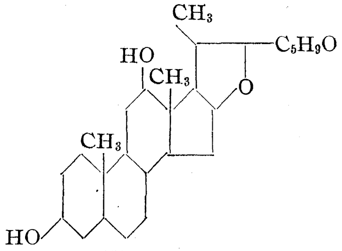

II

In the last paper of this series[1] the tentative formulas, I and II, based on chemical evidence, were proposed for chlorogenin. Formula II was favored because the ketodibasic acid obtained on oxidation did not appear to be either an α- or a β-keto acid as would be required by formula I. The second hydroxyl group was assigned to position 12, since the diketone forms a dioxime which would not be expected if the hydroxyl group is at position 11.

Recent work on the surface films of structurally related compounds[2] indicates that those molecules having one or two hydroxyl groups in the end-ring give incompressible films in which the molecules stand on end and occupy an area that is predicted by models of the compounds. Cholestanol-6 and $\Delta^{4,5}$-cholestenol-7 (ψ-cholesterol) having hydroxyl groups in the second ring give highly compressible films indicating that the molecules are tilted or lying flat at low pressures.[3] Hence it was expected that if formula II is a possibility for chlorogenin, the molecules in surface films would lie flat at low pressures and give a highly compressible film. The data plotted in curve I show that this is actually the case. The molecules occupy at low pressures an even larger area than ψ-cholesterol, the film being gaseous at very low pressures. At higher pressures the curve appears as if it will coincide with that for gitogenin

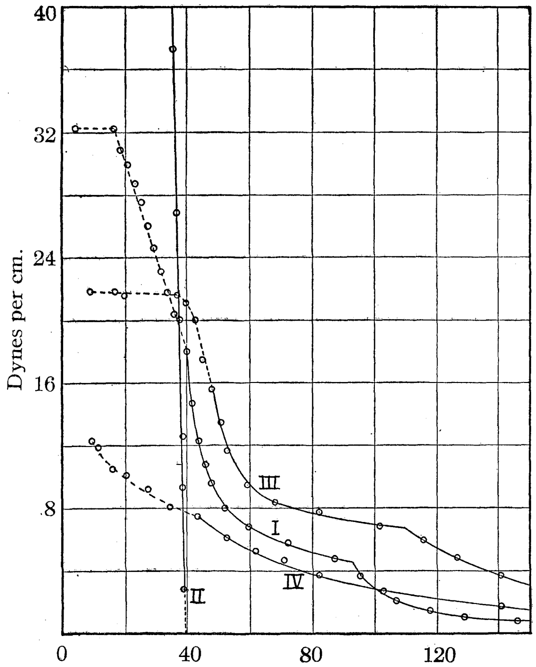

Fig. 1.—Pressure-area curves for surface films of: I, chlorogenin; II, gitogenin; III, chlorogenin diacetate; IV, diketone from chlorogenin.

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(1) Noller, THIS JOURNAL, **59**, 1092 (1937).

(2) Askew, Farmer and Kon, *J. Chem. Soc.*, 1399 (1936).

(3) Adam, Askew and Danielli, *Biochem. J.*, **29**, 1786 (1935).

but contraction begins at a pressure of about 15 dynes per centimeter and at higher pressures the film collapses. However, it remains mobile as shown by dusting with talc, even at 32 dynes per centimeter.

The data for gitogenin (curve II) were obtained using a sample kindly supplied to us several years ago by Dr. W. A. Jacobs of the Rockefeller Institute for Medical Research. The value of 39.5 Å. for the area per molecule at zero pressure is identical with that obtained previously[2] and served to check our technique and procedure. Evidently under pressure the molecules of chlorogenin can be made to stand on end and occupy an area very close to that occupied by gitogenin, thus furnishing additional evidence for the close relationship in the structure of these two compounds.

Chlorogenin diacetate gives a curve, III, which is very similar to that for chlorogenin except that the lower attraction of the acetate groups for water is manifest in the greater tendency to remain in the gaseous state and the greater instability of the close packed film. The diketone obtained by the oxidation of chlorogenin (curve IV) shows no tendency to form a close packed film but collapses at pressures of about 6 dynes per centimeter.

Experimental

The surface pressures were measured on a Cenco Hydrophil Balance by the general procedure developed by Adam and his co-workers.[3] The solvent used was a mixture of eight parts by volume of purified cyclohexane and two parts of purified dioxane. From 0.01 to 0.02 g. of compound was weighed accurately into a tared glass-stoppered 25-cc. Erlenmeyer flask and dissolved in 10–20 cc. of solvent with warming if necessary. After cooling to room temperature the flask was stoppered and the weight of solvent determined.

For placing the solution on the surface a 1-cc. ground-glass syringe was used, whose tip was drawn out and ground so that small drops would form and leave the pipet without wetting the outer surface of the tip. The tip was fitted with a small cap by means of a ground joint to prevent evaporation during the weighing of the syringe. The space between plunger and barrel of the syringe was sealed by a narrow band of glycerol.

All films were spread on 0.02 *N* hydrochloric acid. The films were not examined for collapse with a dark ground illuminator[3] but the phenomenon of contraction was observed shortly before collapse was obvious.

Summary

Measurements on surface films of chlorogenin, chlorogenin diacetate and the diketo derivative are in agreement with the view that the two hydroxyl groups are in different rings in the molecule. They also confirm the close relationship in structure previously assumed to exist between chlorogenin and gitogenin.

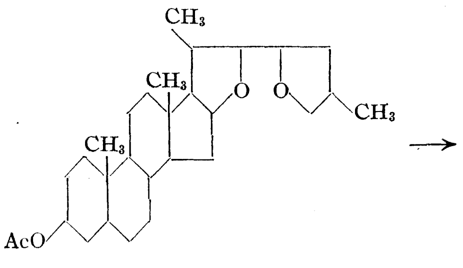
Stanford University, Calif. Received May 4, 1938

[Contribution from the Department of Chemistry of Stanford University]

Saponins and Sapogenins. VII. The Structure of the Side Chain of Chlorogenin

By F. M. McMillan and C. R. Noller

In previous chemical investigations on the structure of chlorogenin,[1] it has been assumed that the two unreactive oxygen atoms of chlorogenin are in a side chain whose structure is similar to that of the isomeric compound gitogenin and of other steroid sapogenins. This side chain is generally believed to consist of two tetrahydrofuran rings, the chief chemical evidence being the oxidation of tigogenin acetate[2] to an acid and a lactone as formulated in the equation



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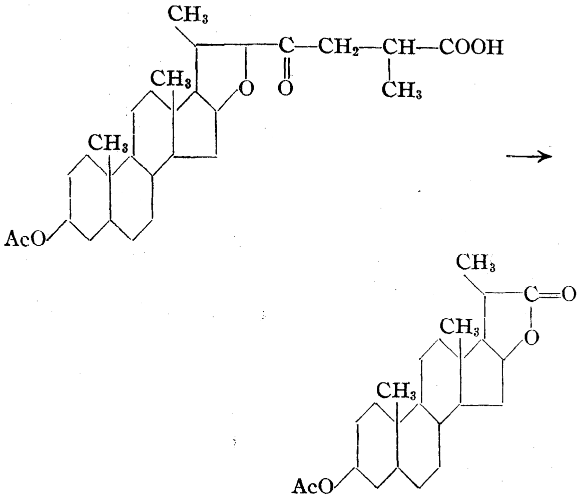
[1] Noller, This Journal, **59**, 1092 (1937); **60**, 1629 (1938).

[2] Tschesche and Hagedorn, *Ber.*, **68**, 1412, 2247 (1935).



Since the present work was completed, Fieser and Jacobsen[3] have reported the isolation of an acid from sarsasapogenin which they have named sarsasapogenoic acid and which is analogous to the acid obtained by Tschesche and Hagedorn from tigogenin. The acetate of the C_{22}-lactone from sarsasapogenin was first reported by Farmer and Kon.[4]

Oxidation of chlorogenin diacetate gives the diacetate of a C_{27}-acid which, in conformity with the nomenclature of Fieser and Jacobsen, we shall call chlorogenoic acid. Conditions have been worked out for obtaining directly the diacetate of the acid in good yields and little difficulty was encountered in its purification. In the case of sarsasapogenin Fieser and Jacobsen found it necessary to saponify the crude acetate and purify the dihydroxy acid. The tigogenoic acid of Tschesche and Hagedorn was likewise isolated after saponification. In both cases removal of the acetyl groups apparently takes place on extracting the acid with aqueous alkali. It is of interest to note the narrow range of temperature in which it is possible to get good yields of chlorogenoic acid diacetate. At 25° chlorogenin diacetate is not attacked whereas at 40° only difficultly crystallizable gums are formed.

Chlorogenoic acid diacetate crystallizes with a molecule of water of crystallization which at first led us to believe that a hydroxy acid was formed in the oxidation. This has been shown definitely to be not the case. Like tigogenoic acid and sarsasapogenoic acid, chlorogenoic acid diacetate does not form a semicarbazone under the usual conditions. We have not tried as yet the more drastic treatment with hydroxylamine by which Fieser and Jacobsen converted sarsasapogenoic acid into the compound $C_{27}H_{44}O_5N_2$.

Under the optimum conditions for preparing chlorogenoic acid diacetate, no neutral oxidation products could be detected. Under more drastic conditions very poor yields were obtained of a compound which has the characteristic properties of a lactone. If this is analogous to the lactones from tigogenin and sarsasapogenin, it should have the empirical formula $C_{26}H_{38}O_6$. Our analyses indicate the formula $C_{27}H_{44}O_7$. Similarly the saponified lactone should have the formula $C_{22}H_{34}O_4$, whereas our analyses indicate $C_{23}H_{40}O_5$. The best explanation seems to be that both of these compounds contain methyl alcohol of crystallization which would lead to the formulas $C_{27}H_{42}O_7$ and $C_{23}H_{38}O_5$, respectively.

Numerous attempts were made to obtain oxidation products intermediate between chlorogenoic acid diacetate and the lactone diacetate, most of which were unsuccessful. In several of the oxidations starting with chlorogenoic acid diacetate, minute amounts of an acid were obtained having the empirical formula $C_{27}H_{42}O_6$. This is the same as that for chlorogenoic acid but the compound is definitely different and we have no evidence concerning its structure.

By heating sarsasapogenin or gitogenin with a mixture of glacial acetic acid and concentrated hydrochloric acid, Jacobs and Simpson[5] obtained a liquid ketone which gave a semicarbazone melting at 119.5–120°. Chlorogenin behaves similarly except that the semicarbazone was extremely difficult to purify and the melting point could not be raised above 114–118°. The amount of this material was vanishingly small in spite of the fact that as much as 10 g. of chlorogenin was used in the decomposition.

It is planned to continue these investigations as soon as we can replenish our stock of raw materials.

Experimental

Chlorogenin Diacetate.—To 7 g. of chlorogenin, m. p. 272–276°, were added 38 cc. of 99% acetic anhydride, 4 cc. of glacial acetic acid and 6.5 g. of fused sodium acetate. The mixture was refluxed over a free flame until all of the sodium acetate dissolved and then heated on a steam-bath for two hours. The solution was poured into 400 cc. of water with rapid stirring. The product separated as an oil which soon crystallized. It was filtered, washed with water, dried and crystallized from 40 cc. of methyl alcohol

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[3] Fieser and Jacobsen, THIS JOURNAL, **60**, 28 (1938).

[4] Farmer and Kon, *J. Chem. Soc.*, 414 (1937).

[5] Jacobs and Simpson, *J. Biol. Chem.*, **105**, 501 (1934).

giving 6.1 g., m. p. 152.5–155°. On recrystallization it melted at 154–155° and a third crystallization did not change the melting point.

Anal.[6] Calcd. for $C_{31}H_{48}O_6$: C, 72.05; H, 9.37; sap. equiv., 258.3. Found: C, 72.14; H, 9.53; sap. equiv., 257.9, 259.3.

Chlorogenoic Acid Diacetate.—A solution of 4 g. of chlorogenin diacetate in 175 cc. of glacial acetic acid was kept at 32–33° in a water-bath while a solution of 5 g. of chromium trioxide in 75 cc. of 90% aqueous acetic acid was added slowly through a motor-driven hollow stirrer in order to ensure rapid mixing. The addition of the reagent required twenty-five minutes and stirring was continued for ten minutes after all the reagent had been added. The solution was poured into water, giving a light-colored gummy precipitate. After standing for several hours the precipitate hardened and was filtered, washed with water and dried. The product, weighing 3.5 g., was dissolved in ether and extracted with three portions of 5% aqueous sodium carbonate and washed with water. The aqueous extracts were counter extracted with ether which was added to the previous ether solution.

Evaporation of the ether solution gave about 0.3 g. of a light-colored glass which after three crystallizations from methyl alcohol gave crystals which were shown by melting point and mixed melting point to be unchanged chlorogenin diacetate.

Acidification of the combined sodium carbonate extracts gave a cream-colored precipitate which was filtered, washed and dried *in vacuo* over potassium hydroxide. It weighed 2.4 g. and melted at 102–106°. It was extremely soluble in all the common organic solvents with the exception of the paraffin hydrocarbons, in which it was only slightly soluble. It crystallized from 70% aqueous acetic acid, 70% aqueous acetone, and from ligroin (100–120°) containing a small amount of absolute ethyl alcohol. After the acid had been purified fairly well from 70% acetone, it could be crystallized readily from 80% aqueous methyl alcohol. It then melted at 114–116° to a viscous glass which gradually gave off bubbles and crystallized on the walls of the melting point tube, after which it melted again at 211–213.5°. This behavior was observed from all aqueous solvents. If, however, the compound was boiled in ligroin (100–120°) and then just sufficient absolute alcohol added to take it into solution, the crystals obtained on cooling melted at 210–211° without first melting at the lower temperature. The same result was obtained by heating at 140° at 20 mm. for five hours. As the analyses show, the acid melting at 114–116° is a monohydrate which goes over above its melting point to the anhydrous acid.

Anal. of hydrate. Calcd. for $C_{31}H_{46}O_8 \cdot H_2O$: C, 65.93; H, 8.57; acetyl, 15.25; OH, 6.00, neut. equiv., 564.7. Found: C, 65.43; H, 8.32; acetyl, 15.30, 14.72; OH (Zerewitinow), 7.03; neut. equiv., 566.3, 563.5, 563.5, 566.9.

Anal. (Anhydrous acid). Calcd. for $C_{31}H_{46}O_8$: C, 68.10; H, 8.49; OH, 3.10; neut. equiv., 546.7. Found: C, 67.87; H, 8.55; OH (Zerewitinow), 3.35; neut. equiv., 548.2.

In order to obtain satisfactory yields of chlorogenoic acid diacetate, the above conditions for the oxidation must be followed closely. If the reaction was carried out at 25° only a trace of acidic material was formed and a large amount of the diacetate was recovered unchanged. When carried out at 40° over a period of one and one-half hours, the acid fraction was a gum which could be recrystallized only with difficulty.

Chlorogenoic acid diacetate does not form a semicarbazone on refluxing for two hours with semicarbazine in 90% ethyl alcohol, nor does it form a triacetate or an unsaturated compound on heating with acetic anhydride.

On heating the hydrate at 140° and 20 mm. for two hours it lost weight equivalent to 3.37% of the original sample as compared with the calculated amount of 3.18% for loss of one molecule of water. The gas evolved on heating at its melting point contained no carbon dioxide and the decrease in volume on washing with ammoniacal cuprous chloride solution corresponded to only 3.5% of the amount calculated for the evolution of one mole of carbon monoxide. No other combustible gases could be detected. The residue after heating was recrystallized and proved to be unchanged chlorogenoic acid diacetate.

On heating the acid with concentrated sulfuric acid, the amount of gas evolved which could be absorbed by ammoniacal cuprous chloride solution corresponded to about 11% of that calculated for the evolution of one mole of carbon monoxide per mole of compound.

Chlorogenoic Acid.—The brown gummy residue remaining after the acetyl determinations on chlorogenoic acid diacetate, partially crystallized on standing. Crystallization from methyl alcohol gave white crystals which shrank from the tube at 161° and melted at 169–170°.

Anal. Calcd. for $C_{27}H_{42}O_6$: C, 70.09; H, 9.16. Found: C, 70.01; H, 9.00.

Methyl Ester of Chlorogenoic Acid Diacetate.—To a solution of 0.50 g. of chlorogenoic acid diacetate in methyl alcohol was added an ether solution of diazomethane until a slight excess was present. The solution was evaporated to a volume of about 4 cc. and filtered hot. On cooling 0.34 g. of methyl ester, m. p. 162.5–163°, crystallized and evaporation of the filtrate from this crop gave 0.15 g., m. p. 159–162°. Recrystallization from methyl alcohol did not raise the melting point above 163°. The same ester was obtained from the acid showing a double melting point as from the dehydrated material.

Anal. Calcd. for $C_{32}H_{48}O_8$: C, 68.54; H, 8.63; OH, none; sap. equiv., 186.9. Found: C, 68.39; H, 8.76; OH (Zerewitinow), 0.71, 0.79; sap. equiv., 187.7, 187.8.

Lactone Diacetate.—When the oxidation of chlorogenin diacetate was carried out under more vigorous conditions than described above, for example, at 40° for one and one-half hours, or 45° for six hours, crystalline chlorogenoic acid diacetate could not be isolated readily but a small amount of a neutral product was obtained from the ether solution after extraction with sodium carbonate. The crude product, m. p. 190–208°, after two crystallizations from methyl alcohol melted at 249–252°, after which there was no further change. The compound did not form an oxime on refluxing with hydroxylamine in methyl alcohol for three and one-half hours.

The compound was insoluble in cold aqueous alkali and

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(6) All carbon and hydrogen analyses are by Dr. A. Schoeller, Berlin.

a solution in 50% aqueous alcohol absorbed no alkali on titration. A few milligrams of the compound was refluxed for forty-five minutes with 1 *N* ethyl alcoholic potassium hydroxide solution after which the solution was poured into water. No precipitation occurred but acidification with hydrochloric acid precipitated a compound which after solution in 50% alcohol absorbed no alkali on titration. These properties indicate that the neutral product is a lactone diacetate which is saponified by alcoholic alkali to a dihydroxy lactone.

Anal. Calcd. for $C_{26}H_{38}O_6$: C, 69.93; H, 6.58. Calcd. for $C_{26}H_{38}O_6 \cdot CH_3OH$: C, 67.76; H, 8.84. Calcd. for $C_{27}H_{44}O_7$: C, 67.46; H, 9.26. Found: C, 67.85; H, 9.36.

Attempts to determine the equivalent weight of the lactone diacetate by saponifying with an excess of standard alkali and back titrating did not give consistent results due to the hydrolysis of the sodium salt and reformation of the lactone. The **dihydroxy lactone** recovered from these saponifications consisted of needles, m. p. 255–256°.

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.88; H, 9.46. Calcd. for $C_{22}H_{34}O_4 \cdot CH_3OH$: C, 70.01; H, 9.71. Calcd. for $C_{23}H_{40}O_5$: C, 69.66; H, 10.17. Found: C, 69.62; H, 10.01.

Oxidation of Chlorogenoic Acid Diacetate.—Of the many attempts made to obtain intermediate oxidation products between the acid and the lactone, the most successful was the oxidation with potassium permanganate. A neutral solution of the sodium salt from 0.1 g. of chlorogenoic acid diacetate was refluxed for thirty minutes with an aqueous solution of 0.038 g. of potassium permanganate. Precipitation of manganese dioxide began almost immediately and the purple color disappeared in a few minutes. After thirty minutes, the solution was filtered and the precipitate washed well with water. Acidification of the filtrate gave a flocculent white precipitate, m. p. 175–190°. After two crystallizations from 70% aqueous acetone and one from acetone it melted at 221–222°. The compound is much more soluble in 70% aqueous acetone than in acetone alone but is precipitated from the 70% acetone on further dilution with water.

Anal. Calcd. for $C_{27}H_{42}O_6$: C, 70.09; H, 9.16; neut. equiv., 462.6. Found: C, 69.81, 70.05; H, 9.23, 8.85; neut. equiv., 484.

The same acid was isolated in small amounts after oxidation of the sodium salt with hydrated manganese dioxide at 65–70° and in one of the chromic oxide oxidations at 40°. In none of the oxidations yielding this acid could the results be duplicated consistently since the acid appears to undergo further oxidation with the formation of oils and gums that could not be crystallized. Chlorogenoic acid diacetate was recovered unchanged after treatment in acetic acid solution with lead tetraacetate.

Cleavage of the Side Chain of Chlorogenin.—A fragrant oil was obtained on treating 10 g. of chlorogenin with acetic acid–hydrochloric acid according to the procedure of Jacobs and Simpson.[5] This was converted into a semicarbazone but extreme difficulty was encountered in attempting to isolate a pure product. Recrystallization from ether–petroleum ether mixtures failed to give a product melting above 100°. A large number of other solvents and solvent mixtures were tried without success. By passing an ether solution of the semicarbazone through a column packed with a mixture of magnesium oxide and Celite, evaporating successive portions of the filtrate separately and rubbing up the solid residues with small amounts of ether, a product was obtained from the middle fractions that melted at 114–118°. This material consisted of tiny microcrystals but was still somewhat gummy and could not be purified further by crystallization. The melting point given by Jacobs and Simpson for the semicarbazone of the ketone from sarsasapogenin and gitogenin is 119.5–120°.

Summary

Oxidative and acid degradation of chlorogenin indicates that the structure of the side chain is very similar to, if not identical with, that of the other steroid sapogenins.

STANFORD UNIVERSITY, CALIF. RECEIVED MAY 10, 1938

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE GENERAL ELECTRIC CO.]

Dielectric Constants of Some Fluorine Compounds

BY RAYMOND M. FUOSS

I. Introduction.—In contrast to the other halogens, the properties of fluorine compounds have been studied comparatively little. Recent technical interest in new refrigerants has, however, made a large number of fluorinated methanes and ethanes available. Below are presented the results of an investigation of the dielectric constants of fifteen fluorine compounds.

II. Materials, Apparatus and Method.—The fluorine compounds were presented to us by the Jackson Laboratory of E. I. du Pont de Nemours and Company, to whom grateful acknowledgment is made.

The bench apparatus consisted of a manifold to which were connected an oil pump, three distilling bulbs with an ascarite tube between the first two, a manometer and a guarded condenser. The ascarite served to remove traces of water or of hydrogen halides which might have been present. The stopcocks were lubricated with a sirup of phosphoric acid and anhydride for the higher boiling compounds; ordinary heavy grease was used for the others. The samples were distilled from the supply cartridges into the first bulb, and then distilled back and forth through the ascarite. After each of the first few condensations, the samples were pumped to remove small amounts of dissolved air. Then the sample was distilled from the first bulb in small portions, and a dielectric constant determination at several pressures was made on each portion. The third bulb was used as a receiver for the initial and final portions, so that the middle fraction could be redistilled to give a check determination. The vapor density of the middle fraction was determined by weighing against a matched counterpoise a bulb (volume 421.3 cc.) filled with the gas at known pressures and temperature.

The measuring condenser was a 100 $\mu\mu$f radio condenser mounted in a vacuum-tight brass case, and insulated from the latter by mica washers. The case was connected to the guard line in the Schering bridge circuit.[1] The leads (high potential and test) to the condenser plates were brought out as tungsten wires through glass insulation fused to fernico tubes which were soldered to the brass case. The condenser case was connected to the manifold by a graded seal between a fernico bushing and the Nonex glass of the manifold. The insulation between the two sets of brass condenser plates was isolantite; the insulation held up very well, but in the course of about six weeks use developed a slightly conducting film. (The original value of tan δ at 60 cycles for the cell was 0.0004; during use, it gradually rose to 0.0014.) The cell was mounted in a wooden box in order to surround it by a dead air space; the cell temperature was determined by means of a thermocouple inserted in a well soldered inside the case.

All measurements were made at 60 cycles and 100 v. across the cell. The temperature varied from about 22 to 30°, depending on room temperature, but the drift in any run was so slow that no appreciable error was introduced due to uncertainty in temperature for a given reading.

The polarization was obtained in several ways from the data, which consisted in a series of pressure and resistance measurements. Since the unknown arm of the bridge was substantially loss free, we have

$$C_x = SR_4/R_3 \tag{1}$$

where C_x is the unknown capacity, S is a 100 $\mu\mu$f standard capacity and R_4 and R_3 are the other two components of the bridge network. But the dielectric constant ϵ' is given by

$$\epsilon' = C_x/C_0 \tag{2}$$

where C_0 is the capacity of the evacuated condenser. In turn

$$C_0 = SR_4^0/R_3^0 \tag{3}$$

In the measurements, R_3 was kept fixed for all readings on a given compound, so that R_3 and S dropped out of the final result

$$\epsilon' = R_4/R_4^0 \tag{4}$$

R_3 was selected to make R_4^0 just above 10,000 ohms, so the bridge was made direct reading in dielectric constant

$$\epsilon' = 1 + 10^{-4}\Delta R_4 \tag{5}$$

where ΔR_4 was the difference between R_4^0 for the evacuated cell and R_4 for the cell filled with gas at pressure p. R_4 could be determined to $\pm 0.2\ \Omega$ which gives an accuracy of about ±0.002% in ϵ'. The polarization P was calculated by the Clausius-Mosotti formula

$$P = \frac{\epsilon' - 1}{\epsilon' + 2}\frac{M}{\rho} \tag{6}$$

where M is the molecular weight and ρ is the density, for the temperature and pressure at which ϵ' was determined. As a check on the consistency of the results $(\epsilon' - 1)/p$ was plotted against p, and P was calculated, using the ideal gas density[2] as follows

$$P = 2.097 \times 10^4\, T \lim_{p \to 0} \left(\frac{\epsilon' - 1}{p_{\text{mm.}}}\right) \tag{7}$$

Finally, a value of P was calculated from the low pressure data (where the deviations from ideal behavior were small) by the formula

$$P = 2.079\, T\,(\Delta R_4/\Delta p) \tag{8}$$

All pressures were corrected to 0° by the formula

$$p_0 = p\,(1 - 0.000175t) \tag{9}$$

Values of P calculated by (6), (7) and (8) for a given compound usually agreed within several per cent. or better. Lack of agreement was an indication of impurities in the sample, because (6) contains the actual density of the sample while (7) and (8) contain only the ideal gas density.

III. Results.—An abstract of the experimental results is given in Table I. The pressures have been corrected to millimeters at 0° and rounded off to three places. In order to make the tables more compact, the dielectric deviation δ is given in place of the dielectric constant ϵ'; the two are related by the equation

$$\epsilon' = 1 + 10^{-3}\,\delta \tag{10}$$

In Fig. 1 are given some examples of $\epsilon' - p$ curves, which illustrate the method of determining polarization by means of (8). It should be pointed out that the scattering of the points from the straight lines of Fig. 1 is a direct measure of the reproducibility of the Schering bridge readings; one unit in the δ-scale corresponds to 10 Ω in R_4. The absolute values of ϵ' are consistent to about ±0.002%, *i. e.*, several units in the fifth place.

Figure 2 illustrates the evaluation of polarization by means of the extrapolation of $(\epsilon' - 1)/p$ to zero pressure. As is well known, the limiting value of $(\epsilon' - 1)/p$ permits P to be calculated using ideal gas densities. It was, however, considered desirable in this work to make direct de-

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(1) Fuoss, This Journal, **59**, 1703 (1937).

(2) Fuchs, *Z. Physik*, **63**, 824 (1930).

TABLE I

DIELECTRIC CONSTANTS OF FLUORINE COMPOUNDS

p	δ	p	δ	p	δ
SF_6, t = 27.5°		CF_2Cl_2, t = 29.0		CHF_2Br, t = 27.2°	
708	1.91	719	3.05	734	7.29
704	1.90	504	2.14	682	6.79
590	1.58	417	1.76	654	6.45
457	1.23	331	1.41	461	4.52
369	0.98	188	0.79	419	4.02
216	.57	157	.65	324	3.13
131	.34	83	.32	214	2.07
				129	1.23
				86	0.83
CF_4, t = 24.8°		$CFCl_3$, t = 26.0°		$CHFCl_2$, t = 30.0°	
723	1.13	498	2.51	719	6.59
629	0.98	448	2.24	709	6.51
515	.81	339	1.67	419	3.79
429	.67	270	1.32	312	2.80
332	.52	189	0.92	222	1.99
223	.36	129	.60	134	1.20
131	.21	73	.35		
CF_3Cl, t = 29.0°		CHF_2Cl, t = 25.4°		CF_2Br_2, t = 28.8°	
619	1.96	711	6.58	718	5.03
607	1.93	611	5.64	652	4.53
484	1.53	509	4.69	617	4.28
330	1.00	410	3.74	519	3.49
211	0.66	311	2.82	411	2.72
99	.31	205	1.87	299	1.99
		154	1.37	210	1.45
		105	0.96	114	0.82
		82	.72	64	.45
CF_3CF_3, t = 23.0°		$CClF_2CClF_2$, t = 26.8°		CH_3CF_3, t = 25.2°	
711	1.97	715	4.04	644	13.23
608	1.69	605	3.40	554	11.34
509	1.40	512	2.87	436	8.91
411	1.14	416	2.30	337	6.83
307	0.86	328	1.80	219	4.43
201	.56	225	1.25	120	2.42
110	.31	150	0.83	83	1.67
61	.17	93	.52	61	1.23
		63	.34	40	0.82
				24	.47
CF_3CF_2Cl, t = 27.4°		$C_2H_2ClF_3$, t = 26.6°		CH_3CClF_2, t = 27.4°	
722	3.34	715	10.25	706	13.38
584	2.71	612	8.74	600	11.31
506	2.36	513	7.30	511	9.59
333	1.58	414	5.86	379	7.09
260	1.23	309	4.37	279	5.21
195	0.93	207	2.95	204	3.79
121	.58	153	2.19	155	2.89
59	.28	107	1.53	123	2.29
		65	0.91	95	1.77
		43	.60	71	1.33
				47	0.87
				34	.64

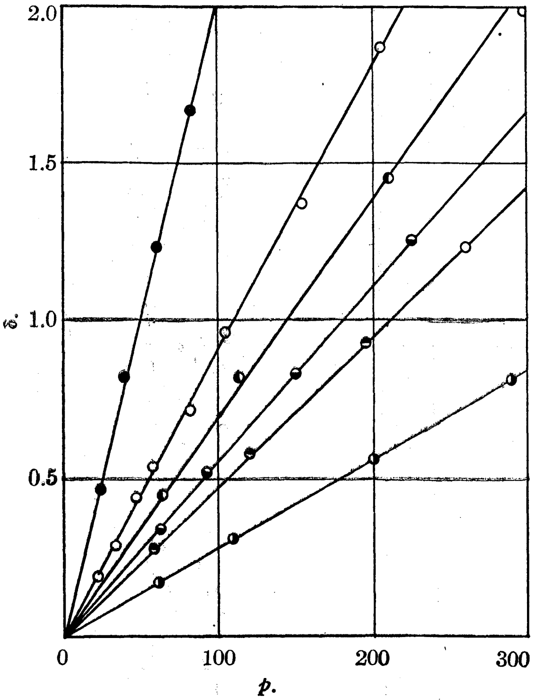

Fig. 1.—Change of dielectric constant with pressure: ◐, CF_2Br_2; ◑, C_2F_6; ●, CH_3CF_3; ◒, $C_2Cl_2F_4$; ◓, C_2ClF_5; ○, CHF_2Cl.

terminations of the vapor densities, in order to check the purity of the samples. The results of the vapor density determinations are given in Table II. The first column gives the formula of the compound, the next two the pressure and temperature corresponding to the density (in mg./cc.) in the fourth column, and the fifth column gives the ratio of the apparent molecular weight to that calculated from the chemical formula. Gases of the type discussed here should give positive deviations up to several per cent.

TABLE II

VAPOR DENSITIES AND POLARIZATIONS OF FLUORINE COMPOUNDS

Compound	p	t	ρ	M/M_0	t	P
SF_6	718.8	27.8	5.650	1.0102	27.5	16.8
CF_4	722.9	23.6	3.451	1.0039	24.8	9.7
CF_3Cl	613.8	28.3	3.430	1.0058	29.0	19.8
CF_2Cl_2	719.3	28.0	4.709	1.0169	29.0	26.2
$CFCl_3$	551.2	27.2	4.138	1.0238	26.0	30.7
CHF_2Cl	711.2	25.4	3.377	1.0223	25.4	56.1
CHF_2Br	466.8	27.0	3.129	0.9584	27.0	60.0
$CHFCl_2$	712.8	29.2	3.958	1.0172	30.0	56.5
CF_2Br_2	654.8	28.6	7.426	1.0172	29.0	43.0
CH_3CF_3	644.2	26.0	2.948	1.0161	25.2	124.2
CH_3CClF_2	706.8	26.6	3.895	1.0252	27.4	115.5
CF_3CF_3	710.5	22.6	5.335	1.0036	22.6	17.2
CF_3CF_2Cl	721.8	27.0	6.007	1.0092	26.2	28.7
$CClF_2CClF_2$	715.2	26.2	6.569	1.0047	26.2	34.5
$C_2H_2ClF_3$	715.6	26.2	4.776	1.0516	26.2	83.6

from ideal behavior. The sixth column gives the temperature at which the polarization was calculated; the polarization is given in the last column. The figure given is an average, based on the direct determinations and on the extrapolated values.

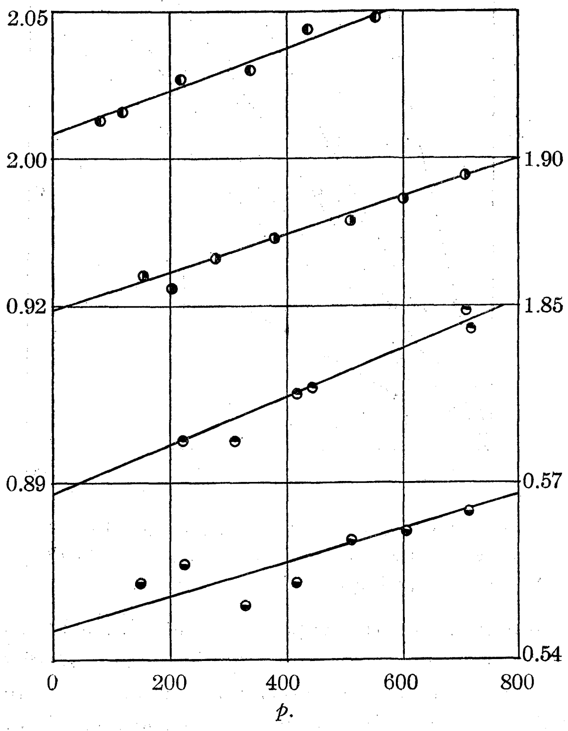

Fig. 2.—Variation of $(\epsilon' - 1)/p$ with pressure: ◐, CH_3CF_3; ◑, CH_3CClF_2; ◓, $CHFCl_2$; ◒, $C_2Cl_2F_4$.

IV. Discussion.—We begin by comparing the results of Table II with previously observed values for the cases where they are available. For SF_6, Watson, Rao and Ramaswany[3] find P_{25° = 16.51 cc. and for CF_4, Watson, Kane and Ramaswany[4] find P_{25° = 10.15 cc.

Four of the fluorinated chloromethanes have been studied by Smyth and McAlpine[5] at a series of temperatures, which permitted a direct determination of P_M, the part of the polarization due to orientation of permanent dipoles. Since the total polarization P is given by

$$P = P_E + P_A + P_M \tag{11}$$

we can calculate values of the moments from the data of Table II by using Smyth's values for P_A, the atomic polarization, together with calculated values for P_E, the electronic polarization. For the latter, the following values of atomic refractivities, extrapolated to infinite wave length by the Cauchy formula,[6] were used: C = 2.37, H = 1.07, Cl = 5.80, Br = 8.53, F = 1.00. The first four figures are conventionally accepted; for fluorine, whose atomic refraction varies with the compound containing it,[7] an average value was chosen which was derived from compounds of the type studied here.[4,7–10] An average value for P_A = 4.0 cc. was used for the fluoromethanes; Smyth and McAlpine's value 0.9 for $CHFCl_2$ seems low compared to the values they find for the other three compounds and to Watson's value of 2.86 for CF_4. We obtain the results given in Table III, where the moments are given in Debye units.

TABLE III

DIPOLE MOMENTS OF FLUOROMETHANES

Compound	(R. M. F.)	(S. and McA.)
CF_4	0.0	—
CF_3Cl	.47	—
CF_2Cl_2	.55	0.51
$CFCl_3$	.53	.45
CHF_2Cl	1.41	1.40
$CHFCl_2$	1.34	1.29
CHF_2Br	1.30	—
CF_2Br_2	0.72	—

It will be seen that the agreement is within the experimental error of the writer's method; the method of Smyth and McAlpine gives one more significant figure in the dielectric constant.

We can compare the result for CF_3Cl with that for the other fluorochloromethanes by the method of vector addition used by Smyth and McAlpine. Using their notation, in which the symbol for a radical or molecule in parentheses denotes its dipole moment corrected for induction,[11] we have

$$\begin{aligned}(CF_3Cl) &= 3(C - F)\cos 70^\circ - (CCl)\\ &= (CF) - (CCl) = 0.47 \text{ (obsd.)}\\ (CFCl_3) &= (CF) - 3(CCl)\cos 70^\circ\\ &= (CF) - (CCl) = 0.53 \text{ (obsd.)}\\ &= 0.45 \text{ (Smyth and McAlpine)}\end{aligned}$$

The moments of the last two compounds in Table III give a value for the difference (CCl) − (CBr). We shall assume an atomic polarization of 11.0 cc. for the bromo compounds; this value was chosen after considering the few data available on atomic polarization of bromoalkanes.

$$\begin{aligned}(CHF_2Br) &= (CH) + {}^1/_3(2CF + CBr) = 1.30\\ (CHF_2Cl) &= (CH) + {}^1/_3(2CF + CCl) = 1.41\end{aligned}$$

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[3] Watson, Rao and Ramaswany, *Proc. Roy. Soc.* (London), **143**, 558 (1934).

[4] Watson, Kane and Ramaswany, *ibid.*, **156**, 130 (1933).

[5] Smyth and McAlpine, *J. Chem. Phys.*, **1**, 190 (1933).

[6] Smyth, *Phil. Mag.*, **45**, 849 (1923).

[7] Swarts, *J. chim. phys.*, **20**, 30 (1923).

[8] Klemm and Henkel, *Z. anorg. allgem. Chem.*, **213**, 115 (1933).

[9] Locke, Brode and Henne, THIS JOURNAL, **56**, 1726 (1934).

[10] Henne and Renoll, *ibid.*, **58**, 887 (1936).

[11] Smallwood and Herzfeld, *ibid.*, **52**, 1919 (1930).

whence (CCl) − (CBr) = 0.33, and

$$(\mathrm{CF_2Br_2}) = (\mathrm{CF}) - {}^1/_3(\mathrm{CF} + 2\mathrm{CBr}) = 0.72$$
$$(\mathrm{CF_2Cl_2}) = (\mathrm{CF}) - {}^1/_3(\mathrm{CF} + 2\mathrm{CCl}) = 0.55$$

whence (CCl) − (CBr) = 0.26. When compared with Morgan and Lowry's[12] value for methyl bromide, it appears that the results for both the bromo compounds are high by about the same amount, as is shown by the following calculation

$$(\mathrm{CHF_2Br}) = (\mathrm{CH}) + {}^1/_3(2\mathrm{CF} + \mathrm{CBr}) = 1.30\ (\text{obsd.})$$
$$(\mathrm{CF_2Br_2}) = (\mathrm{CBr}) - {}^1/_3(2\mathrm{CF} + \mathrm{CBr}) = 0.72\ (\text{obsd.})$$
$$(\mathrm{CH}) + (\mathrm{CBr}) = 2.02$$
$$(\mathrm{CH_3Br}) = (\mathrm{CH}) + (\mathrm{CBr}) = 1.45\ (\text{Morgan})$$

The agreement could, of course, be improved by assigning a larger value to P_A for CF_2Br_2, which would also improve the agreement between the two determinations of the (CCl) − (CBr) difference. However, the available samples of these two compounds were quite small and did not permit a careful fractionation; judging from the vapor density, the CHF_2Br contained an impurity of low molecular weight. The value 11.0 cc. used above for P_A already seems large. If a smaller value is chosen, the following values are obtained: with $P_A = 4.0$ cc. $\mu(CHF_2Br) = 1.43$ and $\mu(CF_2Br_2) = 0.93$, which gives (CH) + (CBr) = 2.36, a value which seems entirely too large. Until data on the temperature coefficients of the polarizations of more bromo compounds are available, the value of their atomic polarizations will have to remain an open question.

The fluoroethanes present an interesting group. Two of them, CF_3CF_3 and $CClF_2CClF_2$, should be non-polar; this fact gives $P_A = 6.5$ for C_2F_6 and $P_A = 14.2$ for $C_2Cl_2F_4$. If we use $P_A = 6.5$ for CH_3CF_3 and CH_3CClF_2, we obtain $\mu(CH_3CF_3) = 2.27$ and $\mu(CH_3CClF_2) = 2.13$. We can compare these figures with the results for the methanes as follows

$$(\mathrm{CH_3CF_3}) = (\mathrm{CH_3C}) + 3(\mathrm{CF})\cos 70° = 2.27$$
$$(\mathrm{CH_3CF_2Cl}) = (\mathrm{CH_3C}) + {}^1/_3(2\mathrm{CF} + \mathrm{CCl}) = 2.13$$

whence (CF) − (CCl) = 0.42, in agreement with the earlier figures. For CF_3CF_2Cl, we have $(P - P_E) = 13.2$, which is smaller than the corresponding figure for the non-polar $C_2F_4Cl_2$. But within the experimental error, we can set $P_A = 12.8$ for CF_3CF_2Cl, which gives it a moment of 0.14, in agreement with the other moments

$$(\mathrm{CH_3CF_3}) - (\mathrm{CH_3CClF_2}) = 0.14$$
$$(\mathrm{CF_3CClF_2}) = 0.14$$

We could, in analogy with 1,1,2,2-tetrachloroethane, for which $\mu = 1.6$,[13] assume that $C_2Cl_2F_4$ had a finite moment, in which case the atomic polarizations for the fluorinated ethanes would be reduced from the values assumed here, and all moments would be correspondingly increased.

Finally, the compound $C_2H_2FCl_3$ will be considered. It was prepared by fluorination of $CHCl_2CHCl_2$ and one naturally would expect it to be $CHFClCHF_2$. However, the dipole moment agrees more closely with the structure CF_3CH_2Cl. If we use $P_E = 15.7$ and $P_A = 12.8$, we find $\mu(C_2H_2F_3Cl) = 1.64$. Then we have

$$(\mathrm{CF_3CH_2Cl}) = (\mathrm{CF_3C}) + {}^1/_3(2\mathrm{CH} - \mathrm{CCl}) = 1.64$$
$$(\mathrm{CF_3CH_3}) = (\mathrm{CF_3C}) + 3(\mathrm{CH})\cos 70° = 2.27$$

whence (CH) + (CCl) = 1.89, which agrees very closely with the value 1.85 used by Smyth and McAlpine for methyl chloride. The other isomer, CF_2ClCH_2F, gives (CH) + (CF) = 1.47, compared to the accepted value 1.81. The vapor density of the sample indicates a small amount of an impurity of higher molecular weight, but it hardly seems possible that the presence of an impurity could raise the moment from 0.1–0.2 expected for $CHFClCHF_2$ to the value observed. The only explanation which can be advanced on the basis of the present evidence is that rearrangement took place during fluorination.

Summary

The total polarization of a series of fluorine compounds has been determined by Schering bridge measurements on the gases. By making reasonable assumptions concerning the electronic and atomic polarizations, values for their dipole moments were obtained as follows: CF_4, 0.0; CF_3Cl, 0.47; CF_2Cl_2, 0.55; $CFCl_3$, 0.53; CHF_2Cl, 1.41; $CHFCl_2$, 1.34; CHF_2Br, 1.30; CF_2Br_2, 0.72; CF_3CF_3, 0.0; $CClF_2CClF_2$, 0.0; CH_3CF_3, 2.27; CH_3CClF_2, 2.13; CF_3CF_2Cl, 0.14; CF_3CH_2Cl, 1.64. These figures are in agreement with the theory of induction between dipole moments.

SCHENECTADY, N. Y. RECEIVED MAY 14, 1938

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[12] Morgan and Lowry, *J. Phys. Chem.*, **34**, 2385 (1930).

[13] Smyth, "Dielectric Constant and Molecular Structure," Chemical Catalog Co., New York, 1931, p. 201.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF NEW HAMPSHIRE]

The Activity and Osmotic Coefficients of Trivalent Metal Chlorides in Aqueous Solution from Vapor Pressure Measurements at 25°

BY CHARLES M. MASON

In a previous communication[1] it was shown how the isotonic or isopiestic method of Robinson and Sinclair[2] could be adapted to the measurement of the vapor pressures of the aqueous solutions of the three-one electrolyte, lanthanum chloride. In the present investigation, with revised technique, this method has been extended to the determination of the vapor pressures of six more three-one electrolytes: namely, aluminum chloride, scandium chloride, yttrium chloride, cerous chloride, praseodymium chloride, and neodymium chloride. In the present work the previous data for lanthanum chloride were extended to higher concentrations and more accurate data obtained in the concentration range below 0.4 molal. All the data obtained in each case have been used to compute the osmotic and activity coefficients for the corresponding salt.

Experimental Details

Apparatus.—The apparatus employed was modified from that described by Mason and Gardner.[3] The brass desiccator used was supplemented by an additional one cast of monel metal. This metal was found to be freer of pinholes and easier to make vacuum tight. For this investigation the metal tee tube formerly used was replaced by a brass needle valve to which was soldered the female half of a brass union. The male half of the union was connected by rubber tubing to the vacuum line. Another male half of the union, interchangeable with the first, was soldered shut and served to keep water out of the needle valve during immersion in the thermostat. A diagram of the metal desiccator as used is shown in Fig. 1.

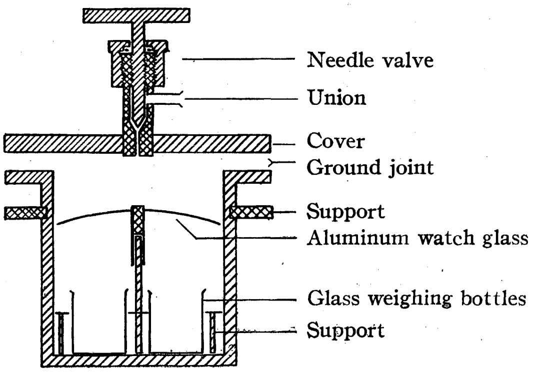

Fig. 1.—Metal desiccator.

With the more concentrated solutions it was found possible to obtain reproducible results using 30-cc. glass-stoppered weighing bottles in the apparatus. The solutions under investigation were weighed in these bottles. In order to ensure more rapid thermal and distillation equilibrium, platinum gauze was placed in the solutions in the glass bottles. This was done in the form of strips of gauze 1 cm. wide by 10 cm. long folded like a bellows and placed edgewise to stand up in the bottom of the weighing bottles. The strips were then about half in and half out of the solution, providing additional surface as well as thermal conduction. The platinum gauze was found to decrease by more than half the minimum time needed to obtain equilibrium. In order to prevent grease and other films from interfering with the wetting of the platinum they were ignited in the Meker burner before each run.

The glass bottles in the desiccator were immersed to a depth of about 0.3 cm. in potassium chloride or sodium chloride solution of the same concentration as that used in the reference bottles. They were held in place by a brass frame which kept them from tipping over and at the same time served as a shield to prevent any of the solution in the bottom from splashing into the bottles themselves. Attached to the frame above the bottles was a watch glass shaped disk of aluminum which acted as a shield to keep any spray from getting into the bottles when air was admitted at the end of a run.

Below 0.5 molal the accuracy obtained with glass bottles decreased rapidly with decreasing concentration. The glass bottles were therefore replaced in this range by similar bottles made of sterling silver and heavily gold plated. Stainless steel was tried but was found not to withstand corrosion. The design of the silver containers is shown in Fig. 2. They were made to fit tightly into recesses in a heavy copper block. A good thermal contact was secured by pressing them firmly against the bottom of the recess with a bakelite collar (to prevent wear) which was in turn forced down by a brass collar screwed into the top of the recess. It was found that equilibrium could be obtained without a contacting solution and so none was used. The air was removed from under the bottles and from under the copper block by putting a drop of water under each silver bottle and several drops under the block in the bottom of the desiccator. This evaporated when the desiccator was evacuated and swept the air out ahead

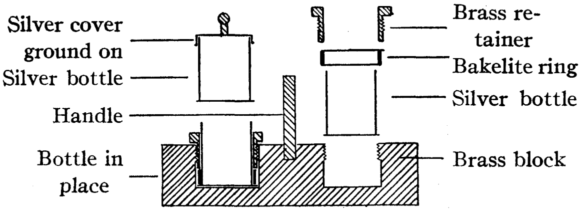

Fig. 2.—Brass block with silver bottles.

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[1] Mason and Ernst, THIS JOURNAL, 58, 2032 (1936).

[2] Robinson and Sinclair, *ibid.*, 56, 1830 (1934).

[3] Mason and Gardner, *J. Chem. Ed.*, 13, 188 (1936).

of it. No water was ever found in these places when a run was completed. In all cases the desiccator was evacuated slowly to prevent boiling and splashing, allowed to stand for one hour or more, and then reëvacuated to remove the last traces of air.

The concentration of the solution in all of the bottles was determined in the usual manner, namely, by weighing. Care was taken to wipe the bottles with a damp cloth before each weighing and thus the weights could always be reproduced within the error of the balance.

All measurements were carried out in a water thermostat at 25 ± 0.01°. The temperature was determined by thermometers checked against thermometers calibrated by the Bureau of Standards. The thermostat was equipped with a shaking device to rock the metal desiccators back and forth, about forty-five times a minute, thereby keeping the solutions in constant agitation.

Materials. (a) **Aluminum Chloride.**—The best commercial grade of hydrated aluminum chloride was dissolved in water, filtered, and recrystallized four times by shaking out of solution with hydrogen chloride gas at 0°. The hydrated salt so obtained was carefully dried in a current of warm air at 50–70° and then ground in an agate mortar to pass 20 mesh. This material was then placed for several weeks over potassium hydroxide in a vacuum desiccator to remove the last traces of hydrogen chloride. The product was analyzed gravimetrically for chloride ion by the usual methods and for the aluminum present by the method of Willard and Tang.[4] The results of the analysis indicated a purity better than 99.97%.

(b) **Cerous Chloride.**—The cerous chloride used had been prepared from a very pure sample of cerium oxalate by the method of Hönigschmid and Holch[5] and was found to be of high purity by spectroscopic analysis. The salt was recrystallized three times by shaking out of solution with hydrogen chloride gas at 0°. A pure white product was obtained entirely free from any trace of ceric cerium. This product was then purified as follows: The hydrated salt was dried in a current of warm air at 50–70° until all traces of hydrogen chloride appeared to be removed. The dried salt was then dissolved in a minimum amount of conductivity water, a few drops of concentrated hydrochloric acid added to prevent hydrolysis, and evaporated to a thick sirup on the steam-bath. This sirup was chilled to 0°, seeded if possible, and stirred vigorously with a motor stirrer. This action produced a mass of very fine crystals which were easily filtered onto a fritted glass plate, sucked free of mother liquor, and air-dried as before. The final drying was accomplished in a vacuum desiccator.

(c) **Hydrochloric Acid.**—All the hydrochloric acid used was obtained by distilling the best commercial grade of arsenic-free acid in an all-glass still and discarding the first and third portions.

(d) **Lanthanum Chloride.**—The lanthanum material had been prepared carefully by repeated crystallization as the oxalate and the hydroxide. The chloride was prepared by ignition of the oxalate to the oxide in an electric muffle furnace and solution of this oxide in hydrochloric acid. After filtering, the solution was evaporated and the chloride shaken out at 0° with hydrogen chloride. The product was purified by the same procedure as for cerous chloride.

(e) **Neodymium Chloride.**—This was prepared in a manner similar to that for cerous and lanthanum chloride.

(f) **Potassium and Sodium Chlorides.**—These salts were the best commercial material twice recrystallized from water and dried for twenty-four hours in an electric oven at 120°.

(g) **Praseodymium Chloride.**—Praseodymium oxalate was obtained from the estate of the late Charles James. It was purified by the method of Brauner[6] to remove cerium and lanthanum. The oxide so obtained was converted to the chloride and purified by the same method as that given for lanthanum and cerous chloride.

(h) **Scandium Chloride.**—Scandium oxalate was converted to the chloride and purified in a manner similar to the lanthanum chloride.

(i) **Yttrium Chloride.**—The yttrium oxalate was ignited to the oxide, dissolved in hydrochloric acid, and reprecipitated as the oxalate five times until all trace of the impurity, sodium, was removed. The chloride was then prepared and purified in a manner similar to that for lanthanum chloride.

Procedure.—In all the experimental work the analysis of the solutions under investigation was obtained from the weight of the bottles containing them. To make the standard reference solutions, enough potassium or sodium chloride, whichever was used, was weighed directly into the bottles to make between 1 and 2 cc. of solution of the concentration desired. The requisite amount of water was then added. Below 0.4 molal the weights of these salts became so small as to introduce weighing errors, and solutions of known concentration were weighed into the bottles instead. These were diluted with the proper amount of water before being placed in the desiccator.

It was not practical to weigh out the hydrated salts directly, so concentrated solutions in conductance water were prepared and carefully analyzed for chloride ion by the gravimetric method. These solutions were weighed directly into the bottles and diluted to the approximate concentration before being placed in the apparatus. All solutions were stored in Pyrex brand glass to prevent introduction of any dissolved material.

In several cases the solutions were also analyzed for rare earth content by precipitation of the oxalate and subsequent ignition to the oxide in the muffle furnace according to the standard procedure. The only divergence in the analyses was for cerium where the method outlined by Moore and Bonardi[7] and modified by Hillebrand and Lundell[8] was employed. In every case the concentration of the solutions checked that obtained from the chloride analysis within the known experimental error.

Density Measurements.—In the theoretical treatment it was necessary to know the concentration in moles per liter, which was calculated from the molality by means of the density. The densities of all these salts in aqueous solution were determined in duplicate at 25° using a 25-g.

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[4] Willard and Tang, THIS JOURNAL, **59**, 1190 (1937).

[5] Hönigschmid and Holch, *Z. anorg. allgem. Chem.*, **177**, 91 (1928).

[6] Brauner, *Coll. Czech. Chem. Comm.*, **5**, 279 (1933).

[7] Moore and Bonardi, *Bur. Mines Bull.*, **212**, 43 (1923).

[8] Hillebrand and Lundell, "Applied Inorganic Analysis," John Wiley and Sons, Inc., New York, N. Y., 1929, p. 434.

TABLE I

ISOTONIC RATIOS AND OSMOTIC COEFFICIENTS OF THE SALT SOLUTIONS

Aluminum Chloride (m_2) against Sodium Chloride (m_1)

m_1	m_2	φ_1	φ_2
6.1440	1.8025	1.2987	2.2132
6.1440	1.8048	1.2987	2.2105
6.1440	1.8065	1.2987	2.2084
5.7681	1.7259	1.2658	2.1151
5.7380	1.7213	1.2630	2.1050
5.5518	1.6819	1.2470	2.0581
5.4913	1.6629	1.2418	2.0504
5.4047	1.6527	1.2346	2.0187
5.3806	1.6442	1.2324	2.0165
5.0535	1.5737	1.2046	1.9341
4.6805	1.4920	1.1725	1.8391
4.6081	1.4735	1.1670	1.8248
4.0092	1.3323	1.1175	1.6814

Aluminum Chloride (m_2) against Potassium Chloride (m_1)

m_1	m_2	φ_1	φ_2
4.6099	1.3350	0.9835	1.6981
4.4577	1.3108	.9785	1.6638
4.2475	1.2650	.9713	1.6307
3.9090	1.2002	.9603	1.5638
3.5684	1.1306	.9500	1.4992
3.4809	1.1167	.9473	1.4765
3.1511	1.0437	.9375	1.4153
2.9196	0.9903	.9308	1.3721
2.7913	.9617	.9272	1.3456
2.7241	.9477	.9254	1.3300
2.3830	.8645	.9165	1.2632
2.0056	.7680	.9082	1.1859
1.8342	.7176	.9053	1.1570
1.3561	.5782	.9004	1.0559
1.3511	.5745	.9004	1.0588
1.3266	.5682	.9002	1.0509
1.0185	.4632	.8985	0.9878
0.9905	.4537	.8984	.9807
.8531	.4039	.8980	.9495
.8150	.3885	.8980	.9419
.6994	.3462	.8980	.9071
.5472	.2792	.8993	.8812
.3916	.2073	.9027	.8526
.3814	.2040	.9029	.8440
.2494	.1370	.9093	.8276
.1851	.1041	.9150	.8134
.1681	.09473	.9169	.8136
.1643	.09230	.9174	.8164
.1488	.08374	.9195	.8170
.1409	.08015	.9208	.8093
.1205	.06811	.9240	.8174
.1034	.05830	.9272	.8222
.09569	.05416	.9287	.8204

Scandium Chloride (m_2) against Sodium Chloride (m_1)

m_1	m_2	φ_1	φ_2
6.1440	1.9549	1.2987	2.0408
6.1440	1.9568	1.2987	2.0388
5.7609	1.8679	1.2663	1.9527
5.7313	1.8596	1.2625	1.9455
5.7247	1.8596	1.2618	1.9422
5.7313	1.8642	1.2625	1.9407
5.4983	1.7993	1.2425	1.8984
5.4047	1.7814	1.2364	1.8756
5.0535	1.6891	1.2046	1.8018
4.6860	1.5960	1.1752	1.7253

Scandium Chloride (m_2) against Potassium Chloride (m_1)

m_1	m_2	φ_1	φ_2
4.8040	1.4599	0.9900	1.6289
4.7704	1.4535	.9887	1.6225
4.4252	1.3790	.9770	1.5676
4.3707	1.3631	.9752	1.5635
4.3618	1.3631	.9750	1.5600
4.3468	1.3596	.9745	1.5578
4.3360	1.3616	.9741	1.5510
3.9044	1.2602	.9602	1.4875
3.8839	1.2653	.9595	1.4726
3.8796	1.2602	.9594	1.4768
3.5077	1.1780	.9483	1.4119
3.3977	1.1493	.9449	1.3970
3.2965	1.1282	.9418	1.3759
3.2788	1.1217	.9413	1.3757
3.1241	1.0845	.9369	1.3495
3.0378	1.0699	.9343	1.3265
2.7903	1.0031	.9272	1.2896
2.7652	0.9980	.9265	1.2835
2.6955	.9812	.9246	1.2700
2.5656	.9471	.9212	1.2477
2.3147	.8834	.9148	1.1985
1.8067	.7387	.9049	1.1066
1.7990	.7339	.9047	1.1088
1.6753	.6978	.9032	1.0842
1.4169	.6160	.9009	1.0361
1.1667	.5313	.8992	0.9873
0.9721	.4602	.8983	.9483
.9359	.4470	.8982	.9403
.7213	.3612	.8980	.8966
.6927	.3483	.8981	.8931
.5634	.2980	.8991	.8499
.5627	.2963	.8991	.8537
.5621	.2919	.8991	.8657
.4849	.2569	.9002	.8496
.4896	.2565	.9002	.8591
.4762	.2598	.9005	.8253
.4345	.2330	.9015	.8406
.4221	.2322	.9018	.8197
.4183	.2322	.9019	.8124
.3916	.2139	.9026	.8262
.3814	.2074	.9030	.8303
.3786	.2113	.9031	.8091
.3587	.1994	.9037	.8128
.2584	.1433	.9087	.8193
.2205	.1270	.9132	.7928
.1626	.09363	.9176	.7966
.1559	.09179	.9185	.7800
.1559	.09140	.9185	.7833

Yttrium Chloride (m_2) against Sodium Chloride (m_1)

m_1	m_2	φ_1	φ_2
6.1440	2.0166	1.2987	1.9784
5.3806	1.8255	1.2324	1.8162
4.6081	1.6235	1.1670	1.6561
4.0092	1.4634	1.1175	1.5531

Yttrium Chloride (m_2) against Potassium Chloride (m_1)

m_1	m_2	φ_1	φ_2
4.8040	1.5118	0.9900	1.5729
4.3663	1.4164	.9752	1.5031
3.8920	1.3051	.9598	1.4311
3.1241	1.1240	.9376	1.3030
2.7652	1.0337	.9265	1.2392
2.3147	0.9114	.9148	1.1617
1.8067	.7617	.9049	1.0732
1.4169	.6337	.9008	1.0071
1.1667	.5449	.8992	0.9627
0.9721	.4715	.8983	.9261
.6927	.3567	.8981	.8720
.6055	.3165	.8989	.8599
.4118	.2266	.9020	.8196
.3494	.1957	.9042	.8072
.2372	.1366	.9102	.7902
.2312	.1347	.9106	.7815
.1974	.1148	.9138	.7856
.1237	.07104	.9235	.8040

Lanthanum Chloride (m_2) against Sodium Chloride (m_1)

m_1	m_2	φ_1	φ_2
6.1440	2.1461	1.2987	1.8629
5.6391	2.0018	1.2544	1.7668
5.3127	1.9103	1.2292	1.7092
5.0510	1.8360	1.2046	1.6569
4.3974	1.6473	1.1493	1.5340

Lanthanum Chloride (m_2) against Potassium Chloride (m_1)

m_1	m_2	φ_1	φ_2
4.2776	1.4573	0.9705	1.4243
4.1533	1.4317	.9679	1.4039
3.8814	1.3663	.9595	1.3629
3.8541	1.3595	.9586	1.3588
3.7674	1.3381	.9559	1.3456
3.5795	1.2908	.9503	1.3176
3.4381	1.2574	.9461	1.2934
3.4075	1.2472	.9450	1.2910
3.2548	1.2071	.9406	1.2681
2.8414	1.0967	.9285	1.2028
2.5870	1.0272	.9217	1.1606
2.4924	0.9985	.9182	1.1460
2.0895	.8767	.9098	1.0842
1.7321	.7618	.9038	1.0274
1.7105	.7548	.9035	1.0238
1.4362	.6603	.9010	0.9798
1.0312	.5069	.8990	.9144
0.7337	.3794	.8980	.8683
.5697	.3063	.8990	.8361
.5440	.2953	.8994	.8284
.3784	.2096	.9031	.8150
.2494	.1439	.9092	.7893
.2003	.1172	.9133	.7811
.1955	.1131	.9138	.7898
.1913	.1103	.9112	.7902
.1698	.09874	.9166	.7880
.1671	.09767	.9170	.7846
.1390	.08117	.9325	.7986
.1385	.08165	.9209	.7820
.1268	.07349	.9230	.7972
.1109	.06424	.9257	.7989

TABLE I (*Continued*)

Cerium Chloride (m_2) against Sodium Chloride (m_1)

m_1	m_2	φ_1	φ_2
6.1440	2.1202	1.2987	1.8817
6.1440	2.1165	1.2987	1.8850
5.6391	1.9821	1.2544	1.7844
5.4913	1.9303	1.2418	1.7662
5.3127	1.8923	1.2292	1.7256
5.0510	1.8210	1.2046	1.6707
5.0535	1.8172	1.2046	1.6750
4.3974	1.6345	1.1493	1.5460

Cerium Chloride (m_2) against Potassium Chloride (m_1)

m_1	m_2	φ_1	φ_2
4.8040	1.5907	0.9900	1.4949
4.3663	1.4851	.9752	1.4335
3.8920	1.3672	.9598	1.3661
3.1241	1.1734	.9376	1.2481
2.8408	1.0861	.9290	1.2149
2.7652	1.0766	.9265	1.1900
2.4474	0.9862	.9182	1.1393
2.0903	.8676	.9097	1.0967
1.7990	.7801	.9047	1.0432
1.7643	.7667	.9043	1.0408
1.6236	.7165	.9026	1.0226
1.4169	.6513	.9008	0.9798
1.3672	.6303	.9005	.9767
1.2461	.5876	.8997	.9540
1.1667	.5616	.8992	.9340
1.0759	.5210	.8988	.9280
0.9721	.4822	.8983	.9055
.6927	.3625	.8981	.8581
.4082	.2263	.9021	.8136
.3482	.1955	.9042	.8052
.2074	.1203	.9126	.7867
.1436	.08461	.9203	.7810
.1276	.07570	.9227	.7777

Praseodymium Chloride (m_2) against Sodium Chloride (m_1)

m_1	m_2	φ_1	φ_2
6.1440	2.1298	1.2987	1.8732
6.1440	2.1346	1.2987	1.8690
5.9287	2.0712	1.2840	1.8377
5.5518	1.9711	1.2470	1.7562
5.4913	1.9515	1.2418	1.7471
5.3806	1.9225	1.2324	1.7245
5.0535	1.8283	1.2046	1.6648
4.6081	1.7076	1.1670	1.5746
4.0092	1.5307	1.1175	1.4634

Praseodymium Chloride (m_2) against Potassium Chloride (m_1)

m_1	m_2	φ_1	φ_2
4.3663	1.4808	0.9752	1.4377
3.8920	1.3665	.9598	1.3669
3.1241	1.1710	.9376	1.2507
2.7652	1.0767	.9265	1.1897
2.3147	0.9465	.9148	1.1186
1.8067	.7908	.9049	1.0337
1.7990	.7854	.9047	1.0362
1.4169	.6540	.9008	0.9758
1.1667	.5635	.8992	.9309
0.9721	.4844	.8983	.9014
.6927	.3648	.8981	.8527
.6055	.3216	.8989	.8461
.4115	.2296	.9020	.8101
.3494	.1977	.9042	.7990
.2372	.1374	.9102	.7857
.2312	.1338	.9106	.7867
.1974	.1158	.9138	.7783
.1355	.08038	.9215	.7767
.1187	.06985	.9244	.7854

Neodymium Chloride (m_2) against Sodium Chloride (m_1)

m_1	m_2	φ_1	φ_2
5.9376	2.0517	1.2848	1.8591
5.9287	2.0517	1.2840	1.8551
5.5518	1.9491	1.2470	1.7760
5.3806	1.9098	1.2324	1.7369
4.6081	1.6908	1.1670	1.5903
4.0092	1.5183	1.1175	1.4754

Neodymium Chloride (m_2) against Potassium Chloride (m_1)

m_1	m_2	φ_1	φ_2
4.6046	1.5254	0.9832	1.4889
4.4254	1.4840	.9772	1.4570
4.4205	1.4841	.9770	1.4550
4.3747	1.4724	.9775	1.4485
4.3264	1.4622	.9642	1.4264
3.9793	1.3783	.9626	1.3886
3.9739	1.3765	.9623	1.3890
3.7302	1.3196	.9547	1.3494
3.6443	1.2998	.9522	1.3349
3.3946	1.2344	.9447	1.2990
3.0498	1.1453	.9345	1.2442
2.9095	1.1085	.9306	1.2213
2.6249	1.0293	.9227	1.1765
2.2975	0.9346	.9144	1.1239
1.8291	.7905	.9051	1.0471
1.5467	.6945	.9019	1.0043
1.2232	.5791	.8485	.9489
0.8961	.4505	.8980	.8932
.6898	.3608	.8981	.8585
.4924	.2695	.9001	.8224
.4724	.2613	.9005	.8140
.4082	.2282	.9021	.8068
.3482	.1960	.9042	.8032
.2686	.1541	.9080	.7913
.2074	.1207	.9126	.7841
.1436	.08443	.9203	.7826
.1276	.07430	.9227	.7923

Regnault specific gravity bottle. The usual precautions were observed and the results are given in Table IV.

Results and Discussion

In most of the experimental runs three samples of the salt solution were allowed to come to isotonic equilibrium with a like number of the standard reference solution. When the silver bottles were used two samples were in equilibrium with the two samples of standard solutions. In some experiments only two samples of the standard solution were used and these were opposed by two or four different salt solutions as the case might be. Ample time, usually more than forty-eight hours, was allowed in every case for the solutions to reach equilibrium with each other. No experiment was considered satisfactory if the deviation between identical samples was greater than one part per thousand.

Potassium chloride was used as a reference salt up to saturation and sodium chloride was used to extend the range of the three–one electrolytes beyond the concentrations which could be obtained with potassium chloride.

The silver bottles gave good results down to about 0.25 molal but below this concentration, although fair results were obtained down to about 0.06 molal, the results were inclined to be quite erratic and had about ten times the error of the results above 0.25 molal. In general, the results for all the salts are of about the same accuracy. The observed values of φ_2 did not, as a rule, deviate more than one per cent. from a smooth curve such as is shown in Fig. 3. The average deviation was about 0.2% in concentrated solutions and 0.5% in dilute. Scandium chloride was more erratic than the rest and gave larger

TABLE II

SMOOTHED OSMOTIC COEFFICIENTS, φ_2

m_1	μ	$AlCl_3$	$ScCl_3$	YCl_3	$LaCl_3$	$CeCl_3$	$PrCl_3$	$NdCl_3$
0.05	0.30	0.826	0.807	0.810	0.800	0.800	0.801	0.797
.1	0.60	.812	.794	.791	.788	.784	.782	.784
.2	1.2	.841	.815	.808	.801	.798	.796	.795
.3	1.8	.890	.858	.847	.831	.832	.828	.828
.4	2.4	.948	.912	.892	.869	.871	.865	.866
.5	3.0	1.009	.970	.940	.910	.914	.906	.909
.6	3.6	1.074	1.028	.990	.952	.958	.950	.954
.7	4.2	1.141	1.088	1.042	.998	1.005	.995	1.003
.8	4.8	1.213	1.150	1.096	1.046	1.055	1.042	1.053
.9	5.4	1.291	1.216	1.155	1.097	1.106	1.094	1.105
1.0	6.0	1.378	1.285	1.217	1.150	1.160	1.148	1.159
1.1	6.6	1.471	1.359	1.283	1.205	1.214	1.206	1.216
1.2	7.2	1.564	1.433	1.351	1.264	1.270	1.267	1.275
1.3	7.8	1.657	1.507	1.420	1.323	1.328	1.327	1.335
1.4	8.4	1.753	1.583	1.491	1.382	1.387	1.388	1.399
1.5	9.0	1.855	1.659	1.564	1.445	1.455	1.447	1.464
1.6	9.6	1.966	1.734	1.639	1.506	1.515	1.508	1.529
1.8	10.8	2.203	1.889	1.796	1.633	1.657	1.638	1.662
2.0	12.0	...	2.040[a]	1.965	1.766	1.796	1.777	1.809
2.2	13.2	...	...	...	1.899	1.935[a]	1.922[a]	1.940[a]

[a] Extrapolated.

deviations. The isotonic data obtained are listed in Table I.

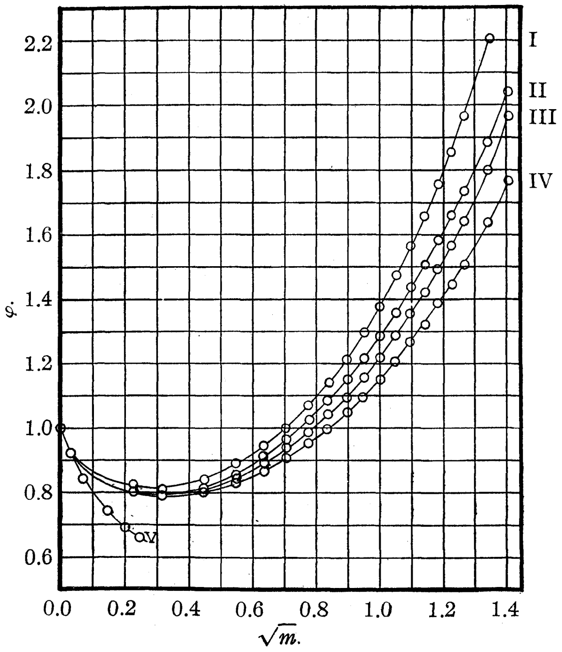

Fig. 3.—Osmotic coefficients of salts: I, $AlCl_3$; II, $ScCl_3$; III, YCl_3; IV, $LaCl_3$; V, φ_0, limiting law.

Table I includes the values of φ_1 and φ_2. The values of φ_1 were taken from those of Scatchard and Wood[9] which were given to me prior to publication by Professor Scatchard. These data represent the best possible evaluation of all the known data for potassium and sodium chlorides. The values of φ_1 in Table I were read from a large-scale plot of the data described above.

φ_2 is defined by the equation

$$\varphi_2 = (55.51/4\ m_2) \ln p_0/p \qquad (1)$$

and φ_1 by the equation

$$\varphi_1 = (55.51/2\ m_1) \ln p_0/p \qquad (2)$$

p_0/p is the same for both salts when at isotonic equilibrium and combining equations (1) and (2) we obtain

$$\varphi_2 = \frac{m_1}{2m_2}\varphi_1 \qquad (3)$$

By means of equation (3) the values of φ_2 in Table I were computed. These values have been smoothed graphically by plotting φ_2 against $m^{1/2}$ on a large scale as shown in Fig. 3. The data which were obtained are listed at round concentrations in Table II.

The activity coefficients have been computed from the osmotic coefficients by a modification of the method of Randall and White[10] using the equation

$$\log \gamma = -\frac{h}{2.303} - \frac{2}{2.303}\int_0^{m^{1/2}} \frac{h}{m^{1/2}}\, dm^{1/2} \qquad (4)$$

From the data of Wyman[11] the intercept on the $h/m^{1/2}$ axis was calculated to be 2.844. When the curve was constructed, as shown in Fig. 4, it was found that a large portion of the area was in the region below 0.25 molal where the data were least

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(9) Scatchard and Wood, unpublished.

(10) Randall and White, THIS JOURNAL, **48**, 2514 (1926).

(11) Wyman, *Phys. Rev.*, **35**, 623 (1930).

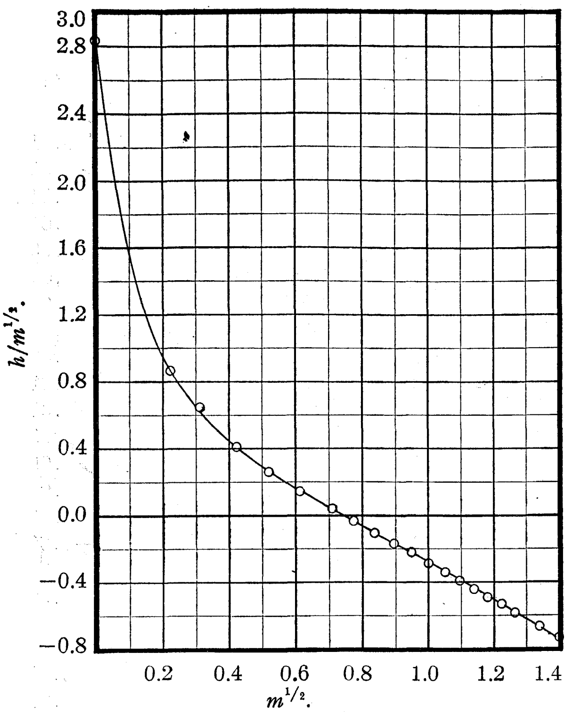

Fig. 4.—Plot of $h/m^{1/2}$ against $m^{1/2}$ for $ScCl_3$ to compute the graphical integration.

accurate and that there was probably a very long error in log γ resulting from this. Furthermore, there was the additional error in drawing this curve that it was impossible to determine how much of a hook or hump should be given to these data in considering their approach to zero concentration. Inasmuch as chlorides are peculiarly sensitive to the formation of complex ions, the area represented by such a hump may be considerable. The following method was adopted to correct this error. Equation (4) was rewritten in the form

$$\log \gamma = -\frac{h}{2.303} - \frac{2}{2.303} Y \qquad (5)$$

where Y represents the correct area under the curve at a given value of m. X was then defined as

$$X = Y + Z \qquad (6)$$

becoming equal to the measured area when Z represents the error introduced.

The right-hand term of equation (5) was then substituted for log γ in the equation of Hückel[12]

$$\log \gamma = -\frac{1.068\sqrt{12c}}{1 + A\sqrt{12c}} + B(12c) - \log(1 + 0.072\,m) \qquad (7)$$

where m is the molality and c is the concentration in moles per liter.

The constants A and B and the correction factor Z were then calculated by substitution of the numerical data for 0.5, 1.0 and 1.5 molal and simultaneous solution of the resulting equations. The numerical values obtained for the correction factors Z were larger than one would expect from an error in the linear extrapolation. This would show that a hook or hump of some sort must exist in the curve shown in Fig. 4 near zero concentration. The values obtained for these quantities are given in Table III.

TABLE III

CONSTANTS IN DEBYE AND HÜCKEL EQUATIONS

Salt	A	B	b	Z
$AlCl_3$	0.32953	0.08623	0.14560	−0.63409
$ScCl_3$	.47040	.06446	.11696	− .41977
YCl_3	.43836	.06186	.11067	− .50656
$LaCl_3$	.44919	.05506	.09413	− .43880
$CeCl_3$	.51556	.05115	.09663	− .45158
$PrCl_3$	.45350	.05485	.09500	− .46729
$NdCl_3$	.50930	.05118	.09771	− .40575

The values obtained for Z were used to calculate the correct areas, Y, in the graphical integrations. These values of Y were then used in equation (5) to compute the activity coefficients given as $\gamma_{\text{corr.}}$ in Table IV. In this same table $\gamma_{\text{obsd.}}$ refers to the values of the activity coefficients obtained directly from the graphical integration of Randall and White.[10] The constants A and B were used in Hückel's equation (7) to compute the values of γ_D recorded in Table IV. In order to compare the corrected activity coefficients with those obtained by equation (7), the values of $\Delta\gamma(\gamma_{\text{corr.}} - \gamma_D)$ have also been included in Table IV and one set for aluminum chloride have been

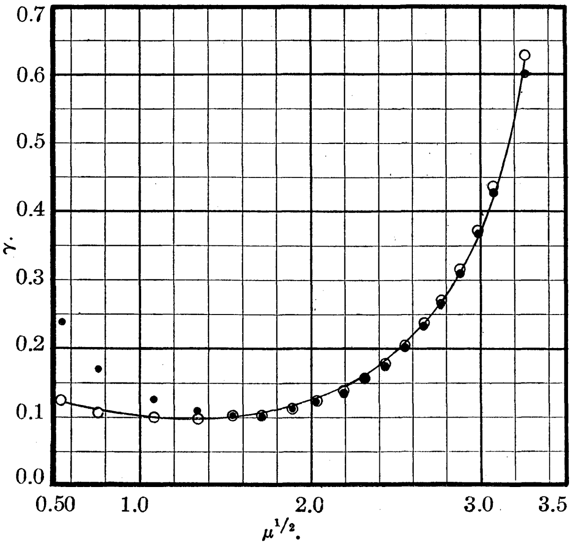

Fig. 5.—Activity coefficients of $AlCl_3$: ●, γ_D; ○, $\gamma_{\text{corr.}}$

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(12) Hückel, *Physik. Z.*, **26**, 93 (1925).

TABLE IV

ACTIVITY AND OSMOTIC COEFFICIENTS OF SALTS

m	Density	$\varphi_{\text{exptl.}}$	φ_D	$\Delta\varphi$	$\gamma_{\text{exptl.}}$	$\gamma_{\text{corr.}}$	γ_D	$\Delta\gamma$
Aluminum Chloride								
0.05	1.0030	0.826	0.718	0.108	0.463	0.130	0.247	−0.117
.1	1.0088	.812	.715	.097	.403	.113	.175	− .062
.2	1.0200	.841	.771	.070	.366	.103	.127	− .014
.3	1.0310	.890	.849	.041	.364	.102	.114	− .012
.4	1.0416	.948	.934	.014	.376	.106	.110	− .004
.5	1.0523	1.009	1.022	− .013	(.398)	.112	.113	− .001
.6	1.0630	1.074	1.112	− .038	.428	.120	.120	.000
.7	1.0739	1.141	1.203	− .062	.465	.131	.130	.001
.8	1.0845	1.213	1.294	− .081	.511	.144	.144	.000
.9	1.0943	1.291	1.384	− .093	.569	.161	.161	.000
1.0	1.1048	1.378	1.476	− .098	(.643)	.181	.183	− .002
1.1	1.1147	1.471	1.567	− .096	.734	.207	.209	− .002
1.2	1.1245	1.564	1.657	− .093	.843	.237	.240	− .003
1.3	1.1341	1.657	1.749	− .092	.971	.273	.277	− .004
1.4	1.1437	1.753	1.839	− .086	1.126	.317	.321	− .004
1.5	1.1532	1.855	1.931	− .076	(1.318)	.371	.374	− .003
1.6	1.1625	1.966	2.022	− .056	1.562	.440	.431	.009
1.8	1.1812	(2.203)	2.203	.000	2.248	.633	.602	.031
Scandium Chloride								
0.05	1.0039	0.807	0.709	0.098	0.416	0.180	0.270	−0.090
.1	1.0101	.794	.715	.079	.357	.154	.201	− .047
.2	1.0231	.815	.737	.078	.317	.137	.156	− .019
.3	1.0359	.858	.797	.061	.310	.139	.137	.002
.4	1.0487	.912	.865	.047	.316	.137	.140	− .003
.5	1.0613	.970	.936	.034	(.330)	.143	.143	.000
.6	1.0738	1.028	1.009	.019	.350	.151	.150	.001
.7	1.0860	1.088	1.082	.006	.375	.162	.161	.001
.8	1.0980	1.150	1.156	− .006	.406	.175	.174	.001
.9	1.1096	1.216	1.230	− .014	.443	.191	.191	.000
1.0	1.1209	1.285	1.304	− .019	(.487)	.210	.210	.000
1.1	1.1321	1.359	1.378	− .019	.541	.234	.235	− .001
1.2	1.1433	1.433	1.452	− .019	.602	.260	.260	.000
1.3	1.1545	1.507	1.526	− .019	.675	.291	.291	.000
1.4	1.1656	1.583	1.600	− .017	.757	.327	.327	.000
1.5	1.1763	1.659	1.673	− .014	(.852)	.368	.368	.000
1.6	1.1870	1.734	1.747	− .013	.961	.415	.415	.000
1.8	1.2088	1.889	1.894	− .007	1.234	.533	.529	.004
2.0	1.2280	(2.040)	2.040	.000	1.588	.686	.677	.009
Yttrium Chloride								
0.05	1.0056	0.810	0.707	0.103	0.451	0.164	0.262	−0.098
.1	1.0141	.791	.694	.097	.385	.150	.197	− .047
.2	1.0315	.808	.729	.079	.340	.123	.144	− .021
.3	1.0485	.847	.786	.061	.329	.120	.128	− .008
.4	1.0652	.892	.850	.042	.331	.120	.123	− .003
.5	1.0820	.940	.917	.023	(.341)	.124	.124	.000
.6	1.0990	.990	.986	.004	.356	.129	.128	.001
.7	1.1154	1.042	1.056	− .006	.376	.137	.135	.002
.8	1.1316	1.096	1.126	− .030	.401	.146	.145	.001
.9	1.1472	1.155	1.196	− .041	.432	.157	.156	.001
1.0	1.1622	1.217	1.266	− .049	(.469)	.170	.170	.000
1.1	1.1765	1.283	1.336	− .053	.513	.186	.187	− .001
1.2	1.1918	1.351	1.406	− .055	.564	.205	.205	.000
1.3	1.2066	1.420	1.476	− .056	.623	.226	.227	− .001
1.4	1.2211	1.491	1.547	− .055	.692	.251	.252	− .001
1.5	1.2357	1.564	1.617	− .053	(.772)	.280	.280	.000
1.6	1.2506	1.639	1.686	− .047	.866	.315	.313	.002

TABLE IV (*Continued*)

m	Density	$\varphi_{\text{exptl.}}$	φ_D	$\Delta\varphi$	$\gamma_{\text{exptl.}}$	$\gamma_{\text{corr.}}$	γ_D	$\Delta\gamma$
1.8	1.2805	1.796	1.826	−0.030	1.101	0.400	0.403	−0.003
2.0	1.3090	(1.965)	1.965	.000	1.430	.519	.493	+ .026

Lanthanum Chloride

m	Density	$\varphi_{\text{exptl.}}$	φ_D	$\Delta\varphi$	$\gamma_{\text{exptl.}}$	$\gamma_{\text{corr.}}$	γ_D	$\Delta\gamma$
0.05	1.0082	0.800	0.702	0.099	0.390	0.162	0.262	−0.100
.1	1.0194	.788	.684	.104	.333	.139	.190	− .051
.2	1.0414	.801	.709	.091	.292	.121	.142	− .021
.3	1.0630	.831	.756	.075	.297	.116	.125	− .009
.4	1.0842	.869	.810	.059	.277	.115	.118	− .003
.5	1.1057	.910	.868	.042	(.282)	.117	.117	.000
.6	1.1265	.952	.927	.025	.290	.121	.119	.002
.7	1.1474	.998	.986	.012	.303	.126	.124	.002
.8	1.1677	1.046	1.047	− .001	.318	.132	.130	.002
.9	1.1877	1.097	1.107	− .010	.338	.140	.139	.001
1.0	1.2075	1.150	1.167	− .017	(.360)	.150	.149	.001
1.1	1.2269	1.205	1.227	− .022	.388	.161	.161	.000
1.2	1.2463	1.264	1.287	− .023	.419	.174	.174	.000
1.3	1.2655	1.323	1.348	− .025	.455	.189	.189	.000
1.4	1.2851	1.382	1.407	− .025	.496	.206	.206	.000
1.5	1.3036	1.445	1.468	− .023	(.543)	.226	.226	.000
1.6	1.3220	1.506	1.528	− .022	.595	.248	.248	.000
1.8	1.3575	1.633	1.647	− .014	.723	.301	.299	.002
2.0	1.3923	(1.766)	1.766	.000	.888	.370	.362	.008
2.2	1.4266	1.899	1.885	.014	1.096	.456	.445	.011

Cerium Chloride

m	Density	$\varphi_{\text{exptl.}}$	φ_D	$\Delta\varphi$	$\gamma_{\text{exptl.}}$	$\gamma_{\text{corr.}}$	γ_D	$\Delta\gamma$
0.05	1.0084	0.800	0.703	0.097	0.462	0.187	0.275	−0.088
.1	1.0195	.784	.685	.099	.393	.159	.205	− .046
.2	1.0420	.798	.712	.086	.344	.140	.158	− .018
.3	1.0640	.832	.761	.071	.330	.134	.142	− .008
.4	1.0853	.871	.816	.055	.329	.133	.136	− .003
.5	1.1074	.914	.875	.039	(.335)	.136	.136	.000
.6	1.1275	.958	.936	.022	.346	.140	.140	.000
.7	1.1480	1.005	.997	.008	.362	.147	.146	.001
.8	1.1700	1.055	1.059	− .004	.382	.155	.156	− .001
.9	1.1912	1.106	1.120	− .014	.406	.164	.164	.000
1.0	1.2120	1.160	1.182	− .022	(.434)	.176	.176	.000
1.1	1.2315	1.214	1.243	− .029	.467	.189	.191	− .002
1.2	1.2515	1.270	1.305	− .035	.504	.204	.206	− .002
1.3	1.2715	1.328	1.367	− .039	.547	.222	.223	− .001
1.4	1.2910	1.387	1.429	− .042	.596	.242	.243	− .001
1.5	1.3100	1.455	1.490	− .035	(.658)	.267	.266	.001
1.6	1.3285	1.515	1.552	− .037	.719	.292	.291	.001
1.8	1.3658	1.657	1.674	− .017	.891	.360	.357	.003
2.0	1.4020	(1.796)	1.796	.000	1.103	.447	.420	.027
2.2	1.4380	1.935	1.918	.017	1.376	.558	.508	.050

Praseodymium Chloride

m	Density	$\varphi_{\text{exptl.}}$	φ_D	$\Delta\varphi$	$\gamma_{\text{exptl.}}$	$\gamma_{\text{corr.}}$	γ_D	$\Delta\gamma$
0.05	1.0089	0.801	0.702	0.099	0.419	0.165	0.264	−0.099
.1	1.0204	.782	.684	.098	.356	.140	.181	− .041
.2	1.0430	.796	.710	.086	.312	.123	.150	− .023
.3	1.0655	.828	.758	.070	.299	.118	.131	− .013
.4	1.0872	.865	.812	.053	.297	.117	.120	− .003
.5	1.1085	.906	.870	.036	(.302)	.119	.119	.000
.6	1.1290	.950	.930	.020	.310	.122	.121	.001
.7	1.1502	.995	.990	.005	.324	.127	.126	.001
.8	1.1717	1.042	1.051	− .009	.341	.134	.132	.002
.9	1.1925	1.094	1.111	− .017	.362	.142	.141	.001
1.0	1.2129	1.148	1.172	− .024	(.387)	.152	.151	.001
1.1	1.2330	1.206	1.233	− .027	.417	.164	.164	.000
1.2	1.2530	1.267	1.293	− .026	.452	.178	.177	.001

TABLE IV (*Concluded*)

m	Density	$\varphi_{\text{exptl.}}$	φ_D	$\Delta\varphi$	$\gamma_{\text{exptl.}}$	$\gamma_{\text{corr.}}$	γ_D	$\Delta\gamma$
1.3	1.2727	1.327	1.354	− .027	.492	.193	.192	.001
1.4	1.2925	1.388	1.415	− .027	.537	.211	.210	.001
1.5	1.3115	1.447	1.476	− .029	(.586)	.230	.230	.000
1.6	1.3300	1.508	1.536	− .028	.643	.253	.253	.000
1.8	1.3674	1.638	1.656	− .018	.782	.307	.306	.001
2.0	1.4047	(1.777)	1.777	.000	.968	.380	.368	.012
2.2	1.4407	1.922	1.896	.024	1.214	.477	.454	.023
			Neodymium Chloride					
0.05	1.0090	0.797	0.703	0.094	0.415	0.184	0.273	−0.089
.1	1.0203	.784	.686	.098	.354	.157	.203	− .046
.2	1.0435	.795	.713	.082	.309	.137	.156	− .019
.3	1.0663	.828	.762	.066	.295	.131	.140	− .009
.4	1.0888	.866	.819	.047	.294	.130	.134	− .004
.5	1.1105	.909	.879	.030	(.299)	.133	.134	− .001
.6	1.1327	.954	.940	.014	.309	.137	.138	− .001
.7	1.1545	1.003	1.002	.001	.323	.143	.143	.000
.8	1.1762	1.053	1.064	− .011	.341	.151	.151	.000
.9	1.1978	1.105	1.126	− .021	.362	.161	.163	− .002
1.0	1.2190	1.159	1.188	− .029	(.388)	.172	.172	.000
1.1	1.2402	1.216	1.250	− .034	.418	.186	.187	− .001
1.2	1.2608	1.275	1.313	− .038	.453	.201	.201	.000
1.3	1.2813	1.335	1.375	− .040	.494	.219	.219	.000
1.4	1.3015	1.399	1.438	− .038	.539	.239	.238	.001
1.5	1.3214	1.464	1.500	− .036	(.592)	.263	.260	.003
1.6	1.3410	1.529	1.562	− .033	.653	.290	.285	.005
1.8	1.3798	1.662	1.686	− .024	.800	.355	.343	.012
2.0	1.4176	(1.809)	1.809	.000	1.0017	.445	.414	.031
2.2	1.4553	1.940	1.932	.008				

( ) show reference points used in theoretical calculations.

plotted against the square root of the ionic strength in Fig. 5. This plot in Fig. 5 is characteristic of all seven salts.

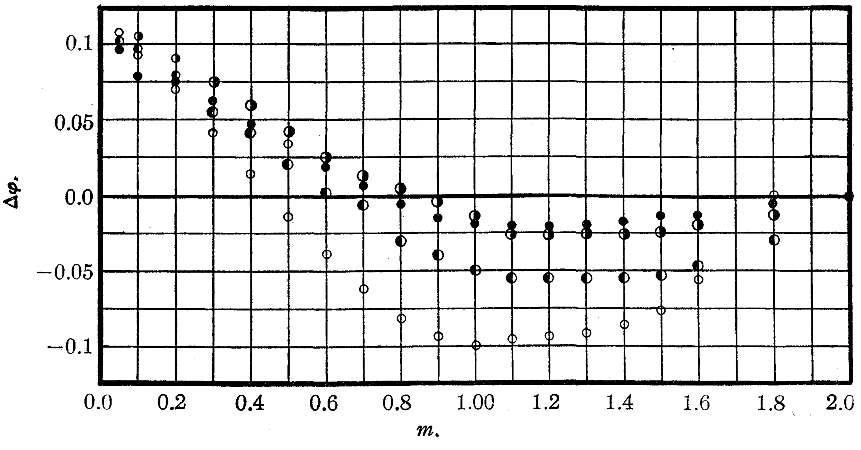

Fig. 6.—Deviations of osmotic coefficients: ○, $AlCl_3$; ●, $ScCl_3$; ◐, YCl_3; ◑, $LaCl_3$.

Examination of the values for $\Delta\gamma$ shows wide divergence in the dilute solutions. This is to be expected and the values for $\gamma_{\text{corr.}}$ are probably too low in this region, because of the increased error in the isotonic measurements at lower concentrations. The values of γ_D fall off above an ionic strength of ten but this is quite readily understood because the linear term in Hückel's equation may not be enough to correct for the variation of the dielectric constant in such concentrated solutions.

The smoothed osmotic coefficients given in Table II have been used to test the equation of Scatchard[13] for osmotic coefficients of salts in concentrated solutions. This equation was used in the form

$$\varphi_D = 1 + \frac{Az_1z_2}{\mu}\left[1 + \sqrt{\mu} - \frac{1}{1 + \sqrt{\mu}} - 2\ln(1 + \sqrt{\mu}\right] + b\mu \quad (8)$$

where μ is the ionic strength and b is the linear constant. The value −1.165 was used for A. b was calculated by fixing $\varphi_D = \varphi_{\text{exptl.}}$ at 2.0 molal and the values so obtained have been included in Table III. The values of φ_D were computed by

(13) Scatchard, *Chem. Rev.*, **19**, 309 (1936).

means of equation (8) and are given in Table IV. The corresponding values of $\Delta\varphi(\varphi_{\text{exptl.}} - \varphi_D)$ have also been calculated and are included in the same table (III). For some of the salts $\Delta\varphi$ has been plotted against m in Fig. 6. Cerium, praseodymium and neodymium chlorides were omitted from the plot because the values of $\Delta\varphi$ for these salts were so close to lanthanum chloride which has been included.

The values of $\Delta\varphi$ representing the deviation from Scatchard's equation are not proportionately large when compared to those given by him for the higher valence sulfates measured by Robinson and Jones.[14] In fact, the actual values of $\Delta\varphi$ found in this investigation are less than those for the sulfates.

I am indebted to Professor Scatchard and Dr. Wood for the use of their data for the osmotic coefficients of potassium and sodium chlorides prior to publication and for several suggestions regarding the use of equation (8). For these courtesies I wish to express thanks.

Summary

1. The osmotic coefficients of aluminum, scandium, yttrium, lanthanum, cerium, praseodymium and neodymium chlorides have been determined in aqueous solution at 25° by the isotonic method of Robinson and Sinclair.[2]

2. The activity coefficients of these salts have been computed from the osmotic coefficients.

3. The data obtained in both 1 and 2 have been compared with theory.

DURHAM, N. H. RECEIVED APRIL 30, 1938

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[14] Robinson and Jones, THIS JOURNAL, **58**, 959 (1936).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NEW YORK UNIVERSITY]

Ternary Systems. XXIV. Calcium Sulfate, Sodium Sulfate and Water

BY ARTHUR E. HILL AND JOHN H. WILLS[1]

Early study of this system by Fritsche[2] disclosed the existence of two double salts, glauberite ($CaSO_4 \cdot Na_2SO_4$) and a salt of the composition $CaSO_4 \cdot 2Na_2SO_4 \cdot 2H_2O$, which has been variously known as syngenite, from a mistaken reading of its composition, and as the labile double salt, from its metastable relationship to other double salts. Isotherms of the system have been studied at 22° by Cameron and Seidell,[3] and at 25° by Cameron and Breazeale,[4] in both cases without inclusion of double salts. Barre[5] compiled the concentrations of isothermally invariant solutions saturated with two salts, glauberite and each of the components of the system and the labile salt with each of the components, giving an outlined polytherm of the system from room temperature to 100°. D'Ans and Schreiner[6] discussed the two double salts and added a point of saturation by glauberite and gypsum at 60°. Van't Hoff[7] determined the invariant points of saturation by each of these double salts with gypsum and mirabilite (Glauber's salt) as 30.2° for the transition involving the labile double salt and 29° for that involving glauberite. The present research contains a repetition of the 25° isotherm and additional isotherms at 35, 50 and 75°, including in addition to the previously known double salts, anhydrite at the higher temperatures and a new double salt, sodium pentacalcium sulfate; these data permit the construction of a fuller polytherm than was previously possible.

In carrying out work in this system in which there occur so many degrees of metastability at any given temperature, much use has been made of van't Hoff's[8] generalization that the retardation of salts in coming to equilibrium with their solutions is related to the mean valence, calculated by dividing the total valence representing all the ions in the formula by the total number of such ions, giving each water molecule in a hydrate an arbitrary mean valence of 4/3; this rule guided us in this research, as in other related researches,[9] in deciding upon appropriate time of contact for

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[1] This paper is an abridgment of the thesis presented by Mr. Wills in partial fulfilment of the requirements for the degree of Ph.D. at New York University, June, 1935.

[2] Fritsche, *J. prakt. Chem.*, **72**, 291 (1857). Glauberite had been prepared previously only in the dry way.

[3] Cameron and Seidell, *J. Phys. Chem.*, **5**, 643 (1901).

[4] Cameron and Breazeale, *ibid.*, **8**, 335 (1904).

[5] Barre, *Ann. chim. phys.*, [8] **24**, 145 (1911).

[6] D'Ans and Schreiner, *Z. anorg. Chem.*, **62**, 129 (1909).

[7] Van't Hoff, *Z. physik. Chem.*, **45**, 257 (1903).

[8] Van't Hoff, "Zur Bildung der ozeanischen Salzablagerungen," F. Vieweg und Sohn, Braunschweig, 1905; Vol. I, p. 32; Vol. II, p. 17.

[9] Hill, THIS JOURNAL, **56**, 1071 (1934); Hill and Yanick, *ibid.*, **57**, 645 (1935).

the different salts, for which periods as short as one or two minutes may sometimes not be exceeded without change, while in other cases weeks or months are necessary. The entire list of salts now known in this system, with the mean valence for each, is as follows:

Name	Formula	Mean valence
Mirabilite	$Na_2SO_4 \cdot 10H_2O$	1.33
(Unnamed)	$(Na_2SO_4 \cdot 7H_2O)$	(1.33)
Thenardite	Na_2SO_4	1.33
Labile salt	$2Na_2SO_4 \cdot CaSO_4 \cdot 2H_2O$	1.43
Gypsum	$CaSO_4 \cdot 2H_2O$	1.50
Glauberite	$Na_2SO_4 \cdot CaSO_4$	1.60
Pentasulfate	$Na_2SO_4 \cdot 5CaSO_4 \cdot 3H_2O$	1.64
(Hemihydrate)	$(CaSO_4 \cdot 0.5H_2O)$	(1.71)
Anhydrite	$CaSO_4$	2.00

Of this series, the second and the eighth, sodium sulfate heptahydrate and calcium sulfate hemihydrate, did not appear spontaneously in any of our experiments, and were omitted from consideration; the others have been considered in the appropriate isotherms. Special attention was paid to the labile salt, concerning which a number of points have apparently remained unsettled in the eighty years since its discovery and of course special attention was likewise given to the new pentasalt after it had appeared in one of the isotherms.

The Labile Salt, Sodium Hemicalcium Sulfate.—The composition of this salt as proposed by Fritsche and its condition as metastable with respect to glauberite as held by van't Hoff were disputed by Cameron, Bell and Robinson,[10] who believed the formula to be $2CaSO_4 \cdot 3Na_2SO_4$ (anhydrous) on the basis of indirect determination of composition in a sodium chloride solution, and also believed that their dilatometric experiments showed it to be stable. Experimental answer to this view appears in the four isotherms presented in this paper, which show by solubility curves that the labile salt is metastable with respect to glauberite between 25 and 75°, in accord with van't Hoff's conclusion based upon the transition temperatures. The matter of the composition of the salt was gone into by D'Ans and Schreiner,[6] who were able to obtain samples sufficiently freed from mother liquor, by use of a hydraulic press, to permit analyses, which agreed well with the formula $CaSO_4 \cdot 2Na_2SO_4 \cdot 2H_2O$. It is worth noting that each of the methods which led to the conflicting results is accompanied by unusual difficulties in the case of this salt, which forms from gypsum in sodium sulfate solution in the form of a network of fine spicules so knitted together that a weight of approximately 2% of the salt will hold the mass in suspension so rigidly that there is no movement upon inversion of the vessel. This condition obviously retards the attainment of equilibrium and may leave a considerable portion of gypsum unchanged, which is probably the cause of Cameron, Bell and Robinson's error. This network retains a large proportion of mother liquor even upon centrifuging at 1800 r. p. m., so that a direct analysis such as D'Ans and Schreiner made is not always possible. We are able, however, to confirm their findings, by the use of both methods; algebraic extrapolation of the tie lines for the labile salt in Table I gave (assuming the water content of the salt correct) agreement with the original formula of Fritsche with an average deviation of 0.75% for the six cases there tabulated, with a maximum deviation of 1.30%, in experiments in which the amounts of solid phase were usually less than 1% of the weight of the system. A sample was also prepared by washing out the mother liquor with alcohol–water mixtures, which was found to contain 29.75% $CaSO_4$ (theory 29.83), 61.57% Na_2SO_4 (theory 62.27), and 8.68% H_2O (theory 7.90), in agreement with the formula $CaSO_4 \cdot 2Na_2SO_4 \cdot 2H_2O$.

With respect to the metastability of the salt, our findings are in agreement with those of Barre and of D'Ans and Schreiner that the salt can be held unchanged for long periods of time in contact with its solutions at lower temperatures (25° *e. g.*), and that only at 75° and above does the change toward glauberite begin at once. The action of the salt when treated at 25° with pure water instead of a sodium sulfate solution with which it is in equilibrium (30–34%) is noteworthy; the decomposition cannot be better described than as explosive, both because of the astonishing speed at which the solid disappears, and also because of the unexpected concentration attained. A sample was treated with cold water and immediately filtered from a small residue of calcium sulfate; the solution was analyzed and found to contain 1.01% calcium sulfate. At 25° the solubility of gypsum is 0.208% and that of anhydrite[11] is 0.274%; the solubility of hemihydrate from the curve of Chassevent[12] is about 0.8%, all figures being considerably less than the value found.

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(10) Cameron, Bell and Robinson, *J. Phys. Chem.*, **11**, 409 (1907).

(11) Hill, THIS JOURNAL, **59**, 2242 (1937).

(12) Chassevent, *Ann. chim. phys.*, [10] **6**, 244 (1926).

This seems to be evidence that the mechanism by which the salt decomposes on treatment with water cannot be a simple change into dissolved sodium sulfate and solid calcium sulfate in one of the three forms noted, since a solution cannot supersaturate itself from a given solid phase; either a fourth solid calcium sulfate is formed (an amorphous body, perhaps, which may be the condition of the oft-quoted "soluble anhydrite") or else the primary change is into dissolved material which only later precipitates. Investigation of this phenomenon of decomposition is being continued.

Microscopic identification of the labile hemisalt is comparatively easy, by two of its properties: first, the unusual slimness of the long needles, which run quite uniformly between 1 and 2 μ in breadth, whatever be the length, and by their refractive index $\gamma = 1.510$ (± 0.003), which is sufficiently different from that of glauberite as given by Larsen[13] ($\gamma = 1.536$) as well as that of the pentasalt given later in this paper. The refractive indices in the other directions could not be determined accurately enough.

Sodium Pentacalcium Sulfate.—The new salt, resembling the pentacalcium sulfates found in the potash series and the ammonia series except as to extent of hydration, was first found at 75° when solutions of about 14% sodium sulfate content were treated with gypsum; in general, it may be prepared easily at temperatures of 60 to 75° in solutions of 10 to 14% sodium sulfate upon addition of gypsum, or more rapidly by introduction of gypsum and glauberite in proportions corresponding to the reaction $4(CaSO_4 \cdot 2H_2O) + CaSO_4 \cdot Na_2SO_4 \longrightarrow 5CaSO_4 \cdot Na_2SO_4 \cdot 3H_2O + 5H_2O$. The reaction is completed in four days or less; if the concentration of the solution is such that the salt is metastable only with respect to anhydrite (see Fig. 4), subsequent change to that solid is very slow and need hardly be taken into consideration, but operation in the concentration where the pentasalt is metastable with respect to glauberite will result in fairly rapid and eventually complete change into that salt. Samples of the pentasalt may be washed free of mother liquor without appreciable decomposition, and are found upon analysis to be in close agreement with the formula given; a sample gave $CaSO_4$ 77.59% (theory 77.63), Na_2SO_4 16.21 (theory 16.20), H_2O 6.20 (theory 6.17). This water content, which was confirmed by a number of analyses giving 6.2% of water or a few tenths higher, corresponds to a trihydrate, whereas the corresponding potassium and ammonium salts have been found by all investigators to be monohydrates.

The salt crystallizes in rather fine needles of an average diameter of about 7 μ, which under the microscope are seen to be prisms (or pinacoid faces) with pyramidal ends. They show oblique extinction; $Z \wedge c$ is 11° (± 2), which is quite close to that found for the corresponding potassium and ammonium salts by Gabriel;[14] the refractive indices found were $\alpha = 1.5557$ (± 0.003), $\gamma = 1.567$ (± 0.003).

Experimental Procedure

The materials used were precipitated gypsum and analyzed anhydrous sodium sulfate. Where salts were expected to form by reaction of these components, they were weighed accurately with weighed quantities of water, to give a known original complex as one of the points to be used in extrapolations for the composition of the solid phases. The materials were rotated in stoppered bottles in thermostats for appropriate times. For analysis, solution was filtered off and a part evaporated to constant weight, first at 100° and finally for a day at 200°; in the remainder of the solution, the calcium was precipitated as oxalate and weighed as oxide. It was found that the precipitated calcium oxalate occluded sodium sulfate in weighable amount, whereas occlusion of potassium sulfate did not occur in our previous work;[9] the most effective method of elimination was found to be the volatilization of the sodium salt from the bottom of the platinum crucible to the lid, which occurred at temperatures reached by a Meker burner or blast lamp, and subsequent volatilization from the lid by heating it in the open; failure to do this would leave the results one per cent. or more too high in calcium.

The 25° Isotherm.—The results at 25° are given in Table I and shown in Fig. 1.

The solubility curve for gypsum passes through a minimum at a concentration of about 1.5% of sodium sulfate, and through a maximum at about 20%. The figures of Cameron and Breazeale[4] are distinctly higher than found by us; the isothermally invariant point for gypsum and mirabilite

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[13] Larsen, "The Microscopic Determination of the Nonopaque Minerals," U. S. Govt. Printing Office, Washington, D. C., 1934, p. 156.

[14] Gabriel, THIS JOURNAL, **57**, 686 (1935).

TABLE I

$CaSO_4$–Na_2SO_4–H_2O AT 25°

Original complex Wt. % Na_2SO_4	Original complex Wt. % $CaSO_4$	Saturated solution Wt. % Na_2SO_4	Saturated solution Wt. % $CaSO_4$	Solid phases
—	—	—	0.209	Gypsum
0.573	3.773	0.595	.148	Gypsum
1.529	3.789	1.601	.139	Gypsum
3.109	2.561	3.200	.144	Gypsum
5.964	3.805	6.251	.161	Gypsum
10.80	1.176	10.93	.181	Gypsum
14.63	3.304	15.23	.194	Gypsum
17.89	1.093	18.09	.197	Gypsum
19.24	3.803	20.15	.198	Gypsum
24.21	1.276	21.75	.197	Gypsum + mirabilite
—	—	25.87	.188	Gypsum(m) + glauberite
—	—	27.98	.180	Gypsum(m)
29.84	0.325	29.78	.174	Gypsum(m) + labile salt
—	—	33.85	.155	Gypsum(m) + thenardite
—	—	21.70	—	Mirabilite
22.29	1.138	21.72	.120	Mirabilite
—	—	33.91	.049	Glauberite + thenardite
—	—	32.61	.065	Glauberite
—	—	29.31	.113	Glauberite
—	—	26.60	.175	Glauberite
36.37	0.358	34.13	.055	Labile salt + thenardite
33.31	.700	32.72	.070	Labile salt
32.84	.426	32.49	.073	Labile salt
31.74	.427	31.41	.094	Labile salt
31.60	.693	31.05	.123	Labile salt
30.69	.317	30.47	.115	Labile salt
31.01	.744	30.34	.141	Labile salt
		34.00	.00	Thenardite

shows very little change in the solubility of mirabilite caused by the small amount of calcium sulfate present. It is not easy to explain Cameron and Breazeale's view that the solubility of mirabilite is considerably depressed. We have continued the measurements in the region of supersaturation with respect to mirabilite, which was accomplished by warming the systems above the transition temperature of mirabilite (32.4°) before immersion in the thermostat at 25°. The points on the curve for the labile salt were obtained by allowing the compound to form from gypsum, after seeding with the labile salt; the reaction required one to two weeks for completion, except where excess solid thenardite was present, in which case the change of gypsum to labile salt is quite rapid. Glauberite, however, did not seem to form at all at this temperature; the measurements were made, therefore, by addition of glauberite prepared at higher temperatures; equilibrium was reached in one day. Anhydrite was not included in the work at this temperature, because of the extreme difficulty in obtaining

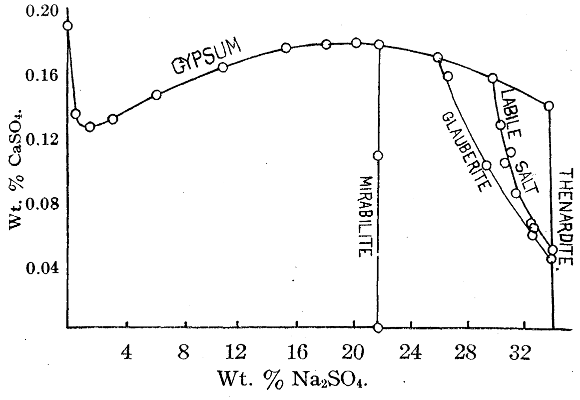

Fig. 1.—$CaSO_4$–Na_2SO_4–H_2O at 25°.

TABLE II

$CaSO_4$–Na_2SO_4–H_2O AT 35°

Original complex Wt. % Na_2SO_4	Original complex Wt. % $CaSO_4$	Saturated solution Wt. % Na_2SO_4	Saturated solution Wt. % $CaSO_4$	Solid phases
—	—	—	0.214	Gypsum
0.489	1.023	0.503	.150	Gypsum
.984	0.974	.988	.142	Gypsum
1.937	.983	1.896	.142	Gypsum
5.916	.978	5.968	.164	Gypsum
13.85	1.064	13.97	.198	Gypsum
—	—	25.16	.204	Gypsum
27.70	0.819	27.93	.199	Gypsum
29.51	1.216	29.89	.190	Gypsum
33.54	0.700	32.85	.178	Gypsum + thenardite
—	—	32.90	—	Thenardite
35.21	.560	32.87	.046	Thenardite + glauberite
29.67	.962	29.31	.084	Glauberite
28.70	.993	28.34	.099	Glauberite
25.73	1.169	25.17	.146	Glauberite
23.68	1.219	23.06	.199	Glauberite
22.96	2.103	22.65	.206	Glauberite + gypsum
33.79	0.734	32.85	.065	Thenardite + labile salt
33.79	2.498	31.66	.078	Labile salt
31.73	0.751	31.18	.088	Labile salt
31.73	1.583	30.48	.102	Labile salt
—	—	27.25	.176	Labile salt
—	—	26.70	.200	Labile salt + gypsum
—	—	27.93	.217	Pentasalt
—	—	30.06	.189	Pentasalt + gypsum
—	—	31.01	.179	Pentasalt
—	—	31.4	.166	Pentasalt
—	—	32.5	.144	Pentasalt
—	—	32.88	.135	Pentasalt + thenardite

equilibrium with that salt at low temperatures;[9,11] it is unquestionably metastable with respect to gypsum in water, with a solubility curve which crosses that for gypsum at a high concentration of sodium sulfate. The new pentacalcium sulfate was also omitted, since the isotherms at higher temperatures make it reasonably sure that it is metastable at 25° with respect to all other salts in the system.

The 35° Isotherm.—The isotherm at 35° was chosen to illustrate conditions just above the temperature at which mirabilite has disappeared. The results are shown in Table II and Fig. 2.

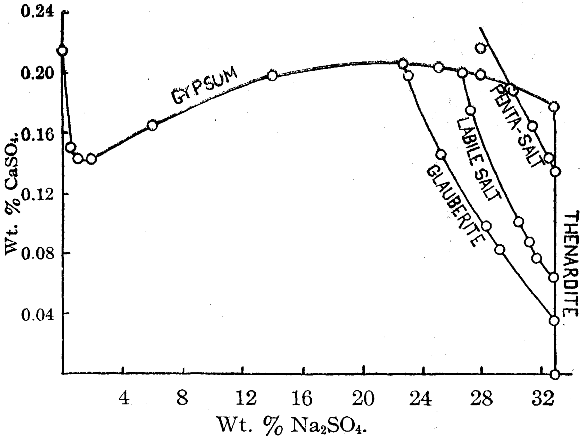

Fig. 2.—$CaSO_4$–Na_2SO_4–H_2O at 35°.

The gypsum curve again shows a maximum and a minimum, as it did at 25°. The salt comes to an equilibrium with its solution within a few minutes, but no need for rapid work resulted, as there was no spontaneous occurrence of double salts in eighteen hours' time up to a concentration of 30% sodium sulfate. In the presence, however, of solid thenardite at the invariant point (32.85%) the formation of labile salt begins immediately and the system becomes constant at the invariant concentration for labile salt and thenardite, the change toward glauberite being suspended. The change of labile salt to glauberite at this temperature is very slow under all conditions of concentration, for which reason some of the points on the glauberite curve were obtained with samples of that salt made at 75°. The labile salt formed from gypsum at 35°, upon seeding, within two to four days, but the extrapolations of the tie-lines fail to agree with the accepted formula by two to three per cent., which may be due either to the presence of unchanged gypsum or to that of glauberite, each of which is higher in calcium sulfate, that being the direction in which the experiments with the labile salt regularly err. Anhydrite was not included in the isotherm. The new pentasalt[15] is found to be metastable with respect to both labile salt and glauberite; the points on its curve were obtained by rotating the salt with sodium sulfate solution until the maximum content of calcium was found by analysis, which point was usually reached between five and twenty-four hours. During this period there was sometimes the appearance of a few glauberite crystals and more frequently formation of the labile salt set in.

The 50° Isotherm.—The isotherm at 50°, which includes a solubility curve for anhydrite in addition to the salts included at lower temperatures, is shown in Table III and Fig. 3. In this table and others which follow, the results in parentheses were obtained by interpolation.

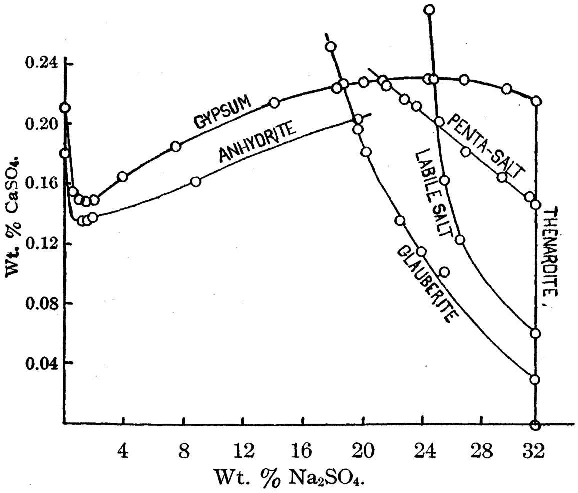

Fig. 3.—$CaSO_4$–Na_2SO_4–H_2O at 50°.

The gypsum curve again shows a minimum and maximum. No spontaneous formation of glauberite from gypsum occurred at any concentration of sodium sulfate; our observation is that it occurs only as a second step after labile salt (or pentasalt) has formed, according to the two equations

$$CaSO_4{\cdot}2H_2O + 2Na_2SO_4 \longrightarrow 2Na_2SO_4{\cdot}CaSO_4{\cdot}2H_2O$$

$$2Na_2SO_4{\cdot}CaSO_4{\cdot}2H_2O \longrightarrow Na_2SO_4{\cdot}CaSO_4 + Na_2SO_4 + 2H_2O$$

In obtaining the points on the gypsum curve any length of time was found possible up to about 25% sodium sulfate; beyond that concentration not more than ten minutes could be allowed

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(15) We are indebted to Dr. John E. Ricci and Dr. Thomas W. Davis for the experimental work with this salt at 35 and at 50°.

TABLE III

$CaSO_4$–Na_2SO_4–H_2O AT 50°

Original complex Wt. %		Saturated solution Wt. %		
Na_2SO_4	$CaSO_4$	Na_2SO_4	$CaSO_4$	Solid phases
—	—	—	0.210	Gypsum
0.449	8.437	0.521	.154	Gypsum
.894	7.576	.989	.149	Gypsum
1.431	3.758	1.521	.148	Gypsum
1.889	3.743	1.981	.149	Gypsum
3.712	3.672	3.908	.164	Gypsum
7.160	3.540	7.496	.185	Gypsum
13.36	3.774	14.05	.214	Gypsum
18.20	0.657	18.28	.224	Gypsum
19.94	.403	20.07	.228	Gypsum
23.11	3.810	24.40	.230	Gypsum
26.43	1.755	26.93	.230	Gypsum
29.76	0.539	29.75	.224	Gypsum
33.59	.525	31.77	.216	Gypsum + thenardite
—	—	31.73	—	Thenardite
—	—	1.236	.135	Anhydrite
1.941	.594	1.529	.135	Anhydrite
1.945	.856	1.942	.138	Anhydrite
8.978	1.006	8.923	.162	Anhydrite
35.38	0.641	31.70	.040	Thenardite + glauberite
29.49	.967	29.08	.058	Glauberite
25.84	.522	25.49	.102	Glauberite
26.71	5.280	23.93	.115	Glauberite
22.77	0.749	22.53	.136	Glauberite
20.14	.195	20.24	.182	Glauberite
20.33	1.172	19.68	.197	Glauberite
19.79	1.299	19.66	.203	Glauberite + anhydrite
18.65	1.096	18.71	.227	Glauberite + gypsum
18.23	1.068	18.44	.233	Glauberite
18.10	0.722	17.88	.252	Glauberite
33.71	.807	31.67	.060	Labile salt + thenardite
—	—	26.61	.124	Labile salt
—	—	25.51	.163	Labile salt
—	—	24.8	.230	Labile salt + gypsum
—	—	24.51	.277	Labile salt
—	—	31.7	.147	Pentasalt + thenardite
—	—	31.3	.153	Pentasalt
—	—	29.4	.165	Pentasalt
—	—	27.0	.182	Pentasalt
—	—	25.2	.202	Pentasalt + labile salt
—	—	23.6	.213	Pentasalt
—	—	22.8	.217	Pentasalt
—	—	21.6	.226	Pentasalt
—	—	(21.4)	(.229)	Pentasalt + gypsum

before the solubility began to drop, and at 31.77% (the invariant concentration) a still shorter time was necessary. The points on the curve for the labile salt were all obtained from undersaturation with material made at 35° and about 30% sodium sulfate; when the attempt was made to obtain results by formation of the labile salt from gypsum, the formation of glauberite began before the formation of the labile salt was complete. Glauberite, it will be observed, is the stable salt over a considerable range of concentrations; at about 25% sodium sulfate it could be formed completely in about two days from gypsum, via the labile salt, and from anhydrite in about two weeks. The invariant point with gypsum could be approached only from lower concentrations of sodium sulfate, that is, by decomposition of glauberite to gypsum, but not from the higher concentrations (change of gypsum to glauberite) because of the non-existence at this concentration of the apparently necessary intermediate compound, the labile salt. The curve for anhydrite was included, this being the lowest temperature at which it was thought feasible to work with that salt. It recently has been shown[11] that anhydrite is stable with respect to gypsum at temperatures down to 42°, as had previously been indicated in the systems containing potassium sulfate and ammonium sulfate.[9] The solid used was an artificial anhydrite made by dehydration of gypsum by sulfuric acid as previously described;[9] the solubility figures represent approach from undersaturation for one week's time, and were found constant for two months; approach from supersaturation did not prove feasible. Experiments were not successful in the region where the anhydrite is metastable with respect to glauberite or the labile salt. The points on the pentasalt curve are all obtained from undersaturation, using a sample of the salt made at 75° and periods of from two to eighteen hours, the time being limited usually by the spontaneous appearance of the labile salt.

The 75° Isotherms.—Table IV and Fig. 4 show the results at 75°, which include curves for the two forms of calcium sulfate and the three double salts.

The gypsum curve has apparently lost the maximum. In obtaining the curve, gypsum could be left in contact with solutions containing up to 12–13% of sodium sulfate for a half day without appearance of double salts; from that point on, there was almost immediate formation of double salts (probably pentasulfate, or labile salt at the higher concentrations) as shown by the extrapolation of the tie-lines; the last four points on the gypsum curve show the presence of double salt, although the filtrations were made within a minute or two. For this reason it is possible that the true solubility curve is slightly higher than we have found; Barre's[5] two figures are very much lower than ours, probably on this same account. The anhydrite figures were obtained from undersaturation, the time being a few days to a week; two points standing slightly above the curve represent approach from supersaturation by a month's decomposition of the pentasulfate. In the region in which anhydrite is metastable with respect to glauberite, it changes to that salt in surprisingly short time, so that the curve could not be continued to higher concentrations. The point on the glauberite curve at 25.78% sodium sulfate was obtained from anhydrite in two days. The points on the curve for the labile salt were obtained wholly from undersaturation, using material obtained at lower temperatures and were contaminated with excess sodium sulfate, for which reason the exact composition of the original complexes is not known; the time was restricted to one-half hour or less to avoid too extensive

Table IV

$CaSO_4$–Na_2SO_4–H_2O at 75°

Original complex Wt. %		Saturated solution Wt. %		
Na_2SO_4	$CaSO_4$	Na_2SO_4	$CaSO_4$	Solid phases
—	—	—	0.192	Gypsum
0.488	2.257	0.506	.142	Gypsum
.978	2.212	1.009	.143	Gypsum
1.461	2.309	1.505	.145	Gypsum
1.944	2.306	1.996	.148	Gypsum
3.890	2.316	4.036	.168	Gypsum
7.766	2.300	8.046	.199	Gypsum
10.05	2.747	10.38	.224	Gypsum
12.17	2.870	12.06	.238	Gypsum
17.96	1.892	17.20	.270	Gypsum
22.56	2.494	23.15	.300	Gypsum
29.61	0.511	29.62	.308	Gypsum
—	—	30.32	.308	Gypsum + thenardite
—	—	30.38	—	Thenardite
0.991	0.980	1.002	.070	Anhydrite
4.955	1.243	5.017	.086	Anhydrite
7.94	4.671	8.93	.113	Anhydrite
9.099	2.536	9.205	.103	Anhydrite
9.62	3.309	9.95	.113	Anhydrite
15.82	0.824	14.47	.117	Anhydrite
18.94	.577	18.92	.128	Anhydrite + glauberite
19.78	.895	19.95	.129	Anhydrite
—	—	30.32	.042	Glauberite + thenardite
28.88	4.619	27.14	.052	Glauberite
28.57	3.815	26.76	.054	Glauberite
28.96	5.253	26.35	.056	Glauberite
25.94	0.410	25.78	.060	Glauberite
23.39	1.756	22.45	.086	Glauberite
19.23	0.808	19.20	.123	Glauberite
—	—	18.16	.138	Glauberite
16.42	.354	16.30	.175	Glauberite
15.43	.523	15.12	.198	Glauberite
14.36	.521	14.16	.225	Glauberite
13.76	2.006	13.85	.247	Glauberite + gypsum
—	—	30.38	.081	Labile salt + thenardite
—	—	29.06	.103	Labile salt
—	—	28.46	.110	Labile salt
—	—	26.17	.154	Labile salt
—	—	25.94	.169	Labile salt
—	—	25.20	.210	Labile salt
—	—	24.20	.292	Labile salt
—	—	(24.0)	(.302)	Labile salt + gypsum
—	—	10.2	.221	Pentasulfate + gypsum
10.85	1.386	10.81	.217	Pentasulfate
11.11	1.478	11.05	.201	Pentasulfate
12.39	5.355	12.10	.208	Pentasulfate
12.99	0.430	13.06	.207	Pentasulfate
13.74	6.490	13.60	.200	Pentasulfate
14.36	2.605	14.25	.197	Pentasulfate
15.00	3.433	15.07	.201	Pentasulfate
14.99	1.117	15.10	.198	Pentasulfate + glauberite
16.97	0.354	17.03	.189	Pentasulfate
19.01	.472	19.08	.185	Pentasulfate
—	—	(26.2)	(.160)	Pentasulfate + labile salt
33.76	.510	30.28	.146	Pentasulfate + thenardite

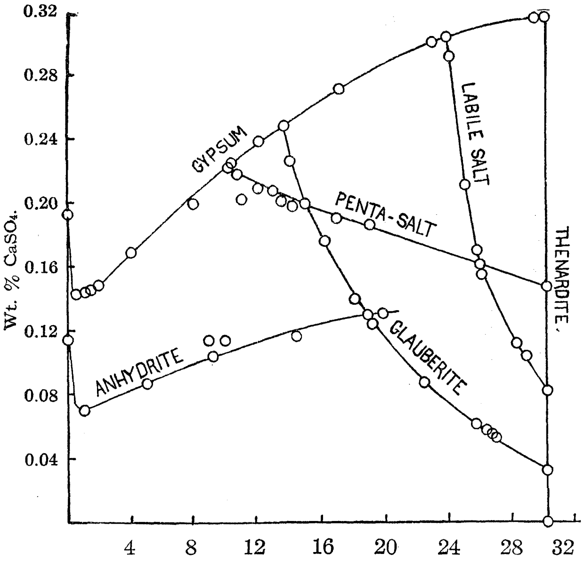

Fig. 4.—$CaSO_4$–Na_2SO_4–H_2O at 75°.

TABLE V

ISOTHERMALLY INVARIANT POINTS IN SYSTEM $CaSO_4$–Na_2SO_4–H_2O

	Wt. % Na_2SO_4 found							
	I Gypsum + mirabilite	II Thenardite with any Ca-salt	III Labile salt + pentasalt	IV Labile salt + gypsum	V Glauberite + anhydrite	VI Glauberite + pentasalt	VII Glauberite + gypsum	VIII Pentasalt + gypsum
25°	21.7	33.9	..	29.8	..	..	25.9	...
35°	..	32.8	..	26.7	..	..	22.65	30.0
50°	..	31.7	25.2	24.8	19.7	..	18.7	(21.4)
75°	..	30.3	(26.2)	(24.0)	18.9	15.1	13.85	10.2

formation of glauberite. The glauberite curve represents formation of the salt from gypsum, by way of labile salt, for periods of approximately one day. The figures for the pentasalt were obtained mostly by formation of the compound from gypsum and glauberite, in a few cases from undersaturation with pure pentasulfate. In general, the time allowed for formation was from two to five days at concentrations of sodium sulfate between 10 and 14%; in no case is any extensive decomposition of the pentasalt indicated by the extrapolation of the tie-lines, which show a solid with a sodium sulfate content of 10.84 to 17.7% (16.2 by theory). At higher concentrations, however, where it is metastable with respect to glauberite, its decomposition is very rapid, and the points on the curve were obtained in times of an hour or less.

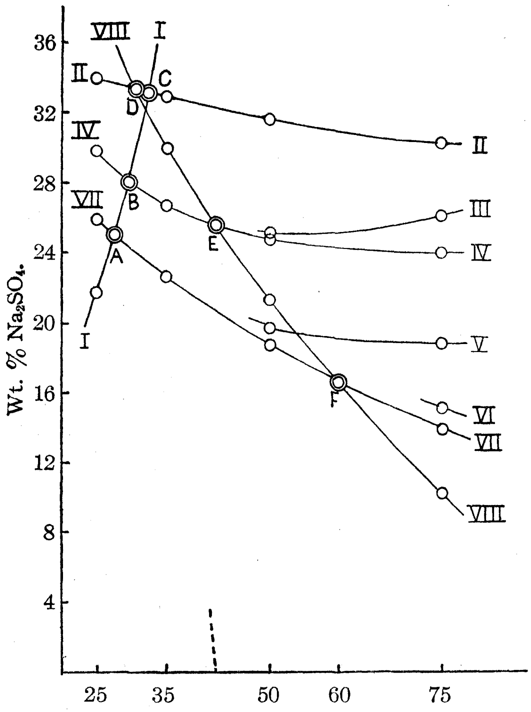

Fig. 5.—Polytherm of system $CaSO_4$–Na_2SO_4–H_2O. Curve I, gypsum and mirabilite; II, thenardite and any calcium salt; III, labile salt and pentasalt; IV, labile salt and gypsum; V, glauberite and anhydrite; VI, glauberite and pentasalt; VII, glauberite and gypsum; VIII, pentasalt and gypsum.

The Polythermal Diagram.—The results at the four temperatures are collected in Table V and in the polythermal diagram, Fig. 5, showing the concentration of sodium sulfate at each point and omitting the small concentrations of calcium sulfate. A corresponding diagram showing the concentrations of calcium sulfate can be constructed from the foregoing tables, but with less clarity.

In Fig. 5, the lines represent saturation with respect to the two salts indicated in each case by the Roman numeral in Table V, but it is to be noted that the areas between lines do not represent fields of saturation with respect to a single salt, as in the usual diagram, since the many degrees of metastability occurring in this system make impossible that simple method of representation. Curve I is the curve for mirabilite and gypsum. Curve II represents saturation with thenardite and any one of the calcium-containing salts; since their solubility is in all cases so slight, it is found that the solutions saturated with two salts show the solubility of thenardite within the errors of analysis. The curves for the labile salt with other salts make a pair (III and IV) running increasingly close together at lower temperatures; Barre's figures[5] for one of these pairs (gypsum and labile salt) are slightly above ours at the lower temperature and below ours at 75°, which we attribute to partial change of his salt to glauberite or pentasalt. The curves for glauberite with another salt make a trio (V–VI–VII) lower down in the diagram; Barre's figures for the gypsum–glauberite curve are above 2% higher than ours, as is also D'Ans' figure at 60°. The curve for gypsum and pentasalt (VIII) shows a markedly different direction, in accord with the fact that the solubility curve of the pentasalt (Figs. 2–4) does not parallel the curves for the other salts.

The system shows a relatively small number of invariant points of saturation with respect to three salts within the temperature range studied. That the number is small may be seen from the four isotherms, in which it appears that four of the seven salts considered change their relative solubility but slightly with change of temperature. The exceptions are anhydrite, mirabilite and pentasalt. With respect to anhydrite, it has been shown lately[11] that its transition temperature with gypsum is 42° instead of the higher temperature (63.5°) assigned at an earlier date by van't Hoff;[16] there must therefore be a series of invariant points below that temperature for anhydrite and gypsum with each of the other salts of the system. Because of the difficulty in obtaining saturation with anhydrite at these lower temperatures, this series of points has not been determined. Mirabilite increases its solubility greatly between 25° and its transition temperature to thenardite, 32.4°, so that its solubility curve (Fig. 1 and Fig. 5, curve I) passes through the solubility curves for gypsum–glauberite (VII), gypsum–labile salt (IV) and gypsum–thenardite (II), giving rise to invariant points A, B and C. A similar change in the solubility of the pentasalt gives rise to the invariant points D, E and F. The interpolated values of the temperature and the concentration of sodium sulfate are collected in Table VI.

TABLE VI

INVARIANT POINTS IN SYSTEM $CaSO_4$–$NaSO_4$–H_2O

Letter in Fig. 5	Saturating salts	Temp., °C.	Wt. % Na_2SO_4
A	Gypsum, Mirabilite, Glauberite	27.5	25.0
B	Gypsum, Mirabilite, Labile salt	29.5	28.0
C	Mirabilite, Thenardite, Gypsum	32.4	33.0
D	Pentasalt, Gypsum, Thenardite	31	33.2
E	Pentasalt, Gypsum, Labile salt	44	25.5
F	Pentasalt, Gypsum, Glauberite	60	16.6

The invariant points A and B of this table were determined previously by van't Hoff[7] and set at 29 and 30.2°, respectively; it is possible that the interpolated figures of Table VI from equilibrium experiments may be closer to the true values. The interpolated values which we have obtained for points D, E and F probably are less close to the true values, since they depend upon equilibria which were less clearly established.

Summary

The system $CaSO_4$–Na_2SO_4–H_2O has been studied and isotherms constructed at four temperatures, 25, 35, 50 and 75°, including solubility determinations for gypsum, anhydrite, glauberite, the labile salt and a new hydrated sodium pentacalcium sulfate, $Na_2SO_4 \cdot 5CaSO_4 \cdot 3H_2O$. The metastability and the composition of the labile salt, $2Na_2SO_4 \cdot CaSO_4 \cdot 2H_2O$, have been confirmed, and a polythermal diagram of the system sketched.

UNIVERSITY HEIGHTS
NEW YORK, N. Y.

RECEIVED APRIL 22, 1938

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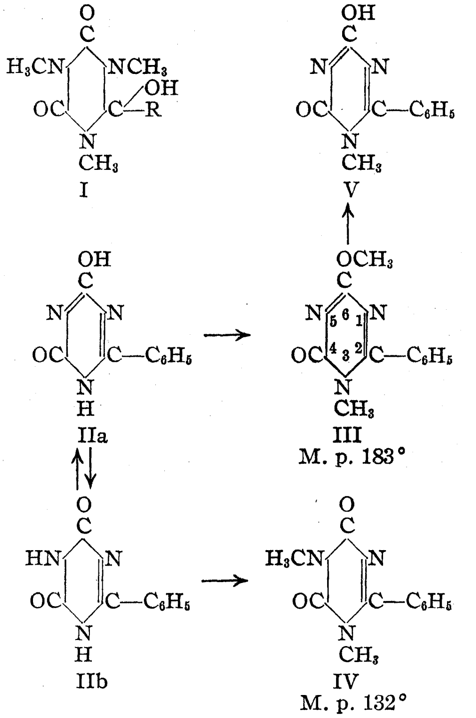
[16] Van't Hoff, *Z. physik. Chem.*, **45**, 257 (1903).

[CONTRIBUTION FROM THE LABORATORIES OF THE MOUNT SINAI HOSPITAL]

Studies on Triazines. II.
Lactim–Lactam Isomerism in Substituted Tetrahydrotriazines

BY EDITH BLOCH[1] AND HARRY SOBOTKA

In a previous communication[2] 1,3,5-trimethyl-2-phenyl(or -alkyl)-2-hydroxy-4,6-dioxohexahydrotriazines (I) were described. In order to corroborate this formulation it was attempted to arrive at a common derivative starting from 2-phenyl-4,6-dioxotetrahydrotriazine (II), the cyclization product of benzoyl biuret, a substance studied extensively by Ostrogovich.[3] In his later communications he ascribes mono-enolic structures to this product and to various homologs, as given in formula IIa. However, the result of catalytic hydrogenation seems to favor IIb, as only two hydrogen atoms can be introduced in the methyl homolog, yielding trigenic acid.[4]



The methylation of 2-phenyl-4,6-dioxotetrahydrotriazine with diazomethane in ether yields a mixture of two isomeric substances $C_{11}H_{11}O_2N_3$. One of them crystallizes in fine needles of m. p. 183°, whereas the other forms heavy, stout platelets of m. p. 132° and is generally more soluble in organic solvents and water. At first it was suspected that the two isomers differ from each other like isocyanurates from cyanurates, the former carrying the methyl groups on nitrogen, the latter on oxygen.

The constitution of the lower melting substance (IV) was confirmed by analysis of its decomposition products. After eight hours of digestion in alkaline solution, benzoic acid could be isolated from the mother liquors and methylamine hydrochloride, as well as ammonium chloride from the distillate, the methylamine hydrochloride definitely exceeding 1 equivalent.

Quantitative methoxyl determinations showed the absence of methoxyl in substance IV and the presence of only 1 methoxyl group in substance III. On treatment with dilute acid or alkali, substance III easily loses one methyl group and a monomethyl derivative (V) is formed. We therefore assign structure III with one methoxyl and one methyl imide group to this product. The location of the methyl groups in position 3 and 6 is not proved definitely, but seems more likely than in 4 and 5 or the highly improbable positions 3 and 4 or 5 and 6. The simultaneous occurrence of oxygen and nitrogen bound methyl groups in the molecule of this substance is the more remarkable, since no such "$^1/_3$ or $^2/_3$-isoesters" occur in the case of cyanuric acid. Hantzsch and Bauer[5] claimed the existence of such compounds, but Slotta and Tschesche[6] disproved their results and attribute the non-existence of such "mixed" esters–isoesters to the great trend toward symmetry in the molecule. In the present case there is, however, a far lesser degree of symmetry in the starting material which makes the unequal methylation more plausible. On treatment with diazomethane the monomethyl derivative V yielded again the mixed ester–isoester III in about 80% yield.[7]

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[1] Hernsheim Fellow in Chemistry.

[2] Sobotka and Bloch, THIS JOURNAL, **59**, 2606 (1937).

[3] A. Ostrogovich, *Gazz. chim. ital.*, **39**, 540 (1909); **44**, 562 (1914); **65**, 229 (1935); *Bul. Soc. Stiinte Cluj*, **4**, 521, 528 (1929).

[4] A. Ostrogovich and G. Ostrogovich, *Gazz. chim. ital.*, **66**, 48 (1936).

[5] Hantzsch and Bauer, *Ber.*, **38**, 1005, 1113 (1905).

[6] Slotta and Tschesche, *ibid.*, **60**, 295, 301 (1927).

[7] The methylation of imino nitrogen by diazomethane seems to depend upon its position in a ring between two CO groups, influencing the acidic character of the imino hydrogen. Cyanuric acid [Palazzo and Scelsi, *Gazz. chim. ital.*, **38**, 659 (1908)], phthalimide [Pechmann, *Ber.*, **28**, 859 (1895)], succinimide and the triazines in the present case react, whereas urea, methyl urea, benzoyl

Although the substances I and IV differ from each other only by the elements of methyl alcohol, it was not possible to convert one into the other. Neither the removal of CH_3OH from substance I nor the addition of the elements of water to the double bond in IV could be achieved. Aqueous or alcoholic sulfuric or hydrochloric acids of various concentrations were tried. However, in each case only the starting material could be recovered, even after heating to 100° in concd. sulfuric acid.

The similarity between substances I and IV is exemplified by their behavior on bromination. The tetrabromide $C_{11}H_{11}O_2N_3Br_4$ is very similar in appearance and properties to the substance $C_{12}H_{14}O_2N_3Br_3$ derived from substance I by bromination under identical conditions.[2] They differ from each other by one methyl group and the replacement of one hydrogen atom by bromine. Debromination of the new tetrabromide with alkali, zinc dust, or silver salts does not yield the starting material or any other crystalline substance.

The pharmacological action of these substances is under investigation.

Experimental Part

Benzoyl Biuret.—Forty grams of urea was dissolved in 120 cc. of dry pyridine and refluxed for two hours. The mixture was allowed to cool to about 80° and 38.5 cc. of benzoyl chloride was added dropwise under stirring, until a uniform solution was obtained, which occurs sharply on addition of the last drop. The solution was warmed for thirty minutes on a boiling water-bath, cooled to room temperature and kept in the refrigerator overnight. The resulting solid mass of crystals was extracted three times with 200 cc. of warm chloroform to remove benzamide and dibenzamide, formed as by-products of the reaction. The residue was heated for five minutes with 400 cc. of water and filtered hot through a Büchner funnel. This extraction with water was repeated twice. Then the residue was extracted twice with 200 cc. of hot methyl alcohol and filtered hot as above. After drying, the residue had a melting point of about 220° and was sufficiently pure for the following reaction; yield 11–12 g. After repeated recrystallization from ethyl alcohol the substance melted at 224–225° (all melting points corrected).

From the combined aqueous and alcoholic extracts and mother liquors a mixture of benzoyl urea and little benzoyl biuret was obtained. It was extracted with water in a Soxhlet extractor for forty-eight hours. A small amount of pure benzoyl biuret could be obtained from the residue in the thimble by recrystallization from ethyl alcohol. From the aqueous extracts benzoyl urea crystallized, which, after recrystallization from ethyl alcohol, melted at 214–216°; yield *ca.* 25 g.[8]

2-Phenyl-4,6-dioxotetrahydrotriazine (II).—Twelve grams of crude benzoyl biuret was dissolved in a solution of 7.5 g. of potassium hydroxide in 350 cc. of water and after standing for one hour the solution was saturated with carbon dioxide. The monopotassium salt crystallized and was redissolved by addition of more water. The solution was now made just acid to congo by addition of 50% acetic acid. On standing overnight the triazine crystallized in beautiful needles, which after recrystallization from ethyl alcohol melted at 297–300°; yield *ca.* 5 g.[8] The substance could be recovered unchanged after two hours of heating with concentrated sulfuric acid on a boiling water-bath.

Methylation of 2-Phenyl-4,6-dioxotetrahydrotriazine.—A solution of diazomethane in ether (from 8 g. of nitrosomethyl urea) was dried for one hour over pellets of potassium hydroxide and then poured over 3 g. of 2-phenyl-4,6-dioxotetrahydrotriazine, suspended in 500 cc. of dry ether. Slow reaction with gradual evolution of nitrogen occurred. After standing for two days at room temperature, the ether was filtered from a small amount of undissolved material and evaporated *in vacuo* to a volume of about 25 cc. After standing in the refrigerator overnight, the crystalline part was filtered on a Büchner, pressed well, to remove as much of the oily material as possible, then recrystallized twice from benzene: m. p. 183°; yield about 0.8–1.0 g. The ethereal and benzene mother liquors were combined and evaporated to dryness under reduced pressure. The partly oily residue was dissolved in 300 cc. of boiling water. On slow cooling and rubbing a small amount of fine needles appeared, which after recrystallization from benzene melted at 183° and were combined with the first lot; yield about 0.1 g The substance forms long fine white needles, very soluble in methanol, ethanol, hot benzene, soluble in chloroform, ether, glacial acetic acid; little soluble in water and in petrolic ether.

Anal.[9] Calcd. for $C_{11}H_{11}O_2N_3$: C, 60.83; H, 5.07; N, 19.30; OCH_3, 14.30. Found: C, 60.83; H, 5.11; N, 19.50; OCH_3, 14.18.

The aqueous mother liquors were extracted three times with 100 cc. of benzene in a separatory funnel, the combined extracts dried over sodium sulfate and evaporated *in vacuo*. The oily residue crystallized on rubbing with a few drops of petrolic ether. The substance was dissolved in 50 cc. of butanol on a hot water-bath. On cooling it slowly crystallized and after standing for several days was filtered on a Büchner funnel and washed several times with a mixture of 1 part of methyl alcohol and 4 parts of petrolic ether: m. p. 120–125°; yield *ca.* 0.5 g. Examination under the microscope proved that the substance still contained needles of the higher melting isomer. By repeated recrystallization from butanol it was finally obtained pure, in heavy, stout platelets melting at 132°. The substance is very soluble in organic solvents, except petrolic ether, also soluble in water. It is easily soluble in concd. hydrochloric acid and can be reprecipitated on neutralization with 10% ammonia.

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urea, benzoyl biuret and glycine anhydride were found to remain unchanged in dry ether, also in wet ether suspension and in acetone-ether mixtures. For the reaction of amino acids see Kuhn and Brydowna, *Ber.*, **70**, 1333 (1937).

[8] Method adapted from A. Ostrogovich, *Bul. Soc. Stiinte Cluj*, **4**, 521, 528 (1929).

[9] We are indebted to Dr. S. A. Morrell for the methoxyl determinations.

Anal. Calcd. for $C_{11}H_{11}O_2N_3$: C, 60.83; H, 5.07; N, 19.30; OCH_3, 0. Found: C, 60.86; H, 4.92; N, 19.56; OCH_3, 0.

Monomethyl Derivative (V).—Five-tenths gram of substance III was heated with 2 cc. of normal sodium hydroxide for ten minutes. After cooling the solution was acidified with dilute sulfuric acid; the product separated at once and was recrystallized from dilute methanol or from a large amount of water, as prismatic glistening white needles, of m. p. 278–280°. The same product was also obtained by heating substance III in aqueous or alcoholic hydrochloric acid.

Anal. Calcd. for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.43; N, 20.49; OCH_3, 0. Found: C, 59.02; H, 4.54; N, 20.22; OCH_3, 0.

Alkali Hydrolysis of Substance IV.—Hydrolysis was carried out in an apparatus similar to that described by Lieber and Smith:[10] 217 mg. of substance III was dissolved in 40 cc. of 25% sodium hydroxide and heated. After the given time intervals the receiver containing a measured amount of acid was changed and the liquid in the distilling flask each time filled up to the original volume The acid was titrated with 0.1 N alkali and from the amounts used by the distilled ammonia and methylamine the percentage hydrolysis was computed. It was 36.7, 56.3, 73.0, 83.2, and 84.6% after one, two, four, six, and eight hours, respectively.

After eight hours the alkaline solution was carefully acidified and the resulting precipitate filtered. After recrystallization from alcohol the substance formed shining plates which proved to be identical in melting point and gave no melting point depression with benzoic acid (122°). In order to determine the nature of the distilling amine, 1 g. of substance IV was hydrolyzed for eight hours with 50 cc. of 25% potassium hydroxide and the distillate absorbed in excess hydrochloric acid. The solution was evaporated to dryness and the residue carefully dried in a vacuum desiccator to constant weight; yield 460 mg. The material was extracted in a Soxhlet extractor with absolute alcohol for four hours. The alcoholic extract on evaporation yielded 350 mg. of methylamine hydrochloride. The residue in the thimble consisted of ammonium chloride.

Reaction of Substance IV with Bromine.—Forty-five hundredths gram of substance IV was dissolved in 2 cc. of glacial acetic acid and 2.5 cc. of an 8% solution of bromine in glacial acetic acid added dropwise. The bromide crystallized at once in beautiful red plates, which on filtering and washing with dry ether became yellow, apparently with loss of hydrobromic acid; yield 0.57 g. The substance was recrystallized from hot glacial acetic acid, containing bromine; it is very soluble in methanol, ethanol, soluble in hot chloroform and glacial acetic acid, insoluble in ether; it is readily debrominated by dilute alkali, also by silver salts in aqueous solution or etheric suspension.

Anal. Calcd. for $C_{11}H_{11}O_2N_3Br_4$: C, 24.58; H, 2.04; N, 7.82; Br, 59.59. Found: C, 24.84; H, 2.30; N, 7.73; Br, 59.87.

Summary

2-Phenyl-4,6-dioxotetrahydrotriazine, the cyclization product of benzoyl biuret, yields two isomeric dimethyl derivatives on methylation with diazomethane. The pair represents a case of lactam–lactim tautomerism involving one of the two methyl groups.

NEW YORK, N. Y. RECEIVED APRIL 18, 1938

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[10] E. Lieber and G. B. L. Smith, THIS JOURNAL, **59**, 2283 (1937).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

A New Synthesis of 3,4-Benzpyrene Derivatives

BY LOUIS F. FIESER AND E. B. HERSHBERG[1]

The only synthesis of the powerfully carcinogenic 3,4-benzpyrene heretofore achieved is that of Cook and Hewett,[2] consisting in the application to pyrene of the general method of constructing an additional ring with the use of succinic anhydride. With the technical improvements in the various steps introduced in this Laboratory,[3,4] by Winterstein, Vetter and Schön,[5] and by Vollmann, *et al.*,[6,7] 3,4-benzpyrene can now be prepared fairly readily by this method in over-all yield of about 36%.[3] The succinic anhydride synthesis, however, is not adaptable to the preparation of many derivatives of the important parent hydrocarbon, and the list of compounds thus far obtained by application of the general synthesis or by utilization of the same intermediates includes only the following substances: 4'-methyl-3,4-benzypyrene[3,8] (and its dihydride[3,8]), 3'(?)-methyl-3,4-benzpyrene,[5] 4'-hydroxy-3,4-benzpyrene,[4] 3,4-benzpyrene-3',4'-dicarboxylic anhydride[9] (and its dihydride[9]), 1',2',3',4'-tetrahydro-3,4-benzpyrene.[3,5,10]

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[1] Lilly Research Fellow.

[2] Cook and Hewett, *J. Chem. Soc.*, 398 (1933).

[3] L. F. Fieser and M. Fieser, THIS JOURNAL, **57**, 782 (1935).

[4] Fieser, Hershberg, Long and Newman, *ibid.*, **59**, 475 (1937).

[5] Winterstein, Vetter and Schön, *Ber.*, **68**, 1079 (1935).

[6] Vollmann, Becker, Corell and Streeck, *Ann.*, **531**, 1 (1937).

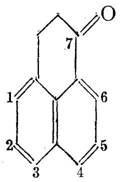
[7] For further comments on the synthesis, see Sannié and Poremski, *Bull. soc. chim.*, [5] **3**, 1139 (1936); Rondoni and Corbellini, *Atti accad. Lincei*, VI, **21**, 128 (1935).

[8] Fieser and Newman, THIS JOURNAL, **57**, 1602 (1935).

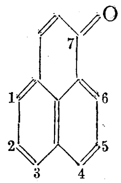
[9] L. F. Fieser, M. Fieser and E. B. Hershberg, *ibid.*, **58**, 1463 (1936).

[10] The analytical sample of this hydrocarbon prepared with Mrs. Fieser[3] (by Clemmensen reduction) formed faintly yellow plates, m. p. 113°, whereas Winterstein, Vetter and Schön[5] subsequently

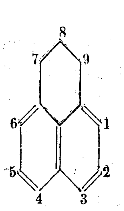
The synthesis of additional derivatives of known structure seemed to us of importance both for the purpose of exploring further the relationship between carcinogenic activity and structure and in order to provide reference substances for use in investigating the course of the oxidation,[6] diazo coupling,[11] and other substitutions[12] of the interesting hydrocarbon.[13] Because of the limitations in the succinic anhydride synthesis, a search was made for an alternate method of constructing the 3,4-benzpyrene ring system, and we can now report the development of a new synthesis which offers promise of considerable variation. An important step of the process involves a Scholl *peri*-condensation of a benzoylnaphthalene derivative, and in this respect the synthesis resembles that discussed but not tried by Cook and Hewett.[2] These authors expressed the view that 3,4-benzpyrene probably could be synthesized by application of the Scholl reaction to the benzoyl derivative of the ketone obtained by Mayer and Sieglitz[14] by the cyclization of β-(1-naphthyl)-propionic acid and regarded by them as having the structure I (for a discussion of the nomenclature of compounds I–III, see footnote[15]).



Perinaphthanone-7
I



Perinaphthenone
II



Perinaphthane
III

Cook and Hewett,[16] however, subsequently found that under certain conditions the cyclization gives a mixture of products, one of which is the unsaturated ketone II, apparently identical with the "pyrene ketone" obtained by Bamberger and Philip[17] in their degradation of pyrene.[17a] The English workers also observed in another connection that 4,5-benzhydrindone-3, a ketone somewhat analogous to I, failed to enter into a typical Friedel and Crafts reaction even at slightly elevated temperatures.[18] It was our plan to attempt to benzoylate not a ketone or diketone,[2] but the corresponding tricyclic hydrocarbon III.

peri-Trimethylenenaphthalene, for which we propose the new name perinaphthane,[15] was first isolated by Langstein,[19] who obtained a small amount of the crystalline hydrocarbon as a product of the degradation of pyrene. A synthesis was accomplished by Fleischer and Retze[20] from naphthalene and malonyl bromide, but the process involved reduction of the resulting diketone with hydrogen iodide and red phosphorus, followed by dehydrogenation of the over-reduced product, and the method is hardly practical for preparative purposes. In seeking a practical method we first considered the possibility of effecting a cyclization of 1-allylnaphthalene[21] into

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reported obtaining colorless needles, m. p. 135°, from methanol. In an effort to account for this discrepancy the earlier experiment in this Laboratory has been repeated (L. F. F.). A pure sample (6.3 g.) of 4′-keto-1′,2′,3′,4′-tetrahydro-3,4-benzpyrene (crystallized from dioxane[4]) was reduced by the Clemmensen method with added dioxane and toluene. The crude, twice distilled product (3.7 g., pale yellow, m. p. 110.5–112°) was crystallized repeatedly from glacial acetic acid and from alcohol, further purified by chromatographic adsorption (E. B. H.), and again crystallized from alcohol, when it formed lustrous, colorless plates, m. p. 112.6–113.1°, corr. This material appears to be a pure individual, and our earlier observation concerning the melting point of the product of Clemmensen reduction is thus confirmed. High pressure hydrogenation of the ketone was reported[3] to give low-melting crude material which affords pure 3,4-benzpyrene on dehydrogenation. We may now add that this crude product, although it appears to contain a considerable quantity of the above tetrahydride, is not homogeneous and probably consists of a mixture of hydro derivatives.

(11) Fieser and Campbell, This Journal, **60**, 1142 (1938).

(12) Windaus and Rennhak, *Z. physiol. Chem.*, **249**, 256 (1937).

(13) Our hydrogenation, oxidation (lead tetraacetate), and reduction studies, This Journal, **59**, 2331, 2502 (1937); **60**, 940 (1938), are also being extended to 3,4-benzpyrene.

(14) Mayer and Sieglitz, *Ber.*, **55**, 1835 (1922).

(15) *Note on Nomenclature.*—Cook and Hewett[16] have noted that three systems of naming these tricyclic compounds have been employed and that none of them is strictly correct. The ketone II has been referred to as pyrene ketone,[17] phenalone-9,[14,16] 1,8-naphthindenone[6] [see also Criegee, Kraft and Rank, *Ann.*, **507**, 177 (1933); Koelsch, This Journal, **58**, 1326 (1936); Wojack, *Ber.*, **71**, 1102 (1938)], and *peri*-naphthindone.[25,26] While we hesitate to add to the confusion of the literature, there is as yet so little agreement or precedent that we venture to propose a system which seems to us more satisfactory than any heretofore employed. For the parent hydrocarbon with a saturated alicyclic bridge, the name *peri*-trimethylenenaphthalene is lengthy and not well adapted to naming *ac*-substitution products, "dihydrobenznaphthene" imputes to the unsaturated hydrocarbon "benznaphthene" [v. Braun and Rath, *ibid.*, **61**, 960 (1928)] a completely aromatic character which it does not possess, "dihydrophenalene" implies a closer relationship to benzene than to naphthalene, and "*peri*-naphthindane" suggests the presence of an indane system and a five-membered ring. The hydrocarbon has been made reasonably easily available in the present work and may assume a position of importance comparable with acenaphthene. The name suggested, perinaphthane, calls to mind significant features of the structure and can be modified to include various possible *ac*-derivatives by the usual conventions (compare cholestane). It does not represent a wide departure from at least one of the names prevously employed, for perinaphthane may be regarded as a condensation of *peri*-naphthindane. A lack of correspondence with parallel compounds of the acenaphthene (ace, from acetic) series is regrettable, but hardly avoidable, since the common name for the latter hydrocarbon does not conform to modern usage with respect to the alicyclic part of the molecule. It would have been more appropriate to use "acenaphthane" for the hydrocarbon with the saturated bridge and "acenaphthene" for its dehydro derivative.

(16) Cook and Hewett, *J. Chem. Soc.*, 365 (1934).

(17) Bamberger and Philip, *Ann.*, **240**, 178 (1887).

(17a) Professor Cook has called our attention to the more recent work of Darzens and Lévy, *Compt. rend.*, **201**, 902 (1935), who obtained a saturated ketone in excellent yield by conducting the cyclization in nitrobenzene solution.

(18) Cook and Hewett, *J. Chem. Soc.*, 1098 (1933).

(19) Langstein, *Monatsh.*, **31**, 867 (1910).

(20) Fleischer and Retze, *Ber.*, **55**, 3280 (1922).

(21) Tiffeneau and Daudel, *Compt. rend.*, **147**, 678 (1908).

the 8-position, but the only smooth transformation discovered gave a different result. When the substance was passed over alumina at 500–550° there was produced a liquid hydrocarbon corresponding in properties to α-propenylnaphthalene.[22]

We next investigated as a possible starting point for the preparation of the desired hydrocarbon in quantity a process described in the patent literature for the synthesis of the unsaturated ketone, perinaphthenone (II). According to an early patent[23] a yellow substance (m. p. 152°) of this probable structure can be obtained by heating either α- or β-naphthol with glycerol and 82% sulfuric acid, the acid presumably functioning as a dehydrating, condensing, and oxidizing agent. Cook and Hewett[16] noted that the reported properties are similar to those of Bamberger and Philip's[17] "pyrene ketone" (m. p. 142°) and of the product (m. p. 153–154°) formed with other substances from β-(1-naphthyl)-propionic acid under the cyclizing and dehydrogenating influence of stannic chloride[16] (or of aluminum chloride, acting on the acid chloride[14]). Finally Vollmann, *et al.*,[6] made a direct comparison of the material prepared according to the patent with a purified sample of "pyrene ketone" (m. p. 152°) and found the two to be identical. Although the original process did not seem very promising, a more recent patent[24] includes a detailed description of an improved procedure in which sodium nitrobenzene sulfonate is employed as the oxidizing agent. Silbermann and Barkow[25] have employed this procedure with success and have recorded further observations concerning the reaction. In our hands the reaction proceeded essentially as described in the patent. After finding a convenient method for recovering the product from the tarry reaction mixture, no difficulty was experienced in preparing the ketone in quantity (200 g.), and although the yield of pure product is only 26% of the theoretical, based on the β-naphthol used, the starting materials are of such a nature that this is not a very important consideration. Our purified perinaphthenone (II) melts at 156–156.5°, corr.

The only recorded attempt to reduce perinaphthenone is an experiment by Silbermann and Barkow[25] in which the ketone was treated with zinc and hydrochloric–acetic acid and the resulting oil distilled over zinc dust. This gave a very small amount of an evidently impure sample of perinaphthane (III). We investigated the hydrogenation of the ketone in the presence of Raney nickel, platinum oxide, and copper chromite catalyst with quite different results. With Raney nickel at atmospheric pressure the ketone in ether–alcohol absorbed 2 moles of hydrogen and gave as the chief product the previously unknown saturated alcohol, perinaphthanol-7. With Adams catalyst there was a rapid initial absorption of gas and a yellowish reaction product soon separated from the alcoholic solution. This substance is very sensitive and decomposes rapidly in solution. Rapid recrystallization gave deep yellow material for which analyses and molecular weight determinations suggest the structure of a dimolecular product of either reduction or reduction and condensation. This was not investigated further.

On hydrogenating the unsaturated ketone in dioxane or ether at high pressure in the presence of copper chromite catalyst we invariably obtained a mixture of the saturated alcohol and the hydrocarbon. As the temperature was increased less alcohol was found in the reaction mixtures, and it seems likely that the alcohol is produced in any case and, at the higher temperatures, is converted into perinaphthane by a process of dehydration and hydrogenation. It appeared, however, that the temperature cannot be increased beyond a certain point without offering opportunity for hydrogenation of the naphthalene nucleus. In order to avoid such over-hydrogenation and still maintain dehydrating conditions, the amount of catalyst was reduced to a minimum. Using but 2.5 mg. of catalyst per gram of ketone, it was found possible to conduct the hydrogenation at 250–260° in a reasonable time and obtain hydrocarbon of high purity in 70–74% yield.

With a satisfactory method available for the preparation of perinaphthane in quantity, little difficulty was experienced in completing the remaining steps of the 3,4-benzpyrene synthesis indicated in the chart. Benzoylation of the hydrocarbon by the Perrier method proceeded smoothly to give a crystalline product which we assume to be 3-benzoylperinaphthane (IV). For conversion into 2,1′-trimethylenebenzanthrone-10 (V) by the Scholl reaction it was found best to

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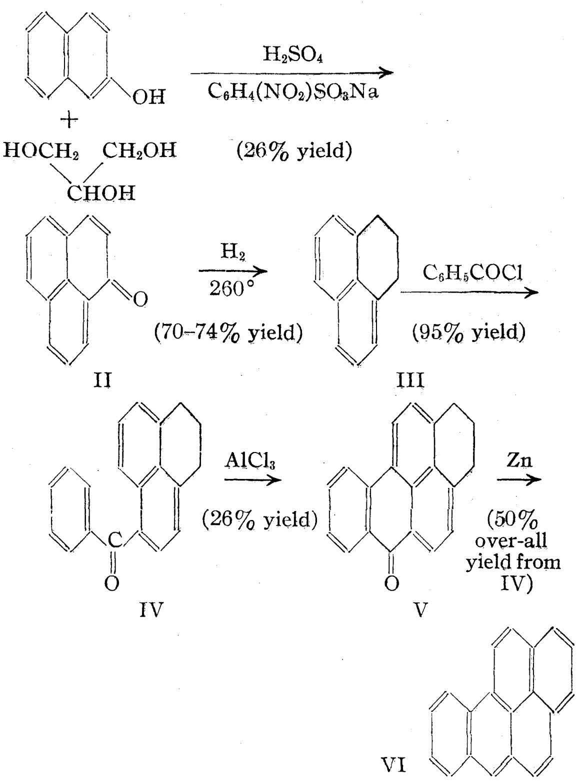
[22] Zal'kind and Zonis, *J. Gen. Chem.*, *U. S. S. R.*, **6**, 988 (1936).

[23] Bad. Anil. u. Sodafabrik, German Patent 283,066 (1915) [*Chem. Centr.*, **86**, I, 814 (1915)].

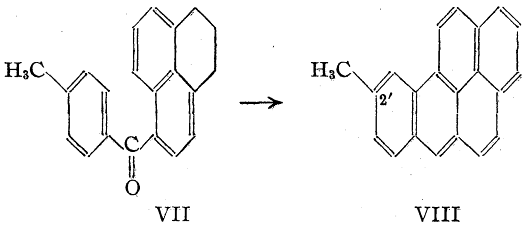
[24] I. G. Farbenindustrie, German Patent 614,940 (1935) [*C. A.*, **29**, 8009 (1935)].

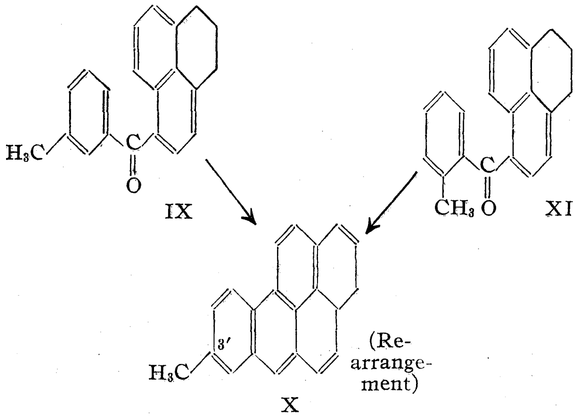
[25] Silbermann and Barkow, *J. Gen. Chem.*, *U. S. S. R.*, **12**, 1733 (1937).

heat the ketone IV in a sodium-aluminum chloride melt at 155° in an atmosphere of oxygen. A pure product was then isolated from the reaction mixture fairly readily, if in low yield, and on distillation with zinc dust it yielded pure 3,4-benzpyrene (VI). It was thought that hydro derivatives of V are probably formed in the Scholl reaction along with the benzanthrone derivative, and indeed the mother liquor material from V gave an additional quantity of 3,4-benzpyrene on zinc dust distillation. It was then found that the over-all yield of the hydrocarbon can be improved greatly by carrying out the cyclization process at a lower temperature without undue exposure to air and submitting the total amount of moist, gummy reaction product to distillation from a mixture with zinc dust. Conducted in this way, the synthesis affords 3,4-benzpyrene in over-all yield of 34% from perinaphthenone, or 9% from β-naphthol. The process is rapid and compares favorably with the older synthesis as a practical method of preparing the carcinogenic hydrocarbon.



In extending the synthesis, we investigated the three ketones resulting from the condensation of the isomeric toluyl chlorides with perinaphthane. The Scholl reaction was conducted under conditions judged from the above experience to give material best suited for conversion into the hydrocarbon rather than for the isolation of the benzanthrone derivatives, and these intermediates were not examined. The hydrocarbons did not prove difficult to purify, and the homogeneity was checked carefully by conversion to the beautifully crystalline, brilliant red trinitrobenzene complexes and recovery of the hydrocarbons by chromatographic adsorption of the trinitrobenzene on alumina from benzene solution. The *p*-toluyl compound VII gave in 42% yield a hydrocarbon which we regard as 2′-methyl-3,4-benzpyrene (VIII), m. p. 140–140.2°, corr. The *m*-toluyl ketone IX and the *o*-toluyl ketone XI gave, in 14 and 22% yield, an identical hydrocarbon, m. p. 147.6–148.1°. This compound is definitely different from the 2′-isomer, for both the hydrocarbon and its picrate give a distinct depression in melting point (the trinitrobenzene derivatives show no depression on admixture). There is reason to believe that the second hydrocarbon is 3′-methyl-3,4-benzpyrene (X), formed normally from the *m*-toluyl ketone and produced in the case of the *o*-toluyl ketone as the result of a migration of the methyl group to the adjacent position in the course of the Scholl reaction. If the *o*-toluyl ketone had reacted normally the hydrocarbon would be identical with the known 4′-methyl-3,4-benzpyrene,[3] m. p. 219.5–220°, corr.,[8] which is not the





case. Since there is little likelihood that both reactions proceed abnormally and still yield the same product, it is safe to assume that the ketone IX undergoes normal cyclization. Furthermore, the hydrocarbon in question corresponds fairly closely in melting point with the methylbenzpyrene (m. p. 143–144°, corr.) synthesized by Winterstein, Vetter and Schön[5] from pyrene and methyl succinic anhydride. This synthesis must give either the 2′- or 3′-isomer and, in analogy with known cases, the 3′-position is the more probable point of attachment. The correspondence between the substances obtained in two syntheses which would be expected to yield the 3′-isomer strengthens the belief that this structure is correct. Further support is derived from the analogy with the behavior of the three isomeric toluyl-α-naphthyl ketones. In extending earlier work, Fieser and Martin[26] proved that the meta and para isomers condense normally to the expected methylbenzanthrone, while the ortho compound gives the same product as the meta isomer, corresponding exactly to the conclusions reached above. The structures assigned in the present work therefore are open to little question.

A number of ramifications of the new synthesis are being investigated, and we can report now the isolation of two additional methylbenzpyrenes resulting from the addition of methyl lithium to the benzanthrone derivative V.

Experimental Part[27]

Isomerization of α-Allylnaphthalene.—For preparation of the hydrocarbon,[21] the Grignard reagent from 207 g. of α-bromonaphthalene and 36 g. of magnesium in ether (600 cc.)–benzene was added in two hours, with stirring under reflux, to 121 g. of allyl bromide in 250 cc. of benzene. After refluxing further for two and one-half hours, the hydrocarbon fraction was separated and distilled, b. p. 220–235° (8 mm.); yield, 154 g. (92%). Fractionation through a 1-meter column gave 137 g. (81%) of material, b. p. 127.5–128.5° (8 mm.), n^{25}D 1.6089.

The picrate, obtained from a cold, concentrated methanol solution, formed orange needles, m. p. 68–69°.

Anal. Calcd. for $C_{13}H_{12}\cdot C_6H_3O_7N_3$: N, 10.59. Found: N, 11.00.

Fifteen grams of α-allylnaphthalene was distilled slowly through a tube of activated alumina at 500–550° at a pressure of 15 mm. The condensate consisted of a light yellow oil, b. p. 125–135° (8 mm.). Treated in alcoholic solution with two successive 5-g. portions of picric acid, the oil yielded 7.9 g. of picrate, m. p. 109–110°, and 6.2 g., m. p. 106–108°. Crystallized to constant melting point, the picrate formed orange needles, m. p. 110–111°.

Anal. Calcd. for $C_{13}H_{12}\cdot C_6H_3O_7N_3$: N, 10.59. Found: N, 10.99.

The hydrocarbon was recovered from the purified picrate by adsorption of the nitro compound on alumina from benzene and obtained as a yellow oil (4.9 g.), b. p. 139–140° (10 mm.), n^{20}D 1.6350. The constants given by Zal'kind and Zonis[22] for α-propenylnaphthalene are b. p. 105–106° (6 mm.), n^{20}D 1.6388. On oxidation of the hydrocarbon with sodium dichromate there was a strong odor of acetaldehyde and α-naphthoic acid, m. p. 158–159°, was isolated in good yield.

Perinaphthenone (II).—For the preparation of a quantity of the ketone the condensation was run conveniently in three lots, which were then combined for recovery of the product. In each lot the charge consisted of 460 cc. of water, 675 cc. of concentrated sulfuric acid, 250 g. of technical sodium nitrobenzene sulfonate, 500 g. of glycerol and 200 g. of β-naphthol. The reagents were mixed in this order in a 3-liter three-necked flask provided with a short condenser in the center opening, a mechanical stirrer (tantalum wire stirrer) working through the condenser, and a thermometer. The mixture was stirred and heated cautiously as required to maintain a temperature of 130–140° for one hour. (The reaction is exothermic and is apt to get out of control if a heating bath is used.) The dark solution was decanted while hot from a tarry residue through a pad of glass wool in a funnel onto 2–3 liters of ice in a series of beakers. After dilution to a total volume of about 6 liters, the mixtures were kept at 0° for one or two hours to allow the precipitated tar to agglomerate and the supernatant liquor was then decanted and discarded. The next two lots of reaction mixture were poured in succession onto ice in the same beakers, discarding the acid liquor and retaining the tar. The total tar, which becomes soft and mobile when warm, was then extracted with six 1-liter portions of benzene, heating the mixture on the hot-plate with mechanical stirring. The decanted extracts were filtered, combined, clarified with decolorizing carbon, and concentrated. After removing the solvent the product was distilled in vacuum, and there was obtained 209 g. of orange-yellow distillate boiling at 190–200° at 1–3 mm. For crystallization this was dissolved in 500 cc. of benzene and 500 cc. of ligroin (b. p. 80–86°) was added at the boiling point. This crystallization gave 196 g. (26%) of product in the form of yellow prisms, m. p. 154.5–155.5°. A sample recrystallized from benzene–ligroin formed elongated, diamond-shaped prisms, m. p. 156–156.5°.

The tar remaining from the benzene extraction dissolves fairly readily in hot water. The proportion of glycerol specified is considerably greater than that specified in the patent[24] and by Silbermann and Barkow,[25] for it was our experience in trial runs that this modification results in a definitely superior product. No advantage was found in increasing the proportion still further. Slow addition of the β-naphthol, as specified by Silbermann and Barkow, did not improve the result, nor did changes in the proportion of the oxidizing agent. In one trial with α-naphthol the yield was not as good as with the β-isomer.

Perinaphthane (III).—In the procedure found most satisfactory the charge consisted of 20 g. of perinaph-

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(26) Fieser and Martin, THIS JOURNAL, **58**, 1443 (1936).

(27) All melting points are corrected. Microanalyses by the Arlington Laboratories, Arlington, Virginia.

thenone, 25 cc. of peroxide-free dioxane, and 50 mg. of copper chromite catalyst 37 KAF. This was placed in the bomb in a glass liner and hydrogenation was conducted at an initial pressure of 1800 lb. (120 atm.) and a temperature of 250–260° for ten hours. On cooling, the solution separated into two layers and dioxane was added to make it homogeneous. After filtering from the catalyst the solvent was removed in vacuum and the product distilled at 8 mm. pressure. The fraction boiling at 140–165° (15.8 g.) consisted largely of the desired hydrocarbon, and the remaining distillate, b. p. 165–190°, was mainly perinaphthanol (see below).

Crystallization of the hydrocarbon fraction from 50–75 cc. of methanol diluted with a few cubic centimeters of water gave 11.7 g. (m. p. 63.5–64.5°) of perinaphthane in the first crop and 1.3 g. (m. p. 62–63°) in the second; total yield 70%. In a duplicate experiment the yield was 74%.

In pilot experiments hydrogenation was tried at temperatures below 200° with ether as solvent and without a solvent, but the yield of hydrocarbon was never better than 45%. It seems advantageous to use a solvent for there is then less gum left as a residue from the distillation. Yields of 45–58% were obtained in 20-g. runs at 200–230° using from 100 to 750 mg. of catalyst, and it was noticed that the use of a large amount of catalyst tended to give material of inferior melting point, possibly because of over-hydrogenation. This suggested the use of a very small quantity of catalyst, a higher temperature, and a pressure as low as possible, as specified in the procedure given above.

Further purification of perinaphthane by repeated crystallization from dilute methanol gave thin, colorless plates of the constant melting point 65.1–65.4°. We cannot confirm the melting point 68–69° reported by Langstein,[19] or 66–67° given by Fleischer and Retze.[20] Our hydrocarbon, like Langstein's, darkens on exposure to light.

The picrate forms fine orange-red needles from methanol and melts at 150–151°.

Anal. Calcd. for $C_{13}H_{12}\cdot C_6H_3O_7N_3$: N, 10.58. Found: N, 10.62.

It is doubtful whether previous investigators had the pure substance in hand, for melting points of 127° (Langstein[19]), 134–135° (Fleischer and Retze[20]), and 132–133° (Silbermann and Barkow[25]) are given, all with previous darkening.

The trinitrobenzene derivative formed long, yellow needles from methanol and melted at 160–161°, in agreement with the value 159–160° reported by Fleischer and Retze.[20]

Perinaphthanol-7.—This alcohol, formed in varying amounts in the above experiments, was obtained as the chief product of hydrogenation under the following conditions. A solution of 5 g. of perinaphthenone in 100 cc. of ether (distilled from a Grignard solution) and 25 cc. of absolute alcohol was shaken with hydrogen at atmospheric pressure in the presence of 0.5 g. of Raney nickel. There was a transient deep brown color at the start and the absorption of gas reached 2 moles in about five hours. After filtering from the catalyst and removing the solvent there was obtained on distillation in vacuum 3.2 g. of pale yellow distillate, b. p. 158–161° (1 mm.), and 0.9 g. of deep red distillate, b. p. 161–200° (1 mm.); considerable tar was left in the flask. The first fraction (solid) on crystallization from ligroin (b. p. 80–86°) gave 2.5 g. (49%) of colorless, crystalline product, m. p. 81–85°. After six further crystallizations the material formed glistening blades, m. p. 91.5–93°, and the picrate formed dull orange needles, m. p. 159–160°, from benzene–ligroin. This sample of the alcohol appears to be less satisfactory than those described below, and the substance seems to be very difficult to purify.

Crystallization from ligroin of the high-boiling fraction from the high-pressure hydrogenation gave a sample of the alcohol melting at 100.5–101.5° and showing no depression when mixed with the lower melting material. The picrate in this case melted at 163–165°. Surprisingly enough, the best sample was obtained from material recovered from an attempted dehydration. One gram of crude alcohol, m. p. 81–85°, was heated with a little potassium bisulfate at 180–200° for five minutes and the product distilled at 10 mm. pressure. There was considerable tarry residue, and the light yellow distillate afforded only 0.25 g. of crude, crystalline product from ligroin (b. p. 60–70°). After six recrystallizations, the sample melted at 105.5–106°. This sample was analyzed.

Anal. Calcd. for $C_{13}H_{12}O$: C, 84.75; H, 6.57. Found: C, 84.96; H, 6.38.

The picrate, prepared from the best sample and crystallized from benzene–ligroin, formed fine, dull orange needles, m. p. 163.5–164.5°.

Anal. Calcd. for $C_{13}H_{12}O\cdot C_6H_3O_7N_3$: N, 10.14. Found: N, 9.92.

Hydrogenation with Adams Catalyst.—A solution of 2 g. of perinaphthenone in 40 cc. of absolute alcohol with 30 mg. of platinum oxide catalyst quickly turned deep brown when shaken with hydrogen at slight positive pressure, and after a few minutes a yellowish solid began to precipitate. (The behavior was the same when a small amount of hydrochloric acid was added to the alcoholic solution.) After the absorption of 1 mole of gas (several hours), the solid was collected with the adhering catalyst and washed with dry ether (weight 1.75 g.). The material was dissolved in 40 cc. of hot dioxane and the solution was quickly filtered and diluted with 50 cc. of hot water. The first crop of crystals (0.25 g.) formed small, orange-yellow needles, m. p. 179–180°, dec. The substance decomposes rapidly in solution and recrystallization usually gives inferior material and is attended with heavy losses. Decomposition was evident in an attempted molecular weight determination in camphor.

Anal. Calcd. for $C_{26}H_{20}O_2$: C, 85.78; H, 5.54; mol. wt., 364. Calcd. for $C_{26}H_{18}O_2$: C, 86.18; H, 5.01; mol. wt., 362. Found: C, 86.06, 85.81; H, 5.41, 5.59; mol. wt. (ebullioscopic in acetone), 320, 348.

3-Benzoylperinaphthane (IV).—The Perrier complex from 45 g. of benzoyl chloride and 43.3 g. of aluminum chloride was dissolved in 500 cc. of carbon bisulfide and added with shaking to 52 g. of perinaphthane in 150 cc. of the same solvent. The clear, deep red solution was refluxed for one-half hour and decomposed with ice and acid. After evaporation of the solvent the oily product was extracted and washed in ether and distilled, giving 79.9 g.

(95%) of material, b. p. 210–215° (2 mm.) which slowly solidified. This was suitable for use in the next step. A sample recrystallized twice from ether–petroleum ether formed massive, faintly cream-colored prisms melting at 62–63°.

Anal. Calcd. for $C_{20}H_{16}O$: C, 88.21; H, 5.92. Found: C, 87.96; H, 5.95.

2,1′-Trimethylene-1,9-benzanthrone-10 (V).—The most satisfactory procedure found for preparing this intermediate, rather than utilize it in the synthesis, was as follows. A melt was prepared from 23 g. of sodium chloride and 80 g. of aluminum chloride, and 19.6 g. of benzoylperinaphthane was added. The mixture was heated for four hours in a bath maintained at 150–155°, while stirring mechanically and passing oxygen over the surface of the melt. The hot melt was then poured onto ice and hydrochloric acid and the brown, gummy precipitate was collected and taken into glacial acetic acid while still wet. Four crystallizations from this solvent, with the liberal use of decolorizing carbon each time, gave in all 5.0 g. (26%) of iridescent golden-yellow leaflets, m. p. 217–218°. The substance is readily soluble in benzene, rather sparingly soluble in glacial acetic acid, and only slightly soluble in alcohol. In very dilute alcoholic solution it exhibits a striking yellow-green fluorescence. The solution in concentrated sulfuric acid shows a brilliant red-yellow fluorescence.

Anal. Calcd. for $C_{20}H_{14}O$: C, 88.86; H, 5.22. Found: C, 89.05; H, 5.24.

The material precipitated from the mother liquors of the above experiment by dilution with water was distilled with zinc dust as described below and yielded 2.2 g. (12%) of 3,4-benzpyrene. A small sample of the pure benzanthrone derivative was converted in the same way into the hydrocarbon.

3,4-Benzpyrene.—A melt was prepared from 23 g. of sodium chloride and 80 g. of aluminum chloride in a 125-cc. Erlenmeyer flask, 15.1 g. of 3-benzoylperinaphthane was added, and the flask was stoppered loosely and heated with occasional shaking in an oil-bath held for three hours at 130–140° and for two hours longer at 145–150°. The ketone dissolves readily in the melt giving at the outset a deep red solution which turns brown as the reaction proceeds. At the end of the time specified this was poured onto ice and acid and the gummy precipitate was collected on a filter, washed with water, and sucked well. The crude, moist material, which darkens appreciably during the washing, was shredded and mixed with 250 cc. of zinc dust in a 300-cc. round-bottomed flask sealed directly to a distilling flask with a sealed-on receiver. The distillation was conducted from a sodium–potassium nitrate bath at a dull red heat and was continued as long as distillate collected in the distilling flask (one-half to one hour). The crude product was then distilled into the second receiver at a pressure of 1–2 mm. This eliminated entrained zinc dust and a tarry residue and gave a clean distillate easily purified by dissolving it in ether, concentrating, and adding successive portions of petroleum ether until crystallization was complete. The first crop (5.8 g.) consisted of light yellow needles, m. p. 176–177°, and the second (1.2 g.) melted at 172–175°; total yield, 50%. When the zinc dust distillation was conducted at too low a temperature, or too rapidly, the product often crystallized in the form of leaflets of lower melting point; this probably is due to contamination with hydro derivatives. When the Scholl reaction was conducted with stirring in the presence of oxygen as above and the crude product put through the zinc dust distillation the yield of hydrocarbon was about half that obtained by the process described.

The hydrocarbon was fully identified by comparison with known material.[3] For further characterization, and for comparison with the new derivatives described below, the hitherto unknown **3,4-benzpyrene–trinitrobenzene** was prepared. It formed glistening, bright red blades from benzene, m. p. 226–227°.

Anal. Calcd. for $C_{20}H_{12} \cdot C_6H_3O_6$: N, 9.03. Found: N, 9.00.

Unlike the corresponding complex from methylcholanthrene,[28] this trinitrobenzene derivative can be cleaved effectively with full recovery of the hydrocarbon by selective adsorption of the nitro component on alumina from benzene solution. The recovered hydrocarbon after crystallization melted at 178.5–179°.

The Isomeric 3-Toluylperinaphthanes.—These were prepared as above from the reaction of the Perrier complex of the appropriate toluyl chloride and perinaphthane (from 8 to 13 g.) in carbon bisulfide solution, distilled in vacuum for use in the syntheses, and crystallized for analysis from ether–petroleum ether or from ether. The properties and yields are given in the table. They all form massive prismatic clusters and were obtained in either a colorless or pale yellow condition.

TABLE I

o-, *m*- AND *p*-TOLUYLPERINAPHTHANE ($C_{21}H_{18}O$)

					Analyses	
Isomer	M. p., °C.	B. p., °C.	Mm.	Yield, %	% C (Calcd. 88.06)	% H (Calcd. 6.33)
Ortho	68–69	210–215	0.2	84	87.83	6.41
Meta	86.5–87	225–230	2	95	88.13	6.42
Para	90–90.5	215–220	0.5	95	88.13	6.29

2′-Methyl-3,4-benzpyrene (VIII).—A solution of 16.9 g. of 3-(*p*-toluyl)-perinaphthane in a melt from 23 g. of sodium chloride and 80 g. of aluminum chloride was heated in a stoppered flask at 140–150° for four and one-half hours. The crude, moist product was mixed with 150 cc. of zinc dust and distilled slowly as before, except that the pressure was reduced to 200–250 mm. to allow for a higher boiling point of the methylated hydrocarbon. Crystallization of the distillate gave in all 6.8 g. (42%) of material melting in the range 130–136°. This was converted into the trinitrobenzene complex, which was crystallized to a constant melting point of 212–213° and then passed in benzene solution through an adsorption tower of alumina. The regenerated hydrocarbon collected from the filtrate was crystallized once from benzene–ligroin and three times from methanol. It forms fluffy, light yellow needles and has a double melting point. When heated slowly it melts almost completely at 138–139°, and after solidification by cooling it remelts at 140–140.2°. It is readily soluble in benzene and ether, moderately soluble in metha-

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(28) Fieser and Hershberg, THIS JOURNAL, **60**, 940 (1938).

nol, and almost insoluble in petroleum ether. The solubility is greater than that of the parent hydrocarbon.

Anal. Calcd. for $C_{21}H_{14}$: C, 94.70; H, 5.30. Found: C, 94.85; H, 5.51.

The trinitrobenzene complex forms glistening red blades from benzene–ligroin, m. p. 211.5–212°.

Anal. Calcd. for $C_{21}H_{14}\cdot C_6H_3O_6N_3$: N, 8.77. Found: N, 8.95.

The **picrate** forms brown needles from benzene–ligroin, m. p. 184–185°.

Anal. Calcd. for $C_{21}H_{14}\cdot C_6H_3O_7N_3$: N, 8.48. Found: N, 8.35.

3′-Methyl-3,4-benzpyrene (X). (a) Normal Reaction.—3-(*m*-Toluyl)-perinaphthane (9.4 g.) was heated with sodium–aluminum chloride in a closed flask at 135–150° for four and one-half hours and the product distilled from zinc dust at atmospheric pressure. The once crystallized distillate melted at 138–142°; yield, 1.3 g. (14%). A benzene solution of this material was passed through a tower of alumina and the recovered product was crystallized six times from ether–ligroin and ether–absolute alcohol. This gave small, faintly greenish-yellow needles. The hydrocarbon apparently exists in two forms of slightly different melting point. When heated slowly the sample melted at 146.5–147°, but when inserted in a bath at 145° it melted at once. The resolidified material melts at 147.6–148.1°. The melting point and appearance remained unchanged on further passage through an adsorption tower and on regeneration from the purified trinitrobenzene derivative. The hydrocarbon is somewhat less soluble than the 2′-isomer.

Anal. Calcd. for $C_{21}H_{14}$: C, 94.70; H, 5.30. Found: C, 94.52; H, 5.04.

The trinitrobenzene complex forms long, brilliant red needles from benzene–ligroin, m. p. 210.5–211°.

Anal. Calcd. for $C_{21}H_{14}\cdot C_6H_3O_6N_3$: N, 8.77. Found: N, 8.55.

The picrate separated from benzene–ligroin as fine brownish-red needles, m. p. 179.5–180°.

Anal. Calcd. for $C_{21}H_{14}\cdot C_6H_3O_7N_3$: N, 8.48. Found: N, 8.42.

Mixtures of the hydrocarbon with the 2′-isomer were found to melt as low as 123–128°, and a depression to 171–173° was noted with a mixture of the two picrates. The trinitrobenzene derivatives melt at practically identical temperatures and no depression was observed with mixtures.

(b) By Rearrangement.—The Scholl reaction was conducted as above with 12 g. of 3-(*o*-toluyl)-perinaphthane (four hours at 150–160°) and the distillation from zinc dust carried out at 100–200 mm. pressure. The redistilled and once crystallized product formed straw-yellow needles, m. p. 143–145°; yield, 2.6 g. (22%). After further crystallization from ether–petroleum ether it melted at 146.5–147.5° and gave no depression when mixed with the first sample (a). The melting points and mixed melting points of the picric acid and trinitrobenzene complexes were also identical with those of the above samples.

Summary

The first step in the synthesis consists in condensing β-naphthol with glycerol essentially as described in a patent. The resulting unsaturated ketone, for which the name perinaphthenone is proposed, can be reduced satisfactorily to the hydrocarbon (perinaphthane, in the suggested system of nomenclature) by high pressure hydrogenation. The benzoyl derivative of the hydrocarbon undergoes the Scholl cyclization fairly smoothly, and 3,4-benzpyrene is obtained in good over-all yield by zinc dust distillation of the product.

Of the isomeric toluyl derivatives of perinaphthane, the meta and para compounds undergo normal cyclization and give as final products of the synthesis 3′- and 2′-methyl-3,4-benzpyrene, respectively, while with the ortho isomer there is methyl migration leading to the ultimate formation of 3′-methyl-3,4-benzpyrene. These results parallel those obtained in the application of the Scholl reaction to the preparation of the corresponding methylbenzanthrones.

CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASS.

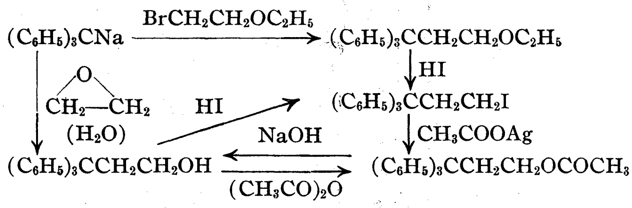
RECEIVED MAY 23, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BROWN UNIVERSITY]

γ,γ,γ-Triphenylpropyl Derivatives

BY CHARLES BUSHNELL WOOSTER, H. D. SEGOOL AND T. T. ALLAN, JR.

The reaction between sodium in liquid ammonia solution and γ,γ,γ-triphenylpropyl iodide which results in the formation of sodium triphenylmethide was reported in a previous paper.[1] Because of the interesting nature of this reaction and of the observed tendency of compounds of the type R_3C-C-CX to undergo unusual reactions,[2] it appeared desirable to establish more thoroughly the constitution of the triphenylpropyl iodide which was used. This has now been accomplished by carrying out the reactions indicated in the flow sheet.



The iodide was prepared originally by cleavage of γ,γ,γ-triphenylpropyl ethyl ether the constitution of which appeared to be reasonably well established by the method of its synthesis. Furthermore, the available evidence demonstrated the presence of a triphenylmethyl group in the iodide. There remained, however, the possibility of molecular rearrangement during the action of hydriodic acid on the ether which might have led to the formation of a triphenylisopropyl iodide instead of the expected triphenyl-*n*-propyl iodide. Accordingly, the synthesis of the same iodide from triphenyl-*n*-propyl alcohol and the regeneration of this alcohol, by conversion to the acetate and hydrolysis, furnish the necessary link in the chain of evidence which shows that the iodide actually has the primary structure.

Experimental Part

The Preparation of γ,γ,γ-Triphenylpropyl Alcohol.—Sodium triphenylmethide was prepared by slowly adding 50 g. of triphenylchloromethane to a solution of 8.3 g. of sodium dissolved in about 500 cc. of liquid ammonia in a one-liter three-necked flask equipped with a mercury-sealed stirrer, a dropping funnel and an outlet for gaseous ammonia. A large excess of ethylene oxide was then added gradually in small portions. This reacted vigorously with the excess sodium, but at first the deep red solution of sodium triphenylmethide showed no evidence of reaction. However, after several hours a voluminous pink precipitate had appeared in the reaction vessel, although the red color of the solution indicated the presence of some unreacted sodium triphenylmethide. These observations suggest that ethylene oxide may form an intermediate, unstable oxonium complex with the organo-alkali compound similar to those which are formed with Grignard reagents.

The addition of water to the reaction mixture discharged the red color and precipitated a yellow plastic mass which solidified on standing in contact with water after it had been washed free of most of the aqua ammonia. The product was recrystallized from commercial hexane and obtained in the form of light yellow crystals, m. p. 106.5–107.5°; yield about 30 g.

Anal. Calcd. for $C_{21}H_{20}O$: C, 87.5; H, 6.94. Found: C, 87.9, 87.7; H, 7.07, 7.05.

Attempts to oxidize this product to tritylacetic acid were unsuccessful, but its structure seems to be sufficiently well established by its thermal stability and the method of preparation. Although "abnormal" reactions with the Grignard reagent (involving isomerization to the aldehyde or ketone structures) have been reported with isobutylene oxide, styryl oxide and *sym*-dimethylethylene oxide[3] no such results have ever been observed with ethylene oxide itself. Furthermore, the triphenylisopropyl alcohol, $(C_6H_5)_3CCHOHCH_3$, which is the only likely alternative structure, would be expected to be thermally unstable since its next lower homolog $(C_6H_5)_3CCH_2OH$, decomposes smoothly into triphenylmethane and formaldehyde when heated slightly above its melting point (107°)[4] and the corresponding decompositions of triphenylacetic acid and triphenylacetaldehyde indicate the generality of such behavior. However, the reaction product was recovered unchanged after heating to 150–170° for an hour and failed to give a test for even a trace of triphenylmethane with a solution of potassium amide in liquid ammonia which instantly produces a deep red solution of potassium triphenylmethide when treated with this hydrocarbon.

Preparation of Triphenylpropyl Iodide from the Alcohol.—Five grams of the alcohol was refluxed for five hours with 40 cc. of constant boiling hydriodic acid. After cooling, the product was separated and purified as previously described[1] and identified by a mixed melting point; yield 1.6 g.

Preparation of Triphenylpropyl Acetate from the Alcohol.—The alcohol seems to be quite unreactive toward many of the usual reagents; it was recovered unchanged after refluxing for one hour with acetyl chloride and thionyl chloride although a product of m. p. 134° (presumably the benzoate) was obtained by refluxing with benzoyl chloride.

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[1] Wooster and Morse, THIS JOURNAL, **56**, 1735 (1934).

[2] Whitmore and Stahly, *ibid.*, **55**, 4153 (1933).

[3] Henry, *Compt. rend.*, **145**, 21, 406 (1907); Tiffeneau and Fourneau, *ibid.*, **146**, 697 (1908).

[4] Schlenk and Ochs, *Ber.*, **49**, 610 (1916).

The determining factor seems to be the boiling point of the reagent since the acetate was obtained in satisfactory yield by the use of acetic anhydride.

Seven and three-tenths grams of the alcohol was refluxed for one hour with excess acetic anhydride, the solution poured into water and, after the hydrolysis of the anhydride was complete, the product was separated by filtration and recrystallized from alcohol: yield 6.4 g., m. p. 114–115°.

Anal. Calcd. for $C_{23}H_{22}O_2$: C, 83.6; H, 6.67. Found: C, 83.3, 83.1, 83.7; H, 6.72, 6.70, 6.75.

Hydrolysis of the Acetate.—Two grams of the acetate was dissolved in 50 cc. of alcohol in which 3 g. of sodium had been dissolved and 10 cc. of water was added. After refluxing for two hours the solution was poured into water, neutralized with hydrochloric acid and filtered. After crystallization from commercial hexane the product was identified as the triphenylpropyl alcohol by a mixed melting point.

Preparation of Triphenylpropyl Acetate from the Iodide.—An attempt to prepare the acetate by refluxing a solution of the iodo compound in glacial acetic acid with silver acetate for ten and one-half hours proved unsuccessful, possibly because the initially formed silver iodide coated over the sparingly soluble silver acetate. The reaction proceeded satisfactorily, however, when an excess of silver acetate was placed in the filter thimble and the acetic acid solution of 1.88 g. of triphenylpropyl iodide was placed in the flask of a Soxhlet apparatus to prevent precipitation of the silver iodide from occurring in the presence of solid silver acetate. After the Soxhlet apparatus had been operated for about twenty hours, the solution in the flask was cooled, filtered, evaporated to small volume, diluted with water, neutralized with sodium carbonate and filtered again. The black gummy solid was crystallized from alcohol by seeding with a sample of the previously prepared acetate. After recrystallization from alcohol it was found to be halogen free and identical (by mixed melting point) with the acetate obtained from γ,γ,γ-triphenylpropyl alcohol and acetic anhydride.

Summary

The product previously obtained by the action of hydriodic acid on γ,γ,γ-triphenylpropyl ethyl ether has been shown to be γ,γ,γ-triphenylpropyl iodide. Evidently no molecular rearrangement occurs during this reaction.

PROVIDENCE, R. I. RECEIVED MAY 5, 1938

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

Semiquinone Radicals in the Indamine and Indophenol Groups

BY G. SCHWARZENBACH[1] AND L. MICHAELIS

The original task of this paper was to extend the search for semiquinone radicals as intermediate steps of reversible oxidation–reduction, to the indamine and indophenol groups. The result not only was successful but in addition presented an excellent opportunity for developing the general principles concerned with the degree of stability of such radicals.

In none of the many representatives of the indophenol dyes investigated by W. M. Clark[2] and associates, was there any evidence for the existence of an intermediate step of reduction. On the contrary, these authors took just these dyestuffs as models to prove their assumption that in reversible bivalent oxidations the two electrons always go on and off in pairs. The experimental results can be confirmed entirely for the dyestuffs selected by these authors and for the *p*H range covered by their experiments. Yet it would be unjustifiable to consider this state of affairs as general. We shall demonstrate for two dyestuffs rather closely related to the group investigated by these authors, that semiquinone radicals are formed in fairly large concentrations as intermediate steps. These two dyestuffs are phenol blue and Bindschedler's green, the formulas of which are given by the T-forms in the table of formulas (Fig. 7). The experimental material will be presented first, and the cause for the different behavior will be treated in the discussion.

The formulas shown in the table are electronic formulas, each stroke representing an electron pair. The totally oxidized forms T, the semiquinone forms S, and the fully reduced forms R are given in the different possible states of ionization. T, R, and S, themselves, denote the forms existing only in very alkaline solutions, where all removable protons are removed. The order represented in this scheme corresponds to the order of the ionization steps as derived from the experiments.

An open structure has been chosen for the T-forms in which the central nitrogen appears surrounded by only six electrons. The fourth electron pair can be said to be delivered by the auxochromic groups $N(CH_3)_2$, OH, and O. These have

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[1] Under a fellowship from the Rockefeller Foundation.

[2] Hygienic Laboratory Bulletin, No. 151, United States Public Health Service, Washington, D. C., 1928.

unshared electron pairs, which can form a double bond with the neighboring carbon atom, whereby the benzene ring, of which this carbon is a part, is converted into a quinoid ring. Both auxochromic groups take part in this electron delivery, the molecule is a resonance system. The valence chemistry and its connection with the absorption spectra and the acidimetric behavior of systems like these have been described by Schwarzenbach and co-workers.[3] In the S-form the odd electron is represented as a dot attached to the central atom, but this should not be regarded as an expression of a definite position of the odd electron.

A. Experimental Part

1. Preparation of the Dyestuffs

Phenol blue was prepared by the method described by Heller,[4] by oxidation of freshly prepared *p*-aminodimethylaniline and phenol with sodium hypochlorite in acetate buffer and at zero temperature. The dye was filtered off and crystallized three times from 95% ethanol. It then forms dark crystals, m. p. 167°.

Bindschedler's green was prepared by the method given by Wieland.[5] *p*-Aminodimethylaniline and dimethylaniline are oxidized with bichromate in acid solution and in the presence of zinc chloride. The zinc double salt forms a beautifully crystallized green product which was not further purified. Recrystallization cannot be accomplished without some decomposition and the recrystallized product is rather less pure than the original material. In concentrated aqueous solutions this green salt is converted partially into red crystals, the longer known of the two modifications of Bindschedler's green, which behave in solution exactly like the green product. Both modifications have been described already by Wieland. Titrations have been carried out mainly with the green crystals, which show certain advantages owing to their greater solubility.

Phenolindophenol was prepared according to the method described by Clark[2] and recrystallized five times from a solution of sodium chloride. It was obtained in beautifully crystalline state of great purity and stability. All these specimens were kept constantly in the ice box to prevent decomposition.

2. The Titrations.—The titrations were mostly reductive. As reductant, reduced rosindulin GG, and in a few cases in the acid *p*H range, where rosindulin becomes insoluble, titanous chloride was used. These reductive titrations were controlled in some cases by a corresponding oxidative titration, the dyestuff being reduced previously by means of hydrogen on colloidal palladium, and bromine or ferricyanide was used as oxidant.

The technique of the titration has been described before. The only modification consisted in adding the dyestuff to the buffer solution just before the titration began. This makes the effect of a possible slow decomposition of these dyestuffs, which are not very stable, almost negligible. Two microburets were introduced through the stopper of the titration vessel which contained 50 cc. of the buffer solution. One of the burets contained a strong solution of the dye (concentration about 4×10^{-3} *M*) in alcohol (in the case of phenol blue) or water (in the case of Bindschedler's green) and the other the reductant or oxidant in the same molar concentration. The air in the titration apparatus was then replaced by hydrogen. Colloidal palladium ensured the removal of the oxygen dissolved and produced a hydrogen potential, which made possible the measurement of the *p*H of the buffer. In the case of an oxidative titration 2 cc. of the dyestuff solution was now added and immediately reduced. After replacement of the hydrogen by nitrogen the titration was started. In the case of a reductive titration, the buffer was bubbled with nitrogen before adding the dyestuff and the titration begun immediately after its addition. After the titration was finished more colloidal palladium was added, hydrogen was passed through the vessel and the hydrogen potential measured. It was found that the change of *p*H value during the reduction was negligible in all titrations of Bindschedler's green, except for some few titrations with titanous chloride. In the experiments with phenol blue the final *p*H value was always somewhat lower than the value before the beginning of the titration. This difference of about 0.07 *p*H unit is due to the addition of alcohol to the buffer solution and not to a change caused by the oxidation–reduction process. In the following tables only the final *p*H value is registered.

In the case of phenol blue we could get excellent titration curves between *p*H 3.7 and 9.1. The potentials could be measured in this *p*H range with the same accuracy achieved in the case of lactoflavin,[6] the limits of error being about ±0.2 mv. In more acid solutions we had difficulties in the determination of the starting point of the reduction and end-point of the oxidation. The potentials at these points are very unsteady due to an irreversible decomposition of phenol blue. But even in solutions of a *p*H of 2 or 3 it could be shown definitely that the titration curve is much too steep for a two-electron process without intermediate. The semiquinone in these solutions could also be detected visually by its color, especially distinctly visible in a nearly completely reduced solution. At *p*H 10 the potentials were again unstable. This is due most probably to a hydrolytic elimination of the dimethylamino group, as can be inferred from the fact that the potentials dropped slowly to the potential range of phenolindophenol which is produced by this process.

Bindschedler's green is more stable in acid solutions and less stable in alkaline solutions in comparison with phenol blue. The potentials were perfectly stable between *p*H 3 and 7, the limits of error being not greater than in the case of phenol blue. At *p*H 7.5 and 8.0 fairly reliable titration curves were still obtained, but at *p*H 9 the dye stuff was hydrolyzed rather quickly to form phenol blue, a well-known reaction for Bindschedler's green. In the acid range fairly good curves were obtained down to a *p*H of 1.5. Here titanous chloride had to be applied as a reductant because rosindulin forms a precipitate. The strong acidity of the titanous chloride solutions impaired some-

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[3] G. Schwarzenbach and co-workers, *Helv. Chim. Acta*, **20**, 490, 498, 627, 654, 1253, 1591 (1937).

[4] G. Heller, *Ann.*, **392**, 47 (1912).

[5] H. Wieland, *Ber.*, **48**, 1087 (1915).

[6] L. Michaelis and G. Schwarzenbach, *J. Biol. Chem.*, **123**, 527 (1938).

what the reliability of the measurements around *p*H 2 due to a change in *p*H during the reduction. Below *p*H 1 Bindschedler's green begins to become very unstable, the green solution being decolorized in a few hours. In phosphate buffer solutions which were used in the *p*H range around 7, zinc phosphate was precipitated, because the zinc double salt was used directly. In some cases this precipitate was filtered off, but it was found that it did not affect the potential measurements at all.

The final concentration of the dye in the titration experiments was usually between 2 and 4 × 10^{-4} mole per liter. The slight solubility of phenol blue did not allow of higher concentrations. Below a concentration of 1 × 10^{-4} the establishment of the potentials was no longer satisfactory.

In Table I the normal potentials E_m against the standard hydrogen electrode in volts and the index potentials E_i against the corresponding E_m value in millivolts are registered for the different buffer solutions. The values are mean values of several duplicate titration experiments at 30°.

TABLE I

Buffer	*p*H	Titration	E_m	E_i
		Phenol blue		
Lactate	3.00	Oxidative ($CrO_4^{=}$, Br_2)	+0.5007	(21)
Lactate	3.00	Reductive (rosindulin)	+ .5000	(22)
Lactate	3.72	Reductive (rosindulin)	.4538	19.5
Lactate	3.84	Reductive (rosindulin)	.4490	20.0
Acetate	4.12	Reductive (rosindulin)	.4262	19.7
Acetate	4.62	Reductive (rosindulin)	.3970	19.6
Acetate	5.04	Reductive (rosindulin)	.3623	18.2
Phosphate	5.96	Reductive (rosindulin)	.2923	15.6
Phosphate	6.86	Oxidative ($[Fe(CN)_6]^{\equiv}$)	.2300	15.0
Borate	9.13	Reductive (rosindulin)	.0945	14.6
		Bindschedler's green		
HCl	1.10	Reductive ($TiCl_3$)	+0.6290	?
HCl	1.53	Reductive ($TiCl_3$)	.5927	15.3
Lactate	2.37	Reductive ($TiCl_3$)	.5325	(15)
Lactate	2.65	Reductive ($TiCl_3$)	.5185	(15)
Lactate	2.95	Reductive (rosindulin)	.4978	15.8
Acetate	3.97	Reductive (rosindulin)	.4152	15.4
Acetate	4.58	Reductive (rosindulin)	.3635	16.4
Acetate	5.50	Reductive (rosindulin)	.2945	17.1
Phosphate	6.78	Reductive (rosindulin)	.2294	17.2
Phosphate	7.18	Reductive (rosindulin)	.2157	16.4
Phosphate	7.47	Reductive (rosindulin)	.2071	16.1
Phosphate	8.03	Reductive (rosindulin)	.1853	16.2

The E_i values in brackets are not certain. Here the titration curves were not very reliable because the dye was not quite stable or the *p*H during the titration could not be kept quite constant.

The results indicate clearly that in both dyes the reduction leads through an intermediate product on an oxidation level of a quinhydrone, since the index potentials are distinctly greater than 14.3 mv. In the case of phenol blue below *p*H 5 the index potentials are so high as to indicate the formation of the quinhydrone in large quantities.

This quinhydrone may be a radical or its dimeric form, a hydrazine derivative. To decide between these alternatives, we carried out some titration experiments with various concentrations of the dyestuff, keeping the *p*H value constant. Table II gives information about these.

TABLE II

Phenol blue *p*H 4.60		Bindschedler's green *p*H 4.58		Bindschedler's green *p*H 6.78	
C	E_i	*C*	E_i	*C*	E_i
0.9 × 10^{-4}	19.8	2.2 × 10^{-4}	16.4	2.8 × 10^{-4}	17.2
1.8 × 10^{-4}	19.5	4.0 × 10^{-4}	16.4	5.6 × 10^{-4}	17.2
3.5 × 10^{-4}	19.5	7.6 × 10^{-4}	16.4	9.0 × 10^{-4}	17.3

These figures show clearly that the quinhydrone is a radical and not a dimeric compound, since the index potential is independent of concentration. This result is not unexpected. The intermediate form of phenol blue has a definite blue color which would not be expected of a valence saturated hydrazine. Furthermore, Wieland states that the radical *bis*-(dimethylaminophenyl)-hydrazine at a concentration of 2 × 10^{-2} *M* in benzene solution is 10% dissociated into radicals. We may expect that the dimerization constant in water is even smaller, but even if this be not the case, the dimeric form could not be formed in the low concentration range used in our titration experiments.

3. The Absorption Spectra.—Phenol blue is a base, which takes up a proton at *p*H 4.9 giving rise to a color change from pure blue to violet. There can be no doubt about the constitution of the molecules involved in this acidity equilibrium: namely, T and HT. The color of the ion and the neutral molecule indicate that both are resonance systems, the quinoid double bonds shifting from one nucleus to the other. This is only possible if we place the added proton in the indicated position. An addition to the electron pair of the dimethylamino nitrogen would destroy the resonance and give rise to the formation of a quinone of a very slight, probably yellow, color.[7] Furthermore the order of magnitude of 10^{-5} must be expected for a dissociation constant of a phenolic hydroxide group which is acidified through a slightly asymmetrical resonance. The addition of the proton to the central nitrogen would give rise to a much smaller change in color as we will see in the case of Bindschedler's green. The absorption spectra of T and HT have been determined with König and Martens' spectrophotometer and are given in Fig. 1, together with the spectra of two forms of Bindschedler's green. It can be seen that the absorption maxima of phenol

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(7) G. Schwarzenbach and co-workers, *Helv. Chim. Acta*, **20**, 490, 627 (1937).

blue in its T and HT state are separated far enough to make a spectrometric determination of the acidity constant possible. It was found by this method that in an acetate buffer solution of a *p*H of 4.55 the ratio of HT/T is 1.81 at 30°, a wave length of 6620 Å. being used for the measurements of the extinctions. This corresponds to a dissociation constant of $K_t = 10^{-4.81}$.

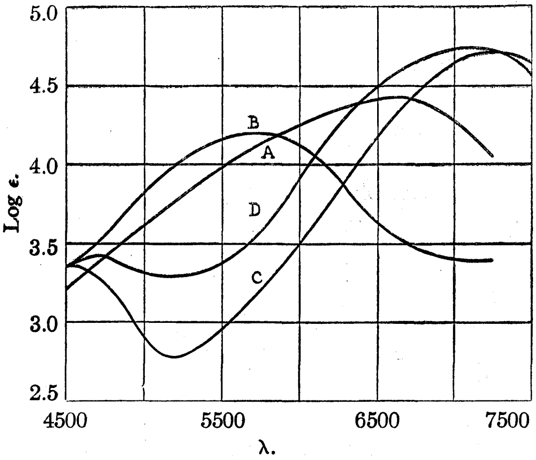

Fig. 1.—The logarithm of the molar extinction coefficient: Curve A, phenol blue *p*H 5.5 (T); Curve B, phenol blue *p*H 3.5 (HT); Curve C, Bindschedler's green *p*H 4.5 (T); Curve D, Bindschedler's green *p*H 2 (HT).

Bindschedler's green gives yellowish-green solutions which on acidifying turn to a more bluish-green. Both solutions have a strong absorption band at the infrared border of the visible part of the spectrum. The maximum of the absorption lies so far in the red that its determination with the visual method (König and Martens' apparatus) is scarcely possible. Photographs on infrared sensitized plates revealed, however, the exact position of the bands. Their maximum is in the infrared quite close to the visible red. The color change on acidifying takes place between *p*H 3 and 4. From Fig. 1 it can be seen that the change in the absorption spectrum is not very pronounced, making a colorimetric determination of the acidity constant difficult. But this acidity constant shows up clearly if we plot the E_m potentials against *p*H. From this curve it follows that this dissociation constant has a value of about $10^{-3.4}$. The place of addition of the proton can only be the central nitrogen atom of the molecule so that the molecules T and HT, with the formulas in the table of formulas, are involved in this acidity equilibrium. An addition to the free electron pair of the dimethylamino nitrogen would give rise to the formation of a strongly asymmetrical structure, which would have a yellow color. Such a color change takes place only at much lower *p*H values, namely, in about 40% sulfuric acid.

Both forms of Bindschedler's green and of phenol blue have two more absorption bands in the region of shorter wave lengths. One lies in all cases in the neighborhood of 2900 Å. The other lies in the case of the acid form of phenol blue also in the ultraviolet at about 3550 Å., whereas in the case of Bindschedler's green and the neutral form of phenol blue this second band which is rather weak lies in the violet and blue region of the visible spectrum (Fig. 1). The whole absorption spectrum has therefore in all cases three bands showing a pronounced similarity to the spectra of the sulfonphthaleins.[8] This is not surprising because the indophenols and indamines represent a resonance system very similar to that of the dyes of the Döbner's violet and benzaurin type (2). On reduction the bands in the visible part of the spectrum and in the nearer ultraviolet disappear, whereas the band at 2900 Å. is strongly increased in intensity.

It has been mentioned that the presence of the semiquinone of phenol blue can be demonstrated by its definite color. If small amounts of bromine are added to a solution of reduced phenol blue in an acid solution (HCl = 0.005 *N*), the color of the solution turns blue, not violet, which in acid solution is the color of the fully oxidized form. Also an absorption appears in the far red which disappears again on further oxidation and is replaced by the band of the fully oxidized substance HT. The absorption in the far red has to be attributed to the radical. Curve A in Fig. 2 represents the extinction of a solution in which 16% of the phenol blue has been reoxidized (concentration of the dyestuff = 10^{-5}). From the semiquinone formation constant, derived from the titration experiments, the concentration of the fully oxidized form HT has been calculated and the absorption due to its presence introduced as curve B in Fig. 2. Curve C is the difference between the curves A and B and represents the absorption of the semiquinone. In the other regions of the spectrum, including the ultraviolet, the presence of the semiquinone does not show up by any specific absorption.

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[8] Mohler, Forster and Schwarzenbach, *Helv. Chim. Acta*, **20**, 654 (1937).

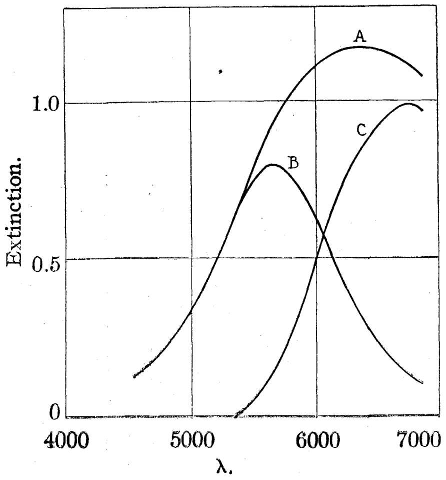

Fig. 2.—A, the extinction of a solution of 10^{-5} molar leuco-phenol blue in 5×10^{-3} molar hydrochloric acid of which 16% has been oxidized; B, the extinction due to the form HT; C, the extinction due to the form H_2S (the free radical).

It is somewhat surprising that the oxydimethylaminodiphenyl nitrogen, the radical derived from phenol blue, has a completely different color from *bis*-(dimethylaminophenyl-)-nitrogen derived from Bindschedler's green, which has been prepared by Wieland[5] and which is yellow. Since the absorption bands of Bindschedler's green are shifted toward the red in comparison with phenol blue, we think it likely that this will be the case also in the two corresponding radicals and we predict for the yellow radical of Wieland another absorption band in the infrared region.

4. The Acid–Base Constants of Reduced Phenol Blue.—The curve of E_m as a function of pH which is shown in Figs. 4 and 5, shows different points where it changes its direction owing to the dissociation of the reduced and oxidized forms. To confirm the exact positions of these bends, the direct determination of the acidity constants of the reduced forms also was desirable. In the case of Bindschedler's green this was not possible because the reduced form is very sparingly soluble, but it could be accomplished easily in the case of leuco-phenol blue, which is a phenol and an aniline at the same time

$$\mathrm{HR^-} \underset{K_r''}{\leftrightarrows} \mathrm{H_2R} \underset{K_r'''}{\rightleftarrows} \mathrm{H_3R^+}$$

K_r''' was derived from an acid titration curve of the leuco-base which is shown in Fig. 3 and K_r'' was computed from the shift of the potential of a hydrogen electrode in a sodium hydroxide solution by addition of phenol blue. The results are

$$K_r''' = 10^{-5.99} \qquad K_r'' = 10^{-10.00}$$

Both figures hold for 30° and an ionic strength of about 0.1.

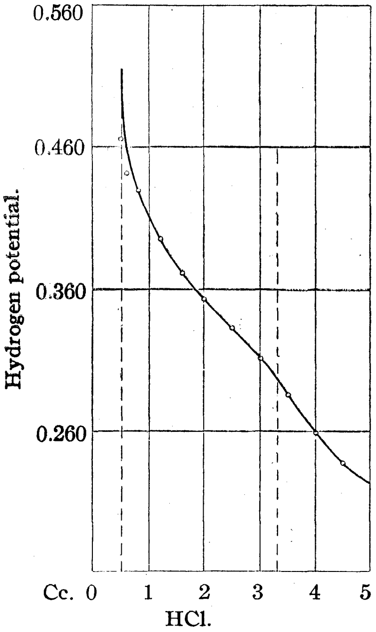

Fig. 3.—Titration of leuco-phenol blue with acid at the hydrogen electrode.

B. The Interpretation of the Potential Measurements

1. The Mean Potentials E_m as a Function of pH and the Dissociation Constants of T and R.—The curve drawn through the experimental points in Fig. 4 for phenol blue shows a bend at pH 4.8 and 6.0 owing to the acid dissociations of T and R described above. At pH 10 there must be another bend indicating K_r'' and then the curve will have, in the more alkaline range, a slope of 30 mv. per pH unit and can be extrapolated safely. In the acid range, where experimental points no longer can be obtained, the extrapolation is not so safe. We will probably soon reach another constant of the T form, a proton being attached to the central nitrogen.

The curve of Bindschedler's green represented in Fig. 5 has a slope of 30 mv. per pH unit in the alkaline solution. The reduced form contains, therefore, one proton more than the oxidized form in this pH range and must be represented by formula HR. The curve will extend with this slope far into the alkaline range, where the proton attached to the central nitrogen atom finally will be lost, the potential becoming independent of *p*H. At *p*H 6.4 and 5.1 the reduced form takes up two more protons, obviously forming the ions H_2R and H_3R. The constants $K_r'' = (H^+) \times (HR)/(H_2R)^+ = 10^{-6.4}$ and $K_r''' = (H^+) \times (H^+) \times (H_2R^+)/(H_3R^{++}) = 10^{-5.1}$ are very reasonable for aromatic dimethylamino groups and also the ratio of K_r''/K_r''', corresponding to 1.3 *p*H units is compatible with the expected value as influence of the ionic charge of the first proton on the acidity constant of the second in this distance. In the case of leuco-phenolindophenol about the same ratio between K_r'' and K_r'' has been observed, the constants being $10^{-9.4}$ and $10^{-10.6}$. Unfortunately the solubility of the base HR is so slight that no good acidimetric titration curves could be obtained in a titration experiment with the hydrogen electrode to confirm the constants above.

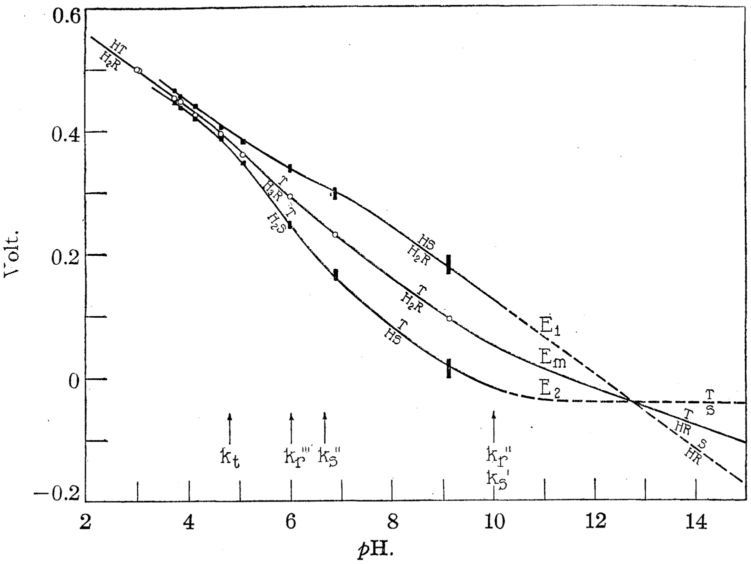

Fig. 4.—Phenol blue: the normal potentials E_m for the system T, R; E_2 for the system T, S; and E_1 for the system S, R. K_t, K_s, and K_r denote the acidity constants of the T, S, and R forms.

At *p*H 3.4 the E_m curve bends from the 90 mv. slope back to the 60 mv. slope owing to the dissociation constant of the T-form described above.

At *p*H 1.5 there is once more a bend indicating a third constant of the reduced form. This is somewhat surprising. Only the ion H_4R can be formed here with salt formation of the weakly basic diphenylamino nitrogen. This constant lies so far in the acid range that a confirmation by means of an acidimetric titration is impossible.

2. The Index Potentials, E_i, the Normal Potentials of the Lower and the Higher Step of Oxidation, E_1 and E_2, and the Semiquinone Formation Constant, k.—From the index potentials we can calculate[9] the semiquinone formation constant k and the maximum ratio of semiquinone to the total dye $(s/a)_{max}$. Table III contains these figures in solutions of different *p*H, as computed from the curves E_1 and E_2 which will be discussed later. Obviously both dyestuffs form free radicals to a large extent. One of these radicals, the one derived from Bindschedler's green, is identical with the *bis*-(dimethylaminophenyl)-nitrogen obtained by Wieland from the corresponding hydrazine.[5] Wieland states that this radical is very sensitive toward water. We can confirm this result but Wieland's viewpoint should be corrected somewhat. The radical does not disappear entirely in the presence of water. There is an equilibrium established according to $2S \rightleftarrows$

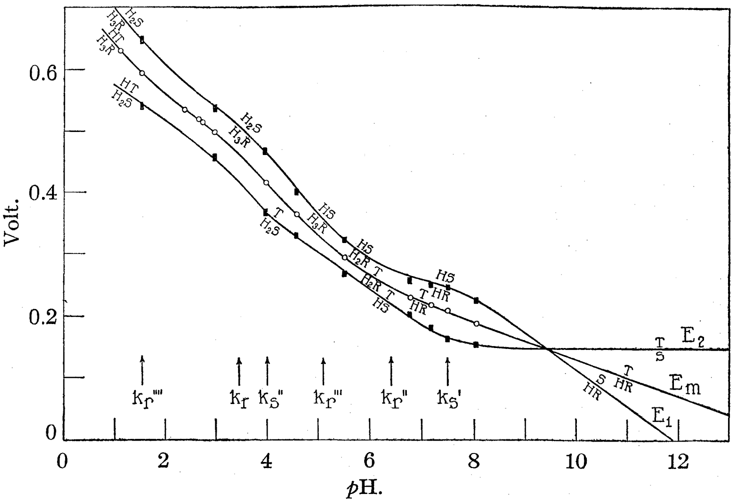

Fig. 5.—Bindschedler's green: The normal potentials E_m for the systems T, R; E_2 for the system T, S, and E_1 for the system S, R. K_t, K_s and K_r denote the acidity constants of T, S, and R.

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[9] The methods of calculation as developed previously will be summarized in *Chem. Rev.*, in press (1938).

TABLE III

$k = s^2/rt$, where s, r and t denote the activities of the S, R and T-forms. $(s/a)_{\text{max.}}$ = maximum ratio of $s:a$, that is to say the ratio $s:a$ in the half-reduced state.

*p*H		1	2	3	4	5	6	7	8	9	10	11	12
Bindschedler's green	k	0.0087	0.030	0.040	0.023	0.100	0.146	0.059	0.059	0.40	4.00	36	1550
	$100 \times (s/a)_{\text{max.}}$	4.5	8.0	9.1	7.0	13.7	16.0	10.8	10.8	24	50	75	95
Phenol blue	k			0.48	0.48	0.25	0.027	0.0041	0.0022	0.0022	0.0047	0.022	0.18
	$100 \times (s/a)_{\text{max.}}$			26	26	20	7.6	3.1	2.2	2.2	3.3	6.9	17.5

R + T, the constant of this equilibrium depending on *p*H. At *p*H 6 as much as 16% of the whole dyestuff is still present in the form of the radical.

It is worth while mentioning that this is the first case in which a radical of the semiquinone type is identical with a radical previously prepared by the classical method, by spontaneous dissociation of its dimeric form in an organic solvent.

If we compare the figures of Table III with the behavior of phenolindophenol we find at first sight a pronounced difference. As can be inferred from the data obtained by W. M. Clark,[2] the latter compound does not form a radical between *p*H 5 and 13. We also have found in these *p*H ranges an index potential not differing from the theoretical minimum value 14.3. But there is an indication that in very strongly alkaline solutions the formation of an intermediate does occur. Satisfactory titration curves could not be obtained owing to an instability of the system, but by reducing a very pure sample of phenolindophenol in strong alkali (> 2 *m* sodium hydroxide) with glucose, a pink color can be observed easily just before the solution decolorizes on forming the fully reduced compound. On re-oxidation with air, the pink color appears again before the solution becomes blue. We do not believe that this phenomenon is due to a decomposition product, but to the formation of a radical as intermediate product. It is analogous in appearance and behavior to the intermediate form of the indigosulfonate as described by Shaffer.[10]

We also have an indication that a semiquinone is formed in more acid solutions. Below *p*H 4 the dye is very unstable, the potentials always drift toward the positive side, probably because quinone-imide is formed with a normal potential above phenolindophenol. This decomposition has the effect of compressing the titration curve (potential plotted against degree of reduction), causing the index potentials to appear lower than they would be without secondary decomposition occurring. So at *p*H 3.7 a curve was obtained with an index potential of only 11.0, but at *p*H 4.6 an index potential of 14.7 and at *p*H 4.02 even one of 15.2 was observed. The corrected values, therefore, would be distinctly greater than 14.3 although accurate figures cannot be given. This is a clear indication that a semiquinone is formed in these *p*H ranges.

We shall discuss the semiquinone formation in terms of the E_1 and E_2 values which, in addition to E_{m}, are plotted in Figs. 4 and 5. These potentials are the normal potentials of the systems T, S and S, R and defined by the equations

$$E = E_2 + \frac{RT}{F} \ln (t/s) = E_1 + \frac{RT}{F} \ln (s/r)$$

where E is the potential observed.

It is comparatively easy to give the correct E_1 and E_2 curves although the index potentials may not be absolutely certain, for these curves can only have a slope of 0.06 or 0.12 v. per *p*H unit. This restriction makes it possible to compute a mean value of the measured index potentials at different *p*H. The slope of the curve informs us about the number of protons by which the semiquinone differs from the t or r forms. We are therefore definitely sure about the state of ionization of the half reduced form. In the *p*H range investigated, the semiquinone formation constant, k, is in the case of both dyestuffs, and of course also in the case of phenolindophenol, so small, that $E_2 - E_1$ becomes negative, the E_1 curve being above the E_2 curve. Here, a wide separation of E_2 and E_1 is equivalent to a small k.

Figure 4 shows that between *p*H 7 and 10 the semiquinone of phenol blue has the form HS and that below *p*H 6.6 the form H_2S exists. These two forms will have the structures given in the table of formulas because it is reasonable to assume that the dissociation constant for an acidic group in the semiquinone lies between the corresponding constants for the T and R forms.

The last value experimentally obtained for phenol blue on the alkaline side is that for *p*H 9. Nevertheless we know, as has been pointed out, the course of the E_{m} curve beyond 10, because the

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[10] P. A. Shaffer, *J. Biol. Chem.*, *Proc.* **105**, lxxviii (1934); *cf.* also L. Michaelis, *Chem. Rev.*, **16**, 243 (1935), on p. 282.

dissociation constant $H_2R \rightarrow HR$ has been measured. At *p*H 10, where the parallel course of these three curves is broken by the constant just mentioned, the semiquinone has still the central proton to lose. The semiquinone formation constant in very alkaline solutions depends on the magnitude of this unknown constant $HS \rightarrow S$. It is certain that this constant must be much greater than the corresponding one for the reduced form $RH \rightarrow R$, and reasonable to assume that it has to lie in the neighborhood of 10^{-10}. As we will see, we have in the case of Bindschedler's green a clear indication that this constant $HS \rightarrow S$ lies below *p*H 8. If we take account of all these arguments, we come to the extensions for the curves in the high *p*H ranges as indicated in Fig. 4, and reach the conclusion that in very strong alkaline solutions we must expect a very large semiquinone formation. The same holds true for the very acid range. At *p*H 3, where the last experimental points could be obtained, we have as semiquinone the form H_2S and a new constant will soon be due, addition of the proton taking place at the dimethylamino nitrogen. Such a constant makes the E_1 and E_2 curves again bend toward the E_m curve, producing an increase in the semiquinone formation.

The case of Bindschedler's green is very similar, but the conclusions reached for the behavior in very alkaline solutions are more certain because the constant of the semiquinone $RS \rightarrow S$ is indicated clearly at *p*H 7.5. It is clearly seen that the semiquinone formation in very alkaline solutions must be very large as indicated also in Table III.

The observations on all three dyestuffs, Bindschedler's green, phenol blue and phenolindophenol, indicate the following general behavior: strong semiquinone formation in alkaline and acid range and comparatively small semiquinone formation in the middle *p*H range. In the case of phenol blue the acid range of large semiquinone formation is reached exceptionally early and already begins at *p*H 4.

The above statement for the very alkaline range is not astonishing. We know that the formation of R and T forms in non-aqueous solutions, from a free radical, is generally negligible and that we find only the equilibrium between the dimeric compound and the radical. Such solutions are similar to a solution of very high *p*H, because the R form has not the possibility of taking up a proton. The sensitivity of these equilibria toward water now becomes quite clear. The addition of water, a proton donator, has an effect equivalent to that of a strong lowering in *p*H by converting the R form into HR

$$R + H_2O \longrightarrow RH + OH'$$
$$2S + H_2O \longrightarrow T + RH + OH'$$

This is the main reason for the dismutation which has been found in many cases by addition of water to the radicals and has been especially described for the case of the radical derived from Bindschedler's green by Wieland. If we dissolve small quantities of the semiquinone or its dimeric product in water, Bindschedler's green is produced immediately and by the action of the OH ions, formed by the reaction just mentioned, hydrolyzed to phenol blue.

C. Discussion

The general treatment of oxidations and reductions of organic compounds has to take account of the following equilibria

$$\begin{tikzcd} R \arrow[r, shift left, "\epsilon"] & S \arrow[l, shift left] \arrow[r, shift left, "\epsilon"] \arrow[d, shift left] & T \arrow[l, shift left] \\ & {}^1/_2D \arrow[u, shift left] & \end{tikzcd} \qquad (1)$$

The reaction $D \rightleftarrows 2S$ has been the classical one to prepare radicals and has been investigated always in non-aqueous solutions. On the other hand, oxidations and reductions $R \rightleftarrows T$ have been investigated extensively in aqueous solution by means of the potentiometric method. The general belief was that the bivalent reversible oxidation–reduction in organic compounds would occur in a single bivalent step. There was no reason to link the reversible oxidation with the problem of free organic radicals, until almost simultaneously Friedheim and Michaelis[11] and Elema[12] found that in some cases during such reductions and oxidations free radicals are formed even in aqueous solutions. Later on, Michaelis and Fetcher[13] also found the dimeric form of the radical to exist in the equilibrium. Thus the complete picture of the scheme (1) was revealed.

The semiquinones, however, still seemed to have little connection with the substances commonly known as free radicals. As pointed out by Michaelis, the semiquinones were in all cases compounds which contained two equal atoms (other

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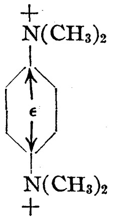
[11] E. A. H. Friedheim and L. Michaelis, *J. Biol. Chem.*, **91**, 355 (1931).

[12] B. Elema, *Rec. trav. chim.*, **50**, 907 (1931).

[13] L. Michaelis and E. S. Fetcher, This Journal, **59**, 2460 (1937).

than carbon), symmetrically located in the molecule, as in the case of Wurster's blue



These two atoms could be regarded as carriers of the odd electron, ε, which was assumed to resonate symmetrically between the two positions. The older free radicals, on the other hand, contained one atom which might be considered as the carrier of the odd electron, so that it was reasonable to speak of trivalent carbon, or divalent nitrogen or univalent oxygen. These latter radicals were found to be very sensitive toward water.

The present paper has filled the gap between the two groups of radicals: radicals of the second type, with so called divalent nitrogen, have been found to exist in aqueous solution in equilibrium with the oxidized and reduced forms. These findings are quite in agreement with the theory of stability of the free radicals. As Hückel[14] and Pauling[15] have shown, all free radicals owe their existence to resonance energy. The odd electron and the π electrons of the aromatic nuclei cannot be placed in a definite position, rather their charge is on a time average distributed over a wide range of the molecule.[16]

The equilibria constants of the above scheme are of course dependent on pH. The equilibrium R $\rightleftarrows$ T is expressed in the potential E_m and the equilibria R $\rightleftarrows$ S and S $\rightleftarrows$ T in the potentials E_1 and E_2. To understand their magnitude, we must know something about the relative stability of the molecules involved in the equilibrium, this is to say, of all the molecules whose formulas are given in the table of formulas (Fig. 7) for the T-, R- and S-forms.

This stability cannot yet be calculated by quantum mechanical methods. Even in simpler cases, where the molecules contain no other atoms than carbon and hydrogen, different approximation methods (Hückel and Pauling) yield widely differing results. We will try here to express the stability of a molecule in terms of the more qualitative valence chemistry, starting from the concept of an ideal state of a molecule exhibiting maximum stability. The instability of a molecule is then measured in terms of the tendency of its atoms to reach this ideal state.

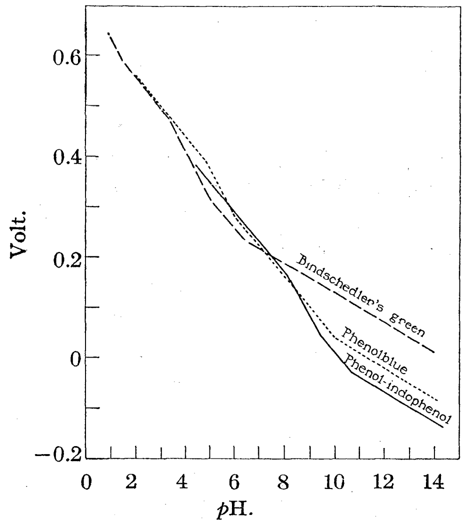
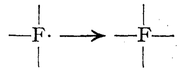


Fig. 6.—The mean normal potentials of Bindschedler's green, phenol blue and phenolindophenol.

An atom in the ideal state would be surrounded by four electron pairs which are all equal and indistinguishable. For example, the C-atom in methane or the helium atom can be regarded as being in this ideal state. Any reactivity can be attributed to one of the two following reasons:

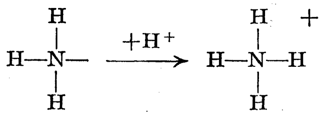
1. A deviation from the stable electron number 8, giving rise to a tendency for oxidation or reduction as for instance in the fluorine atom



$$\text{—F·} \longrightarrow \text{—F—}$$

This kind of instability will be called oxidation–reduction instability.

2. A deviation from the ideal state of equality of the four electron pairs, giving rise to acid–base reactions as in ammonia



$$\text{H—}\overset{\text{H}}{\underset{\text{H}}{\text{N}}}\text{—} \xrightarrow{+\text{H}^+} \text{H—}\overset{\text{H}}{\underset{\text{H}}{\text{N}}}\text{—H}^{+}$$

We will call this instability an acid–base instability.

Both tendencies must be regarded as equally important, because the free energies of acid–base reactions and oxidation–reduction reactions are of the same order of magnitude.

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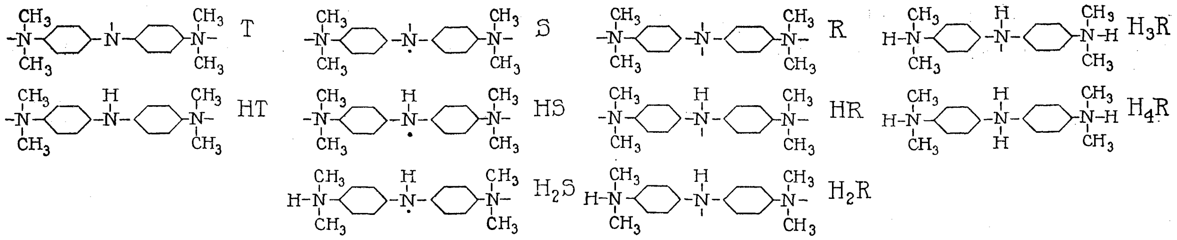
(14) E. Hückel, *Z. Physik*, **83**, 632 (1933); *Trans. Faraday Soc.*, **30**, I, 41 (1934).

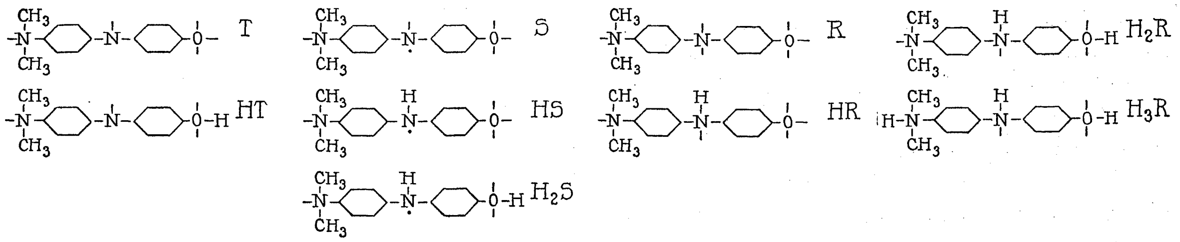
(15) L. Pauling and G. W. Wheland, *J. Chem. Phys.*, **1**, 362 (1933).

(16) C. K. Ingold, *Trans. Faraday Soc.*, **30**, 52 (1934).



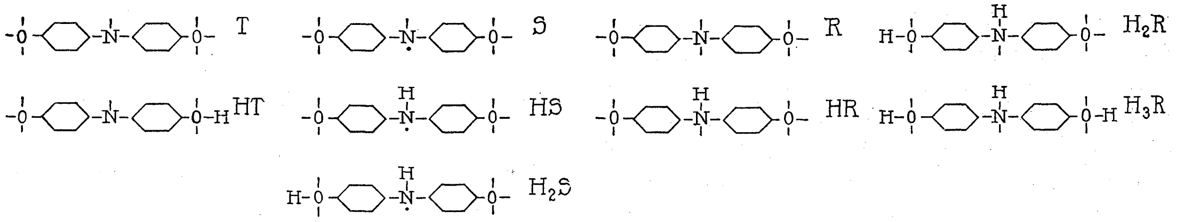
T-Forms S-Forms R-Forms

Bindschedler's green.



T-Forms S-Form R-Forms

Phenol blue.



T-Forms S-Forms R-Forms

Phenolindophenol.

Fig. 7.

If we regard the stability of all the ions and molecules involved in the equilibrium $R \rightleftarrows S \rightleftarrows T$ in all possible pH ranges, we arrive at the following conclusions.

1. **The Stability of the R-Forms.**—The R-forms of our dyestuffs show primarily an acid–base instability, all atoms being surrounded by an electron octet. (In the formulas in the table of formulas (Fig. 7) 4 strokes belong to every atom.) The instability is manifested in the basic character of these molecules, the central N-atom and the auxochromic groups having unshared electron pairs. It is easily understood that the instability will be great in strongly alkaline solution, where even the central N atom has lost a proton and is strongly basic. In extremely acid solutions a maximum stability is reached. This means that all equilibria will be displaced in favor of the R form on decreasing the pH.

2. **The Stability of the T-Forms.**—The fact that the R-forms can be oxidized to the S- and T-forms even in acid solutions, is due to the fact that the oxidized forms exhibit a new type of resonance, which is missing in the R forms. The nature of this resonance is different for the S and for the T forms. In the T forms we have resonance between the two moieties of the molecule, one of quinoid structure, the other of benzenoid structure. Their acid–base instability is much decreased in comparison with the R forms, but instead an oxidation–reduction instability arises. In these substances the fourth electron pair of the central nitrogen is delivered by the auxochromic groups. The stability will therefore depend on the tendency of these groups to share their electron pairs with the neighboring carbon atom, in other words, to form a double bond with this carbon atom. This tendency is strongly related to the basicity of the auxochromic groups. The stability will be great if the auxochromic groups are strongly basic. We have, therefore, the maximum stability in solutions of a high pH. As we go

to more acid solutions we block the unshared electron pairs of the auxochromic groups ($T \rightarrow HT$) and the central nitrogen is more and more deprived of its electrons, giving rise to an increased tendency to take up an electron pair from outside. It has to be assumed that all symmetrical forms, in which the two auxochromic groups are equal, have a greater stability than the corresponding unsymmetrical forms. This is due to the larger resonance energy of the symmetrical forms.

The stabilities of the R and T-forms change, therefore, in just the opposite sense as we change the *p*H. In acid solutions R is especially stable and in alkaline solutions T is especially stable. This corresponds to the general fact that the normal potentials all become more negative as we raise the *p*H. A more positive potential means that T is more easily reduced to R and a more negative potential means that R is more easily oxidized to T.

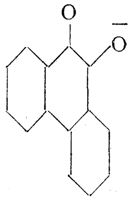
In this respect a comparison of the E_m values of phenolindophenol, phenol blue and Bindschedler's green, as demonstrated in Fig. 6, is of interest. Above *p*H 10, the three curves are parallel, the value for Bindschedler's green being the most positive and the one for phenolindophenol the most negative. The same must hold true for still more alkaline solutions, where the potentials become independent of *p*H. The relative values of the three normal potentials can be understood easily, because the instability (basicity) of the three R forms will increase in the following sequence

Bindschedler's green < Phenol blue < Phenolindophenol

whereas the instability of the T forms will increase in just the opposite order, the more basic ionic oxygen group forming a more stable resonance system than the less basic amino group. This brings about the sequence in the normal potentials of these three dyestuffs.

3. The Stability of the Radical S.—It is much more difficult to predict the stability of a radical even qualitatively. Quite generally it must be assumed that a valence-unsaturated compound is less stable than R or T. The S form arises from the reaction $R + T \rightleftarrows 2S$ only if R and T are relatively unstable; this means, in general, in very acid and in very alkaline solution. We have shown experimentally that this really is the case in our examples. However, although it is difficult to make any statement about the stability of a radical in a general way, there may exist one quite obvious electronic structure in a radical which greatly enhances its existence. We may say that the semiquinones, which are radicals stable to a well measurable extent even in an aqueous solution, show this type of electronic arrangement. This is a resonance phenomenon, which differs essentially from the resonance of the T form mentioned above. It is not concerned necessarily with a resonance between two rings, but may be confined entirely within one single ring which contains two atoms of the same kind, either two N atoms, or two O atoms in symmetrical positions—that is to say, either in ortho or in para positions; either attached to, or within this ring. They are within the ring in phenazine, attached to the ring in Wurster's dyes. Instead of one ring, it may be the double ring of the biphenyl type, as in benzidine and γ,γ'-dipyridyl. The experience with the Wurster's dyes shows that the atom groups attached to each of the two N atoms need not necessarily be alike. They are alike in Wurster's blue, which has a very great stability. They are not alike in Wurster's red, which still has a fair stability. Also the semiquinone of phenol blue may be considered as comparable to Wurster's red, symmetrical with respect to the two N atoms at one ring, but not symmetrical with respect to the groups attached to the two N atoms. Phenolindophenol does not show this type of symmetry at all, but Bindschedler's green does.

This type of resonance furthermore is greatly influenced by *p*H, as was formerly explained on several occasions, *e. g.*, for the semiquinone of phenanthrenequinone,[13] and for the purple radical prepared by partial reduction of benzil.[17]



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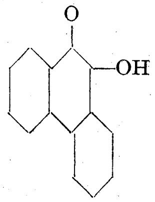

II

So, in alkaline solution (I), there is resonance with respect to the negative charge which may be at the one or the other O atom. But in acid solution (II), the attachment of the proton fixes the electron in one of the two possible positions thus decreasing the resonance and so the stability.

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[17] L. Michaelis and E. S. Fetcher, THIS JOURNAL, **59**, 1246 (1937).

These considerations convey, at least qualitatively, an understanding about the stability of the radicals as depending on the constitution of the particular dye and on *p*H. We may emphasize once more, at this occasion, that practically none of the organic radicals that had been known prior to the discovery of the semiquinones, exhibit that particular type of strongly symmetrical resonance structure which has just been described as characteristic of the semiquinones. Correspondingly, those older radicals are usually not stable enough to be capable of any appreciable existence in the presence of water, in contrast to the semiquinone radicals.

Summary

Potentiometric oxidative and reductive titrations of Bindschedler's green and phenol blue at various *p*H's have been carried out. The slope of the titration curves indicates that an intermediate semiquinone radical is formed. The ionization constants for the reduced, half-oxidized, and oxidized forms of these dyes as well as the semiquinone formation constant have been determined. The latter depends on *p*H.

The ionization constants have been checked by spectrophotometric measurements. The absorption bands of all the three forms of each of these two dyestuffs are shown.

The discussion correlates the stability of the three forms, and especially that of the free radical, with general ideas about molecular stability derived from the electronic theory of the chemical bond and the principle of resonance. The type of resonance stabilizing the free radical is very different from the type of resonance stabilizing the oxidized form of the dye itself. The relative stability of the three forms of a dyestuff (oxidized, half-reduced radical, and reduced) is accounted for, qualitatively at least. The results are summarized in Figs. 4, 5, 6.

New York, N. Y. Received April 22, 1938

[Contribution from the Laboratories of The Rockefeller Institute for Medical Research and the Physics Department of Columbia University]

Potentiometric and Magnetometric Study of the Duroquinone System

By L. Michaelis, M. P. Schubert, R. K. Reber,[1] J. A. Kuck[1] and S. Granick

Among the numerous reversible bivalent two-step oxidation–reduction systems studied so far only a few cases of simple quinones have been subjected to an experimental study. They are concerned with orthoquinones. This paper adds an example of a paraquinone. A suitable representative avoiding the difficulties due to the instability of most quinones in alkaline solution, is duroquinone (tetramethylbenzoquinone). Although there is a limit to the stability of duroquinone also, no observable irreversible alteration by alkali occurs at all, during the period of time necessary for the experiments, at the temperature, 30°, even at the highest *p*H that reasonably may be used for experiments of this type. Because of its slight solubility, the experiments were performed with buffer solution containing 20 volume per cent. of pyridine, which, though reacting chemically with other quinones, serves only as a solvent for duroquinone. The process of reduction was studied both by the potentiometric and the magnetometric methods. Both methods agree in the final result. In sufficiently alkaline solution a free semiquinone radical of brown color is formed as intermediate step of the reversible reduction. This radical is strongly paramagnetic. In contrast to the semiquinone of phenanthrenequinonesulfonate, which is a representative of the orthoquinones, the semiquinone of duroquinone has no measurable tendency to form a valence-saturated, dimeric form in the dissolved state.

1. Potentiometric Experiments

Reductive titration with leuco-rosinduline G G was used. In sufficiently alkaline solutions, *p*H >9, the potentials are instantaneously and reproducibly established at concentrations down to 6×10^{-5} molarity. At lower *p*H values, the establishment of the potentials in low concentrations, about 10^{-4} *m*, is relatively sluggish, though eventually leading to definite and reproducible values. For this reason titration curves for duroquinone at *p*H < 9 are somewhat less accurate than those at *p*H > 9. This uncertainty has no

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[1] Members of the staff of the College of the City of New York.

TABLE I

Molar concn., of duroquinone $\times_k 10^4$	pH	100 cc. of the buffer contains 20 cc. of pyridine, and	Mean normal potential, E_m, v.	Index potential E_i Left: right of the titration curve, mv.		Average	$\sqrt{k}$ (k = semiquinone formation constant)	$E_2 - E_1$, mv.
2.4	7.40	47 cc. 0.067 *M* KH_2PO_4 + 23 cc. 0.067 *M* Na_2HPO_4	−0.226	13	14	..	~ 0	$\sim -\infty$
2.4	7.56	40 cc. 0.067 *M* KH_2PO_4 + 40 cc. 0.067 *M* Na_2HPO_4	− .2285	13	15	..	~ 0	$\sim -\infty$
2.4	8.71	2.00 g. sodium veronal + 2.5 cc. 1 *M* HCl	− .299	15	14	..	~ 0	$\sim -\infty$
2.4	11.50	70 cc. 0.067 *M* Na_2HPO_4 + 2.2 cc. of 1.086 *N* NaOH	− .4645	15.7	15.8	15.75	0.19	−87
2.4	11.76	70 cc. 0.067 *M* Na_2HPO_4 + 3.2 cc. of 1.086 *N* NaOH	− .4805	17.5	18.0	17.75	0.45	−42
2.4	12.26	1.6 cc. 1.086 *N* NaOH 0.74 g. KCl	− .504	20	21	20.5	0.84	− 9.1
2.4	12.74	5 cc. 1.086 *N* NaOH 0.74 g. KCl	− .524	26	26	26.0	1.62	+25.1
2.4	12.92	7.5 cc. 1.086 *N* NaOH 0.74 g. KCl	− .530	29.5	29.5	29.5	2.15	+39.9
4.9	13.01	10 cc. 1.086 *N* NaOH 0.74 g. KCl	− .533	31	32	31.5	2.46	+46.9
1.2	13.00	Same	− .532	29.5	30.5	30.0	2.21	+41.3
0.6	12.96	Same	− .532	32	32	32	2.54	+48.6
2.4	13.01	Same	− .532	33	32	32.5	2.62	+50.2
2.4	13.28	20 cc. 1.086 *N* NaOH 0.74 g. KCl	− .538	36	36	36	3.23	+60.0
2.4	13.51	40 cc. 1.086 *N* NaOH 0.74 g. KCl	− .548	39	39	39	3.79	+69.4

noticeable bearing on the values of E_m, the mean normal potential, but it affects somewhat the values for E_1 and E_2, the normal potentials of the lower and the higher steps of oxidation, since at $p\text{H} < 9$ the index potential E_i is very close to its minimum value 14.3 mv., and under these circumstances a small error in E_i involves a distinct error in E_1 and E_2. It will be seen, however, that no uncertainty in the construction of the curve (Fig. 1) ensues herefrom, except for the fact that the ionization constant of the radical cannot be determined with accuracy. All that we can say is that it is greater than 10^{-11}. Probably it is very much greater than 10^{-11}, by analogy with the semiquinone of phenanthrenequinonesulfonate.[2] The titration experiments are summarized in Table I, and the normal potentials, plotted against pH according to calculations from these experiments, are shown in Fig. 1. The bend correlated to the acid dissociation of the radical has been located tentatively at pH 11; it may be in reality at a much smaller pH value. In any case, it can be seen that the radical is practically incapable of existence in neutral or acid solution.

The initial concentration of duroquinone has been varied in these experiments in the ratio 1:16 without producing any variation in the shape of the titration curve at any given pH, in contrast to the case of phenanthrenequinonesulfonate.[3] This clearly indicates that there is no measurable tendency to dimerization of the radical. This result is confirmed by the magnetic method up to much higher concentrations.

One striking difference of this paraquinone from the two orthoquinones previously investigated is this. An *o*-quinone shows an acidic ionization, at pH around 9, due to the addition of an *OH⁻ ion* in alkaline solution. A *p*-quinone does not show this type of ionization, obviously because the acidifying influence of one CO group upon another is distinct only if the two CO groups are in close proximity. In any case, within the pH range experimentally available no ionization is noticeable. A consequence of this fact is that the E_1 and the E_2 curves do not run parallel in strongly alkaline solution, and hence the maximum ratio of semiquinone to total dye $(s/a)_{\text{max.}}$ continuously increases with increasing pH, whereas in the two orthoquinones investigated[2,4] it reaches a maximum value constant for any $p\text{H} > 11.5$.

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[2] L. Michaelis and M. P. Schubert, *J. Biol. Chem.*, **119**, 133 (1937).

[3] L. Michaelis and E. S. Fetcher, THIS JOURNAL, **59**, 2460 (1937).

[4] L. Michaelis, *ibid.*, **58**, 873 (1936).

Magnetometric Measurements

The method used was what may be called the slow-reduction method as described in a previous paper[5] with the magnetic balance of Wills and Boeker, modified by Woodbridge.[6] The change of magnetic susceptibility of the solution was measured during the period of reduction. The duration of this reductive period depends on *p*H and on the concentrations. The concentration of glucose was usually adjusted so as to stretch the time of reaction approximately over one hour.

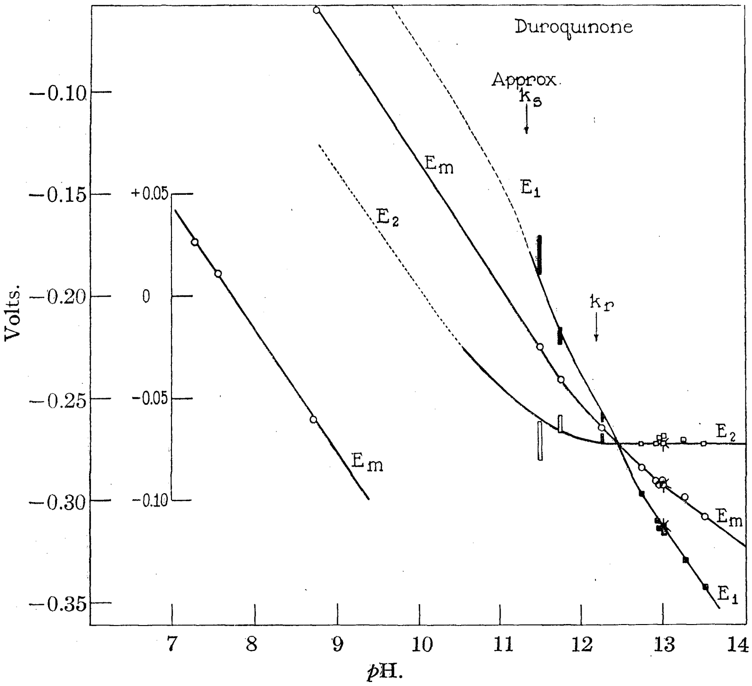

Fig. 1.—The mean normal potential, E_m; the normal potential of the lower step of oxidation, E_1, and the normal potential of the higher step of oxidation, E_2, of duroquinone plotted against *p*H. The left-hand curve is an extension of the main curve. The point designated ȯ- corresponds to three separate experiments with coinciding results.

In order to compare these measurements with those obtained potentiometrically one has to know the *p*H of the solution. In general, the *p*H will not be constant during the reduction. First, from the non-acid duroquinone the acidic semiquinone and the acidic hydroquinone are formed gradually. Since in these experiments the concentration of the quinone has to be taken much higher than in the potentiometric experiments, this fact has to be taken into consideration. Second, as the sugar acts as a reductant it is oxidized to various acids. So a sufficient excess of sodium hydroxide has to be added in order to minimize the effect of these acidic molecular species on the *p*H during the reduction. The following experiments will show that the experimental conditions chosen were such as to render any change of *p*H during the reduction negligible. All of these experiments were carried out by measuring the potential of the platinum electrode after adding some drops of 1% colloidal palladium, and while bubbling with hydrogen until the reduction was complete and the hydrogen potential was constant. (1) A solution just as used for the magnetic experiments no. 12 to 15, containing sodium hydroxide and pyridine, but without duroquinone and without glucose, showed *p*H 13.05. (2) The same solution, containing glucose, showed *p*H 13.01. (3) After adding in addition the duroquinone and rapidly reducing it by PdH_2 in the electrode vessel to the hydroquinone, *p*H was 12.99. (4) The same solution, containing glucose and the duroquinone as in (3) was allowed to stand at 30° in a closed bottle until the reduction by glucose was complete. Then the solution was poured into the electrode vessel, and after addition of colloidal palladium the potential in hydrogen was measured. This showed *p*H 13.00.

These experiments show that addition of glucose slightly shifted the *p*H of the sodium hydroxide solution, as may be expected, but that the effect on *p*H of any chemical reaction during the reduction is within the limits of error in the measurement of *p*H in such strongly alkaline solutions.

So we may put for experiments 12, 13, 14, and 15, *p*H = 13.00. For this *p*H we derive from the curve Fig. 1, $E_2 - E_1$ = 40 mv. Hence the semiquinone formation constant k = 4.64; and $(s/a)_{\text{max.}}$ = 0.517 ± 0.01. The limits of error are based on the assumption that the limit of error in the index potential, E_i, from which $E_2 - E_1$ has to be calculated, is ± 0.5 mv. The magnetic measurement yields $(s/a)_{\text{max.}}$ = 0.519 as average for the four parallel experiments, 12

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(5) L. Michaelis, G. F. Boeker and R. K. Reber, This Journal, **60**, 202 (1938); L. Michaelis, R. K. Reber and J. A. Kuck, *ibid.*, **60**, 214 (1938).

(6) A. P. Wills and G. F. Boeker, *Phys. Rev.*, **42**, 687 (1932); D. B. Woodbridge, *ibid.*, **48**, 672 (1935).

to 15. The agreement is satisfactory. The calculation of $(s/a)_{\max.}$ is based on the difference in the value of susceptibility of its maximum point in the half reduced state, and the final, time-independent value after the completion of the reduction, and on the principle set forth in the previous paper[5] by assuming that the contribution of one mole of the free radical to the total susceptibility, in the direction of paramagnetism, amounts to $2.94/T$ units, where T is the absolute temperature. According to Van Vleck, "all odd polyatomic molecules should presumably conform to this formula."[7] Certainly this radical does.

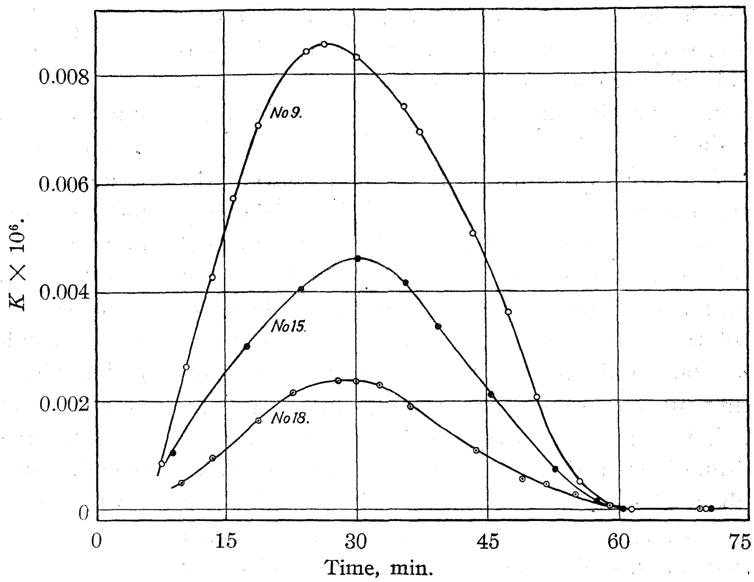

Fig. 2.—Magnetic susceptibility of duroquinone plotted against time, for three of the experiments tabulated in Table II. The time-independent diamagnetic susceptibility after the completion of the reduction is taken as zero point.

It should be ascertained also that the oxidation of glucose itself does not entail any measurable change in magnetic susceptibility. This was proved in the following experiment.

TABLE II

Expt.	T, °C.	P	G	S	a	$K \times 10^6$	s	$s/a_{\max.}$
1	20	3	61.1	0.52	0.0142	0.00945	0.00750	0.528
2	20	3	419	.52	.0143	.00417	.00331	.226[a]
3	20	3	243	1.00	.0147	.01020	.00810	.550
4	30	3	53.4	1.00	.01337	.00915	.00745	.557
5	30	3	52.4	2.00	.0139	.01045	.00850	.612
6	30	3	300	2.00	.01427	.01095	.00893	.625
7	30	3	302.2	2.00	.01427	.01108	.00902	.632
8	30	3	90.2	0.60	.01445	.00788	.00642	.444
9	30	2	80.4	.61	.01431	.00850	.00692	.482
10	30	2	78.6	.60	.01440	.00810	.00659	.457
11	30	2	72.8	.60	.01430	.00831	.00677	.473
12	30	2	39.2	.60	.00712	.00430	.00351	.493
13	30	2	39.2	.60	.00754	.00491	.00400	.531
14	30	2	39.2	.60	.00717	.00461	.00375	.523
15	30	2	39.2	.60	.00703	.00457	.00373	.530
16	30	2	20.0	.60	.00355	.00217	.00177	.500
17	30	2	20.1	.60	.00353	.00228	.00186	.527
18	30	2	24.0	.60	.00356	.00238	.00194	.540

P = ml. of pyridine in 10 ml. of solution.
G = mg. of glucose in 10 ml. of solution.
S = ml. of 2.00 N NaOH in 10 ml. of solution.
s = calculated molar concentration of the semiquinone radical.
a = molar concentration of duroquinone added.
K = difference between the susceptibility at the maximum point and the time independent value at the end of the reaction.

[a] The exceptionally low value of $(s/a)_{\max.}$ in experiment no. 2 is due to the fact that the amount of glucose in comparison with that of sodium hydroxide is so high that pH is considerably lower than in experiment no. 1.

A fresh solution just as in the magnetic experiment, but without duroquinone, was measured in the magnetic balance. Another portion of this solution was bubbled for five hours with air under conditions such as to avoid any evaporation and to keep the volume unchanged, and was then put in the magnetic balance. The oxidation of the sugar had not been allowed to proceed too far in order to ensure the absence of dissolved oxygen during the magnetic observation. The result was that the diamagnetic susceptibility was the same as without previous oxidation, within the limits of error ($\pm$ 0.0002 $\times$ 10^{-6} unit).

Discussion of the Problem of Dimerization

With regard to the formation of either a paramagnetic free semiquinone radical or a dimeric, valence-saturated, non-paramagnetic molecular species on the oxidation level of a quinhydrone, the following statements may serve as actual material for the discussion.

(1) For the benzoquinone system, no statement can be made for alkaline solution because of the instability of benzoquinone in alkali. In acid solution, on mixing benzoquinone and hydroquinone, the solid crystals of quinhydrone are precipitated, and the remaining mother liquor contains practically nothing but a mixture of quinone and hydroquinone. The crystals of

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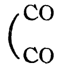
[7] J. H. Van Vleck, "Electric and Magnetic Susceptibilities," Oxford University Press, 1932, p. 274.

quinhydrone are diamagnetic[8] and so are representatives of a dimeric form, which may be considered as a compound of quinone and hydroquinone with the same justification as a dimerized radical.

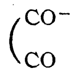
(2) For duroquinone in alkaline solution the free paramagnetic semiquinone radical is the only form in which the quinhydrone arises. In acid solution, no quinhydrone can be detected at all on mixing duroquinone and durohydroquinone in solution. It is extremely difficult also to obtain a solid quinhydrone. When a mixture of duroquinone and durohydroquinone, say in methanol, is evaporated even to dryness, no quinhydrone is formed. On heating the dry residue to about 200°, a dark brown mass is formed which on cooling again becomes yellow. If it is cooled very rapidly, dark brown crystalline specks may survive, which disappear either spontaneously or on gently warming. If the hot brown mass is cooled down sufficiently slowly, all the brown color may disappear. It is formed over again on heating strongly. Obviously the formation of duroquinhydrone is a strongly endothermic reaction. The substance is not capable of existence at room temperature except in a metastable or transient state.

(3) Phenanthrenequinone-3-sulfonate, an orthoquinone, forms a paramagnetic radical in alkaline solution, which, when present in not too low a concentration, is in equilibrium with its non-paramagnetic dimeric compound. In acid solution, the free radical cannot be detected in any safely measurable concentration at all, whereas the dimeric compound is easily formed to a great extent in solutions of sufficiently high concentration of the parent substances.

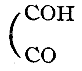
These facts may be interpreted as follows: Let (I) be the symbol for any quinone. Then (II) is the semiquinone radical in a sufficiently alkaline solution, and (III) the same in a sufficiently acid solution. In (II) there is a strong symmetrical resonance, one electron oscillating from the one O atom to the other. This is not the case in (III) where the fixed proton fixes the electron, too. So (II) should be more stable than (III). This greater stability may find its expression in two ways: (a) the tendency of dismutation is smaller in (II) than in (III). This accounts for the fact that the semiquinone radical is more stable in alkaline than in acid solution, indicated by the fact that the semiquinone formation constant increases with increasing pH for all quinones that have been amenable to measurement yet. (b) The tendency toward dimerization is smaller in (II) than in (III). This explains why the dimerization constant should be greater in acid than in alkaline solution.[2]


$\left(\begin{matrix}\text{CO}\\ \text{CO}\end{matrix}\right.$

(I)

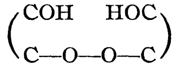

$\left(\begin{matrix}\text{CO}^-\\ \text{CO}\end{matrix}\right.$

(II)


$\left(\begin{matrix}\text{COH}\\ \text{CO}\end{matrix}\right.$

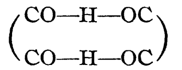
(III)

As regards the structure of the dimeric compound, one suggestion is the peroxide structure (IV).


$\left(\begin{matrix}\text{COH} & & \text{HOC}\\ \text{C—O—O—C}\end{matrix}\right)$

(IV)

The peroxide of Goldschmidt and Steigerwald[9] derived from chlorophenanthrol is colorless; the color appears only when the radical is formed by dissociation of the peroxide. So, one has to resort to the meriquinone structure proposed long ago by Willstätter and Piccard.[10] Expressing their idea in modern terms, one may assume two hydrogen bonds as in (V) for the dimeric form in the solid state. This hydrogen bond involves a resonance between two fictitious structures, in which alternately the one and the other half of the molecule is in the quinoid or in the benzenoid state, in the same way as is the case for any quinoid dyestuff, say of the indophenol type. This accounts for the deep color much more plausibly than does a peroxide structure.


$\left(\begin{matrix}\text{CO—H—OC}\\ \text{CO—H—OC}\end{matrix}\right)$

(V)

The same structure will hold for the soluble dimeric quinhydrone of phenanthrenequinonesulfonate, which represents the quinhydrone practically as it exists in acid solution, and as it exists in equilibrium with the free radical in alkaline solution. This dimeric molecule (V) is such a weak acid that it can exist, to a certain extent, even in rather strongly alkaline solution, provided it can exist in an acid solution.

So we have to discuss on what the existence of this dimeric form depends. The answer is that there must be no steric hindrance for a sufficiently close approach of each pair of atoms which are to be bridged by the hydrogen bond. If the quinone

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[8] Some time ago Dr. C. D. Coryell in Professor L. Pauling's laboratory, at our request, measured the susceptibility of crystalline benzoquinhydrone and found it to be diamagnetic, in confirmation of unpublished experiments of several physicists about which we had personal information.

[9] St. Goldschmidt and Ch. Steigerwald, *Ann.*, **438**, 202 (1924).

[10] R. Willstätter and J. Piccard, *Ber.*, **41**, 1458 (1908).

is an orthoquinone, there is no steric restriction on forming these bonds. In a paraquinone, however, the two bonds can be formed only by putting the planes of the two six-carbon rings flatly one upon the other. This will be easily possible in benzoquinone, but in duroquinone the voluminous side chains prevent a sufficiently close approach. It may be briefly and preliminarily mentioned that the ease with which a solid quinhydrone is formed by mixing a quinone with the corresponding hydroquinone, decreases with the number of CH_3 groups which substitute the H atoms. In the tetramethyl compound, duroquinone, no quinhydrone is formed at all at room temperature.

The authors are deeply indebted to Columbia University for the use of their facilities.

Summary

Duroquinone in a strongly alkaline solution forms a free paramagnetic semiquinone radical of brown color as intermediate step of the reduction. There is no dimeric form of this radical; in other words, no compound corresponding to the ordinary crystalline benzoquinhydrone, which is a dimeric diamagnetic molecule, is formed from duroquinone and durohydroquinone either from alkaline or acid solutions. Solid benzoquinhydrone is a compound formed from quinone and hydroquinone by two hydrogen bonds. These bonds cannot be formed in duroquinone due to steric hindrance.

The maximum percentage of the duro-semiquinone radical in equilibrium with its parent substances continuously increases with increasing *p*H. At *p*H 13 this maximum is about 50%, a result which is the same whether derived from potentiometric or magnetic observations.

NEW YORK, N. Y. RECEIVED MAY 2, 1938

[CONTRIBUTION FROM THE MALLINCKRODT CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Influence of Surface Tension on the Measurement of Viscosity
The Viscosity of Methanol

BY GRINNELL JONES AND HOLMES J. FORNWALT

Introduction

In recent years many measurements of viscosity of solutions of salts in water and in methanol have been carried out in this Laboratory by an improved technique.[1] The various sources of experimental error in determining the measurement of the viscosity of dilute solutions have been studied and discussed in an earlier paper. When measurements were extended to concentrated solutions and especially when the viscosity of methanol was compared with that of water it became apparent that the possibility of two additional sources of error which are negligible for relative measurements of dilute solutions should be considered, namely, errors due to unequal drainage and errors due to surface tension. The drainage error has recently been studied by Jones and Stauffer[2] with results which show that this source of error may be disregarded safely in measurements on methanol.

Surface tension can influence the measurement of viscosity by the Ostwald viscometer because the effective hydrostatic head which drives the liquid through the capillary is not solely determined by the dimensions and mounting of the instrument and the volume of liquid contained therein but is influenced by the capillary rise of the liquid in the two arms of the viscometer. Since this capillary rise is a function of the surface tension divided by the density, it will be different for the solutions and for the pure solvent.[3]

In this paper is given a mathematical analysis of the problem that has led to the development of a method of estimating the magnitude of the correction which should be applied to the results obtained with the Ostwald viscometer. This analysis guided the design of another instrument in which the error due to surface tension was minimized as much as other considerations of design permitted. The viscosity of methanol was then measured with reference to water in both the old and new instruments. The results are compared

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[1] Grinnell Jones and co-workers, THIS JOURNAL, **51**, 2950 (1929); **55**, 624, 4124 (1933); **57**, 2041 (1935); **58**, 619, 2558 (1936); **59**, 484 (1937); *Physics*, **4**, 215 (1933).

[2] Grinnell Jones and R. E. Stauffer, THIS JOURNAL, **59**, 1630 (1937).

[3] M. P. Applebey [*J. Chem. Soc.*, **97**, 2013 (1910)] has applied a correction for the effect of surface tension by a method which is a rough approximation.

before and after applying the computed corrections for surface tension.

Experimental

The source of the methanol was the same as that previously described[4] and the treatment similar except that it was more thorough. Lund and Bjerrum's method[5] of dehydration by distillation from magnesium methylate was carried out twice on each batch and in some cases there was an additional treatment with metallic sodium. The methanol was distilled through a good fractionating column 75 cm. long. The maximum range in the boiling point of the portions collected and used was only 0.04°. The four different batches which were used for the viscosity measurements gave the following densities, respectively: $d^{25}{}_4$, 0.786527, 0.786523, 0.786527, 0.786525. These results are slightly lower and more consistent than had been obtained with many batches which had been given a single treatment with magnesium methylate. The average density of these earlier batches was 0.786545. A comparison with the best results which have been found in the literature is given in Table I.

TABLE I

DENSITY OF METHANOL AT 25°

	$d^{25}{}_4$
E. C. McKelvy and D. H. Simpson, THIS JOURNAL, **44**, 110 (1922)	0.78658
F. K. Ewart and H. R. Raikes, *J. Chem. Soc.*, 1907 (1926)	.78641
H. Lund and J. Bjerrum, *Ber.*, **64B**, 213 (1931)	.78651
J. A. V. Butler, D. W. Thompson and W. H. Maclennan, *J. Chem. Soc.*, 675 (1933)	.78643
R. E. Cornish, R. C. Archibald, E. A. Murphy and H. M. Evans, *Ind. Eng. Chem.*, **26**, 399 (1934)	.78656
Grinnell Jones and H. J. Fornwalt, this paper	.786525

The freezing point of this methanol was determined by Mr. Edwin E. Roper in this Laboratory by the use of a platinum resistance thermometer to be −97.68 ± 0.02° (see the succeeding paper).

The first viscometer (designated herein as instrument T) was originally built for and used by S. K. Talley. The quartz-blower was instructed to make the surfaces connecting the constrictions and the cylindrical part of the upper bulb as nearly conical with a 60° angle as possible. Except for some necessary rounding at the line of contact with the cylinders above and below, he accomplished this objective approximately. In the calculations given below, the conical form is assumed. The values used for the angles are based on measurements made on the finished instrument. The lower reservoir was a vertical cylinder of much larger radius than the upper bulb. This larger radius was chosen in order to minimize the error due to variations in the working volume.

In the new instrument (designated here as F) there were three changes in design for the purpose of minimizing the surface tension correction: (1) the lower reservoir was made a cylinder of the same radius as the cylindrical part of the upper bulb; (2) the hydrostatic head was increased; (3) the quartz blower was instructed to make the upper dome and lower bowl as nearly hemispherical as he could. It is easier to meet this specification than to make the surfaces conical. The essential dimensions in centimeters which were used in the calculations are given below. The significance of the symbols will be understood by reference to Fig. 1.

TABLE II

DIMENSIONS OF THE VISCOMETERS IN CENTIMETERS

	w	*r*	*R*	*J*	*a*	*b*	*c*	*e*	*f*
T	0.05	0.90	3.58	24.3	23.8	22.3	18.5	17.5	16.5
F	.05	.848	0.848	28.5	27.43	26.59	21.95	21.1	20.7

T: Upper dome, $\tan\theta = -0.567$; $\theta = -29°30'$: lower bowl, $\tan\psi = +0.85$; $\psi = +49°38'$.

F: Radius of hemisphere, $r = 0.848$.

The first erratic results for the relative viscosity of methanol obtained with the new instrument were traced to the fact that variations in working volume have a greater effect on the hydrostatic head and, therefore, on the time of flow in the new instrument owing to the narrow lower reservoir. It was found by suitable independent experiments that in the old T viscometer a variation of 0.01 ml. in the working volume of methanol will cause an error of 0.007 second in the total time of 417 seconds; in the new F viscometer a variation of 0.01 ml. causes an error of 0.191 second in 682 seconds. The usual practice of delivering the working volume from a special pipet and determining the weight delivered by the loss of weight of the pipet is adequate when using water even with the F viscometer. However, due to the greater volatility of methanol the results with the old technique were erratic. A technique of transferring by distillation in a vacuum was developed. The methanol was placed in a suitable flask provided with a stopcock and a ground joint beyond the stopcock, and weighed. The flask and the viscometer were then connected by means of their ground joints to the same wide tube, which was also connected to a vapor trap and a stopcock leading to a good mechanical vacuum pump. The ground joints were not greased but were made vacuum tight by an external mercury seal. The vapor trap was chilled with a mixture of solid carbon dioxide and ether, and then the entire system was evacuated through the trap without losing any methanol. After a good vacuum had been established the stopcock to the pump was closed, the viscometer chilled by solid carbon dioxide and ether, and the weighing flask and trap warmed gently, thus distilling the methanol completely into the vis-

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(4) Grinnell Jones and H. J. Fornwalt, THIS JOURNAL, **57**, 2041 (1935).

(5) H. Lund and J. Bjerrum, *Ber.*, **64B**, 210 (1931).

cometer. The empty flask was then weighed, which gave the amount of methanol transferred to the viscometer. This method of transfer by distillation in a vacuum gave more consistent results with methanol and was used in all of the experiments recorded in Table III. With water there was no significant difference between the results obtained by the old and new methods of transfer to the viscometer.

TABLE III

VISCOSITY OF METHANOL RELATIVE TO THAT OF WATER AT 25° UNCORRECTED FOR SURFACE TENSION EFFECTS

Batch	d^{25}_4	Relative Viscosity T	F
35	0.786527	0.60554	0.60831
		.60539	
36	.786523	.60571	.60798
		.60567	.60849
37	.786527	.60562	.60877
		.60584	
38	.786525	.60576	.60794
		.60582	
Average	0.786525	0.60567	0.60830
Probable error of mean		± .00004	± .00010
Ratio F/T = 1.0043			

This table shows that the two instruments give results which differ in the ratio of 1.0043. This difference is substantially greater than the "probable error" of the mean for each instrument, which proves that there is a systematic error in the results obtained with one or both instruments.

The next step is to attempt to compute the correction which must be applied for the error due to surface tension in order to determine whether or not it is large enough to account for the systematic difference.

Computation of the Error in Viscosity Measurements with the Ostwald Viscometer Due to Surface Tension.—The effective hydrostatic head in the Ostwald viscometer will be the geometric head minus the capillary rise in the upper bulb plus the capillary rise in the lower bulb. The capillary rise will depend on the liquid used, and will also depend on the shape of the upper and lower bulbs. The effective hydrostatic head will vary continuously during the flow. It will, therefore, be necessary to derive a differential equation for the time of flow and integrate it over the total volume.

Poiseuille's law of flow may be put in the form

$$\mathrm{d}t = \frac{8l\eta \mathrm{d}V}{\pi s^4 g\rho H} = \frac{A\eta \mathrm{d}V}{\rho H} = \frac{B\mathrm{d}V}{H} \qquad (1)$$

where s is the radius and l the length of the capillary, g the acceleration of gravity, η the viscosity, ρ the density, and H the effective hydrostatic head (geometric head minus the capillary rise) and $\mathrm{d}V$ is the differential volume which flows in the time $\mathrm{d}t$; and for the sake of abbreviation we write $A = 8l/\pi s^4 g$; and $B = A\eta/\rho$. A will have a definite numerical value for any given instrument. B will depend both on the instrument and on the viscosity and density of the liquid used, but will be independent of the surface tension. H will depend on the dimensions of the instrument and the ratio of surface tension to density σ/ρ, but will be independent of the viscosity.

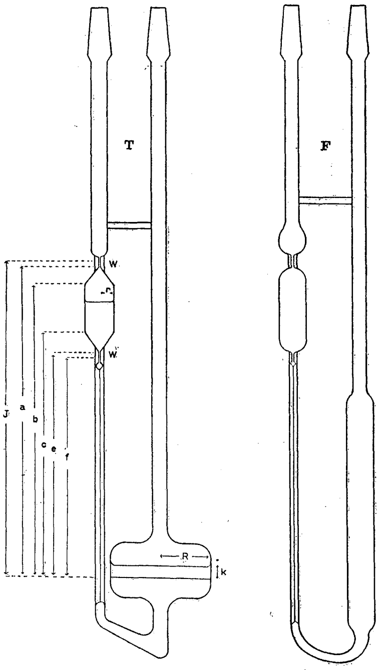

Fig. 1.

The definite integral obtained from Equation (1) should express the time of flow as a function of the instrumental constants which determine A and influence H, and the viscosity, density and surface tension of the fluid. The total time is determined experimentally and the density is also determined independently as a routine part of the viscosity measurements. The surface tension can be measured independently and therefore in mathematical theory may be regarded as a known quantity. However, if it can be shown that with a suitable design of the viscometer the surface tension correction becomes negligible or can be estimated sufficiently well without a precise knowledge of the surface tension, then the precise measurement of viscosity will be greatly simplified.

The absolute measurement of viscosity is an experimental problem of great difficulty. However, for the many theoretical purposes values of the viscosity of solutions relative to that of pure water are sufficient. By making measurements of the total time of flow of water in the same instrument, the instrumental constant A may be eliminated, thus making it unnecessary to measure the length and radius of the capillary.

The definite integral of Equation (1) may be expressed

$$t_c = B_c \int_0^V \frac{\mathrm{d}V}{H_c} = A\,\frac{\eta_c}{\rho_c} \int_0^V \frac{\mathrm{d}V}{H_c}$$

for methanol or for the solution of concentration c, and

$$t_0 = B_0 \int_0^V \frac{\mathrm{d}V}{H_0} = A\,\frac{\eta_0}{\rho_0} \int_0^V \frac{\mathrm{d}V}{H_0}$$

for water. Hence the relative viscosity is given by the expression

$$\frac{\eta_c}{\eta_0} = \frac{t_c\rho_c}{t_0\rho_0}\,\frac{\int_0^V \frac{\mathrm{d}V}{H_0}}{\int_0^V \frac{\mathrm{d}V}{H_c}} \qquad (2)$$

It has been commonly assumed in this and other laboratories that $\int_0^V \frac{\mathrm{d}V}{H_0} = \int_0^V \frac{\mathrm{d}V}{H_c}$, which amounts to the assumption that the effect of surface tension is negligible. The magnitude of the error caused by this assumption will be considered in the succeeding pages.

In order to integrate the equation $\mathrm{d}t = B\mathrm{d}V/H$ it is necessary to know the shape and dimensions of both the upper and lower bulbs. To facilitate this integration it is practically necessary to assume that the geometric form is a comparatively simple one. It is assumed that the working part of the lower reservoir, the upper and lower constrictions where the transits are timed at the beginning and end of the flow, and the central part of the upper bulb are all right circular cylinders having the internal radii R, w and r, respectively, and that the axes of these cylinders are vertical. The upper dome (from a to b) and the lower bowl (from c to e) of the upper bulb may be assumed to be either cones or hemispheres. Although a good quartz blower can make these portions of the instrument approximately hemispherical or conical as desired, the actual geometrical form of the instrument will not correspond exactly to the assumed geometrical form, especially near the lines of contact with the cylindrical parts of the instrument, and, therefore, these assumptions unavoidably introduce some error in the resulting calculations. Moreover, there will be some experimental error in the measurement of the essential dimensions after the instrument has been constructed. The calculations are, therefore, at best only approximations and they are so laborious that they are entirely impractical as a regular part of the routine of viscosity measurements.

In the integration of the fundamental equation $\mathrm{d}t = B\mathrm{d}V/H$ the geometrically distinct parts of the instrument must be treated separately and the definite integrals for the several parts added together.

In the operation of the viscometer a standard working volume of the liquid is added. The liquid is sucked above the mark in the upper constriction and then allowed to fall under the influence of gravity. The timing is started at the instant the meniscus passes the upper mark. The origin from which all vertical or horizontal distances are measured is in the axis of the upper bulb and at the level of the liquid in the lower reservoir when the instrument contains the standard volume and the upper meniscus is at the reference mark on the upper constriction assuming that there is no distortion of the surfaces by surface tension effects. Let J represent the height of the upper mark above this base level. J as thus defined depends solely on the dimensions of the instrument and the standard working volume and is independent of the liquid used.

Now consider a particular instant of time when the meniscus has passed the upper mark and is flowing downward through the upper constriction at a height y above the base level. We may then write

$$\mathrm{d}V = -\pi w^2\mathrm{d}y \qquad (3)$$

and

$$H = +y - h + j - k \qquad (4)$$

where

$$h = 2\sigma/gw\rho \qquad (5)$$

is the capillary rise in the upper constriction; and

$$j = 2\sigma/gR\rho \qquad (6)$$

is the capillary rise in the lower reservoir; and

$$k = \frac{w^2}{R^2}(J - y) \qquad (7)$$

is the increase in height of the liquid in the lower reservoir, because a volume of liquid equal to that in the constriction between the initial mark and the height y has entered the lower reservoir.

When

$$y = a \qquad k = k_a = \frac{w^2}{R^2}(J - a) \qquad (7a)$$

The correction, j, must be applied even if the lower reservoir is so wide that it has a flat portion at its center because the instrument is filled with a standard volume of liquid and the withdrawal of a part of this volume into the meniscus lowers the effective hydrostatic level in the reservoir and thus increases the effective head.

Substituting these values in (1) gives

$$\mathrm{d}t = \frac{B\mathrm{d}V}{H} = \frac{-\pi B w^2 \mathrm{d}y}{y - \frac{2\sigma}{gw\rho} + \frac{2\sigma}{gR\rho} - \frac{w^2}{R^2}(J - y)} \qquad (8)$$

Now integrate between the initial limit of $y = J$ and the final limit $y = a$, which gives

$$t_J^a = \frac{B\pi w^2}{1 + w^2/R^2} \ln \frac{J - \frac{2}{g}\left(\frac{1}{w} - \frac{1}{R}\right)\frac{\sigma}{\rho}}{J - \frac{2}{g}\left(\frac{1}{w} - \frac{1}{R}\right)\frac{\sigma}{\rho} - \left(1 + \frac{w^2}{R^2}\right)(J - a)} \qquad (9)$$

It is evident from this equation that in order to minimize the effects of variations in σ/ρ, J should be made large, and $(J - a)$ and w small. Since $\frac{2}{g}\left(\frac{1}{w} - \frac{1}{R}\right)\frac{\sigma}{\rho}$ is small in comparison with J and with $J - (1 + w^2/R^2)(J - a)$, the error due to the neglect of the surface tension will be almost a linear function of σ/ρ.

The upper dome of the upper bulb may be constructed so that it may be treated either as a cone or as a hemisphere. We have not found an equation for the capillary rise in a conical tube in the literature. An exact solution of this problem would require an exact knowledge of the shape of the meniscus expressed as an equation for the surface. The problem of finding such an equation has not been fully solved even for cylindrical tubes, much less for conical tubes. However, we have succeeded in deriving an approximate equation for the capillary rise in conical tubes which is sufficiently good for the present purpose by a method which is similar to that commonly used to derive the equation for the rise in a cylindrical tube. The details of this derivation are omitted for the sake of brevity. Assume that a conical tube open at both ends is dipped with its axis vertical into a large surface of liquid (see Fig. 2), then the rise of liquid inside the cone above the free surface will be approximately

$$h = \frac{2\sigma(1 - \sin\theta)}{gx\,\rho\cos\theta} \qquad (10)$$

where x is the radius of the circle formed by the intersection of the cone with the horizontal plane at the height h above the free surface, and θ is the angle between the vertical axis of the cone and the sides. By substituting $\theta = 0$ this reduces to the correct form for a cylinder. If the narrow end of the cone is upward the angle θ must be taken as negative and therefore will have a negative sine and a positive cosine, therefore

$$0° > \theta > -90°$$

$$1 > \frac{1 - \sin\theta}{\cos\theta} > +\infty$$

The capillary rise in the cone with the tip upward is greater than in a cylinder of the same effective diameter.

If the narrow end of the cone is downward the equation has the same form but the angle which is called ψ in Fig. 2 is in the first quadrant and is taken as a positive angle; therefore if

$$0° < \psi < 90°$$

$$1 > \frac{1 - \sin\psi}{\cos\psi} > 0$$

Therefore the capillary rise in a cone with the narrow end downward is less than in a cylinder of the same effective diameter.

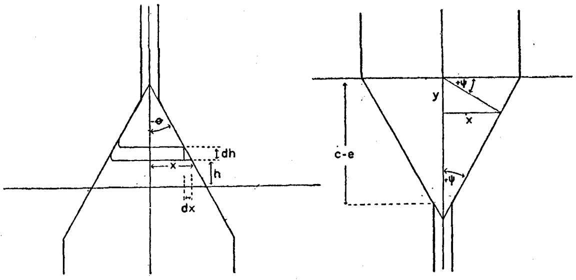

Fig. 2.

The differential equation for the time of flow of the meniscus from a to b in the upper conical dome may now be derived in a manner similar to that given above. The first step is to compute J_a, the geometrical head at the beginning of the conical part of the tube without allowance for surface tension effects. This will be the height, a, above the base level minus the increased level in the lower reservoir, k_a, owing to the transfer of the liquid from the upper constriction to the lower reservoir.

$$J_a = a - k_a = a - \frac{w^2(J - a)}{R^2} \qquad (11)$$

Now consider the particular instant of time when the meniscus is in the cone at a distance y above the base level and let x be the radius of the circle formed by the intersection of the cone with a horizontal plane at the height y.

$$H = y - h + j - k - k_{\mathrm{a}} \qquad (12)$$

$$(x - w)/(y - a) = \tan \theta \qquad (13)$$

here $a > y$ and θ is negative

$$y = a + (x - w) \cot \theta \qquad (14)$$

$$\mathrm{d}y = \cot \theta \, \mathrm{d}x \qquad (15)$$

$$\mathrm{d}V = -\pi x^2 \mathrm{d}y = -\pi x^2 \cot \theta \, \mathrm{d}x \qquad (16)$$

$$\pi R^2 k = \int \mathrm{d}V = -\pi \cot \theta \int_w^x x^2 \mathrm{d}x \qquad (17)$$

$$k = -\frac{(x^3 - w^3) \cot \theta}{3R^2} \qquad (18)$$

When $y = b$, then $x = r$, and

$$k = k_{\mathrm{b}} = -\frac{(r^3 - w^3) \cot \theta}{3R^2} \qquad (18a)$$

h is given by Equation (10) and j by Equation (6) as before, therefore

$$\mathrm{d}t = \frac{B\mathrm{d}V}{H} = \frac{-B\pi x^2 \cot \theta \, \mathrm{d}x}{J_{\mathrm{a}} + (x - w)\cot \theta - \frac{2\sigma(1 - \sin \theta)}{\rho g x \cos \theta} + \frac{2\sigma}{gR\rho} + \frac{(x^3 - w^3) \cot \theta}{3R^2}} \qquad (19)$$

then an algebraic rearrangement gives

$$\frac{\mathrm{d}t}{3R^2B\pi} = \frac{-x^3\mathrm{d}x}{x^4 + 3R^2x^2 + (3R^2J_{\mathrm{a}} \tan \theta - 3R^2w - w^3)x + \frac{6R\sigma x}{g\rho} \tan \theta - \frac{6R^2\sigma \sin \theta}{g\rho(1 + \sin \theta)}} \qquad (20)$$

This equation must now be integrated between the lower limit $x = w$ and the upper limit $x = r$. It has not been found possible to integrate this equation in general terms, but if numerical values are assigned to w, r, R and θ for any particular instrument, and to σ/ρ for any particular liquid, the integration is then possible, although laborious. By a purely algebraic device this equation can be transformed into an equation of the form

$$\frac{\mathrm{d}t}{3R^2B\pi} = \frac{M\mathrm{d}x}{x - m} + \frac{N\mathrm{d}x}{x - n} + \frac{P(2x + p)dx + Q\mathrm{d}x}{x^2 + px + q} \qquad (21)$$

with known numerical values for all of the quantities except B. The integral of this equation has the form

$$\frac{t_{\mathrm{a}}^{\mathrm{b}}}{3R^2B\pi} = \Bigg[M \ln (x - m) + N \ln (x - n) + P \ln (x^2 + px + q) + \frac{2Q}{\sqrt{4q - p^2}} \tan^{-1} \frac{2x + p}{\sqrt{4q - p^2}}\Bigg]_{x = w}^{x = r} \qquad (22)$$

From this equation (22) a numerical value of $t_{\mathrm{a}}^{\mathrm{b}}/B$ can be computed for each special case.

The calculation of $t_{\mathrm{b}}^{\mathrm{c}}$ for the cylindrical part of the bulb between b and c is so similar to that for the cylindrical upper constriction that it is only necessary to write down the equation similar to Equation (9).

$$t_{\mathrm{b}}^{\mathrm{c}} = \frac{B\pi r^2}{1 + \frac{r^2}{R^2}} \ln \frac{J_{\mathrm{b}} - \frac{2}{g}\left(\frac{1}{r} - \frac{1}{R}\right)\frac{\sigma}{\rho}}{J_{\mathrm{b}} - \frac{2}{g}\left(\frac{1}{r} - \frac{1}{R}\right)\frac{\sigma}{\rho} - (b - c)\left(1 + \frac{r^2}{R^2}\right)} \qquad (23)$$

where J_{b} is the geometric head at the beginning of the flow through the cylinder;

$$J_{\mathrm{b}} = b - k_{\mathrm{a}} - k_{\mathrm{b}} = b - \frac{w^2}{R^2}(J - a) + \frac{(r^3 - w^3) \cot \theta}{3R^2} \qquad (24)$$

Here it should be pointed out that if the instrument is so designed that $r = R$, then the term involving the surface tension drops out entirely so that the time of flow through this part of the apparatus is not influenced by the surface tension regardless of the magnitude of $b - c$. This is because the capillary rise in the upper bulb is exactly compensated by the capillary rise in the lower bulb. The lower bowl, like the upper dome, may be assumed to be either a cone or a hemisphere. If it is assumed to be a cone, the derivation is similar to that given for the dome, except that the half angle, ψ, is to be taken as a positive angle, and of course the initial geometric head J_{c} is different.

$$J_{\mathrm{c}} = c - k_{\mathrm{a}} - k_{\mathrm{b}} - k_{\mathrm{c}} = c - \frac{w^2}{R^2}(J - a) + \frac{(r^3 - w^3) \cot \theta}{3R^2} - \frac{r^2}{R^2}(b - c) \qquad (25)$$

$$H = y - h + j - k - k_{\mathrm{a}} - k_{\mathrm{b}} - k_{\mathrm{c}} \qquad (26)$$

$$y = e + (x - w) \cot \psi \qquad (27)$$

$$h = \frac{2\sigma}{gx\rho} \frac{(1 - \sin \psi)}{\cos \psi} \qquad (28)$$

$$k = \frac{(r^3 - x^3) \cot \psi}{3R^2} \qquad (29)$$

Making these substitutions followed by a purely algebraic transformation gives the equation

$$\frac{\mathrm{d}t}{3R^2B\pi} = \frac{-x^3\mathrm{d}x}{x^4 + 3R^2x^2 + (3R^2J_{\mathrm{c}} \tan \psi - 3rR^2 - r^3)\, x + \frac{6R\sigma x \tan \psi}{g\rho} - \frac{6R^2\sigma \sin \psi}{g\rho\, (1 + \sin \psi)}} \qquad (30)$$

This equation must be integrated between the initial limit of $x = r$ and the final limit of $x = w$. To accomplish this numerical values are substituted and the procedure described above for Equation (20) is carried out.

The equation for the lower constriction is similar to that for the upper constriction. If the dome and bowl are conical

$$J_{\mathrm{e}} = e - k_{\mathrm{a}} - k_{\mathrm{b}} - k_{\mathrm{c}} - k_{\mathrm{e}} = e - \frac{w^2}{R^2}(J - a) - \frac{(r^3 - w^3)(\cot\psi - \cot\theta)}{3R^2} - \frac{r^2}{R^2}(b - c) \qquad (31)$$

$$t_{\mathrm{c}}^{\mathrm{b}} = \frac{B\pi w^2}{1 + \frac{w^2}{R^2}} \ln \frac{J_{\mathrm{e}} - \frac{2}{g}\left(\frac{1}{w} - \frac{1}{R}\right)\frac{\sigma}{\rho}}{J_{\mathrm{e}} - \frac{2}{g}\left(\frac{1}{w} - \frac{1}{R}\right)\frac{\sigma}{\rho} - (e - f)\left(1 + \frac{w^2}{R^2}\right)} \qquad (32)$$

If the upper dome and lower bowl are blown so as to make them as nearly as possible hemispheres instead of cones, the calculation is similar to that for a cone but different in detail. The time of flow through the upper constriction, $t_{\mathrm{j}}^{\mathrm{a}}$, is computed by Equation (9) just as before. The upper dome is considered to be a hemisphere of radius, r, whose center has the coördinates $y = b$ and $x = 0$ cut by a vertical cylinder of radius w. It is convenient to introduce an abbreviation $z = y - b$. Then $x^2 + z^2 = r^2$ and $\tan\theta = -z/x$; $\sin\theta = -z/r$; and $\cos\theta = x/r$. The minus signs are due to the fact that θ must be taken as a negative angle but z is a positive quantity.

$$\mathrm{d}V = -\pi x^2 \mathrm{d}y = -\pi(r^2 - z^2)\mathrm{d}z \qquad (16')$$

$$H = y - h + j - k - k_{\mathrm{a}} \qquad (12)$$

$$h = \frac{2\sigma}{\rho g x}\,\frac{(1 - \sin\theta)}{\cos\theta} = \frac{2\sigma}{\rho g x^2}(r + z) = \frac{2\sigma}{\rho g(r - z)} \qquad (10')$$

$$\pi R^2 k = \int \mathrm{d}V = -\int_{(a-b)}^{z} \pi(r^2 - z^2)\mathrm{d}z \qquad (17')$$

$$k = \frac{1}{R^2}\left[r^2(a - b) - \frac{(a - b)^3}{3} - r^2 z + \frac{z^3}{3}\right] \qquad (18')$$

When $y = b$, $z = 0$ and

$$k = k_{\mathrm{b}} = \frac{r^2(a - b)}{R^2} - \frac{(a - b)^3}{3R^2} \qquad (18'a)$$

$$J_{\mathrm{b}} = b - k_{\mathrm{a}} - k_{\mathrm{b}} = b - \frac{w^2}{R^2}(J - a) - \frac{r^2}{R^2}(a - b) + \frac{(a - b)^3}{3R^2} \qquad (24')$$

$$\mathrm{d}t = \frac{B\mathrm{d}V}{H} = \frac{-B\pi(r^2 - z^2)\mathrm{d}z}{J_{\mathrm{b}} + z - \frac{2\sigma}{\rho g(r - z)} + \frac{2\sigma}{\rho g R} + \frac{3r^2 z - z^3}{3R^2}} \qquad (19')$$

Then a purely algebraic transformation gives

$$\frac{\mathrm{d}t}{3R^2 B\pi} = \frac{-(r^2 - z^2)(r - z)\mathrm{d}z}{z^4 - rz^3 - 3(R^2 + r^2)z^2 + (3R^2 r + 3r^3 - 3R^2 J_b)z - \frac{6R\sigma z}{g\rho} - \frac{6R(R - r)}{g}\sigma/\rho + 3R^2 r J_b} \qquad (20')$$

This equation must be integrated between the initial limit of $z = (b - a)$ and the final limit of $z = 0$. This cannot be done except by introducing numerical values. A numerical value of $t_{\mathrm{a}}^{\mathrm{b}}/B$ can then be computed by introducing the appropriate numerical values for R, r, J_{b} and integrating between the initial limit of $z = b - a$ and the final limit of $z = 0$.[6]

The equation for the time of flow in the cylindrical part of the upper bulb, $t_{\mathrm{b}}^{\mathrm{c}}$, is the same as Equation (23) above except that J_b is given by Equation (24′) above instead of by Equation (24).

The differential equation for the time of flow in the lower bowl considered as a hemisphere has the same form as Equation (20′) above except that in place of J_{b} we must insert

$$J_{\mathrm{c}} = c - k_{\mathrm{a}} - k_{\mathrm{b}} - k_{\mathrm{c}} = c - \frac{w^2}{R^2}(J - a) - \frac{r^2}{R^2}(a - b) + \frac{(a - b)^3}{3R^2} - \frac{r^2}{R^2}(b - c) \qquad (25')$$

The integration must be carried out between the initial limit of $z = 0$ and the final limit of $z = e - c$.

The equation for the time of flow through the lower constriction has the same form as Equation (32) above except that J_{e} is given by

$$J_{\mathrm{e}} = e - \frac{w^2}{R^2}(J - a) - \frac{r^2}{R^2}(a - e) + \frac{(a - b)^3 + (c - e)^3}{3R^2} \qquad (31')$$

Table IV gives the results of the numerical calculations carried out by the use of these equations for the instrument T using the dimensions

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(6) There is one disturbing subtlety in these calculations which deserves a footnote: the assumption that the shape of the upper dome is a hemisphere of radius $r = 0.848$ cm., intersected by a vertical cylinder of radius $w = 0.05$ cm., and that the equation (10) holds for values of θ which are near $-90°$ gives a value of $h > J_{\mathrm{a}}$ which makes $H < 0$ and the time of outflow infinite. But as a matter of fact the actual instrument does empty itself, which shows that the conditions mentioned above do not prevail. This means that as a matter of practical quartz blowing the vertical cylinder is somewhat flared before it meets the hemisphere, so that there is in effect a short conical tube inserted between the cylinder and the hemisphere so that values of θ which are nearly $-90°$ do not occur in the actual instrument. At the level where the hemisphere starts x is large enough and θ sufficiently different from $-90°$ so that $h < J_{\mathrm{a}}$ and $H > 0$. The calculations of the results shown in Table V are based on the assumption that there is a truncated cone with $\theta = -45°$ and a height of 0.07 cm. between the vertical cylinder of radius, $w = 0.05$ cm., and the hemisphere of radius, $r = 0.848$ cm. This makes the initial limit for the integration of Equation 20′, $z = \sqrt{0.848^2 - (0.05 + 0.07)^2} = 0.8394665$, which avoids the mathematical paradox described above. Essentially the same result may be obtained in a much less laborious manner by arbitrarily taking as the initial limit for z a value which is slightly smaller than the value which would make $H = 0$, and $t = \infty$.

TABLE IV

ERRORS IN VISCOSITY MEASUREMENTS DUE TO SURFACE TENSION

Values of the definite integral $\int dV/H$ for parts of the viscometer T for water, methanol and solutions having values of σ/ρ equal to 0.9, and 0.8 of that of water, respectively.

		Water	Solution	Solution	Methanol
	σ/ρ	72.18	64.962	57.744	28.19
	$\frac{\sigma_c\rho_0}{\sigma_0\rho_c}$		0.9	0.8	0.3906
Upper constriction	t_J^a/B	0.000186	0.000183	0.000181	0.000171
Upper cone	t_a^b/B	.060399	.060295	.060195	.059784
Upper cylinder	t_b^c/B	.482138	.481843	.481548	.480345
Lower cone	t_c^e/B	.050238	.050218	.050197	.050119
Lower constriction	t_e^f/B	.000569	.000558	.000546	.000505
Total	t_J^f/B	0.593530	0.593097	0.592667	0.590924
	$\frac{\int dV/H_0}{\int dV/H_c}$		1.0007_3	1.0014_6	1.0044_1

given in Table II. These calculations have been carried out for water, assuming that $\sigma = 71.97$ dynes per centimeter at 25° and $\rho = 0.99707$, giving $\sigma/\rho = 72.18$; and for two hypothetical aqueous solutions for which σ/ρ is taken as 0.9 and as 0.8 of that of water, or 64.962 and 57.744, respectively; and for methanol[7] assuming that $\sigma = 22.17$ dynes per centimeter, and $\rho = 0.78652$, giving $\sigma/\rho = 28.19$.

The experimental data recorded in Table III for methanol with viscometer T give $t_c\rho_c/t_0\rho_0 = 0.60567$ and therefore, according to Equation (3), we have $\eta_c/\eta_0 = 0.60567 \times 1.0044_1 = 0.6083_4$ as the value for the relative viscosity of methanol corrected for the surface tension as determined with the old T viscometer.

Similar calculations have been carried out with the new F viscometer and the results are recorded in Table V. The dimensions used in the calculations are given in Table II.

TABLE V

ERRORS IN VISCOSITY MEASUREMENTS DUE TO SURFACE TENSION

Values of the definite integral $\int dV/H$ for parts of the viscometer F for water and for methanol.

		Water	Methanol
	σ/ρ	72.18	28.19
Upper constriction	t_J^a/B	0.000377	0.000356
Upper dome	t_a^b/B	.048368	.048125
Upper cylinder	t_b^c/B	.498199	.498199
Lower bowl	t_c^e/B	.078955	.079115
Lower constriction	t_e/B	.000254	.000224
Total	t_J^f/B	0.626153	0.626019

$$\frac{\int dV/H_0}{\int dV/H_c} = 1.0002_1$$

A comparison of Tables IV and V shows clearly the effectiveness of the new design in reducing the error due to surface tension. One important result of making the radius of the lower reservoir equal to that of the cylindrical part of the upper bulb is that for this part of the apparatus $\int dV/H_0 = \int dV/H_c$, thus completely eliminating the correction for a large fraction of the total time. Moreover, another result is that the effect in the lower bowl partly compensates the effect in the upper dome. For the upper dome $\int dV/H_0 - \int dV/H_c = +0.000243$, whereas for the lower bowl $\int dV/H_0 - \int dV/H_c = -0.000160$.

The experimental data recorded in Table III for methanol with viscometer F give $t_c\rho_c/t_0\rho_0 = 0.60830$, and, therefore, according to Equation (2), we have $\eta_c/\eta_0 = 0.60830 \times 1.0002_1 = 0.6084_3$.

The values obtained with the two different instruments agree much better after applying the surface tension correction (0.60834 with viscometer T, and 0.60843 with viscometer F) than they did before the correction was applied (0.60567 and 0.60830). Averaging the results, giving greater weight to the F instrument because the correction is so much smaller, gives $\eta_c/\eta_0 = 0.6084$. If the absolute viscosity[8] of pure water at 25° is taken as 0.008949 poise, then the absolute viscosity of methanol is 0.005445 poise.

At least sixteen different determinations of the viscosity of methanol at 25° are recorded in the literature, but the references and results are not given in detail. In most cases the results are quite discordant because the measurements were incidental to some other purpose and the technique was crude, or the density of the methanol was so high that it is evident that the sample contained water. The best of the previous results are given below.

The data given in Table IV show that the cor-

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(7) "International Critical Tables," Vol. IV, pp. 447–448.

(8) "I. C. T.," Vol. V, p. 10.

TABLE VI

ABSOLUTE VISCOSITY OF METHANOL

	$d^{25}{}_4$	Poises
Dunstan, Thole and Benson, *J. Chem. Soc.*, **105**, 784 (1914)	?	0.00546
H. Goldschmidt and H. Aarflot, *Z. Physik. Chem.*, **122**, 374 (1926)	0.7869	.00544
F. K. Ewart and H. R. Raikes, *J. Chem. Soc.*, 1907 (1926)	.78641	.00545
Grinnell Jones and H. J. Fornwalt, this paper	.78652	.005445

recting factor for viscometer T is very nearly a linear function of σ/ρ so that

$$\int\frac{dV}{H_0}\Big/\int\frac{dV}{H_c} = 1 + 0.0074\,\frac{(\sigma_0/\rho_0 - \sigma_c/\rho_c)}{\sigma_0/\rho_0} = 1.0074 - \frac{0.0074\,\sigma_c\rho_0}{\rho_c\sigma_0}$$

However, no systematic attempt will be made at this time to estimate the corrections which should be applied to the viscosity data which have been published from this Laboratory, because the surface tension data are not available in most cases. An improved method of measuring surface tension has been developed[9] and data on a few salts obtained, but it is necessary to postpone a general revision of the data for the viscosity of concentrated solutions until the surface tensions of these solutions have been measured. One illustrative example, in which the correction is exceptionally high, must suffice for the present. Jones and Talley,[10] who used our instrument T, report that the relative viscosity of a 2.962 normal potassium chloride solution at 25° is 1.03211. From the data of Jones and Ray the value of $\sigma_c\rho_0/\rho_c\sigma_0$ may be found by a slight interpolation to be 0.9445. This gives a correcting factor of 1.00041 or a relative viscosity corrected for the effect of surface tension of 1.03253.

The Design of the Ostwald Viscometer

With an Ostwald viscometer, where the liquid depends on its own hydrostatic head for driving pressure, an approximate value for the viscosity relative to that of water is computed by the simple equation $\eta = \eta_c/\eta_0 = t_c\rho_c/t_0\rho_0$, but to obtain the maximum precision it may be necessary to apply one or more of the following corrections unless the instrument can be designed so as to make the corrections negligible. The four corrections are (1) the drainage correction; (2) the working volume correction; (3) the kinetic energy correction; (4) the surface tension correction.

It is obvious that the first requirement for precise viscometry is accuracy in the timing and in the determination of the densities. However, the technique of making these measurements has been developed so that the real precision depends on the reliability of the corrections.

The instrument should be designed so as to make the corrections negligible if possible, or at least to minimize them as much as other considerations of design, such as convenience and speed of operation, permit. Unfortunately, details of design which may be helpful in minimizing one of the corrections may increase some other correction or cause trouble in operation or other errors so that the best design is a matter of compromise.

It has been shown in a recent paper from this Laboratory[2] that if the design is suitable in other respects the drainage correction is negligible except for extremely viscous liquids or for viscometers of a very short time of efflux.

The correction for variations in working volume can be applied with most confidence because its theoretical basis is beyond criticism, and the experimental determination of the magnitude with sufficient precision is easy in the case of aqueous solutions if the lower reservoir is not too narrow.

In the case of the kinetic energy correction there is some doubt, or at least a difference of opinion among the authorities, as to the proper way to compute the correction. Some authorities even deny that the correction should be applied at all. Although we believe that the correction should be applied, we also believe it wise to use every feasible artifice of design to reduce the magnitude of the correction, and thereby reduce the error due to inaccuracy in its computation. In designing the viscometer it is possible to control within practical limits the length and radius of the capillary, the hydrostatic head, the volume and shape of the measuring bulb, and the radius of the lower reservoir. The kinetic energy correction is diminished by any change in design which increases the time of outflow, except increasing the volume of the measuring bulb. The correction in principle always can be made negligible by using an instrument with a sufficiently long time of outflow, but this may cause serious inconvenience and delay in making measurements. Reducing the radius of the capillary and reducing the hydrostatic head both increase

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(9) Grinnell Jones and W. A. Ray, THIS JOURNAL, **59**, 187 (1937).

(10) Grinnell Jones and S. K. Talley, *ibid.*, **55**, 624, 4124 (1933).

the time of flow and hence reduce the kinetic energy correction proportionally to the increase in time of flow. However, reducing the radius of the capillary has the disadvantage that it may increase the number of erratic results due to dust particles. Reducing the hydrostatic head will increase the error due to surface tension and make the reproducibility of the mounting more critical. The most useful and unobjectionable way to reduce the kinetic energy correction is to increase the length of the capillary. The time of flow increases proportionally with the length but the correction varies inversely as the square of the length. Variations in volume and shape of the upper bulb and variations in the radius of the lower reservoir have no direct influence on the kinetic energy correction.

Similarly, it is desirable to make the surface tension correction negligible by suitable design of the instrument if feasible. Although the theory of the correction as developed above seems to be mathematically logical and the correction clearly should be applied, nevertheless, it has the weakness that (1) the actual instrument does not have the exact shape and dimensions assumed in the calculations; (2) the equation for the capillary rise in conical or hemispherical tubes used in the calculations is an approximation; (3) the surface tension of the solution may not be known with sufficient accuracy; (4) the calculations are so laborious that they can never become popular.

As has been pointed out above the effective way to minimize the surface tension correction is to design the upper bulb so that as large a part of its volume as is feasible is in the cylindrical portion, and to make the radius of the lower reservoir the same as the radius of the cylindrical part of the upper bulb. If this common radius is too small, the correction for the variation of working volume will be troublesome, especially when dealing with volatile liquids, which may make it difficult to determine the actual volume added with sufficient precision. On the other hand, if, in order to avoid this difficulty, the common radius is made larger, the time of outflow may be made inconveniently long. If the attempt is made to remedy this difficulty by increasing the radius of the capillary there will be an increase in the kinetic energy correction. The best radius will, therefore, be a compromise.

For use with dilute aqueous solutions having a viscosity and surface tension and density nearly the same as water, the compromise can favor the working volume correction by choosing a larger radius for the lower reservoir than for the upper bulb. If the liquids to be studied differ substantially from water, then it will be advisable to make the radius of the lower reservoir the same as that of the upper bulb, to minimize the surface tension correction; and if this common radius is made large in an effort to minimize the working volume correction, then either the kinetic energy correction will be large or the time of outflow inconveniently long.

Similarly, increasing the hydrostatic head will lower the surface tension correction and the working volume correction, but increase the kinetic energy correction by lowering the time of outflow. However, the latter effect can be compensated by a decrease in the radius of the capillary without introducing any other unfavorable result except more trouble from dust particles. Therefore the hydrostatic head should be made as great as mechanical considerations permit without undue inconvenience.

Viscometer T, which was originally designed for dilute aqueous solutions, has proved in the light of our experience to be well designed for this purpose, except that the original specification that ends of the bulb should be made as nearly conical as possible has been found to be unnecessary. Hemispherical ends would be slightly better. Viscometer F, which was designed for methanol, a volatile liquid differing substantially from water in viscosity, surface tension and density, is satisfactory for such liquids and for concentrated aqueous solutions, except that it would have been better to have made the areas of the cross section of the lower reservoir and upper bulb 1.5 or 2 times as great as they actually are.

Summary

1. It is demonstrated by mathematical analysis and by experiments on methanol and water that surface tension effects may influence the measurement of viscosity with the Ostwald viscometer.

2. A method of computing the error due to surface tension for an instrument of known dimensions is given.

3. The viscosity of methanol at 25° relative to that of water is 0.6084.

4. The principles of design of the Ostwald

viscometer to give high precision without unnecessary sacrifice of convenience and speed in operation are discussed.

CAMBRIDGE, MASS. RECEIVED DECEMBER 24, 1937

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY]

The Freezing Point of Methanol; A Simple Type of Cryostat Applicable to Freezing Point Determinations

BY EDWIN E. ROPER

A very pure sample of methanol had been prepared by Jones and Fornwalt[1] for their work on the relative viscosity and on the density. It appeared desirable to determine some physical constants as accurately as possible. Since a cryostat had been constructed by the author and a standardized resistance thermometer was available, Professor Jones requested a determination of the freezing point of their best samples of carefully purified methyl alcohol. The reported physical constants in the literature for methanol appear to be somewhat erratic and, in view of the difficulty involved in thoroughly freeing this material from water, in all probability the main cause of the discrepancies may be assigned to the presence of this impurity.

Experimental Procedure

Temperature Measurement and Standardization.—The temperature of the alcohol sample was measured by means of a four-lead coiled-filament 25-ohm platinum resistance thermometer.[2] The thermometer resistance was measured by a standardized Mueller type Wheatstone bridge, which was thermostated (25.0 ± 0.1°) in an oil-bath. The reproducibility of the measurements was *ca.* 0.0001 ohm, corresponding to 0.001°. The thermometer was standardized by accepted methods[3] at the sulfur boiling point, the steam point, the ice point and compared against the vapor pressure thermometers of carbon dioxide and of oxygen. The temperatures of the fixed points above 0° were taken as recommended by the International Temperature Scale specifications[3] and below 0° as given by Heuse and Otto.[4] The temperature of the ice point on the thermodynamic temperature scale was taken as 273.16°K.[5] The thermometer constants fulfilled all specifications[3] for pure platinum. The absolute accuracy at −100° is probably ±0.02° and the precision ±0.001°. A single junction copper–constantan thermel was used as an aid in adjusting the cryostat. This thermel was standardized at the same fixed points as was the resistance thermometer, with the exception that the freezing point of a National Bureau of Standards sample of tin replaced the sulfur boiling point. The e. m. f. of the thermel was determined with a special type K potentiometer to one microvolt. The e. m. f. was converted into temperature by the accepted method of constructing a deviation curve[6] in conjunction with the reference tables of Southard and Andrews.[7] The accuracy is about ±0.05°.

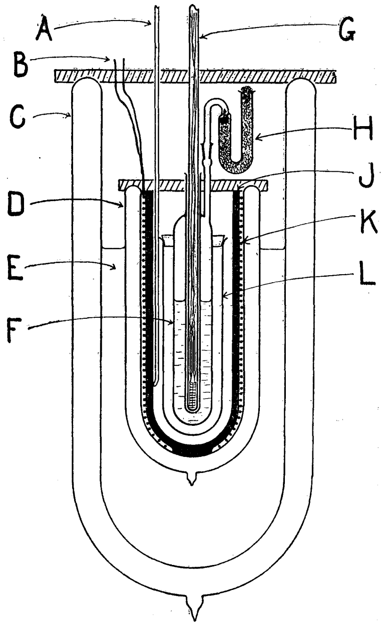

Fig. 1.—Freezing point apparatus showing details of cryostat. A is the environment thermel, B the heater leads, C the outer Dewar containing the refrigerant, D is the inner Dewar, E is the refrigerant, F is the freezing point tube, G the resistance thermometer, H a protective tube of Dehydrite, J is the copper tube, K is the heater wound on the surface of J, L is a glass jacket about the freezing point tube. Not drawn to scale.

Temperature Control.—The cryostat, somewhat similar to the one of Southard and Andrews,[7] is shown diagrammatically in Fig. 1. The copper shell J was 4 mm. wall thickness, 52 mm. outside diameter and 200 mm. long. The outer surface was so machined that after the heater winding was in place, the assembly fitted quite closely

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[1] Jones and Fornwalt, THIS JOURNAL, **60**, 1683 (1938).

[2] (a) Meyers, *Bur. Stds. J. Res.*, **9**, 807 (1932). (b) This thermometer and bridge are the same as were used for the ice point investigation, Roper THIS JOURNAL, **60**, 866 (1938).

[3] Burgess, *Bur. Stds. J. Res.*, **1**, 635 (1928).

[4] (a) Heuse and Otto, *Ann. Physik*, **9**, 486 (1931); (b) *ibid.*, **14**, 181, 185 (1932).

[5] (a) Heuse and Otto, *ibid.*, **2**, 1012 (1929); (b) Roebuck, *Phys. Rev.*, **50**, 370 (1936).

[6] "Inter. Crit. Tables," Vol. I.

[7] Southard and Andrews, *J. Franklin Inst.*, **207**, 323 (1929).

into the Dewar tube D. The heater winding K consisted of 14.1 meters (136 ohms) of number 30 D. S. C. constantan wire wound non-inductively on the tube J, a good thermal contact being ensured by coating the completed winding with Bakelite lacquer, which was subsequently baked. Two slide resistances and an 0–150 milliammeter in series with the heater served to control the energy input. A lag of but a few seconds was found between the heater and the thermel. A glass test tube L about F served to damp out sudden temperature changes in J; this baffle introduced a thermal lag of sixty to eighty seconds between J and F. The outer Dewar tube C was 13 × 52 cm., while the smaller Dewar was 5.4 × 21 cm., both inside dimensions. Liquid air was placed in the outer Dewar to serve as a cold reservoir; the rate of cooling could be controlled within limits by varying the liquid air level. Approximately 100 milliamperes (1.36 watts) d. c. in the heater was sufficient to maintain the assemply at −100°. A given temperature setting could be held constant for several hours, but during this time the decrease in the liquid air level had to be compensated by a manual decrease in the energy input to the cryostat. However, this type of cryostat is particularly suited to freezing point determinations below 0°, where a slow but steady decrease in the environment temperature is required.

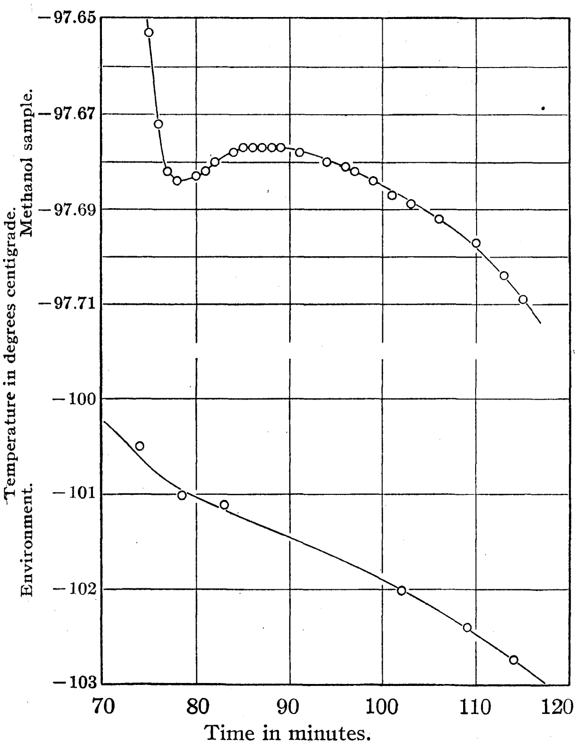

Fig. 2.—Typical freezing point data obtained. The upper curve shows the temperature of the sample of methanol as measured by the resistance thermometer while the lower curve is the course of the environment temperature measured by means of the thermel.

Methanol Samples.—The freezing point of two different portions was investigated. The data on the original samples as determined by Jones and Fornwalt are presented in Table I. The sample no. 31 contained some water as shown by means of the relative viscosity and the density. The sample no. 37 was classed as anhydrous by these investigators. The alcohol was distilled directly into the freezing point tube through the ground joint at the top and then the protective tube of Dehydrite immediately placed in position. Fifty cc. of alcohol was used in the freezing point tube F; this covered the thermometer with 5 cm. of alcohol, which should be sufficient to eliminate heat conduction down the thermometer leads.

TABLE I

Sample	Relative viscosity	Density, d^{25}_4, g./ml.
31	0.6094	0.786 65
37	.6084	.786 53

Procedure.—The alcohol was precooled to *ca.* −90° and the freezing point tube placed in position in the cryostat, which was at about the same temperature. The energy input to the heater was then decreased so that an approximately constant rate of cooling ensued. The temperature of the environment as indicated by the thermel was closely followed. Upon nearing the freezing point, readings of both the thermel and the resistance thermometer were taken at suitable intervals of time. If the environment temperature is not known and carefully controlled, there is no means of predetermining (if no supercooling takes place) whether the freezing point "flat" has been reached or whether the sample is merely approaching the temperature of the environment.

Results Obtained

Figure 2 gives a typical set of data obtained for one particular determination of the freezing point. It can be seen that the temperature of the alcohol sample is constant to 0.01° for twenty-four minutes, while during the same interval the environment temperature dropped 1.1°. The temperature of the alcohol sample does not fall off as abruptly as would be expected, and this might indicate slight traces of water. However, this falling off is a function of the thermal head and conductivity between J and F. Mair[8] takes as the principal criterion of purity the slope of the approximately horizontal portion of the freezing point curve. Table II gives the freezing points found for the two samples and also rough calculations of the amount of water present in sample no. 31 on the assumption that sample no. 37 is anhydrous. The value based on the relative viscosities was calculated on the basis of an estimate made by Jones and Fornwalt[9] on the effect of water upon the viscosity of methanol. The value obtained from the difference in densities was calculated on the basis of a linear relationship be-

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(8) Mair, *Bur. Stds. J. Res.*, **9**, 459 (1932).

(9) Jones and Fornwalt, THIS JOURNAL, **57**, 2041 (1935).

tween density and composition, while the value calculated from the observed freezing point depression was obtained by the application of the approximate thermodynamic equation connecting the mole fraction of impurity, the true freezing point, the freezing point depression and the heat of fusion, the latter value being taken from the calorimetric work of Kelley.[10]

TABLE II

Sample	Freezing point, °C.	Percentage of water in sample from: rel. vis.	density	f. p. dep.
31	−97.75 ±0.02	0.04	0.06	0.05
37	−97.68 ± .02	(.00)	(.00)	(.00)

Discussion

It is very probable that the value −97.68° represents the true freezing point of anhydrous methanol to within the thermometric accuracy in relation to the thermodynamic temperature scale, namely, ±0.02°. An attempt has been made to correlate the freezing point with the density of methanol. Table III gives data taken from three other precision researches and Fig. 3 shows the data plotted, a rough estimate of the estimated accuracy being shown by the diameters of the plotted points. It can be seen that the results of Parks and of Timmermans and Hennaut-Roland are not in agreement with the data of Kelley and of this research. The latter two appear to be the more precise measurements and the density–freezing point curve has been passed through the data as shown.

TABLE III

Freezing point, °C.	d^{25}_4, g./ml.	Author
−97.8 ±0.1	0.7864[a]	Parks[11]
−97.88 ± .05	.786 75	Kelley[10]
−97.0	.786 75	Timmermans & Hennaut-Roland[12]
−97.68 ± .02	.786 52	This research
−97.75 ± .02	.786 65	This research

[a] Calculated value from that given for 22°.

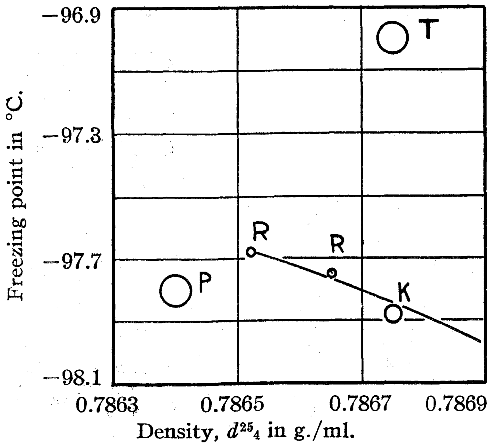

Fig. 3.—Data of different investigators plotted in order to attempt to determine the course of the freezing point–density of the liquid curve: K, Kelley; P, Parks; R, Roper; T, Timmermans.

Acknowledgments.—The author wishes to express his appreciation to Professor Arthur B. Lamb, in whose laboratory the cryostat was developed, for the use of the resistance thermometer, the cryostat and other apparatus and facilities. Professor Grinnell Jones and Dr. H. J. Fornwalt kindly supplied the methanol samples and furnished data concerning their respective relative viscosities and densities. Dr. Fornwalt filled the freezing point tubes with the samples and aided in measuring the environment temperatures in part of the determinations.

Summary

A simple cryostat is described which is applicable to the determination of freezing points below 0° and data are appended describing the operation of the cryostat during the freezing point determination of a methyl alcohol sample. The freezing point of a particularly pure sample of methanol prepared by Jones and Fornwalt was determined to be −97.68 ± 0.02°. A short discussion is given of the freezing point–density relationship.

CAMBRIDGE, MASS. RECEIVED DECEMBER 24, 1937

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(10) Kelley, THIS JOURNAL, **51**, 180 (1929).

(11) Parks, *ibid.*, **47**, 338 (1925).

(12) Timmermans and Hennaut-Roland, *J. chim. phys.*, **27**, 401 (1930).

[CONTRIBUTION FROM THE WILLIAM H. CHANDLER CHEMISTRY LABORATORY OF LEHIGH UNIVERSITY]

The Solubility Curves of the Systems Carbon Tetrachloride–Branched Chain Alkyl Acids–Water at 25°

BY HILTON A. SMITH AND HAROLD TAYLOR

In an earlier paper[1] the effect of the length of the carbon chain of normal organic acids on the solubility curves of the systems carbon tetrachloride–*n*-alkyl acids–water was demonstrated. The present paper gives the results of investigations concerning the effect of branched chain acids on the solubility curves of similar systems.

Experimental

All acids used were the best grade of Eastman chemicals. C. P. carbon tetrachloride was used without further purification since the solubility of water in pure carbon tetrachloride is not great enough to affect the results within the limit of experimental error.

As in the earlier investigation, the limits of mutual solubility of the three components were determined by titration of mixtures of two of the components with the third until two phases merged into a single phase or, when the two starting components were miscible, until a second phase separated. In the case of acids which were only partially miscible with water, the mutual solubility of each in the other was also determined by titration methods.

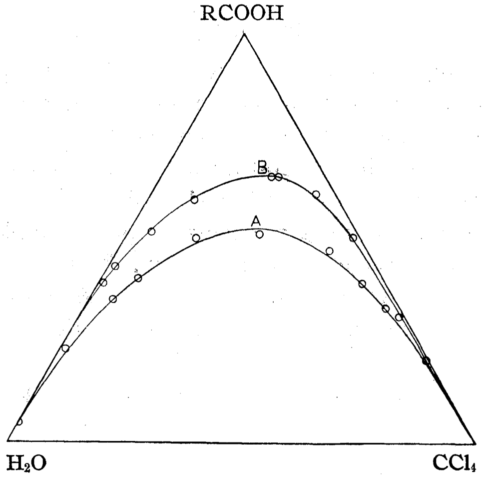

Fig. 1.—Solubility curves of the systems CCl_4–C_3H_7COOH–H_2O at 25°: A, *n*-butyric acid; B, isobutyric acid.

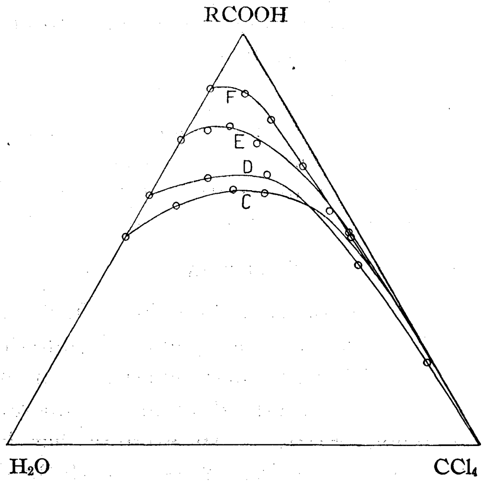

Fig. 2.—Solubility curves of the systems CCl_4–C_4H_9COOH–H_2O at 25°: C, *n*-valeric acid; D, isovaleric acid; E, methylethylacetic acid; F, trimethylacetic acid.

Results and Discussion

The results of the determinations are given in Table I. The values represent the maximum mole per cent. of carbon tetrachloride which may be dissolved in the indicated mixtures of acid and water. As in the earlier paper, the solubility of water in carbon tetrachloride and that of carbon

TABLE I

Mole % CCl_4	Mole % acid	Mole % H_2O	Mole % CCl_4	Mole % acid	Mole % H_2O
Isobutyric Acid			Isovaleric Acid		
0.01	0	99.99	0.01	0	99.99
1.3	39	60	0	0.95	99.05
1.8	43	55	0	60.60	39.40
5.0	51.5	43.5	10	65	25
10	59	31	22	66	12
22	62	16	52	44	4.0
23	65	12	79	20	1.0
25	65	10	99.9	0	0.1
40	59	0.8			
49	51	.5			
99.9	0	.1			
Methylethylacetic Acid			Trimethylacetic Acid		
0.01	0	99.99	0.01	0	99.99
0	0.56	99.44	0	0.55	99.45
0	74.0	26.0	0	86.4	13.6
4.3	76.5	19	7.9	85	7.5
8.7	77	14	17	79	4.4
17	73	10	28	68	3.8
35	62	3.0	48	50	1.7
46	52	1.9	99.9	0	0.1
99.9	0	0.1			

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[1] Smith and Berman, THIS JOURNAL, **59**, 2390 (1937).

tetrachloride in water were calculated from the data of Clifford,[2] Rosenbaum and Walton[3] and Gross and Saylor.[4]

Figure 1 shows the solubility curves of the systems carbon tetrachloride–acid–water at 25° for butyric and isobutyric acids. The curve for *n*-butyric acid was taken from the data of Smith and Berman.[1] Figure 2 shows the diagrams for similar systems using *n*-valeric acid, isovaleric acid, methylethylacetic acid, and trimethylacetic acid. Again the curve for *n*-valeric acid was taken from the data of Smith and Berman.[1]

An examination of these curves shows that in all cases the mutual solubility area is decreased by substitution of a branched chain acid for a normal acid. The curves for isovaleric acid and methylethylacetic acid indicate that a methyl group substituted in the alpha position is more effective in decreasing the mutual solubility area than a methyl group substituted in the beta position.

Summary

The solubility curves at 25° of the systems CCl_4–RCOOH–H_2O have been studied for the following acids: isobutyric, isovaleric, methylethylacetic, and trimethylacetic. The curves show that the mutual solubility area decreases with increased chain branching.

BETHLEHEM, PENNA. RECEIVED MAY 13, 1938

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[2] Clifford, *Ind. Eng. Chem.*, **13**, 631 (1921).

[3] Rosenbaum and Walton, THIS JOURNAL, **52**, 3568 (1930).

[4] Gross and Saylor, *ibid.*, **53**, 1744 (1931).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AT THE OHIO STATE UNIVERSITY]

The Action of Aluminum Chloride on Fluorinated Compounds

BY ALBERT L. HENNE AND MELVIN S. NEWMAN

In an effort to establish the orientation effect of a CF_3 group by the synthesis of $CF_3C_6H_4COCH_3$, benzotrifluoride was allowed to react with acetyl chloride and aluminum chloride. Instead of the expected products, the reaction gave benzotrichloride and aluminum fluoride in excellent yield and purity. In the absence of acetyl chloride, the reaction was not clean-cut and produced a large amount of tar; only a small quantity of benzotrichloride was isolated. In neither reaction was there a copious evolution of hydrogen halide; in the first case only hydrogen chloride came off, while in the second case a small amount of hydrogen fluoride was present in the hydrogen chloride.

From these results, it is concluded that the principal reaction is an exchange of halogen atoms between the organic fluoride and the inorganic chloride. In the presence of acetyl chloride, a complex presumably is formed between this compound and the aluminum chloride, and the exchange of halogen atoms is smooth because it occurs between the complex and the organic fluoride. In the absence of acetyl chloride, the exchange occurs directly and the benzotrichloride produced is subjected to the action of free aluminum chloride. This is known to cause tar formation.[1] The fact that some hydrogen fluoride comes off indicates that either benzotrifluoride or the intermediate benzofluorochloride is also involved in the condensation.

The replacement of organically bound fluorine by chlorine in the presence of aluminum chloride suggests a reason for the repeated failures[2] to effect Friedel–Crafts condensations between organic fluorides and chlorinated ethylenes or benzene.[3] The reactions involving only aliphatic compounds always gave tarry materials, which were abandoned. The reactions involving benzene were tried with the following fluorides: CCl_2FCCl_2F, CCl_2FCClF_2, $CClF_2CClF_2$, $CHClF_2$ and CCl_2F_2. In the last two cases, the fluorinated compound was passed as a gas through benzene containing aluminum chloride. In the other cases, aluminum chloride was dropped in small portions into a cooled solution of the fluoride in an excess of benzene. In general, a vigorous but controllable reaction started at once but soon stopped; it was started again every time a portion of aluminum chloride was added. The gas evolved was mostly hydrogen chloride which contained only a very small amount of hydrogen fluoride. After completion of the reaction, and decomposition with water in the usual way, the

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[1] Wohl and Wertyporoch, *Ann.*, **481**, 30 (1930).

[2] Henne and Leicester, THIS JOURNAL, **60**, 864 (1938).

[3] The use of metalloid fluorides instead of aluminum chloride is now under investigation.

products were tarry, somewhat elastic masses which were either fluorine-free, or almost so. From these masses, only fluorine-free substances were isolated by extraction with benzene, chloroform or dioxane, followed by precipitation with alcohol, ether or acetic acid. These substances had molecular magnitudes of about one thousand. The aluminum salt separated from the aqueous portion invariably tested very strongly for fluorine.

Even in the absence of benzene, the effect of aluminum chloride on stable aliphatic fluorides is apparent after a relatively short period of heating. After forty-eight hours of refluxing over aluminum chloride, CCl_2FCClF_2 generated a small quantity of CCl_3CClF_2, which was isolated, and some higher boiling material which no longer contained any fluorine. In a similar experiment with $CHCl_2$-$CClF_2$ the fluorine was more easily removed, hydrogen fluoride was evolved slowly and steadily and tar formation was more pronounced. In both cases, the aluminum salt tested positively for fluorine.

It is fitting to recall an old experiment[4] which was performed in order to establish the structure of $CHCl_2CHF_2$. This derivative was exposed to the action of chlorine in sunlight, in the presence of aluminum chloride, and from 60 g. of product only 4 g. of impure CCl_3CClF_2 was isolated, while the remainder was predominantly hexachloroethane. More recent work[5] has established that chlorination in sunlight follows a perfectly normal course if the aluminum salt is omitted, and pure CCl_3CClF_2 is obtained quantitatively from $CHCl_2CHF_2$. In the older experiment, the mechanism of the reaction was not well understood. It is probable that an exchange of halogens between the organic fluoride and the aluminum salt took place first, and that the small amount of CCl_3-CF_2Cl obtained owed its formation to the fortuitous fact that an insufficient quantity of aluminum chloride was present to take care of all the organic fluorine.

From this series of experiments it is concluded that it would be futile to use aluminum chloride to effect condensations between a fluorinated derivative and either an aliphatic or an aromatic compound.

Experimental

Benzotrichloride from Benzotrifluoride.—To a solution of 78 g. (1 mole) of acetyl chloride in 540 g. (450 cc.) of benzotrifluoride was added 140 g. (1.05 mole) of powdered anhydrous aluminum chloride over a period of one-half hour, the reaction flask being cooled to prevent the temperature from rising above 40°. A greenish solid seemed to form on the surface of the aluminum chloride at first. After the mixture had been stirred at 30–40° for one hour and then slowly heated to 70° during another hour, the solid gradually dissolved to give a deep red solution. During this latter period a slow steady stream of hydrogen chloride was evolved. A test for hydrogen fluoride was negative and the glass apparatus was not etched during the reaction. After stirring for two hours more at 65–70° the mixture was cooled, poured on ice (very little heat evolved) and steam distilled. By observing the distillate a crude separation of benzotrifluoride and benzotrichloride was effected. Upon fractional distillation there was obtained 135 g. (0.69 mole) of pure benzotrichloride, f. p. −4.4°, b. p. (10 mm.) 89.0–89.5°, $d^{20}{}_4$ 1.3741, $n^{20}{}_D$ 1.55789, *MR* calcd. 45.54, found 45.67. *Anal.* Calcd. for $C_7H_5Cl_3$: C, 43.01; H, 2.58; Cl, 54.41. Found: C, 43.02; H, 2.62; Cl, 53.02, 53.07. In addition, about 20 g. (0.165 mole) of benzoic acid was isolated, which resulted from hydrolysis of the benzotrichloride during steam distillation (benzotrifluoride is not hydrolyzed[2] under similar conditions). Thus the total yield based on the aluminum chloride amounted to 86%. The analysis of the aluminum salt proved it to be aluminum fluoride slightly contaminated by chloride.

Summary

The condensation of fluorinated substances with aliphatic or aromatic compounds cannot be obtained with aluminum chloride, because an exchange of halogen atoms takes place between the organic fluoride and the aluminum salt. A particularly clean-cut exchange was observed when benzotrifluoride reacted with a mixture of aluminum chloride and acetyl chloride. Benzotrichloride of unusual purity was thus obtained in good yield.

COLUMBUS, OHIO RECEIVED MAY 7, 1938

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[4] Swarts, Mémoire couronne, *Acad. roy. soc. Belg.*, **61**, 68–70 (1901).

[5] Henne and others, THIS JOURNAL, **58**, 402, 404, 888 (1936); **59**, 1201, 2434 (1937).

NOTES

The Catalyst in the Gattermann Reaction

By Richard T. Arnold and Joseph Sprung

The modification of Gattermann's synthesis for aromatic aldehydes has greatly increased the popularity of this reaction as a synthetic method.[1] It is noteworthy, however, that the zinc cyanide usually prepared in the laboratory is not pure, but it is stated that the material "contains no impurity that interferes with the Gattermann synthesis." We have reason to believe that these impurities are essential to the successful use of this method. An attempt to use pure zinc cyanide (prepared by Eimer and Amend, New York) for the preparation of 4-hydroxy-α-naphthaldehyde resulted in complete failure and after five hours the only product which we could isolate was the starting substance α-naphthol. We have shown repeatedly, however, that the addition of potassium chloride (0.33 mole) to this zinc cyanide will cause the reaction to take place as described when the zinc cyanide was prepared just before using. If the potassium chloride is added at the beginning of the reaction, the mixture may be decomposed after seventy minutes to give the reported yield. It also has been shown that the zinc cyanide usually employed for this reaction will not function if it is thoroughly washed with water before being dried. We have found one sample of commercial zinc cyanide (Eimer and Amend) which did not require an additional salt and gave good yields in seventy minutes. This material was partially leached with water and filtered. The filtrate gave a strong test for chloride ion. The residue after drying underwent the Gattermann reaction in one hundred minutes. The addition of sodium chloride cut this reaction time to seventy minutes.

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[1] Adams and Levine, This Journal, **45**, 2373 (1923).

Department of Chemistry
University of Minnesota
Minneapolis, Minnesota

Received May 16, 1938

The Stability of Chlorine–Water Vapor Mixtures in Light

By James E. Cline and George S. Forbes

The photochemical reaction involving chlorine and liquid water has been the subject of many papers since its discovery by Berthollet in 1785. The most definite results are those of Allmand, Cunliffe and Madison.[1,2] They found that solutions of hypochlorous acid as well as those of chlorine yield hydrochloric acid, oxygen and chloric acid in the same relative amounts. For each quantum absorbed, two molecules of chlorine or of hypochlorous acid are decomposed.

A search of the literature failed to disclose any investigation of the photochemical behavior of mixtures of chlorine and water vapor. Allmand, Cunliffe and Madison[1] concluded merely that the reaction, if any, in 3 cc. of vapor phase was negligible in comparison with that in 220 cc. of liquid phase.

The apparatus and method used by us to detect and measure a minimal amount of oxygen photochemically evolved from mixtures of chlorine and water vapor was a modification of that previously used for investigation of the photolysis of hydrogen sulfide.[3] Purified chlorine and water were distilled separately into the quartz reaction cell. The pressure of water vapor was read on a mercury manometer and the pressure of chlorine estimated from its volume as a liquid in a calibrated tube. Capillary seals which could be broken by magnetic hammers were used consistently instead of stopcocks. Several distillations under high vacuum served effectively to remove gases not condensable at liquid air temperature. After long exposure of the cell to radiation the extremely small amount of non-condensable gases was determined by use of a McLeod gage as previously described.[3]

Each value of ϕ in the last column was calculated upon the assumption that the radiation considered was the sole effective one. The small amounts of non-condensable gases found might have escaped from the walls of the cell, so that the values of ϕ may be considered as upper limits.

Schwab[4] found that oxygen does not react perceptibly with chlorine atoms, so that oxygen once formed in our reaction mixture could scarcely have been eliminated. The experiments described above therefore indicate the absence of any photo-

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[1] Allmand, Cunliffe and Madison, *J. Chem. Soc.*, **127**, 822 (1925).

[2] Allmand, Cunliffe and Madison, *ibid.*, **131**, 655 (1927).

[3] Forbes, Cline and Bradshaw, This Journal, **60**, 1431 (1938).

[4] Schwab, *Z. physik. Chem.*, **178A**, 123 (1937).

DATA

Source	λ considered	P_{Cl_2} mm.	P_{H_2O} mm.	Estimated quanta absorbed	P_{O_2} mm.	Molecules O_2	$\phi \frac{O_2}{\text{quanta}}$
Mazda	Visible	2000	7.2		$<7 \times 10^{-4}$		
Hg arc	365 mμ	77	13	$>0.8 \times 10^{20}$	$<3 \times 10^{-4}$	$<8 \times 10^{15}$	$<1 \times 10^{-4}$
	313 mμ			$>1 \times 10^{20}$			$<0.8 \times 10^{-4}$
"Fluorolight"	254 mμ	2000	7.2	$>1 \times 10^{20}$	$<5 \times 10^{-4}$	$<1.3 \times 10^{15}$	$<1.3 \times 10^{-4}$

chemical reaction between chlorine and water vapor, unless the improbable hypothesis is made that all products are completely condensable at liquid air temperature.

MALLINCKRODT CHEMICAL LABORATORY
HARVARD UNIVERSITY
CAMBRIDGE, MASS.

RECEIVED MAY 13, 1938

COMMUNICATIONS TO THE EDITOR

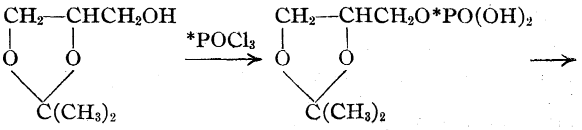
SYNTHESIS OF A RADIOACTIVE ORGANIC COMPOUND: α-GLYCEROPHOSPHORIC ACID

Sir:

The use of radioactive elements as labels in the study of metabolic processes, as initiated by G. Hevesy, already has given highly significant results in a number of cases. Most of the biochemical work accomplished so far has made use of the unstable phosphorus isotope $^{32}_{15}P$. The usual experimental procedure involves the administration to animals of a sodium phosphate solution containing a minute amount of radioactive sodium phosphate and the study of the distribution of the radioactive phosphorus in various organs or chemical fractions isolated from them. While valuable results may be obtained in this manner, it is obvious that the application of organic derivatives of radioactive phosphorus offers even greater possibilities. The development of methods for the synthesis *in vitro* of such compounds is therefore of interest. Biochemical synthesis, while theoretically possible, would be expected to yield products of lower activity and less definitely controllable composition.

For these reasons the synthesis of radioactive phosphorus oxychloride, $*POCl_3$,[1] was carried out, which, as is well known, is an excellent reagent for the introduction of phosphoric acid into organic compounds. The radioactive phosphorus was obtained by the action of fast neutrons liberated by a radon-beryllium source on carbon disulfide. For this material we are indebted to Dr. J. R. Dunning of the Department of Physics of Columbia University. To the reddish residue remaining after the evaporation of the carbon disulfide [*cf.* O. Chievitz and G. Hevesy, *Kgl. Danske Videnskab. Selskab., Biol. Medd.*, **13,** 9 (1937)] a small amount of dry red phosphorus was added and the mixture converted into the chlorides which were sublimed at a pressure of 10^{-5} mm. The sublimate was converted into $*PCl_3$, diluted with ordinary PCl_3 and rectified by distillation. The radioactive PCl_3 obtained was oxidized to $*POCl_3$ by means of potassium chlorate [F. Ullmann and A. Fornaro, *Ber.*, **34,** 2172 (1901)], and the *radioactive phosphorus oxychloride* was purified by fractionation.

With this material the synthesis of *radioactive α-glycerophosphoric acid* was carried out according to E. Fischer and E. Pfähler [*Ber.*, **53,** 1606 (1920)]. The synthesis involved the following steps:



Isopropylidene glycerol

Radioactive isopropylidene α-glycerophosphoric acid

$CH_2(OH)CH(OH)CH_2O{*}PO(OH)_2$

Radioactive α-glycerophosphoric acid

The barium salts of the radioactive α-glycerophosphoric acid and of its acetone derivative were both obtained in crystalline form, the former

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[1] In writing formulas, analytical figures, etc., for compounds containing an unstable isotope it is proposed to express this fact by using an asterisk before the letter symbol for the particular element, *e. g.*, *P, *S.

crystallizing from hot water as clusters of fine needles (calcd. for $C_3H_7O_6PBa$: P, 10.1; Ba, 44.7; found: P, 9.8; Ba, 44.3).

The radioactivity of the various samples was measured by means of a sensitive Geiger–Müller counter; the substances, in aqueous solution, being contained in a standardized glass cell. This technique, in contrast to the usual method of ignition and measurement of the activity of the ash, makes it possible subsequently to manipulate the radioactive substances unchanged. It leads, however, to considerably lower activity counts than those obtained with the ashed residues. Representative solutions of sodium glycerophosphate and of phosphoric acid (from the phosphorus oxychloride originally employed), containing 84.8 and 70.9 mg. of phosphorus, respectively, yielded respective counts of 0.797 and 0.815 impulses per minute per mg. of phosphorus when examined under strictly comparable conditions. As was to be expected, the ratio ${}^{32}_{15}P$: ${}^{31}_{15}P$ was constant in all compounds prepared, after allowance had been made for the natural decay of the unstable isotope.

This work has been made possible by a grant from the John and Mary R. Markle Foundation.

DEPARTMENT OF BIOLOGICAL CHEMISTRY
COLUMBIA UNIVERSITY ERWIN CHARGAFF
NEW YORK, N. Y.

RECEIVED JUNE 4, 1938

THE TRANSIENT INHIBITION OF THE THERMAL DECOMPOSITION OF BUTANE BY NITRIC OXIDE

Sir:

It has been shown by the writers [Echols and Pease, THIS JOURNAL, **59,** 766 (1937)] that the decomposition of butane is inhibited by nitric oxide. Subsequent study of the reaction has clearly indicated that the inhibition by nitric oxide is a *transient effect.* Careful analysis of the reacted gases has shown that this is not the result of removal of the nitric oxide by reaction.

For example, with 200 mm. of butane and 20 mm. of nitric oxide at 520° it is found that the initial slope of the reaction curve is nearly zero, but that the slope slowly rises with time until at 20% reaction it is very nearly that of the uninhibited reaction at the same percentage decomposition. Under these conditions less than 10% of the nitric oxide has reacted.

It has been found that these facts, together with all of the data so far obtained on the phenomenon, may be very nearly quantitatively explained by the assumption that the nitric oxide forms an unstable compound with chain carriers leading to an equilibrium of the form:

$$R + NO \rightleftarrows NOR$$

where R is the chain carrier, presumably a free radical.

This equilibrium is slowly established in the initial stages of the reaction and as the equilibrium is approached the "feed-back" of radicals neutralizes the inhibition, producing a normal rate of the butane decomposition. A detailed discussion of the facts will be presented shortly.

FRICK CHEMICAL LABORATORY L. S. ECHOLS
PRINCETON UNIVERSITY R. N. PEASE
PRINCETON, N. J.

RECEIVED JUNE 20, 1938

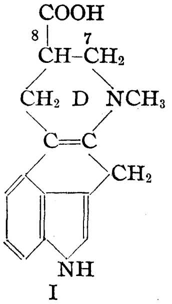
THE POSITION OF THE CARBOXYL GROUP IN LYSERGIC ACID

Sir:

We have reported previously [*J. Biol. Chem.,* **113,** 760 (1936)] that dihydrolysergic acid, contrary to lysergic acid which loses carbon dioxide and methylamine somewhat above 200°, can be sublimed at 25 mm. from a bath heated at 300°. *Anal.* Calcd. for $C_{16}H_{18}O_2N_2$: C, 71.06; H, 6.72. Found: C, 71.3; H, 6.61.] However, more recent investigation of the sublimation of α-dihydrolysergic acid has shown that a chemical change accompanies such sublimation which is accentuated by raising the temperature to 350°. A neutral substance was isolated from the chloroform solution of the sublimate after extraction of dihydrolysergic acid with dilute potash. After recrystallization from methyl alcohol, the substance was obtained in a yield of 33% (m. p. 305–307° with decomposition) $[\alpha]^{25}_{D} -219°$ (*c,* 0.48 in pyridine). Analysis showed that its formation involved loss of water. [*Anal.* Calcd. for $C_{16}H_{16}ON_2$: C, 76.15; H, 6.40; N, 11.11; (N)CH_3, 5.96. Found: C, 76.10; H, 6.58; N, 11.02; CH_3, 5.04.] Contrary to dihydrolysergic acid, it no longer dissolved in dilute acid or alkali, but it still gave the characteristic Keller color reaction unimpaired. Also contrary to the dihydro acid, it was found to be unsaturated since on catalytic hydrogenation it absorbed 1 mole of hydrogen with the formation of a neutral dihydro derivative which melted with decomposition at 336°. [*Anal.* Calcd. for $C_{16}H_{18}ON_2$: C, 75.54; H, 7.14. Found: C, 75.50; H, 7.12.]

In a communication by L. C. Craig, T. Shedlovsky, R. G. Gould, Jr., and W. A. Jacobs which is now in press, an investigation of the dissociation constants of lysergic acid and its derivatives has been reported, which has made it necesssary to revise our previous tentative conclusion that the COOH group of lysergic acid is in position 7, *i. e.*, on the carbon atom adjoining the N atom of Ring D. Such an arrangement would place it in the category of a substituted α-amino acid like proline. Instead, the evidence indicates a β-amino acid derivative and that the point of attachment of the COOH group is the carbon atom β to the N atom or position 8 as shown in formula I.

The formation of the above neutral pyrolysis product from dihydrolysergic acid fits in well with such β-substitution of the COOH group and must be interpreted as an unsaturated cyclic amide possessing either formula II or III.



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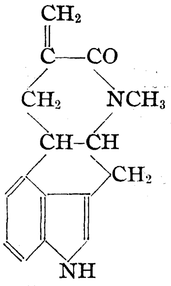
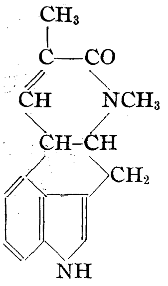


II



III

It is well known that β-amino acids, in contradistinction to the α-acids, decompose readily into unsaturated acids and ammonia. For instance, β-alanine gives readily ammonia and acrylic acid. In accordance with this property, dihydrolysergic acid should cleave between the N atom and carbon atom 7 to give an unsaturated complex secondary amino acid which would at once lactamize. Model experiments with the various piperidine carboxylic acids are now in progress to verify the nature and formation of this pyrolysis product of dihydrolysergic acid.

THE LABORATORIES OF
THE ROCKEFELLER INSTITUTE
FOR MEDICAL RESEARCH
NEW YORK, N. Y.

WALTER A. JACOBS
LYMAN C. CRAIG

RECEIVED JUNE 21, 1938

ENOL ETHERS OF STEROID KETONES

Sir:

The following is a report of the synthesis of enolic ethers of unsaturated ketonic sterols. For the preparation of these compounds the modification of Arbuzov and Mikhailova [*J. Gen. Chem.* (*U. S. S. R.*), **6**, 390 (1936)] of the classical Claisen method was used. Instead of obtaining the expected ketal, the reaction yielded directly the enol ether, one molecule of alcohol having been split out.

As a class, these compounds are stable in a solid state, but quite unstable in solution. From Table I it may be seen that in chloroform solution at room temperature the rotation changes rapidly from a negative to a positive one, the final rotation in each case being that of the free ketone. Very probably the traces of hydrochloric acid in the chloroform are the cause of the rapid splitting of the ethoxyl group, since in pyridine solution the rotation remained practically unchanged. By hydrolyzing the testosterone enol ether propionate with alcoholic potash it was possible to remove the propionic acid group without splitting the ethoxyl out of the molecule.

TABLE I

Time, hours	Specific rotation of enol ethyl ethers Cholestenone[a]	 Testosterone benzoate[b]	 Testosterone propionate[c]
0	−102.3	− 42.5	−140
0.5	− 33.8	+130	−114
1	+ 18.2	+142	
2	+ 67.6	+143	+60
24	+ 87.7		+88 (48 hours)

[a] 1.1% in chloroform. [b] 1.01% in chloroform. [c] 1.2% in chloroform.

In pyridine solution the specific rotations were −96.0° for cholestenone enol ethyl ether, and −67.5° for testosterone benzoate enol ethyl ether. These values changed only slightly after standing for several hours.

The fact that all the new substances show initially a negative rotation would indicate that one of the double bonds is in ring A, the other in ring B [Ulrich Westphal, *Ber.*, **70**, 2128 (1937)].

These substances are prepared by dissolving 5 g. of the ketone in 10 cc. of ethyl orthoformate and 1 cc. of formic acid. The solution is cooled to 20° and one drop of concentrated sulfuric acid added. The mixture is warmed on the water-bath to 50° with constant stirring, held at this temperature for ten minutes. After standing overnight at room temperature, ether is added and the solution washed with water, soda and finally with water until neutral. After drying, the ether is evaporated and the residue recrystallized from acetone or ligroin.

Table II gives the physical constants of these compounds as well as the substances isolated from the solutions on which the rotations were determined. Table III summarizes the analytical results.

TABLE II

	Enol ethyl ethers	Cholestenone	Testosterone propionate	Testosterone benzoate
M. p., °C.	Freshly prepd. material	83.5–85, clear 95	143–150	Soften 175, 181–192
	Mixed with free ketone	69–70	103–133	Soften 130, 156–168
	Recl. $CHCl_3$ from rotn.	79–81	...	185–189
	Mixed with free ketone	80–81	...	186–190
Rotation	Initial	−102.3	−140	− 42.5
	Final	+ 87.7	+ 88	+143
	Free initial ketone	+ 87	+ 88	+148

TABLE III

FORMULAS AND ANALYSES

Enol ethyl ethers		Cholesterone	Testosterone propionate	Testosterone benzoate
Formulas		$C_{29}H_{48}O$	$C_{24}H_{36}O_3$	$C_{28}H_{36}O_3$
Carbon, %	Calcd.	84.46	77.42	80.00
	Found	84.2	76.89	...
Hydrogen, %	Calcd.	11.65	9.67	8.57
	Found	11.53	10.12	...
C_2H_5O, %	Calcd.	10.92	12.09	10.71
	Found	9.77	...	10.25

SCHERING CORPORATION
BLOOMFIELD, N. J.

E. SCHWENK
G. FLEISCHER
B. WHITMAN

RECEIVED JUNE 15, 1938

THE QUANTITATIVE DETERMINATION OF AMINO ACIDS

Sir:

One of the methods frequently employed for the estimation of individual amino acids in protein hydrolysates involves the selective precipitation of the respective amino acids in the form of salts. It is the object of such methods to precipitate as much of the salt as possible, 100% isolation being the ultimate goal. Unfortunately, most of the salts that are precipitated selectively are not precipitated quantitatively. Such an incomplete precipitation may be used to advantage, however, in a newly developed analytical principle which permits a rather precise determination of individual amino acids. It depends upon the fact that the amount of an amino acid salt precipitated at equilibrium is a function of the concentration of its ions in solution.

In order to demonstrate this, let us assume that an acidic reagent, RH, forms, with an amino acid, A, the binary salt, AH·R. In many cases the so-called solubility product of the participating ions was found to be approximately a constant.

$$[AH^+] \times [R^-] = \text{const.} \qquad (1)$$

Figure 1 illustrates an experiment in which increasing amounts r', r'', r''' of the reagent are added to several equal portions of a solution, each containing Y moles of amino acid. In each sample a precipitate is formed. Were it completely insoluble, the course of precipitation would follow the straight line OB. In reality, however, the precipitation follows a hyperbolic curve passing through the points C', C'', C''', C''''.

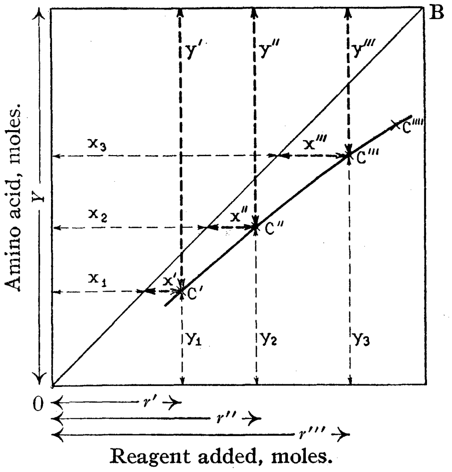


Fig. 1.—Determination of amino acids by means of the solubility product.

The precipitate obtained with an amount of reagent r' contains equivalent amounts x_1 of the reagent, and y_1 of the amino acid; the amounts x' of the reagent and y' of the amino acid remain in solution. Similarly, in a precipitation with an amount of reagent r'' the amounts x'' and y'' remain in solution. From equation (1) it follows that

$$x' \times y' = x'' \times y'' = x''' \times y''' \qquad (2)$$

Experimentally we have found the requirements of equation (2) to be fulfilled satisfactorily for the precipitation of proline by rhodanilic acid [M. Bergmann, *J. Biol. Chem.*, **110**, 471 (1935)], of glycine, alanine and leucine by dioxpyridic acid [M. Bergmann, *ibid.*, **122**, 569 (1938)], and of tyrosine by dioxanilic acid. In all cases where equation (2) is valid, the amount Y of an amino acid can be determined in a solution of unknown content. For this purpose equation (2) may be written in the following manner:

$$x'(Y - y_1) = x''(Y - y_2) = x'''(Y - y_3) \quad (3)$$

In equation (3) all values, with the exception of Y, may be determined experimentally.

In order to demonstrate the precision of such determinations, we report the following analyses:

	Present, mole	Found, mole
Glycine	0.0100	0.0103
l-Alanine	.00297	.00300
l-Leucine	.00255	.00269
l-Proline	.00420	.00435

The results obtained by the application of this type of analysis to protein hydrolysates will be reported elsewhere.

THE LABORATORIES OF
THE ROCKEFELLER INSTITUTE
FOR MEDICAL RESEARCH
NEW YORK, N. Y.

WILLIAM H. STEIN
CARL NIEMANN
MAX BERGMANN

RECEIVED JUNE 6, 1938

NEW BOOKS

Fortschritte der Photographie. (Progress in Photography.) Edited by E. STENGER, Berlin-Charlottenburg, assisted by H. STAUDE, Berlin-Tempelhof. Vol. V. of "Ergebnisse der angewandten physikalischen Chemie." Akademische Verlagsgesellschaft m. b. H., Sternwartenstrasse 8, Leipzig, Germany, 1938. xiv + 415 pp. 78 figs. 16.5 × 24 cm. Price, RM. 33; bound, RM. 35.

Modern photography dates back to the introduction of the silver bromide–gelatin emulsion in the eighth decade of the last century. Since that time, there has been no basic change in the photosensitive material of the plate, film and paper—silver halides dispersed in gelatin. During the sixty years that the silver bromide–gelatin emulsion has been known, no substitute has been found which in any way approaches it in sensitivity to light, adaptability to varied purposes, and ability to reproduce tones satisfactorily.

The study of the photographic process by the methods of scientific research received its first important impetus in England in the hands of Hurter and Driffield in 1890, and Sheppard and Mees in the first decade of the present century. These investigators laid the foundations for the quantitative interpretation of the action of light on the plate and film. At the same time, the pioneer work on spectral sensitization was done in Germany, and extensive study of the development process was made in Germany and France. It was not until the years following 1918, however, that systematic research in Europe and the United States produced information which permitted clarification of the basic principles governing the action of light on the emulsion. These studies were made largely in the research laboratories of the photographic manufacturing concerns, particularly the Eastman Kodak Company in this country, the Agfa Company in Germany, and the British Photographic Research Association in England.

In Germany alone has the photographic process been the object of much research in the Universities. In reading the book under review, one is struck by the opportunities offered by photography as a subject for research in the Universities of this country. Even in those fields where the plate or film is used as an instrument for research on other subjects, many of the results are open to doubt because the investigator displayed lack of knowledge of the capabilities and limitations of his tools. With the increasing use of photography as an instrument, there is growing need for courses of study in its principles. If these were associated with research on some of the infinity of unsolved problems, much of the misuse of photography in its applications to science and industry would eventually be avoided, and the results could not fail to be applied to an improvement of the product.

The photographic literature is singularly diluted by a large proportion of perfectly useless papers, written by people having no broad appreciation of the field, or no scientific training to guide their practical approach. It is very difficult for those not closely associated with scientific research in the subject to select the valuable material from that of doubtful basis. The book under review should provide a reliable guide for them. It is edited by Dr. Erich Stenger, head of the photographic and photochemical department of the Berlin Technische Hochschule, with particular assistance from Dr. H. Staude, who was trained at Dresden under Dr. Robert Luther, dean of German photographic research, and aided by a number of other competent co-workers. The book aims at surveying recent progress in the important fields of photographic research, and has succeeded singularly well. It is the most useful of the photographic textbooks which have appeared in recent years, considered from the point of view of those interested in the scientific aspects. It presupposes a moderate chemical and physical knowledge on the part of the reader. Its perusal will provide an excellent understanding of the state of knowledge of the subject up to the summer of 1937, for it covers not only the scientific and photographic publications, but the patent literature as well.

The first Chapter, compiled by W. Meidinger, treats of the photolysis of crystals of the alkali and silver halides, and of the latter in the presence of gelatin, as in the photographic emulsion, and closes with a survey of theories of the latent image. Progress in the technique of making photographic emulsions is handled by H. Socher, while H. Staude deals with the nature of developers and the theories of their action, and the problems of hypersensitizing, desensitizing, fixing, washing and drying. There is a very comprehensive survey by K. Meyer of recent research in photographic sensitizing dyes, in which field so much progress has been made in the past ten years, and which has been largely responsible for the recent outstanding advances in photographic plates and films, and particularly in color photography. W. Falta writes of the manufacture, properties and handling of photographic papers, W. Petzold of exposure meters, and M. P. Schmidt of diazotype papers and films. The important subject of color photography is treated in two chapters by F. Lührig and K. Räntsch. The chemical and optical aspects are considered, although not so fully as the remaining subjects in the book. This is deliberate on the part of the editor, for the fundamental principles are not new, whereas the practical development of the art is undergoing such rapid changes at the moment, that a useful evaluation of it is not yet possible. There is adequate material provided, however, for a fair basis for understanding developments likely to occur in the near future. In any case, the chapters give the fullest general survey of current trends in color photography which has yet been published.

The book is an indispensable reference source for those concerned with a knowledge of the present state of the theory and practice of photography. The material is critically selected, and its study will give an excellent idea of the ramifications of photography in the fields of physics, and physical and organic chemistry, and of its suitability as a subject for research.

The work is most appropriately dedicated to Professor Robert Luther, outstanding son of the Ostwald school, and leader of German photographic research, who attained his seventieth birthday on January 2nd of this year.

Walter Clark

Piezoelektrizität des Quarzes. (Piezoelectricity of Quartz.) By Dr. Adolf Scheibe, Physikalisch-technische Reichsanstalt. Verlag von Theodor Steinkopff, Residenzstrasse 32, Dresden-Blasewitz, Germany, 1938. xii + 233 pp. 175 figs. 15.5 × 22.5 cm. Price, RM. 20; bound, RM. 21.

This book is volume 45 of the "Wissenschaftliche Forschungsberichte, Naturwissenschaftliche Reihe," edited by Liesegang. The author, a member of the Physikalisch-technische Reichsanstalt, was associated with Dr. E. Giebe in a number of important investigations on piezoelectric crystals. In recent years in collaboration with U. Adelsberger he has designed the extraordinarily precise quartz clocks at the Reichsanstalt, which exceed in constancy the best astronomical clocks. As is to be expected, his own contributions are described in considerable detail. That the book is not for this reason one-sided is attested by the fact that the bibliography at the end contains three hundred and eleven references from foreign as well as German journals, all of which are at least mentioned in the text, while many are fully discussed.

In the main, the book deals exclusively with the piezoelectric properties of quartz and their applications in high-frequency circuits. It is only to a slight extent mathematical, but is considerably broader in scope than Vigoureux's "Quartz Resonators and Oscillators," which is now the only book on this subject in the English language.

Part A, on the static piezoelectricity of quartz, contains an excellent account of the various methods of measuring the piezoelectric constants, which should provide future investigators in this field with sufficient guidance without recourse to the original sources. Ten pages are also devoted to a very complete classified list of all known piezoelectric crystals. The relation of piezoelectric to elastic properties and their dependence on temperature also receives fairly full consideration, although the general vibration equations are not derived.

Part B, on the quartz crystal as resonator, occupies the greater part of the book. The treatment includes full discussions of quartz resonators in the form of bars, plates and rings, their modes of vibration, overtone frequencies, temperature coefficients of frequency, construction of thermostats, methods of mounting, and devices for the detection and measurement of resonance. The luminous resonators developed by Giebe and Scheibe are minutely described and well illustrated. The space given to the equivalent electric constants of the resonator and to the analysis of the resonator as a circuit element, while adequate for a general survey, is hardly complete enough to be of much value to the research worker. The same remark may be made with respect to the brief treatment of the quartz filter. This part closes with an account of various optical methods for the investigation of vibrating crystals. It is to be regretted in this connection that nothing is said in regard to the use of polarized light for the detection of twinned regions in quartz crystals.

Part C deals with the construction and performance of the quartz piezo-oscillator, including various forms of the quartz clock.

Part D, on miscellaneous piezoelectric effects, contains a very brief account of the use of quartz as a source of ultrasonic waves and for a few other special purposes, and of the effect of vibration upon the Laue X-ray patterns of quartz crystals. It is to be regretted that this portion of the book is not sufficiently complete to be as useful as it might for purposes of reference.

Presswork and diagrams are uniformly excellent. Among the few errors noted may be mentioned the statement on page 35 that of the 32 crystal classes 21 are piezoelectric (instead of 20); the assertion on page 50 that β-quartz is not piezoelectric; wrong numbering of an equation on page 57; reference (279) on page 71 should apparently be (284); on page 129 the words "äusseren" and "inneren" should be interchanged. At a few points such matters as notation, the orientation of crystals shown in illustrations, and directions of vibration are either not specified or are ambiguous.

These are minor criticisms. As a whole this book is probably the most complete and authoritative treatment of the piezoelectric properties and applications of quartz that has yet appeared.

Walter G. Cady

Principles of Organic Chemistry. By H. P. Starck, M.A., The Technical College, Kingston-on-Thames, England. Chemical Publishing Company of New York, Inc., 148 Lafayette Street, New York, N. Y., 1938. viii + 664 pp. 14 × 20.5 cm. Price, $5.00.

This new textbook of organic chemistry offers enough new and significant features to justify its intrusion into a field that may, at first thought, seem to be supplied adequately with good texts. The author's approach has been largely experimental and a much larger amount of theoretical and practical information is included than is usually found in such volumes.

"The present work originated," according to the author, "in connection with the author's teaching of organic chemistry to students reading for Pre-medical, First M. B., National Certificate, Pharmaceutical and General examinations in Chemistry. The theoretical sections cover the syllabuses of the Higher School Certificate courses of the Universities of Oxford, Cambridge, and London, and of various professional bodies." The introduction of complex compounds at an early stage in the text, before their methods of preparation and characteristic properties have been described, has been avoided. The treatment does not claim to be exhaustive. The author has sought to present the underlying principles as clearly as possible, in the hope of giving the student a sound foundation which will enable him to take full advantage of his further studies, whether in Chemistry, Biochemistry, Pharmacy, or Medicine. The first 486 pages are devoted to theoretical items, and the remaining 150 pages to practical work including tests for the elements, qualitative and quantitative analysis, and laboratory preparations. The appendix includes numerous tables, logarithms, first aid directions, a description of the Svedberg Ultracentrifuge, and answers to numerical questions.

The reviewer regrets that certain portions of this book, which otherwise might have been a valuable and unique addition to the list of organic textbooks, have not been somewhat modernized. The formulas frequently used for glucose, fructose, and other carbohydrates do not conform to the best modern usage, and the author on page 373 admits as much and yet seeks to justify this discrepancy on the basis of simplicity for the student. The references to the Grignard reagents and to the acetoacetic ester synthesis are again of the traditional, orthodox type, even though these explanations have now been proved to be either inadequate or incorrect. The directions for carbon and hydrogen determinations, as outlined beginning on page 497, might be improved by the use of "Ascarite" and "Dehydrite" and more modern absorption tubes. The naming of compounds might profitably be made to coincide more nearly with the Geneva system.

The valences of carbon, as shown on pages 53 and 62, may be confusing to beginning students. The index might logically and profitably be extended. The portions of the text devoted to organic qualitative analysis are not organized so as to permit of any systematic identification of unknown compounds. The preparation of 3,5-dinitrobenzoates might be superior to that of *p*-nitrobenzoates as derivatives for alcohols. Some twenty-six laboratory preparations and experiments are scattered throughout the first 486 pages or theoretical portion of the text. While they seem to be well organized, they are not of a suitable type, length, or number to constitute a complete laboratory program. Neither are they listed at any point in the index or table of contents. This number of experiments is, however, greatly supplemented by numerous additional exercises in Part II or the practical portion of the text. The reviewer also questions the wisdom of the preparation of hydrocyanic acid by students as outlined on page 331.

However, in spite of these adverse criticisms, the desirable features of this book far outweigh any objections that might be cited. The amounts and arrangement of theoretical and practical material is unique and far greater than usually found in elementary organic texts. Every chapter is concluded with a long list of splendid review and study questions. Important and related facts and properties are frequently summarized in convenient tables. There is a greater intermingling of the aliphatic and aromatic compounds than is usually found in such texts, thereby making the transition from one series to the other much easier and more logical. Important facts and conclusions are emphasized with large bold-faced type. The book is neatly and attractively printed and well bound. It is remarkably free from typographical errors.

The volume can be recommended to instructors who desire a new type of organic textbook that develops the subject largely from an experimental and theoretical standpoint, and then points out numerous organic applications to industrial and home activity.

RALPH E. DUNBAR

The Biological Standardisation of the Vitamins. By KATHARINE H. COWARD, D.Sc., Reader in Biochemistry, University of London. William Wood and Company, Mt. Royal and Guilford Avenues, Baltimore, Maryland, 1938. viii + 227 pp. 44 figs. 15 × 22.5 cm. Price, $4.50.

The author, who is Head of the Nutrition Department of the Pharmaceutical Society of Great Britain, is a recognized authority on methods of vitamin assay. It is fitting, therefore, that the first book to be published in English covering all essential details of biological determinations of vitamins, should come from the pen of one who has contributed so much to the establishment of our present international standards of vitamin unitage.

As the title suggests, the book is devoted exclusively to questions involving the quantitative accuracy of vitamin assays. She has confined her discussion to those vitamins (A, B_1, C and D) the methods for which have been standardized and which have received the approval of the International Vitamin Standards Committee of the League of Nations.

The book is divided into two parts. Part I is devoted to practical phases of vitamin work and may be used without reference to Part II. The latter has to do with the biometrical phases of vitamin work and emphasizes the value of statistical treatment of assay data.

Part I contains seven chapters dealing with such topics as "General Principles which Govern the Biological Methods for the Determination of the Vitamins," "Animals Suitable for the Determination of Vitamins by Biological Methods," "The Determination of Vitamin A, B_1, C and D" (one chapter devoted to each vitamin) and "The Interdependence of the Vitamins."

Each chapter which deals with the determination of a vitamin is preceded by an outline of the material which is to be discussed. The following outline of Chapter III, "The Determination of Vitamin A," is typical of the plan and treatment followed in discussing vitamin assay problems:

1. The International Standard of Reference and Unit of Vitamin A Activity.
    A. The dilution of the standard of reference for dosing.
    B. The need for a simultaneous test of the Standard whenever a determination of vitamin A is made.
    C. The general arrangement of the test for a determination of the vitamin A potency of a substance in terms of the International Standard.
2. The Preparation of Rats for Vitamin A Determinations.
    A. Animals suitable for the test.
    B. Housing of the animals.
    C. Vitamin A-free diet.
3. Criteria for the Measurement of the Response of Rats to Doses of Vitamin A.
    A. Increase in weight.
    B. Occurrence of xerophthalmia.
    C. Changes in the vaginal contents.
    D. Comparison between prophylactic and curative methods.
    E. Comparison between (a) the "increase in weight" method, (b) the "xerophthalmia" method and (c) the "vaginal contents" method.
4. Physical Properties of Vitamin A by means of which it may be Measured.
5. References.

Part II consists of five chapters dealing with "The Standard Deviation" and "The Accuracy Obtainable in Determinations of Vitamin A, B_1, C and D." An appendix consisting of ten pages contains a report of the Second International Conference on Biological Standardisation and a table of Vitamin Content of Some Common Foods, expressed in International Units.

The author shows remarkable familiarity with the various methods and laboratory practices prevailing in the best European and American laboratories. Even the experienced worker will find Part I (practical) of great value and it is the reviewer's opinion that every vitamin assay laboratory should have the book available, since Dr. Coward has brought together material which is widely scattered in the literature.

Part II, however, contains information that is even less readily available than that referred to in Part I. Furthermore, most workers are not familiar with the use of statistical methods. Dr. Coward has the happy faculty of making statistical methods usable and understandable for the average worker.

The author has shown excellent judgment in her choice of photographs, tables and charts which illustrate the points emphasized in the text. No worker in vitamin research can afford to be without this very useful book

R. Adams Dutcher

The Economics of the Sulfuric Acid Industry. By Theodore J. Kreps, Stanford University Press, Stanford University, California, 1938. xiii + 284 pp. 20 figs. 16 × 23 cm. Price, $5.00.

Announced as the first of a series of four volumes in the field of chemical economics, this work deals preëminently with the sulfuric acid industry in the United States. The author has collated and arranged, in this volume, a vast array of statistics and other data relating to the sulfuric acid industry. With unstinted labor he has delved into the archives of Government bureaus and into the files of technical periodicals, and has made conveniently accessible a mass of figures which might otherwise have been lost in oblivion.

The sulfuric acid industry is here displayed in an unusual light, interesting to both the economist and the technician. After the Introduction and two chapters tracing historical developments, the current status of the industry, including the dominance therein of the United States, is presented in Chapter IV. Then ensue eight chapters on different phases of competition, concluding with a chapter on Intercommodity Competition, and the "Outlook for Sulfuric Acid." The presentations of all these different aspects are interesting, and one must admire the painstaking care with which the author has handled his data, and the conscientious manner in which he has drawn his inferences. However, the experienced technician will be unable to agree that the premises are always adequate, or the conclusions always right.

The chapter on Interprocess Competition might well have been expanded to include some subdivisions of this title, such as Intercatalyst Competition and Competition between Tower- and Chamber-Processes. The "idealized" table of comparative operating costs of chamber and contact plants (p. 72) may be objected to as established on incorrect data and forced into balance. Chapter VI contains an interesting account of the struggle between brimstone and pyrite, but why do the statistical tables stop with the year 1934? The discussion of the minor and potential sources of sulfur in Chapter XII seems to belong in Chapter VI.

Quite inadvertently, no doubt, some elements of unfairness seem to have crept into the text here and there. A good deal of publicity is given to one firm of contact-plant contractors to the exclusion of its competitors. In fact the influence of the intense pressure for business on the part of competing vanadium-mass contact-plant builders on (1) the displacement of platinum catalysts; (2) the relative decline in the production of chamber-plant acid; and (3) the creation of an over-supply of acid-plant capacity in the United States, has been omitted altogether. In the last chapter, the tendencies toward curtailment in sulfuric acid demand in certain industries are detailed without any mention of offsettnig new uses and expanding consumption in certain other industries.

The author, Associate Professor of Business Economics at Stanford University, shows a remarkable grasp of many of the technicalities of sulfuric acid manufacture. It is true, however, that some inaccuracies and debatable statements have been included. The solution of the "vanadium mass problem" is ascribed to the wrong man (p. 54); the chamber process is erroneously said to have completely lost the market for oil of vitriol (p. 65); copper ores are said to enter the United States free of duty (p. 79), whereas a duty has been imposed since 1932; it is incorrectly implied (pp. 110 and 264) that vanadium mass can use pyrite gas without gas-purification; for the recent progress of America in contact-process technique, too much credit is given to vanadium mass, and too little to other developments (p.

55); and on p. 187 it is stated that many manufacturers of joint-cost products "do not even attempt to find particular costs for particular products, but are quite happy when the receipts from the totality of their operations show a profit over the totality of their outlays," which is in direct conflict with the practice of all manufacturers of joint-cost products with whose accounting methods the reviewer is familiar.

Several misprints (such as "turbo-dispenser" for turbo-disperser, pp. 60 and 264; "niter coke" for niter cake, p. 61; "carts" for cars, p. 90; and "767 caustic soda" for 76% caustic soda, p. 261), besides faulty English on p. 192 (line 14) and at the top of p. 215, escaped the proofreaders. It seems probable that a pre-publication critical review by a competent sulfuric acid engineer would have served to avoid most of these errors, as well as to guide the author to better sources of information and to bring the data more nearly up to date.

On the whole, this book, the first of its kind, is a valuable contribution to the literature of sulfuric acid, and will be welcomed in the libraries of the economist, the business executive and the technologist.

ANDREW M. FAIRLIE

Annual Tables of Constants and Numerical Data. N. THON, Editor-in-Chief. Vol. XI. Published for the International Union of Chemistry by Hermann et Cie.: McGraw-Hill Book Company, Inc., 330 West 42d Street, New York, N. Y., 1937. 17 × 25.5 cm.

This volume, No. XI, Part 1, is the first to be issued by the Managing Board appointed at the Twelfth Conference of the International Union of Chemistry at Lucerne in 1936. It contains numerical data which have been published during the years 1931–1934 classified in twenty-five sections and in addition a list of forty-four sections in which the other numerical data to be included in subsequent volumes will be classified. It is printed in a smaller and therefore more convenient size than the previous volumes of these Tables. Two other sections, namely, No. 26, Raman Effect, and No. 27, Rotatory Power, printed in the older, larger format, are available as separate monographs.

The Editors state that in this new series of Annual Tables emphasis will be placed on the selection and critical examination of the numerical data without abandoning the ideal of complete presentation to which Annual Tables have adhered in the past. Quantitative data are often divergent because of the different methods employed in, or the different conditions prevailing during, their determination; also because of the different methods of computation or different standard values which have been employed. It is very difficult to assign proper weights to these various factors and it would be unwise to select one single determination and discard the rest. The Editors believe that the best results will be obtained if, after elimination of data which are clearly inaccurate or are dependent upon uncertain factors, the remaining data are simultaneously tabulated and adequate information as to the attendant conditions and the methods or hypotheses involved in their determination is added.

The Editors consider it impossible to include all the data relative to industrial materials, so that in this field a few typical examples will have to suffice.

Data for the years 1935–1936 belonging in the above twenty-seven sections will be included in the forthcoming Volume XII, Part 1; data for the years 1931–1936 belonging in the remaining forty-four sections will appear in Parts 2 and 3 of the forthcoming combined Volumes XI–XII. The Managing Board states that the preparation and printing of these three volumes are progressing rapidly. Prior to their publication the separate sections will be issued in the form of monographs containing one to three sections.

Finally, the Managing Board points out that the publication of these volumes has been possible only because of a substantial grant received from the French Government.

Workers in the physical sciences everywhere will be gratified not only at this continuation of Annual Tables but particularly at the prospect of prompt publication of future volumes.

ARTHUR B. LAMB

The Chemistry of Plant Constituents. By OLE GISVOLD and CHARLES H. ROGERS. Burgess Publishing Company, Minneapolis, Minn., 1938. 309 pp. $3.50.

The authors state in the preface to the first (present) edition that the subject matter deals with the chemistry of plant constituents, with various possible reactions involved in their formation, and that "a rather complete bibliography is presented." When a book covers a vast field, the reviewer's critical competency must be limited to the topics with which he is intimately acquainted. His approval or disapproval of the book as a whole depends upon the thoroughness of his sampling of these topics.

The synthesis of hexoses *in vitro* by Baly (p. 6) is complete to 1928. No mention is made of the work of Ramsperger and Porter, nor of the work of Dhar and associates. The criticisms of Barton Wright (1930), the detailed discussion by Spoehr (1933), the Cold Spring Harbor Symposium (1934) are all ignored. Credit is given (p. 30) to Ehrlich for our "quite complete knowledge about the pectin molecule." Yet Norris and Resch (1937) point out the difficulty of distinguishing the essential structure from incidental adjunct. The authors make no reference to the work of Nanji, Paton and Ling, Carré, nor to the review by Bonner (1936). The work of Myers and Baker (1931, 1934), of Stoep (1928) and the important contributions of Link are all ignored. They suggest (p. 32) that the name pectin should be retained for substances now known as "urpectin" and "protopectin." This is contrary to the A. C. S. committee nomenclature (1927). The suggestion is made (p. 33) that the "definite ratio of calcium and magnesium in the pectin molecule might well explain the necessity of a balanced calcium and magnesium supply for normal plant development." A perusal of Norman ("Biochemistry of Cellulose, the Polyuronides and Lignin," 1937) shows how grossly inadequate is the present treatment.

The carotenoids (chapter X) were next examined. Reviews of this topic tend to conform to a set pattern but, in the reviewer's opinion, this chapter does not compare with the extremely readable account contributed by

Bogert to Gilman's "Organic Chemistry" (1938). Loose statements are frequent. Although Bogert uses xanthophyll synonymously with lutein (to the reviewer's regret, as it has for long been associated with the non-hydrocarbon carotenoids of the leaf), the present authors (p. 178) devote brief paragraphs to (1) *xanthophyll* and (2) *lutein or leaf xanthophyll.* This they state has been isolated from Dotter (sic) pigments. (*Egg-yolk*, Eidotter, or *Dodder?*) Strain has shown that leaf xanthophyll is not synonymous with lutein. They point out (p. 178) that rhodoxanthin does not have a double bond in the center of the molecule and therefore has a different type of symmetry. Application of Pauling's discussion on resonance (Gilman) to a conjugated system of double bonds indicates this to be illusory. On p. 184 they offer a confused discussion of water-soluble yellow pigments, carotenoids, and the autumnal coloring of leaves. "Some of the red colors are developed by the oxidation of the yellow ones. In the tomato, the yellow pigments are masked by the predominating red pigment, lycopin." The sentences, in juxtaposition, entirely unrelated, illustrate the confusion. The contribution of the late K. W. Hausser (1934) to color and bond conjugation might well have been mentioned. The improved method for isolating carotene by Homes (Holmes) and Leicester is hardly their most important contribution, and it has not found wide application because of the re-introduction of the Tswett column, of which but brief mention is made.

Russell's spectrographic evidence in favor of flavpinacol formation in phlobatannins might well have been stressed, and his lucid review (1934) should have settled the undesirability of including caffetannins and chlorogenic acid with the true tannins. The term *leucocyanin* has been substituted (p. 166) for leuco-*antho*cyanin. The development of color was first noted by Willstätter, explained by Rosenheim (1920), but this is not mentioned.

A discussion of chlorophyll is wedged (p. 272) into the chapter on enzymes. The sole reference to chlorophyll chemistry is Hans Fischer's review (1937). Willstätter and Conant are to be remembered, not for their positive chemical contributions, but by less valuable suggestions as to the photosynthetic mechanism. The theory of Muller (p. 272) is put forward, though it has no widespread acceptance, while the views of van Niel on assimilation, and of Emerson and Arnold, Gaffron, on a possible photosynthetic unit are ignored.

Let us set to one side the irritations caused by numerous typographical errors, the indifference to accepted spelling, (carotinoid, lycopin interchangeably with carotenoid, lycopene), the innovations on nomenclature. Limitations of space necessitate compression and even omission. Instead of a highly incomplete bibliography, a critically selective one is required. A further ground for uneasiness lies in the general framework into which the facts are set. Let us examine pp. 1–4 in some detail. "In general, the greater the water supply, the smaller the root system. Too much water will result in the death of most plants." Solution culture technique is overlooked, and no hint is given that oxygen supply is an essential factor. "(Leaves) are the laboratories in which 'nuclear' or simple materials are synthesized." When did chemist or biologist use nuclear in this sense? "Fruits...have the lowest percentage of ash, and leaves have the highest. The latter is probably due to the fact that the water leaves the ash behind as it evaporates from them in transpiration." There is no differentiation of constituents immobilized to a great extent, notably iron and calcium, and those of great mobility, particularly phosphorus and potassium, and we are told the ash is left behind as the water evaporates.

The book shows evidence of uncritical compilation, typographical errors are inexcusably numerous, the style is in places too staccato, and many expressions are both irritating and unscientific, (*e. g.*, p. 1 "a myriad number," p. 5 "a myriad of organic reactions," p. 14 "a myriad of plant products"). It is fair to add that these remarks apply to five of the fifteen chapters, and to slightly less than one-third of the book. The residue is certainly much more free from irritating or obvious defects, and appears to be more carefully reasoned. Unfortunately the reviewer has already limited his field of critical competency, but drastic changes must be made if this book is to survive.

G. Mackinney

Handbuch der Lebensmittelchemie. A. Bömer, A. Juckenack and J. Tillmans. Dritter Band. **Tierische Lebensmittel.** (Handbook of Food Chemistry. Vol. III. Animal Foodstuffs). Edited by A. Bömer. Verlag von Julius Springer, Linkstrasse 22-24, Berlin W 9, Germany, 1936. xvi + 1049 pp. 174 figs. 17.5 × 26 cm. Price, RM 129; bound, RM 132.60.

The first two volumes of this series are devoted to those constituents of the plant and animal world which constitute, or are a part of, man's food. Reviewed and described, also, are the relevant analytical procedures. In the third volume, and so to continue in the others which are contemplated, individual foods are treated. Unlike the practice followed by others, for example König, volume I and supplements of his "Chemie der Menschlichen Nahrungs- und Genussmittel," no attempt has been made at compiling the voluminous data on the proximate composition of foods which have appeared within the past century. Claimed as a novel feature which has been introduced to extend the serviceability of the work for the (German) food chemist in official or private practice is the inclusion of a digest, written by members of the profession (Holthöfer and Bames), of the legal aspects, both domestic and foreign, of the regulations under which the various substances are sold.

An excellent monograph of some 540 pages on milk and milk products, the work of A. Gronover and R. Strohecker who had the assistance of several others on certain special topics; similarly one on meats and meat products (359 p.) by A. Beythien and others; and a 74-page section by J. Grossfeld on the subject of eggs represent the major points of emphasis in this volume. Of lesser interest, although not without value, are the following topics: proprietary foods (23 p.) and sampling and preparation of material for analysis (17 p.) by A. Beythien; a brief discourse on foods and nutritive values (4 p.) by A. Bömer; and German food and food label laws (18 p.) by H. Holthöfer (18 p.).

References to the German literature on all of the topics are rather complete. That apparent ignoration of the world literature against which criticism was directed in respect to an earlier volume (This Journal, 57, 2017

(1935)) appears to have been avoided by the present authors, who have gone beyond their own frontiers in their attempts to bring into the picture the work of other scientists. Keeping pace with the advances in a field as large as that defined by the term food chemistry is, indeed, a large task. The authors have simplified this task for the many by bringing together in condensed form the vast amount of information now extant on this subject. The fact that methods of analysis have not been presented critically may perhaps disappoint some. Inasmuch as the reviewer does not understand that this work was to be primarily a treatise of this kind, he is of the opinion that the project has not missed its mark; rather that it should prove to be an invaluable aid to the worker in these fields.

H. A. SCHUETTE

BOOKS RECEIVED

May 15, 1938–June 15, 1938

MEYER BODANSKY. "Introduction to Physiological Chemistry." Fourth edition. John Wiley and Sons, Inc., 440 Fourth Ave., New York, N. Y. 686 pp. $4.00.

ADOLF BRÄUER and JOSEF REITSTÖTTER. "Fortschritte des chemischen Apparatewesens. Werkstoffe." Lieferungen 1–2. Akademische Verlagsgesellschaft m. b. H., Sternwartenstrasse 8, Leipzig C 1, Germany. 128 + 192 pp. RM. 56; to subscribers, RM. 40.

STUART R. BRINKLEY. "Introductory General Chemistry." Revised edition. The Macmillan Company, 60 Fifth Ave., New York, N. Y. 731 pp. $3.50.

C. H. DOUGLAS CLARK. "The Fine Structure of Matter. Part II. Molecular Polarization." John Wiley and Sons, Inc., 440 Fourth Ave., New York, N. Y. 242 pp. $4.50.

C. H. DOUGLAS CLARK. "The Fine Structure of Matter. Part III. The Quantum Theory and Line Spectra." John Wiley and Sons, Inc., 440 Fourth Ave., New York, N. Y. 186 pp. $4.50.

FARRINGTON DANIELS. "Chemical Kinetics." Cornell University Press, 124 Roberts Place, Ithaca N. Y. 273 pp. $3.25.

J. DUCLAUX. "Mouvement Brownien. I. Partie Expérimentale." Hermann et Cie., Éditeurs, 6 Rue de la Sorbonne, Paris, France. 96 pp. Fr. 25.

THOS. H. DURRANS. "Solvents." Fourth edition. D. Van Nostrand Co., Inc., 250 Fourth Ave., New York, N. Y. 238 pp. $5.00.

A. EUCKEN, Editor. "Der Chemie-Ingenieur. Band II. Chemische Operationen. Teil 2. Apparative Durchführung chemischer Operationen." Akademische Verlagsgesellschaft m. b. H., Sternwartenstrasse 8, Leipzig C 1, Germany. 523 pp. RM. 50; bound, RM. 52.

C. FAULCONER FLINT. "The Chemistry and Technology of Rubber Latex." D. Van Nostrand Co., Inc., 250 Fourth Ave., New York, N. Y. 715 pp. $14.00.

M. J.-A. GAUTIER. "La Pyridine. Étude de Quelques α-Pyridones." Hermann et Cie., Éditeurs, 6 Rue de la Sorbonne, Paris, France. 78 pp. Fr. 18.

M. GUICHARD. "I. De la Sensation à la Méthode de Mesure." "II. Essai Historique sur les Mesures en Chimie. (a) Avant Lavoisier. (b) Avec Lavoisier." "(c) Après Lavoisier." Hermann et Cie., Éditeurs, 6 Rue de la Sorbonne, Paris, France. 120 pp. Fr. 10 + 10 + 10.

MORRIS B. JACOBS. "The Chemical Analysis of Foods and Food Products." D. Van Nostrand Co., Inc., 250 Fourth Ave., New York, N. Y. 537 pp. $6.00.

I. KOPPEL, Editor. "Abeggs Handbuch der anorganischen Chemie. Vierter Band, dritte Abteilung, zweiter Teil, A, Lieferung 3. Eisen und seine Verbindungen." Verlag von S. Hirzel, Königstrasse 2, Leipzig C 1, Germany. 165 pp. RM. 20.

P. LEBEAU and G. COURTOIS. "Traité de Pharmacie Chimique." Second edition, Vols. 1–2. Masson et Cie., Éditeurs, 120 Boulevard St.-Germain, Paris VI^e, France. 1206 + 2128 pp. 280 + 460 fr.

BERNARD LEWIS and GUENTHER VON ELBE. "Combustion, Flames and Explosion of Gases." The Macmillan Company, 60 Fifth Ave., New York, N. Y. 415 pp. $5.50.

A. SMITS. "Die Theorie der Komplexität und der Allotropie." Verlag Chemie, G. m. b. H., Corneliusstrasse 3, Berlin W 35, Germany. 372 pp. RM. 19.50.

EMIL STARKENSTEIN. "Lehrbuch der Pharmakologie, Toxikologie und Arzneiverordnung." Verlag Franz Deuticke, Helferstorferstrasse 4, Wien I, Germany. 758 pp. RM. 20; bound, RM. 23.

JOHN ARREND TIMM. "An Introduction to Chemistry." McGraw-Hill Book Company, Inc., 330 West 42d St., New York, N. Y. 568 pp. $3.50.

HARRY BOYER WEISER. "Inorganic Colloid Chemistry. Vol. III. The Colloidal Salts." John Wiley and Sons, Inc., 440 Fourth Ave., New York, N. Y. 473 pp. $6.00.

JOHN H. YOE. "A Laboratory Manual of Qualitative Analysis." John Wiley and Sons, Inc., 440 Fourth Ave., New York, N. Y. 219 pp. $2.50.

"Annual Reports on the Progress of Chemistry for 1937. Vol. XXXIV." The Chemical Society, Burlington House, London W 1, England. 540 pp. 13s./0d.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

Halogenation of 1-Hexyne in Methanol[1]

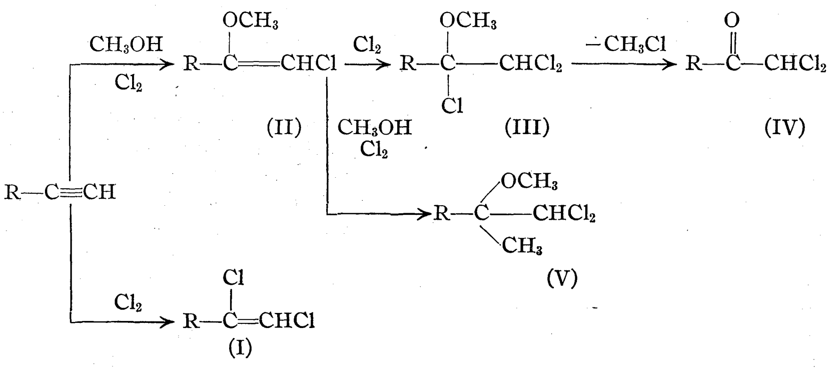
BY J. J. VERBANC AND G. F. HENNION

Introduction

Relatively little attention has been directed toward the halogenation of alkylacetylenes. It is generally accepted that di- and tetrahalogen addition products result from such reactions when conducted in inert solvents. However, there are numerous synthetic possibilities if a third reagent is present, *e. g.*, a reactive solvent such as methanol.

Goldschmidt, Endres and Dirsch[2] treated phenylacetylene with ethyl hypochlorite in carbon tetrachloride solution. They obtained dichloroacetophenone and not the anticipated diethoxydichloro addition product. Jackson[3] chlorinated phenylacetylene in methanol and obtained 1-phenyl-1,1-dimethoxy-2,2-dichloroethane. Similar studies with aliphatic acetylenes have not been reported. In the present investigation 1-hexyne has been chlorinated under a variety of conditions using both methanol and carbon tetrachloride as solvents. All likely addition products have been isolated or prepared by independent methods.

Chlorination of 1-hexyne in methanol at 0–5° yielded a mixture of 1,2-dichloro-1-hexene (I) and 1,1-dichloro-2,2-dimethoxyhexane (V). At 25–30°, 1,1-dichloro-2-hexanone (IV) was obtained in addition to the above products. The formation of these compounds may be represented by the following scheme of reactions (R is n-C_4H_9).



Compounds (II) and (III) were not isolated. The reactivity of (II) precludes the possibility of isolation from the chlorinated mixture. Compounds of type (III) spontaneously decompose, as has been shown previously.[4] During these experiments the formation of methyl chloride was observed, confirming the mechanism of dihaloketone (IV) formation.

The absence of (II) and the monochloro analogs of (IV) and (V) prompted us to synthesize these in another manner. The following reactions were employed, starting with 1-hexyne.

The 1-chloro-2-methoxy-1-hexene (II) thus obtained was dissolved in methanol and treated with chlorine at 25°. Compound (V) was ob-

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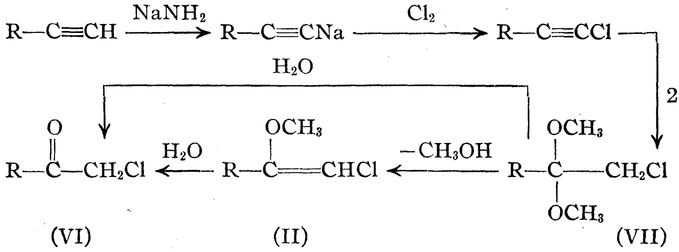
[1] Paper XXVI on the chemistry of the alkylacetylenes and their addition products; previous paper, THIS JOURNAL, **60**, 1159 (1938).

[2] Goldschmidt, Endres and Dirsch, *Ber.*, **58**, 572 (1925).

[3] Jackson, THIS JOURNAL, **56**, 977 (1934).

[4] Baum and Hennion, *ibid.*, **60**, 568 (1938).



tained in 60% yield, thereby confirming, in part, the mechanism proposed above.

Chlorination of 1-hexyne in carbon tetrachloride yielded only the anticipated 1,2-dichloride.

Bromination of 1-hexyne yielded the 1,2-dibromide, irrespective of whether the reaction was conducted in carbon tetrachloride or methanol. Neither methoxy bromides nor bromo ketones could be prepared under the conditions employed.

Experimental

Reagents.—1-Hexyne[5,6] and 1-chloro-1-hexyne[7] were prepared as previously described. All other materials were c. p. stock reagents.

Reaction of Chlorine with 1-Hexyne in Methanol.—Into a two-liter three-necked flask with a reflux condenser, mechanical stirrer and a gas inlet tube, was placed 400 cc. of anhydrous methanol and 82 g. of 1-hexyne. A moderately rapid stream of chlorine, measured by a flowmeter, was introduced over the surface of the rapidly agitated mixture. The absorption of chlorine was quite rapid and the reaction was accompanied by a moderate rise in temperature. The initial temperature, 25–30°, was maintained by moderate cooling. After the theoretical amount of chlorine had been added the mixture was allowed to stir for an additional hour after which it was washed with water, dilute carbonate solution and again with water. The organic layer was dried over calcium chloride and fractionated. Distillation through an efficient column yielded the following compounds listed in order of increasing boiling point.

1,2-Dichloro-1-hexene (I).—Obtained 29 g. (18% yield); b. p. 60–61° at 34 mm.; d^{28} 1.0511; $n^{28}\text{D}$ 1.4535; *MR* (calcd.), 39.17; *MR* (obsd.), 39.10.

Anal. Calcd. for $C_6H_{10}Cl_2$: Cl, 46.4; mol. wt., 153.0. Found: Cl, 46.1; mol. wt., cryoscopic in benzene, 151.3.

1,1-Dichloro-2-hexanone (IV).—Obtained 60.3 g. (37% yield); b. p. 64–66° at 10 mm.; d^{26} 1.1344; $n^{26}\text{D}$ 1.4533; *MR* (calcd.), 39.65; *MR* (obsd.), 40.0.

Anal. Calcd. for $C_6H_{10}Cl_2O$: Cl, 42.0; mol. wt., 169.0. Found: Cl, 42.2; mol. wt., cryoscopic in benzene, 167.7.

1,1-Dichloro-2,2-dimethoxyhexane (V).—Obtained 75 g. (35% yield); b. p. 76–78° at 2 mm.; d^{29} 1.120; $n^{29}\text{D}$ 1.4530; *MR* (calcd.), 52.1; *MR* (obsd.), 51.8.

Anal. Calcd. for $C_8H_{16}Cl_2O_2$: Cl, 32.81; mol. wt., 216. Found: Cl, 32.7, 32.55, 32.50; mol. wt., cryoscopic in benzene, 215, 218.

A similar experiment was carried out employing a reaction temperature of 0–5°. This reaction resulted in a 20% yield of 1,2-dichloro-1-hexene and a 30% yield of 1,1-dichloro-2,2-dimethoxyhexane. Approximately 24% of 1-hexyne was recovered.

Bromination of 1-Hexyne in Methanol.—Into a two-liter three-necked flask with a reflux condenser, mechanical stirrer, and a gas inlet tube, was placed 500 cc. of anhydrous methanol, and 82 g. of 1-hexyne. Two hundred and forty grams of bromine was placed in a 250-cc. wide-mouthed bottle equipped with an inlet and outlet tube. The bromine bottle was connected by means of rubber tubing to the reaction flask and to a nitrogen tank. A slow stream of nitrogen was bubbled through the liquid bromine for four hours, sufficient to transfer all the bromine. The reaction flask was cooled in an ice-bath during the addition. The mixture was stirred for an additional hour, after which it was washed with water, dilute carbonate solution and again with water. The organic layer was dried over calcium chloride and distilled through an efficient column. The yield of 1,2-dibromo-1-hexene was 223 g. (92.5% yield). The compound had the following characteristics: b. p. 89–91° at 30 mm.; d^{22} 1.608; $n^{22}\text{D}$ 1.5080; *MR* (calcd.), 44.97; *MR* (obsd.), 44.80.

Anal. Calcd. for $C_6H_{10}Br_2$: Br, 66.1; mol. wt., 242. Found: Br, 65.9; mol. wt., cryoscopic in benzene, 239.

Chlorination of 1-Hexyne in Carbon Tetrachloride.—Into a one-liter three-necked flask with a reflux condenser, motor driven stirrer, and a gas inlet tube, was placed 82 g. of 1-hexyne and 500 cc. of carbon tetrachloride. An additional 100 cc. of solvent to which had been added 3 cc. of antimony pentachloride was added slowly to the agitated mixture. A moderate stream of chlorine was passed over the surface until the theoretical amount had been added. The reaction mixture was stirred for an additional hour after which it was washed with water, dilute carbonate solution and again with water. The organic layer was dried over calcium chloride and distilled. The yield of product was 38 g. (25% of the theoretical). Considerable polymer (tar) was also obtained. The 1,2-dichloro-1-hexene had the following characteristics: b. p. 62–65° at 36 mm.; d^{27} 1.0525; $n^{27}\text{D}$ 1.4540; *MR* (calcd.), 39.17; *MR* (obsd.), 39.10.

Proof of Structure of 1,1-Dichloro-2-hexanone.—Ten grams of 1,1-dichloro-2-hexanone and 20 g. of calcium hypochlorite were mixed with 100 cc. of distilled water. The mixture was refluxed for thirty minutes after which it was subjected to distillation. The following compounds were obtained: 3.5 g. of chloroform, b. p., 57–58° at 746 mm.; d^{25} 1.481; $n^{25}\text{D}$ 1.4438, and 1.5 g. of *n*-valeric acid, identified by its characteristic odor and *p*-bromophenacyl ester, m. p. 63°.

Identification of Methyl Chloride.—A solution of 82 g. of 1-hexyne in 500 cc. of methanol was chlorinated at 40–50° as described above. The exit gas was passed through two wash bottles containing 25% sodium hy-

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(5) Picon, *Compt. rend.*, **158**, 1346 (1914); **169**, 32 (1919).

(6) Vaughn, Hennion, *et. al.*, *J. Org. Chem.*, **2**, 1 (1937).

(7) McCusker and Vogt, THIS JOURNAL, **59**, 1307 (1937).

droxide solution, then through a calcium chloride drying tube, and finally into a 500-cc. flask cooled to −75° with carbice and acetone. About 20 cc. of condensate was obtained, identified as methyl chloride by conversion to methylmagnesium chloride, then to acetic acid (b. p. 118–119°), in turn converted to acetanilide (m. p. 114°). The chlorinated methanol solution yielded 39 g. of 1,2-dichloro-1-hexene and 38 g. of 1,1-dichloro-2-hexanone.

Addition of Methanol to 1-Chloro-1-hexyne.—This reaction was carried out using the method previously reported.[8] From 116.5 g. of 1-chloro-1-hexyne there was obtained 150 g. (83% yield) of 1-chloro-2,2-dimethoxyhexane: b. p. 77–80° at 14 mm.; d^{25} 0.9873; $n^{25}\text{D}$ 1.4305; *MR* (calcd.), 47.30; *MR* (obsd.), 47.20.

Anal. Calcd. for $C_8H_{17}O_2Cl$: Cl, 19.65; mol. wt., 180.5. Found: Cl, 19.40; mol. wt., cryoscopic in benzene, 179.8.

Preparation of 1-Chloro-2-methoxy-1-hexene.—Employing the general procedure already reported,[9] 90.3 g. of 1-chloro-2,2-dimethoxyhexane was desaturated using *p*-toluenesulfonic acid as a catalyst. The yield of 1-chloro-2-methoxy-1-hexene was 68.5 g. (92.5% yield). The following characteristics were determined for this compound: b. p. 90–91° at 65 mm.; d^{23} 0.9725; $n^{23}\text{D}$ 1.4460; *MR* (calcd.), 40.57; *MR* (obsd.), 40.65.

Anal. Calcd. for $C_7H_{13}OCl$: Cl, 24.9; mol. wt., 148.5. Found: Cl, 24.8; mol. wt., cryoscopic in benzene, 147.1.

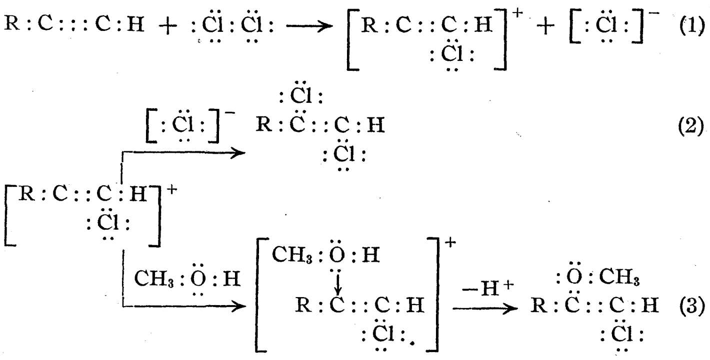
Chlorination of 1-Chloro-2-methoxy-1-hexene.—Forty grams of 1-chloro-2-methoxy-1-hexene was added dropwise (below the surface) to 200 cc. of methanol, while chlorine was passed over the surface. The temperature was maintained at 25–30°. At the completion of the reaction the excess chlorine and hydrogen chloride formed were exactly neutralized with sodium methylate–methanol solution, using phenolphthalein as an indicator. The sodium chloride was filtered off and the filtrate distilled. There was obtained 35 g. (60% yield) of 1,1-dichloro-2,2-dimethoxyhexane.

Hydrolysis of 1-Chloro-2-methoxy-1-hexene.—Fifteen grams of 1-chloro-2-methoxy-1-hexene was added to a mixture of 15 cc. of water and 50 cc. of methanol to which had been added 0.2 g. of *p*-toluenesulfonic acid. The solution was placed in a 250-cc. flask equipped with a reflux condenser and heated for a period of two hours. The excess water was removed by addition of anhydrous sodium sulfate and the clear supernatant liquid fractionated. The yield of 1-chloro-2-hexanone was 11 g. (82%). The ketone had the following properties: b. p. 73–74° at 20 mm.; d^{24} 1.007; $n^{24}\text{D}$ 1.4370; *MR* (calcd.), 34.79; *MR* (obsd.), 34.80.

Anal. Calcd. for $C_6H_{11}ClO$: Cl, 26.38. Found: Cl, 26.3.

Discussion

It is extremely unlikely that methoxychloro addition products of 1-hexyne result through direct addition of methyl hypochlorite. In accord with modern electronic concepts, we prefer to consider a series of repeated fragmentary additions as shown below with electronic formulas.



Equations (1) and (2) represent the normal course of halogenation in inert solvents. Equation (3) shows how a reactive solvent may coordinate with the "positive fragment" from (1), the complex then stabilizing by rejection of a hydrogen ion.

While direct proof of such mechanisms cannot be offered, these electronic concepts have proved extremely useful in predicting a number of other mixed addition reactions now under investigation.

Summary

1-Hexyne has been chlorinated in methanol and in carbon tetrachloride. Chlorination in methanol yielded 1,2-dichloro-1-hexene, 1,1-dichloro-2,2-dimethoxyhexane, and 1,1-dichloro-2-hexanone. In carbon tetrachloride 1,2-dichloro-1-hexene was formed. Bromination in methanol gave exclusively the 1,2-dibromide.

NOTRE DAME, INDIANA RECEIVED APRIL 14, 1938

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[8] Hennion, Killian, *et. al.*, THIS JOURNAL, **56**, 1130 (1934).

[9] Killian, Hennion and Nieuwland, *ibid.*, **57**, 544 (1935).

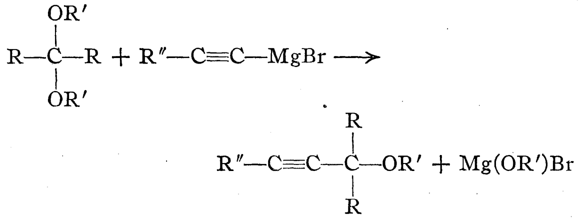
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES, UNIVERSITY OF NOTRE DAME]

Reactions of Dialkoxyalkanes with Alkynylmagnesium Bromides[1]

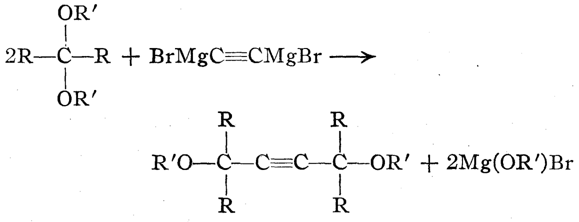
BY A. L. KRANZFELDER AND R. R. VOGT

Introduction

It has been shown by Spaeth[2] and by Tschitschibabin and Jelgasin[3] that several common acetals react with certain alkyl- and arylmagnesium halides to yield various amounts of ethers through replacement of one alkoxyl group by the hydrocarbon radical. This reaction has been applied in the present research by utilizing the acetylenic magnesium bromides and acetal-type compounds for the synthesis of alkyl ethers of alkynyl carbinols and glycols, according to the following type equations, in which (R′) and (R″) represent alkyl groups and (R) may be an alkyl radical or hydrogen atom



$$\mathrm{R{-}\overset{OR'}{\underset{OR'}{C}}{-}R + R''{-}C{\equiv}C{-}MgBr \longrightarrow R''{-}C{\equiv}C{-}\overset{R}{\underset{R}{C}}{-}OR' + Mg(OR')Br}$$



$$\mathrm{2R{-}\overset{OR'}{\underset{OR'}{C}}{-}R + BrMgC{\equiv}CMgBr \longrightarrow R'O{-}\overset{R}{\underset{R}{C}}{-}C{\equiv}C{-}\overset{R}{\underset{R}{C}}{-}OR' + 2Mg(OR')Br}$$

Several ethers of acetylenic glycols as well as certain methoxybutynes have been prepared previously by the action of halomagnesium or sodium compounds of acetylenes on various haloethers, as shown below[4–7]

$$\mathrm{CH_3OCH_2Cl + BrMgC{\equiv}C{-}CH_3 \longrightarrow CH_3OCH_2{-}C{\equiv}C{-}CH_3 + MgBrCl}$$

$$\mathrm{CH_3OCH_2CH_2Br + NaC{\equiv}CH \longrightarrow CH_3OCH_2CH_2{-}C{\equiv}CH + NaBr}$$

$$\mathrm{2ROCH_2Cl + BrMgC{\equiv}CMgBr \longrightarrow ROCH_2C{\equiv}CCH_2OR + 2MgClBr}$$

By treating propargylic acetal, obtained from acrolein, with methyl-, ethyl- and phenylmagnesium bromides, Grard[8] prepared the corresponding 3-ethoxy-1-alkynes. The methyl ethers of some acetylenic carbinols also have been synthesized from methyl sulfate and the sodium alcoholates.[9]

The object of this investigation was to study the reactivity of different types of dialkoxyalkanes toward acetylenic Grignard reagents, and to determine the practicability of the reaction as a general method for the synthesis of various classes of acetylenic ethers. The method lends itself particularly well since the intermediate acetals and ketals are readily prepared directly from acetylene and the alkylacetylenes

$$\begin{tikzcd}
\mathrm{HC{\equiv}CH} \arrow[r, "+2\mathrm{ROH}"] \arrow[d, "\mathrm{Na\ +\ RBr}"] & \mathrm{CH_3{-}CH(OR)_2} \\
\mathrm{RC{\equiv}CH} \arrow[r, "+2\mathrm{ROH}"] & \mathrm{R{-}C(OR)_2CH_3}
\end{tikzcd}$$

The reactions carried out are listed in Table I, along with the physical constants of the acetylenic ethers obtained. Table II shows the analysis of the ethers not reported in the literature. All compounds distilled as water-white liquids having very pleasant odors.

Experimental

Reagents.—1-Hexyne and 1-heptyne were prepared by a modification of the Picon synthesis.[10] Ethyl orthoformate was synthesized according to the method described in the literature.[11] Ethylal and *n*-propylal were Eastman Kodak Company products, and were purified by distillation before use.

Preparation of 1,1- and 2,2-Dialkoxyalkanes.—1,1-Diethoxyethane and 2,2-dimethoxyhexane were obtained by the addition of ethanol and methanol to acetylene[12] and to 1-hexyne,[13] respectively, by means of a mercuric oxide–boron trifluoride catalyst.

The preparation of 1,1-diethoxypropane was effected by the addition of an ether solution of 1.0 mole ethylmagnesium bromide to a solution of 222 g. (1.50 moles) of ethyl orthoformate in dry ether. The method employed was similar to the general procedure described below. Special precautions were taken, however, to use an excess of ester to ensure reaction of only one alkoxyl group. Hy-

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[1] Paper XXVII on the chemistry of the alkylacetylenes and their derivatives; previous paper, THIS JOURNAL, **60**, 1711 (1938).

[2] Spaeth, *Monatsh.*, **35**, 330, 463 (1914).

[3] Tschitschibabin and Jelgasin, *Ber.*, **47**, 48, 1843 (1914).

[4] Yvon, *Compt. rend.*, **180**, 748 (1925).

[5] Lespieau, *ibid.*, **144**, 1161 (1907); **194**, 287 (1932).

[6] Kroeger and McCusker, THIS JOURNAL, **59**, 213 (1937).

[7] Gauthier, *Ann. chim. phys.*, [8] **16**, 334 (1909).

[8] Grard, *Ann. chim.*, **13**, 336–383 (1930).

[9] Gredy, *Compt. rend.*, **198**, 2254 (1934).

[10] Vaughn, Hennion, *et al.*, *J. Org. Chem.*, **2**, 1 (1937).

[11] "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1932, p. 253.

[12] Hinton and Nieuwland, THIS JOURNAL, **52**, 2892 (1930).

[13] Killian, Hennion and Nieuwland, *ibid.*, **56**, 1384 (1934).

TABLE I

DIALKOXYALKANES WITH ALKYNYLMAGNESIUM BROMIDES

			Ether						
No.	Dialkoxyalkane	RMgBr R—	Formula	B. p., °C.	Mm.	d^{25}_4	n^{25}_D	MR Calcd.	MR Obsd.
1	$H_2C(OC_2H_5)_2$	$C_4H_9C\equiv C—$	$C_4H_9C\equiv CCH_2(OC_2H_5)$	90	24	0.8530	1.4391	43.41	43.12
2	$H_2C(OC_3H_7)_2$	$C_4H_9C\equiv C—$	$C_4H_9C\equiv CCH_2(OC_3H_7)$	61	4	.8315	1.4340	48.03	48.20
3	$CH_3CH(OC_2H_5)_2$	$C_5H_{11}C\equiv C—$	$C_5H_{11}C\equiv CCHCH_3(OC_2H_5)$	108	40	.8144	1.4302	52.65	53.38
4	$C_2H_5CH(OC_2H_5)_2$	$C_4H_9C\equiv C—$	$C_4H_9C\equiv CCHC_2H_5(OC_2H_5)$	105	25	.8290	1.4335	52.65	52.70
5	$C_6H_5CH(OC_2H_5)_2$	$C_4H_9C\equiv C—$	$C_4H_9C\equiv CCHC_6H_5(OC_2H_5)$	115	4	.9406	1.5033	67.51	67.97
6	$C_4H_9C\equiv CCH—C_2H_5(OC_2H_5)$	$C_4H_9C\equiv C—$	$(C_4H_9C\equiv C)_2CH(OC_2H_5)$	121	4	.8550	1.4505	69.12	69.24
7	$C_4H_9C\equiv C—CH(OC_2H_5)_2$	$C_4H_9C\equiv C—$	$C_4H_9C\equiv CC(C_4H_9)CH_3(OCH_3)$	83	4	.8191	1.4412	63.25	63.13
8	$CH_3OC_2H_4OCH_3$	$C_4H_9C\equiv C—$	$C_4H_9C\equiv CC_2H_4OCH_3$	91	30	.8285	1.4317	43.41	43.68
9	$CH_3CH(OC_2H_5)_2$	$HC\equiv C—$	$HC\equiv C—CH(OC_2H_5)CH_3$	88	750	.7986	1.4009	29.01	29.71
10	$C_6H_5CH(OC_2H_5)_2$	$HC\equiv C—$	$HC\equiv C—CH(OC_2H_5)C_6H_5$	103	15	1.0425	1.5328	47.96	47.58
11	$CH_3CH(OC_2H_5)_2$	$—C\equiv C—$	$CH_3CH(OC_2H_5)C\equiv CCH(OC_2H_5)CH_3$	179	730	0.8929	1.4328	49.67	49.53
12	$H_2C(OC_3H_7)_2$	$—C\equiv C—$	$C_3H_7OCH_2C\equiv CCH_2(OC_3H_7)$	150	20	.8892	1.4322	49.67	49.60

TABLE II

ANALYSES OF NEW ACETYLENIC ETHERS

No.	Empirical formula	Mol. wt.[a] Calcd.	Mol. wt.[a] Obsd.	% Alkoxyl[b] Calcd.	% Alkoxyl[b] Obsd.
1	$C_9H_{16}O$	140	142	32.11	31.24
2	$C_{10}H_{18}O$	154	153	...	...[c]
3	$C_{11}H_{20}O$	168	167	26.76	25.85
4	$C_{11}H_{20}O$	168	165	26.76	25.79
5	$C_{15}H_{20}O$	216	219	20.83	20.04
6	$C_{15}H_{24}O$	220	221	20.45	19.42
7	$C_{13}H_{24}O$	196	198	15.81	16.36
8	$C_9H_{16}O$	140	138	22.13	21.54

[a] Cryoscopic in benzene. [b] Zeisel method. [c] *Anal.* Calcd. for $C_{10}H_{18}O$: C, 77.92. Found: C, 77.17. (By wet combustion method.)

drolysis was carried out by the careful addition of dilute acetic acid, and the product was neutralized immediately to minimize conversion to the aldehyde. The yield amounted to 100 g. (75% of the theoretical), b. p. 122–123°.

Ethyl orthoformate, treated in a similar manner with phenylmagnesium bromide, gave a 55% yield of benzylidene acetal, b. p. 92–93° at 10 mm.

1,1-Diethoxy-2-heptyne (not previously reported) was obtained analogously, utilizing hexynylmagnesium bromide. The yield was 69%, b. p. 97–98° at 10 mm.; n^{27}_D 1.4320; d^{25}_4 0.8668.

Preparation of 1,2-Dimethoxyethane.—A modification of the reported method[14] was employed, which resulted in increased yields and a purer product.

Seventeen grams (0.75 mole) of metallic sodium was added in small portions to 228 g. (3.0 moles) of ethylene glycol monomethyl ether (Methyl Cellosolve) after which 94.5 g. (0.75 mole) of methyl sulfate was added dropwise, with stirring, during thirty minutes. After heating for an additional fifteen minutes at 85–90° on an oil-bath, the product was distilled through a short Vigreux column. All material boiling below 100° was collected and this fraction redistilled. The amount of product boiling at 82–83° was 54.5 g. (81% yield).

Reaction of Dialkoxyalkanes with Hexynylmagnesium Bromide.—The following represents the general procedure employed for all reactions.

Ethylmagnesium bromide was prepared in the usual manner, using 12 g. (0.50 mole) of magnesium turnings in anhydrous ether, and sufficient ethyl bromide to react with all the metal. To this solution was added dropwise and with stirring 41 g. (0.50 mole) of 1-hexyne, diluted with an equal volume of dry ether. The reaction mixture was allowed to stand for twelve hours, and was then stirred and refluxed vigorously for two hours longer. After allowing to cool, this solution was transferred to a dropping funnel and added slowly to 0.55 mole of the dialkoxyalkane dissolved in 100 cc. of anhydrous ether. The 1-liter, 3-necked flask used for preparation of the Grignard reagent was employed and constant agitation was effected by means of a sealed mechanical stirrer. Throughout the addition the reaction mixture was kept at a temperature sufficiently high, by heating on a water-bath, to distil off the ether at a constant rate. It was found advantageous to add the Grignard reagent through a short, upright water-cooled condenser to prevent evaporation of the ether and solidification in the funnel stem. Stirring was continued for one hour with the water-bath at 95°, after which the semi-solid mixture was hydrolyzed in the cold with dilute hydrochloric acid. The organic layer was dried and distilled under reduced pressure. It was found that merely refluxing the reactants in dry ether with stirring for two to three hours gave lower yields of acetylenic ether than those obtained by removing the ether continuously and heating as described above.

In the reaction involving 1,2-dimethoxyethane, the reaction mixture was heated on a near-boiling water-bath for three hours after the ether had been removed. The remainder of the procedure was the same as that given.

Reaction of Dialkoxyalkanes with Ethynylmagnesium Bromides.—Acetylene dimagnesium bromide was obtained by bubbling acetylene gas, purified by passing through concentrated sulfuric acid and a calcium chloride tower, through a solution of ethylmagnesium bromide in anhydrous ether during the course of eight to ten hours with constant stirring. After refluxing to remove ethane and excess acetylene, the Grignard reagent was added to twice its molal quantity of dialkoxyalkane in the usual manner. In addition to the ethers shown in Table I, 0.50 mole of the reagent, when treated with ethyl orthoformate, gave 69 g. of the diacetal, 1,1,4,4-tetraethoxy-2-butyne, b. p. 107° at 4 mm.; n^{30}_D 1.4315; d^{22}_4 0.9525.

By adding bromobenzene to magnesium turnings in dry ether and simultaneously passing acetylene gas into the solution, as above, with vigorous refluxing, a Grignard reagent was obtained which, by its reactions with acetals proved to be mainly ethynylmonomagnesium bromide.

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[14] Clarke, *J. Chem. Soc.*, **101**, 1802 (1912).

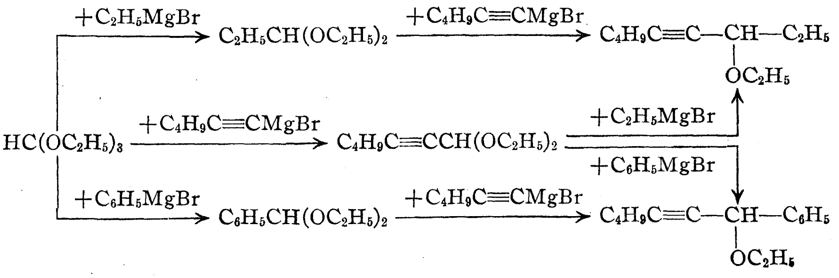
With orthoformic ester, 0.50 mole of the reagent gave 24 g. of the monoacetal, 3,3-diethoxy-1-propyne, b. p. 35° at 10 mm.; $n^{22}D$ 1.4139; $d^{22}{}_4$ 0.8942.

Reaction of 1,1-Diethoxyethane with Sodium Acetylides.—Ninety-six grams (1.0 mole) of 1-heptyne was added slowly to a solution of approximately 1.0 mole of sodamide in liquid ammonia. When most of the ammonia had evaporated, the solid acetylide was suspended in 600 cc. of anhydrous ether. To this solution was added 147 g. (1.25 moles) of ethyl acetal and the mixture refluxed with stirring for two hours. After hydrolysis the organic layer was purified, and distillation yielded 7 g. of 2-ethoxy-3-nonyne, b. p. 108° at 40 mm.

Since liquid ammonia was found to be an excellent solvent for ethyl acetal, the reaction with sodium amyl acetylide was carried out in this medium as well as in *m*-xylene at 120°. In one case the solid acetylide was treated with excess acetal and heated for three hours. In each instance some 2-ethoxy-3-nonyne was obtained, but the yields were quite low. No acetylenic ether could be identified among the reaction products when sodium acetylide was employed in the above media.

Discussion of Results

That the reaction studied in this investigation proceeds through replacement of one alkoxyl group of the acetal or ketal by the acetylenic radical was clearly demonstrated by synthesizing 1-phenyl-1-ethoxy-2-heptyne and 2-ethoxy-3-nonyne by two independent methods, involving the use of different intermediates. Such a mechanism accounts for the formation of identical products when the following reactions were carried out



Each reaction of dialkoxyalkane with hexynylmagnesium bromide was carried out under identical conditions of time, temperature and concentration of reactants, and a very marked variation in the reactivity of the different types of alkoxy compounds was noted. 1,2-Dimethoxyethane, given a longer reaction period, produced only 15% of acetylenic ether. Under the standard conditions, the acetals of formaldehyde yielded 31 to 35% of ether, acetaldehyde and propionaldehyde, 46 to 49%, 2-hexanone, 57%, *n*-butylpropiolaldehyde, 62% and benzaldehyde, 66%.

This method of acetylenic ether synthesis is a very general one, in so far as alkyl ethers of primary, secondary or tertiary acetylenic carbinols may be obtained, depending on whether acetals of formaldehyde, higher aldehydes or ketones are used as starting materials. In addition, the intermediates needed for the secondary and tertiary acetylenic ethers are obtainable directly from acetylene and the alkylacetylenes, thus obviating the use of haloethers or acetylenic carbinols as such.

Summary

Various acetals and ketals have been found to react with alkynylmagnesium bromides to yield ethers of primary, secondary and tertiary acetylenic carbinols and glycols. The latter two types of acetylenic ethers were synthesized from intermediates obtained from acetylene and alkylacetylenes.

Acetals of formaldehyde, higher alkyl aldehydes, ketones and benzaldehyde exhibited a definite increase in reactivity, in the order named, which is explainable electronically.

Sodium acetylides have been shown to react only to a slight extent with acetals in various solvents.

Several new acetylenic ethers have been reported.

A convenient method for the synthesis of 1,2-dimethoxyethane in good yields has been described.

Notre Dame, Indiana Received May 2, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

Some Reactions of Dialkylacetylenes[1]

BY EDWARD A. BRIED AND G. F. HENNION

Introduction

A previous communication[2] in this series reported a rapid preparation of dialkylacetylenes involving the simultaneous interaction of sodium acetylide, sodamide and alkyl halides in liquid ammonia. This work has been extended with three objectives in mind: (1) to study the behavior of higher alkyl halides in the dialkylacetylene synthesis; (2) to study reactions of dialkylacetylenes; and (3) to prepare dialkylacetylene derivatives suitable for rapid identification. Definite results have been obtained only with regard to the first two objectives. A number of noncatalytic addition reactions have been investigated, but in no case have solid derivatives been found suitable for ready identification.

The rapid dialkylacetylene synthesis[2] is limited definitely to the usage of alkyl halides of moderate molecular weight and appreciable solubility in liquid ammonia. Whereas *n*-butyl bromide gave a 70% yield of dibutylacetylene, *n*-amyl bromide gave a 30% yield of diamylacetylene[2] and *n*-hexyl bromide a 38% yield of dihexylacetylene. *n*-Octyl bromide, when treated with sodium acetylide and sodamide in liquid ammonia at atmospheric pressure, gave a 57% yield of octylacetylene and a 15% yield of dioctylacetylene. At 120 lb. per sq. in. (8 atm.) the yield of dioctylacetylene increased to 27%, while the yield of octylacetylene amounted to 15%. Decyl bromide gave decylacetylene and decylamine.

Oxidation of dibutylacetylene with 68% nitric acid in the presence of mercuric nitrate resulted in good yields of *n*-valeric acid. Dibutylacetylene rapidly absorbed hydrogen quantitatively at 55 lb. per sq. in. (3.7 atm.) in the presence of Raney nickel to give *n*-decane. In this connection it seems the hydrogenation of dialkylacetylenes may well serve as a source of pure long chain paraffin hydrocarbons. Addition of bromine to dibutylacetylene yielded a dibromide boiling over a 20° range and therefore likely a mixture of *cis* and *trans* isomers. Hydration of dibutylacetylene, using the method recently reported,[3] gave 5-decanone in excellent yield. Catalytic addition[4] of methanol, ethylene glycol and acetic acid to dibutylacetylene proceeded readily.

Addition of thiocyanogen to diphenylacetylene yielded a crystalline addition compound previously reported by Söderbäck.[5] Treatment of dibutylacetylene under identical conditions failed to give a derivative. Addition of iodine monobromide to dioctylacetylene in ether yielded a brownish-black solid which decomposed upon heating.

Experimental

Reagents.—Octyl alcohol and decyl bromide were kindly supplied for this work by the du Pont Company.

Reaction of Hexyl Bromide with Sodium Acetylide and Sodamide.—Hexyl bromide (124 g., 0.75 mole) was added dropwise to a mixture of 0.69 mole of sodium acetylide and 0.78 mole of sodamide[2] in three liters of liquid ammonia during the course of forty-five minutes. The mixture was evaporated to dryness. Ether (200 ml.) and one liter of crushed ice were added, the organic layer separated and treated in the usual manner. Fractionation *in vacuo* through a 30-cm. Vigreux column yielded 27.5 g. (38% yield) of dihexylacetylene boiling at 132–134° at 21 mm. Redistillation gave a product with the following physical constants: b. p. 124° (15 mm.), 140° (25 mm.), 144° (30 mm.); $n^{25}\text{D}$ 1.4330; d^{25} 0.7991; *MR* (calcd.), 64.85; *MR* (obsd.), 64.5.

Anal. Calcd. for $C_{14}H_{26}$: C, 86.51; H, 13.49. Found: C, 85.66; H, 13.46.

Reaction of Octyl Bromide with Sodium Acetylide and Sodamide.—The same procedure was employed as described above. The yield of dioctylacetylene was 14.2 g. (15% yield). There was a recovery of 59.5 g. (57% yield) of octylacetylene and 5.6 g. of octyl bromide. The addition of 100 ml. of dry ether, when half of the octyl bromide had been introduced, did not increase the yield of dioctylacetylene. Octylacetylene (61.6 g., 59% yield) and dioctylacetylene (7 g., 7% yield) were recovered. Preparation of dioctylacetylene in the autoclave at 120 lb. per sq. in. (8 atm.), using the general method previously described,[2] yielded 25 g. (27% yield) of dioctylacetylene and 15 g. (15% yield) of octylacetylene. Distillation gave dioctylacetylene with the following physical constants: b. p. 163–164° (7 mm.); $n^{25}\text{D}$ 1.4488; d^{25} 0.8022; *MR* (calcd.), 83.32; *MR* (obsd.), 83.71.

Anal. Calcd. for $C_{18}H_{34}$: C, 86.31; H, 13.69. Found: C, 85.76; H, 13.15.

Reaction of Decyl Bromide with Sodium Acetylide and Sodamide.—Two experiments were performed, using 27.6

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[1] Paper XXVIII on the chemistry of the alkylacetylenes and their addition compounds; previous paper, THIS JOURNAL, **60**, 1714 (1938).

[2] Bried and Hennion, *ibid.*, **59**, 1310 (1937).

[3] Thomas, Campbell and Hennion, *ibid.*, **60**, 718 (1938).

[4] Hennion, Nieuwland, *et al.*, *ibid.*, **56**, 1130, 1384, 1802 (1934); **57**, 2006 (1935).

[5] Söderbäck, *Ann.*, **443**, 142 (1925).

g. (0.125 mole) of decyl bromide with 0.075 mole of sodium acetylide and 0.082 mole of sodamide in each case.

An experiment at atmospheric pressure gave 15 g. of a decyl bromide–decylacetylene mixture, b. p. 72° (3 mm.).

An experiment conducted in the autoclave at 120 lb. per sq. in. (8 atm.) gave 12 g. of decylacetylene and 6 g. of decylamine, weighed as the hydrochloride, m. p. 193°, confirming that reported by Komppa.[6]

Oxidation of Dibutylacetylene.—Seventy-nine grams of 68% nitric acid was placed in a 500-ml. three-necked flask equipped with a dropping funnel, mercury-sealed motor-driven stirrer and water condenser. One gram of mercuric nitrate was dissolved in the nitric acid and 34.5 g. (0.25 mole) of dibutylacetylene added dropwise. The reaction was highly exothermic and it was found possible to maintain a temperature of 80° by controlling the rate of addition of the dialkylacetylene. Stirring was continued for one hour. Benzene (100 ml.) was added, the organic layer separated, washed with water, and fractionated through a 50-cm. Vigreux column. The yield of *n*-valeric acid, after the first distillation, was 34.5 g. (68%). Redistillation gave 30 g. (60% yield) of product boiling at 90–91° (19 mm.). The neutralization equivalent was 100 (molecular weight, calcd., 102).

Hydrogenation of Dibutylacetylene.[7]—A catalytic reduction machine similar to the apparatus described by Adams and Voorhees[8] was used. A solution of dibutylacetylene (24.2 g., 0.175 mole) in 100 ml. of methanol with 3 g. of Raney nickel catalyst, prepared according to the method of Covert and Adkins,[9] was shaken in an atmosphere of hydrogen for a period of ninety minutes. The pressure rapidly fell from 55 to 20 lb. per sq. in. (3.7 to 1.3 atm.), corresponding to the absorption of approximately 0.4 mole of hydrogen. The product was washed with 100 ml. of water, the organic layer separated and dried over powdered anhydrous potassium carbonate. Fractionation through a 30-cm. column gave 15.3 g. of product boiling at 62–63° (15 mm.). Successive treatments with concentrated sulfuric acid, water, dilute sodium carbonate and finally with distilled water, followed by distillation, yielded *n*-decane, b. p. 66–67° (17 mm.); $n^{25}\text{D}$ 1.4093; d^{25} 0.7269; *MR* (calcd.), 48.39; *MR* (obsd.), 48.4.

Bromination of Dibutylacetylene.—Bromine (40 g., 0.25 mole) was added dropwise at reflux temperature to a solution of 34.5 g. of dibutylacetylene (0.25 mole) in 200 ml. of dry chloroform. After stirring for one hour, the product was washed successively with water, dilute sodium carbonate, finally with distilled water and dried over calcium chloride. Distillation through a 30-cm. Vigreux column gave a product (50.2 g.) boiling at 113–132° (17 mm.). Repeated fractionation *in vacuo* gave two fractions: (a) b. p. 123–124° (17 mm.); $n^{25}\text{D}$ 1.4975; d^{25} 1.3473; *MR* (calcd.), 63.45; *MR* (obsd.), 64.8; (b) b. p. 127–128° (17 mm.); $n^{25}\text{D}$ 1.5005; d^{25} 1.3749; *MR* (calcd.), 63.45; *MR* (obsd.), 63.8.

Anal. Calcd. for $C_{10}H_{18}Br_2$: Br, 53.67. Found: for fraction (a), Br, 53.91; for fraction (b), Br, 53.94.

Hydration of Dibutylacetylene.—Using the general procedure previously described,[3] dibutylacetylene (69 g., 0.5 mole) was added dropwise to 225 g. of 70% isopropyl alcohol, in the presence of mercury catalyst, at 80°. Distillation through a 30-cm. column gave 62.4 g. (80% yield) of 5-decanone: b. p. 106–108° (27 mm.); $n^{24}\text{D}$ 1.4225; d^{24} 0.8115; *MR* (calcd.), 48.92; *MR* (obsd.), 48.6.

Anal. Calcd. for $C_{10}H_{20}O$: C, 76.84; H, 12.91. Found: C, 76.48; H, 12.77.

It was found impossible to prepare any of the common ketone derivatives from 5-decanone.

Addition of Methanol to Dibutylacetylene.—Dibutylacetylene (34.5 g., 0.25 mole) was added dropwise to 32 g. (1 mole) of anhydrous methanol, containing the usual catalytic mixture of mercuric oxide, boron fluoride, and trichloroacetic acid.[4] The product was isolated in the usual manner. The 5,5-dimethoxydecane was found to decompose slowly on distillation. After one distillation the following constants were obtained: b. p. 98–99° (10 mm.); $n^{25}\text{D}$ 1.4245; d^{25} 0.8549; *MR* (calcd.), 60.91; *MR* (obsd.), 60.4.

The decomposition of the dimethoxy compound was accelerated by distillation with a trace of *p*-toluenesulfonic acid.[10] In this manner 32 g. of 5,5-dimethoxydecane gave 27 g. of 5-methoxy-5-decene: b. p. 94–95° (20 mm.); $n^{25}\text{D}$ 1.4310; d^{25} 0.8212; *MR* (calcd.), 54.18; *MR* (obsd.), 53.6. Analysis indicated that the product was impure.

Anal. Calcd. for $C_{11}H_{22}O$: C, 77.57; H, 13.03; CH_3O, 18.2. Found: C, 75.0; H, 11.8; CH_3O, 12.0.

Addition of Acetic Acid to Dibutylacetylene.—Using the general procedure and catalyst described above, 69 g. (0.5 mole) of dibutylacetylene was added dropwise to 36 g. (0.6 mole) of glacial acetic acid containing 5 g. of acetic anhydride. The product was extracted with 150 ml. of ether and the extract washed successively with water, dilute sodium carbonate, finally with distilled water and dried over calcium chloride. Fractionation gave 59 g. (60% yield) of 5-acetoxy-5-decene boiling at 95–97° (10 mm.). The following physical constants were obtained: $n^{25}\text{D}$ 1.4320; d^{25} 0.8663; *MR* (calcd.), 58.81; *MR* (obsd.), 59.3.

Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.66; H, 11.19. Found: C, 72.04; H, 11.08.

This ester was very resistant both to saponification with alcoholic potassium hydroxide and to hydrolysis with dilute sulfuric acid.

Addition of Ethylene Glycol to Dibutylacetylene.—Dibutylacetylene (69 g., 0.5 mole) was added dropwise to 37.2 g. of ethylene glycol (0.6 mole) according to the general method previously described.[4] The two liquid phases, which originally prevailed, gradually became homogeneous as the reaction progressed. After distillation the fraction boiling at 105–106° (10 mm.) was retained. Redistillation gave 86.5 g. (86% yield) of 2-butyl-2-amyl-1,3-dioxolane: b. p. 103–105° (10 mm.); $n^{25}\text{D}$ 1.4339; d^{25} 0.8862; *MR* (calcd.), 58.71; *MR* (obsd.), 58.8.

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[6] Komppa, *J. prakt. Chem.*, **135**, 193 (1932).

[7] The authors are indebted to Mr. M. J. O'Connor, who is now studying the hydrogenation of acetylenes in this Laboratory, for the use of the hydrogenation equipment.

[8] "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1932, p. 53.

[9] Covert and Adkins, THIS JOURNAL, **54**, 4116 (1932).

[10] Killian, Hennion and Nieuwland, *ibid.*, **57**, 544 (1935).

Anal. Calcd. for $C_{12}H_{24}O_2$: C, 71.93; H, 12.08. Found: C, 71.98; H, 12.04.

Hydrolysis with a small quantity of sulfuric acid gave 5-decanone, b. p. 106–107° (27 mm.); $n^{25}D$ 1.4225.

Reaction of Thiocyanogen and Iodine Monobromide with Dialkylacetylenes.—A benzene solution of thiocyanogen was prepared according to the method of Söderbäck.[5] To one-half of this solution was added 1.3 g. of diphenylacetylene in 25 ml. of dry benzene, while to the other was added a comparable quantity of dibutylacetylene. The two solutions were placed in the dark for twenty hours. The diphenylacetylene deposited a crystalline product melting at 192–193°, as previously reported by Söderbäck.[5] Dibutylacetylene failed to give a derivative.

Dioctylacetylene (2 g.) was added to an ether solution of iodine monobromide (4 g.). After twenty-four hours at room temperature a brownish-black solid was obtained which decomposed upon heating.

Acknowledgment.—The authors acknowledge the kind assistance of Messrs. H. I. Lipsie and C. J. Kelley in a number of experiments.

Summary

1. The action of hexyl bromide, octyl bromide and decyl bromide on mixtures of sodium acetylide, and sodamide in liquid ammonia is described.

2. Oxidation, hydrogenation, bromination, hydration and the addition of methanol, acetic acid and glycol to dibutylacetylene are described.

3. No solid addition compound of dialkylacetylenes, suitable for identification purposes, has been found to date.

NOTRE DAME, INDIANA RECEIVED MAY 4, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF KWANGSI, CHINA]

Pyrimidine Research: The Molecular Rearrangement of 4-Methyl-5-*n*-butyl-2,6-dimethoxypyrimidine[1]

BY YUOH FONG CHI, CHI WEI AND NAW SHAUNG PAN

It has long been known that lactim ethers of configuration I will undergo rearrangement to their isomeric and stable lactam form II. These transformations are irreversible and can be brought about by the application of heat with or without the presence of special catalytic agents, and have been observed to take place in both acyclic and cyclic compounds.

$$\underset{\text{I}}{\overset{|}{N}=\overset{|}{C}-OCH_3} \qquad \underset{\text{II}}{CH_3\overset{|}{N}-\overset{|}{C}=O}$$

This interesting rearrangement recently has been illustrated by Hilbert and Johnson[2] in the pyrimidine series. They showed that 2,6-dialkoxypyrimidines and 2-oxy-3-alkyl-6-alkoxypyrimidines easily undergo rearrangement on heating without catalytic reagents, at an elevated temperature to form the corresponding 1,3-dialkyl-uracils. Nevertheless, 2,6-dialkoxypyrimidine, containing two lactim configurations within the same pyrimidine molecule, will only undergo partial rearrangement by treatment with methyl iodide at a much lower temperature to form 2-oxy-3-alkyl-6-alkoxypyrimidines.

In this paper, the authors have extended this study and describe the conditions under which 4-methyl-5-*n*-butyl-2,6-dimethoxypyrimidine III, rearranges to (a) 1,3,4-trimethyl-5-*n*-butyl-uracil IV, and (b) 2-oxy-3,4-dimethyl-5-*n*-butyl-6-methoxypyrimidine V. Thus far, it has been found that the 2,6-dimethoxypyrimidine III easily undergoes transformation into its isomeric and stable lactam configuration, 1,3,4-trimethyl-5-*n*-butyl-uracil IV, by merely heating at 250–270° for three hours. On the other hand, it was only transformed into 2-oxy-3,4-dimethyl-5-*n*-butyl-6-methoxypyrimidine V, under the catalytic influence of methyl iodide at 50 or at 100°. Such partially rearranged pyrimidines like 2-oxy-3,4-dimethyl-5-*n*-butyl-6-methoxypyrimidine V, were only stable, however, at this lower temperature, and undergo further transformation into the isomeric and completely rearranged modification IV by heating. These respective changes are expressed by the formulas.

1,3,4-Trimethyl-5-*n*-butyl-uracil, IV, was identical with the pyrimidine prepared by methylation of 4-methyl-5-*n*-butyluracil. 2-Oxy-3,4-dimethyl-5-*n*-butyl-6-methoxypyrimidine very easily underwent hydrolysis by treatment with dilute hydrochloric acid yielding 3,4-dimethyl-5-*n*-butyl-uracil. The dimethoxypyrimidine III required for this research was synthesized by the action of

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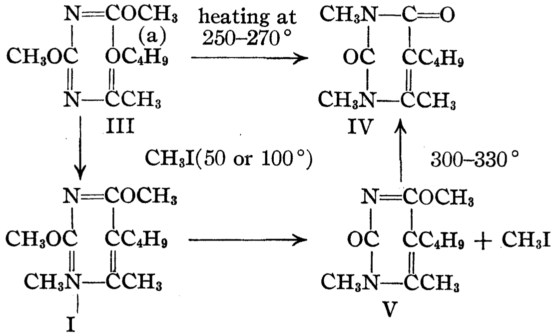
[1] This paper was constructed from a dissertation presented by C. Wei and N. S. Pan to the Faculty of Chemistry at the University of Kwangsi in partial fulfilment of the requirements for the degree of B. Sci. in June, 1937. The authors especially desire to acknowledge the personal assistance of Professor Treat B. Johnson of Yale University in the preparation of the paper for publication.

[2] Hilbert and Johnson, THIS JOURNAL, **52**, 2001 (1930).



(a) C_4H_9 = *n*-butyl

sodium methylate upon 4-methyl-5-*n*-butyl-2,6-dichloropyrimidine, which was obtained by treating its corresponding uracil precursor previously described by Chi,[3] with a mixture of phosphorus oxychloride and phosphorus pentachloride.

Experimental Part

4-Methyl-5-*n*-butyl-2,6-dichloropyrimidine.—One hundred and ten grams of 4-methyl-5-*n*-butyluracil was dissolved in a cold mixture of 500 cc. phosphorus oxychloride and 50 g. of phosphorus pentachloride. This was then heated in an oil-bath at 120° until hydrogen chloride gas ceased to be evolved. This required about ten hours. The excess of phosphorus oxychloride was distilled off under diminished pressure at water-bath temperature, when there was left behind a dark brown, resinous residue. In order to decompose any phosphorus compounds, this product was cooled by an ice–salt mixture, and then treated with cracked ice. Care must be taken to add a very small piece of ice at each time and to observe that the temperature does not rise above 20°. This precaution must be observed in order to avoid hydrolysis of the dichloro compound to the corresponding uracil derivative. After this treatment, the mixture was extracted with ether, the ethereal solution washed with water and dried over calcium chloride. After distilling off the solvent there was left an oil which was distilled under diminished pressure whereupon we obtained the pure dichloropyrimidine boiling at 171° at 23 mm. pressure. The yield was 106 g. or 80% of the theoretical.

Anal. Calcd. for $C_9H_{12}N_2Cl_2$: N, 12.79. Found: N, 12.87, 12.84.

4-Methyl-5-*n*-butyl-2,6-dimethoxypyrimidine.—Four and six-tenths grams of sodium was dissolved in 50 cc. of absolute methyl alcohol. To this cold alcoholic solution of sodium methylate 21.9 g. of 4-methyl-5-*n*-butyl-2,6-dichloropyrimidine dissolved in 50 cc. of absolute methyl alcohol was added slowly. There separated immediately solid sodium chloride. After allowing to stand for one hour to complete the reaction, the sodium chloride was filtered off and washed thoroughly with methyl alcohol. The excess of alcohol was then removed by heating when we obtained an oil. This was shaken with 30 cc. of 30% sodium hydroxide solution, in which the required pyrimidine-2,6-dimethyl ether is insoluble and separated as the upper layer of the solution and was extracted with ether. 4-Methyl-5-*n*-butyl-2,6-dimethoxypyrimidine distilled as a colorless oil, boiling at 159° at 29 mm. The yield was 20 g. or 95% of the theoretical.

Anal. Calcd. for $C_{11}H_{18}O_2N_2$: N, 13.33. Found: N, 13.28, 13.21.

Further alkoxypyrimidines of this type that we prepared according to this procedure are recorded in Table I.

TABLE I

DIALKOXYPYRIMIDINES

4-Methyl-5-*n*-butyl-2,6-	B. p., °C.	Yield, %	Formula	Analyses, % N Calcd.	Found	
Diethoxy-pyrimidine	174 at 27 mm.	87.6	$C_{13}H_{22}O_2N_2$	11.76	11.80	11.82
Di-*n*-propoxy-pyrimidine	193–4 at 23 mm.	98.8	$C_{15}H_{26}O_2N_2$	10.52	10.56	10.74
Di-*n*-butoxy-pyrimidine	219 at 29 mm.	86.5	$C_{17}H_{30}O_2N_2$	9.52	9.71	9.60
Dialloxy-pyrimidine	192–3 at 31 mm.	96.0	$C_{15}H_{22}O_2N_2$	10.68	10.74	10.53

The Molecular Rearrangement of 4-Methyl-5-*n*-butyl-2,6-dimethoxypyrimidine, III. A. Rearrangement to 1,3,4-Trimethyl-5-*n*-butyluracil, IV.—Five grams of the pyrimidine III was heated in an oil-bath at 250–270° for three hours. At first there was a vigorous ebullition which gradually subsided and finally ceased as the proportion of the rearranged compound increased. On cooling, the pale brown reaction product completely solidified. This was purified by dissolving in hot benzene, to which petroleum ether was gradually added to turbidity. After cooling a solid amorphous mass separated. After filtering, this reaction product was dissolved in dry benzene, and then petroleum ether added just to turbidity. On cooling, more amorphous material separated. The clear combined filtrates were then heated at 100° to expel the solvents when an oil was obtained which solidified on cooling. It was purified by recrystallization from a benzene–petroleum ether mixture (1:40), whereupon a compound melting at 54–55° separated in colorless needles.

Anal. Calcd. for $C_{11}H_{18}O_2N_2$: N, 13.33. Found: N, 13.8.

This compound, melting at 54–55°, proved to be identical with 1,3,4-trimethyl-5-*n*-butyluracil, IV, which has not been described previously in the literature. It was prepared as follows.

Synthesis of 1,3,4-Trimethyl-5-*n*-butyluracil, IV.—Five grams of 4-methyl-5-*n*-butyluracil was dissolved in 150 cc. of a sodium hydroxide solution containing 2.6 g. of sodium hydroxide. To this cold solution, 6.9 g. of dimethyl sulfate was then added slowly from a dropping funnel, and during its addition the fluid was stirred vigorously. It was then heated to boiling for one hour. After cooling, the product was extracted with benzene and the solution dried over calcium chloride. After distilling off the benzene we obtained an oil which solidified on cooling. It was purified by crystallization from a mixture of benzene and petroleum ether, from which pure 1,3,4-trimethyl-5-*n*-butyluracil separated. It melted at 54–55° and its melting point was not depressed on mixing with 1,3,4-trimethyl-5-*n*-butyluracil described in the preceding experiment.

Anal. Calcd. for $C_{11}H_{18}O_2N_2$: N, 13.33. Found: N, 12.86, 13.17.

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[3] Chi, THIS JOURNAL, 58, 1151 (1936).

Rearrangement of 4-Methyl-5-*n*-butyl-2,6-dimethoxypyrimidine, III, to 2-Oxy-3,4-dimethyl-5-*n*-butyl-6-methoxypyrimidine, V. Method A.—Five grams of 4-methyl-5-*n*-butyl-2,6-dimethoxypyrimidine, III, was mixed with 14.2 g. of freshly distilled methyl iodide and the solution was heated in a sealed tube at 100° for six hours. The excess of methyl iodide was removed by a blast of air and the residue distilled under a vacuum. Pure 2-oxy-3,4-dimethyl-5-*n*-butyl-6-methoxypyrimidine boiled at 235–236° at 31 mm. pressure with slight decomposition and at 183–184° at 1 mm. pressure without decomposition. This compound is a light yellow and very viscous oil which showed no signs of solidifying.

Anal. Calcd. for $C_{11}H_{18}O_2N_2$: N, 13.33. Found: N, 13.48.

Method B.—Five grams of 4-methyl-5-*n*-butyl-2,6-dimethoxypyrimidine was heated with 14.2 g. of freshly distilled methyl iodide in a sealed tube at 50° for ten hours; from which the partially rearranged pyrimidine 2-oxy-3,4-dimethyl-5-*n*-butyl-6-methoxypyrimidine was isolated as described above. It boiled at 183–184° at 1 mm. pressure.

Anal. Calcd. for $C_{11}H_{18}O_2N_2$: N, 13.33. Found: N, 13.22.

The structure of this compound was established by its behavior on hydrolysis.

Hydrolysis to 3,4-Dimethyl-5-*n*-butyluracil.—2-Oxy-3,4-dimethyl-5-*n*-butyl-6-methoxypyrimidine was heated with dilute hydrochloric acid for one hour. The solution was then evaporated to dryness on a water-bath. The residue dissolved in hot water, whereupon 3,4-dimethyl-5-*n*-butyluracil crystallized on cooling in long needles melting at 151–152°.

Anal. Calcd. for $C_{10}H_{16}O_2N_2$: N, 14.28. Found: N, 14.21, 14.75.

In another experiment, 4-methyl-5-*n*-butyl-2,6-dimethoxypyrimidine was exposed to freshly distilled methyl iodide in the presence of methyl alcohol at room temperature for two weeks, from which a trace of 3,4-dimethyl-5-*n*-butyluracil was isolated. Probably it was produced due to the secondary hydrolytic effect of methyl alcohol upon the partially rearranged product, 2-oxy-3,4-dimethyl-5-*n*-butyl-6-methoxypyrimidine, first formed in the reaction.

Method C. Rearrangement of the Pyrimidine V into the Uracil Compound IV.—2-Oxy-3,4-dimethyl-5-*n*-butyl-6-methoxypyrimidine, V, was heated at 300–360° for three to four hours. The above reaction mixture was dissolved in benzene, to which a large volume of petroleum ether was then added. After cooling, the benzene–petroleum ether solution was decanted from the insoluble portion. The solvent being removed from the benzene–petroleum ether solution, there remained an oil which solidified on cooling. It was recrystallized from benzene–petroleum ether and melted at 54–55°. This proved to be identical with 1,3,4-trimethyl-5-*n*-butyluracil, IV, obtained by heating 4-methyl-5-*n*-butyl-2,6-dimethoxypyrimidine, III.

Summary

1. 4-Methyl-5-*n*-butyl-2,6-dichloropyrimidine has been prepared by the action of phosphorus oxychloride and phosphorus pentachloride upon its corresponding uracil compound.

2. 4-Methyl-5-*n*-butyl-2,6-dialkoxypyrimidines are formed smoothly by interaction of 4-methyl-5-*n*-butyl-2,6-dichloropyrimidine with sodium alcoholates.

3. 4-Methyl-5-*n*-butyl-2,6-dimethoxypyrimidine and 2-oxy-3,4-dimethyl-5-*n*-butyl-6-methoxypyrimidine are found to undergo a transformation into their isomeric and stable lactam modification, 1,3,4-trimethyl-5-*n*-butyluracil, on heating at an elevated temperature. On the other hand, 4-methyl-5-*n*-butyl-2,6-dimethoxypyrimidine will rearrange only partially on heating with methyl iodide at 50 or 100° giving 2-oxy-3,4-dimethyl-5-*n*-butyl-6-methoxypyrimidine.

KWANGSI, CHINA RECEIVED APRIL 7, 1938

[CONTRIBUTION FROM NATIONAL RESEARCH INSTITUTE OF CHEMISTRY, ACADEMIA SINICA, CHINA]

Pyrimidine Research. Synthesis of 4-Methyl-5-*n*-propylcytosine[1]

BY YUOH FONG CHI AND KOU-JEN CHANG

In this short paper is described a method for synthesizing 4-methyl-5-*n*-propylcytosine III. Starting with 2-thio-4-methyl-5-*n*-propyl-6-oxypyrimidine, which is prepared by condensing ethyl *n*-propylacetoacetate with thiourea, the corresponding 2-ethylmercapto compound I is obtained by alkylation in the usual manner, and the resulting mercapto derivative is then treated with phosphorus oxychloride to give 2-ethylmercapto-4-methyl-5-*n*-propyl-6-chloropyrimidine. This new chloropyrimidine derivative reacts with alcoholic ammonia in a normal manner giving the corresponding 6-amino compound II. On digesting the latter with concentrated hydrobromic acid 4-methyl-5-*n*-propylcytosine hydrobromide is formed. The free cytosine base III is liberated by treatment with a slight excess of ammonia.

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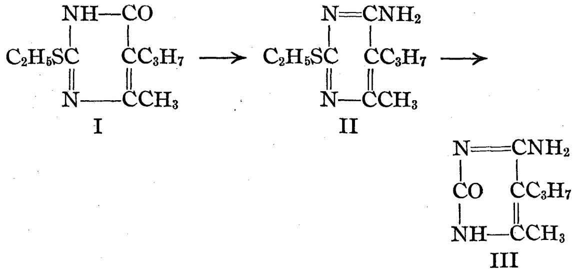
[1] The authors wish to express their thanks to Mr. Yao-Tseng Huang for his assistance in making micro-analyses of the compounds described in this paper. They are also indebted to Professor Treat B. Johnson of Yale University for his personal help in the preparation of this report for publication.



Experimental Part

2-Thio-4-methyl-5-*n*-propyl-6-oxypyrimidine.—Twenty-three grams of metallic sodium was dissolved in 400 cc. of absolute alcohol. One hundred and seventy-two grams of ethyl *n*-propylacetoacetate and 84 g. of thiourea were then added to the solution. The mixture was heated on a water-bath for four hours. After distilling off the solvent the residue remaining behind was dissolved in cold water. This was acidified with dilute acetic acid, when the desired thiopyrimidine separated. After being recrystallized from boiling water, it separated in needles and melted at 209–209.5°. The yield was 103 g. For analysis, the compound was dried over phosphorus pentoxide in a vacuum at 80°.

Anal. Calcd. for $C_8H_{12}ON_2S$: N, 15.21. Found: N, 15.5, 15.5.

2-Methylmercapto-4-methyl-5-*n*-propyl-6-oxypyrimidine.—Twenty-three hundredths gram of sodium was dissolved in 20 cc. of absolute alcohol. To this solution, 1.84 g. of the above thiopyrimidine and 1.55 g. of methyl iodide were added and the mixture heated on a water-bath for four hours. On cooling, the methylmercapto compound separated in needles. It was recrystallized from absolute alcohol and melted at 180–181° to a clear oil. The yield was 1.2 g. The substance was dried over phosphorus pentoxide in a vacuum at 80°.

Anal. Calcd. for $C_9H_{14}ON_2S$: N, 14.14. Found: N, 14.5, 14.1.

2-Ethylmercapto-4-methyl-5-*n*-propyl-6-oxypryrimidine I.—One hundred and fifteen grams of sodium was dissolved in 1 liter of absolute alcohol and 92 g. of the thiopyrimidine and 60 g. of ethyl bromide were added to the solution. The mixture was heated on a water-bath for four hours and the solution then filtered from the insoluble sodium chloride. After distilling off the excess of alcohol the residue was triturated with cold water and filtered. The pyrimidine was recrystallized from dilute alcohol, and melted at 92–93°. The yield was 87.5 g. The substance was dried for analysis over phosphorus pentoxide in a vacuum at 80°.

Anal. Calcd. for $C_{10}H_{16}ON_2S$: C, 56.55; H, 7.60. Found: C, 56.55; H, 7.68.

2-*n*-Propylmercapto-4-methyl-5-*n*-propyl-6-oxypyrimidine.—Twenty-three hundredths gram of sodium was dissolved in 20 cc. of absolute alcohol, to which 1.84 g. of thiopyrimidine and 1.55 g. of *n*-propyl bromide were then added. The experiment was carried out as described above, whereby the *n*-propylmercaptopyrimidine was obtained melting at 89–90°. It was recrystallized from dilute alcohol and separated in needles. The substance was dried over phosphorus pentoxide in a vacuum at 80°.

Anal. Calcd. for $C_{11}H_{18}ON_2S$: N, 12.39. Found: N, 12.6, 12.2.

$\overline{NHCONHC(CH_3)=C(C_3H_7)CO}$, **4-Methyl-5-*n*-propyluracil.**—This pyrimidine is formed quantitatively by digesting any one of the preceding mercaptopyrimidines with hydrobromic or hydrochloric acid. It is also easily prepared by digesting the corresponding 2-thiopyrimidine described above with chloroacetic acid in aqueous solution. The uracil derivative crystallizes from hot water in the form of needles melting at 247–248°.

Anal. Calcd. for $C_8H_{12}O_2N_2$: C, 57.10; H, 7.20. Found: C, 57.36, 57.04; H, 7.17, 7.26.

Ethyl 4-Methyl-5-*n*-propyl-6-oxypyrimidine-2-thioglycolate was obtained easily by alkylation of the above 2-thiouracil derivative in alcohol solution with ethyl chloroacetate. It was purified by crystallization from dilute alcohol and melted at 100–101°.

Anal. Calcd. for $C_{12}H_{18}O_3N_2S$: C, 53.29; H, 6.71. Found: C, 53.40; H, 7.04.

4-Methyl-5-*n*-propyl-6-oxypyrimidine-2-thioglycolic Acid was prepared by saponification of the above ethyl ester with alcoholic potash solution. The acid crystallized from hot water as plates melting at 105–106°. The compound contained water of crystallization.

Anal. Calcd. for $C_{10}H_{14}O_3N_2S$: N, 11.57; H_2O, 6.92. Found: N, 11.4, 11.45; H_2O, 6.74.

2-Ethylmercapto-4-methyl-5-*n*-propyl-6-chloropyrimidine.—Twenty-one and two-tenths grams of 2-ethylmercapto-4-methyl-5-*n*-propyl-6-oxypyrimidine was dissolved in cold phosphorus oxychloride. The solution was heated for twelve hours at 120–130°. After the excess of phosphorus oxychloride was removed, the residue was then treated with cracked ice, the solution extracted with ether and the ether solution dried over calcium chloride. After distilling off the ether the pyrimidine chloride distilled at 165–166° at 11 mm. pressure.

Anal. Calcd. for $C_{10}H_{15}N_2SCl$: C, 52.02; H, 6.56. Found: C, 52.26; H, 6.47.

2-Ethylmercapto-4-methyl-5-*n*-propyl-6-aminopyrimidine II.—Six grams of the above 6-chloropyrimidine was heated with alcoholic ammonia at 160–170° for three hours. The solution was evaporated to dryness and the residue triturated with cold water. The crude pyrimidine dissolved in petroleum ether, from which the 6-amino compound separated in needles, melting at 86–87°.

Anal. Calcd. for $C_{10}H_{17}N_3S$: N, 19.90. Found: N, 20.01, 19.9.

4-Methyl-5-*n*-propylcytosine, III.—The above 6-aminopyrimidine was digested with concentrated hydrobromic acid for sixteen hours, and the solution then evaporated to dryness. After dissolving the residue in boiling water and cooling, the hydrobromide of 4-methyl-5-*n*-propylcytosine separated in prisms. It melted at 253–254°. The salt was dried over phosphorus pentoxide in a vacuum at 80°.

Anal. Calcd. for $C_8H_{13}ON_3 \cdot HBr$: C, 38.70; H, 5.69. Found: C, 38.90; H, 5.79.

The free base was obtained by treating the aqueous solution of the above hydrobromide with ammonia. It was recrystallized from water and melted at 317–318° with decomposition. The substance was dried over phosphorus pentoxide in a vacuum at 80°.

Anal. Calcd. for $C_8H_{13}ON_3$: C, 57.44; H, 7.84. Found: C, 57.81; H, 7.92.

Hydrochloride.—The above cytosine derivative dissolved in dilute hydrochloric acid, and on cooling the hydrochloride separated in prisms, melting at 235°.

Anal. Calcd. for $C_8H_{13}ON_3 \cdot HCl$: C, 47.15; H, 6.93. Found: C, 46.78; H, 6.65.

Summary

1. Ethyl *n*-propylacetoacetate condenses with thiourea in alcohol solution in the presence of sodium ethylate to give 2-thio-4-methyl-5-*n*-propyl-6-oxypyrimidine.
2. 2-Thio-4-methyl-5-*n*-propyl-6-oxypyrimidine is alkylated on sulfur by treatment with methyl iodide, ethyl bromide, *n*-propyl bromide and ethyl monochloroacetate to form the corresponding 2-mercaptopyrimidine derivatives, respectively.
3. 2-Ethylmercapto-4-methyl-5-*n*-propyl-6-chloropyrimidine is obtained from its corresponding 6-oxypyrimidine compound by heating the latter with phosphorus oxychloride.
4. This chloropyrimidine interacts with alcoholic ammonia to form 2-ethylmercapto-4-methyl-5-*n*-propyl-6-aminopyrimidine.
5. Treatment with concentrated hydrobromic acid converts 2-ethylmercapto-4-methyl-5-*n*-propyl-6-aminopyrimidine into 4-methyl-5-*n*-propylcytosine hydrobromide, from which the free base is obtained by neutralization with ammonia.

KWANGSI, CHINA RECEIVED APRIL 7, 1938

[CONTRIBUTION FROM THE NATIONAL RESEARCH INSTITUTE OF CHEMISTRY, ACADEMIA SINICA]

The Alkaloids of Chinese Gelsemium, Kou Wen[1]

BY YUOH FONG CHI, YEE-SHENG KAO AND YAO-TSENG HUANG

Chou[2] has isolated the following alkaloids from the plant Kou Wen: (A) koumine $C_{20}H_{22}N_2O$, m. p. 170°, (B) kouminine, (C) kouminicine and (D) kouminidine. Of these four alkaloids, koumine only was obtained in a good crystalline state and kouminidine was probably not very pure on account of small traces of impurity present, while kouminine and kouminicine were only obtained in an amorphous condition. Recently, Chou[3] isolated the following alkaloids from Ta-Cha-Yeh: (Z) koumine $C_{20}H_{22}N_2O$, m. p. 170°; (B) kouminine in the form of its hydrochloride; (C) gelsemine, $C_{20}H_{22}N_2O_2$, m. p. 178°; and kounidine $C_{21}H_{24}N_2O_5$. In this short paper the authors give a report of their investigation of the alkaloids of Kou Wen. Besides koumine, m. p. 168°, they succeeded in separating Chou's kouminine into gelsemine and other impure bases. From the kouminidine fraction, they isolated a base, m. p. 299° (instead of 200°), to which the original name, kouminidine, was assigned.

Experimental Part

Twenty-two and seven-tenths kilograms of Kou Wen in the form of stems, roots and leaves was powdered and percolated with cold 95% alcohol. The alcoholic extract was evaporated under diminished pressure, and the resin left over was taken up with a sufficient quantity of 2% hydrochloric acid. When the insoluble resinous matter was filtered off the acid extract was allowed to stand for about two weeks, when there deposited a further quantity of neutral resinous material. The clear solution, obtained after removing the insoluble non-basic resinous matter, was finally neutralized with sodium carbonate and extracted thoroughly, first with ether several times (A), and then with chloroform (B).

Isolation of Koumine.—After removing the solvent from the ethereal solution (A), the crude basic residue weighed 38 g. This was dissolved in a small quantity of acetone, and the solution allowed to stand in an ice-box for several days; whereupon koumine deposited in the form of colorless prisms. This was recrystallized from acetone several times or until the melting point became constant at 168°. It was readily soluble in alcohol, chloroform and benzene and slightly soluble in hot water.

Anal. Calcd. for $C_{20}H_{22}N_2O$: C, 78.38, H, 7.24; N, 9.15. Found: C, 78.52, 78.37; H, 7.31, 7.39; N, 9.37, 9.35.

Acetylation of Koumine.—When Koumine was treated with acetic anhydride, the original alkaloid melting at 168° was recovered.

Isolation of Gelsemine.—The acetone mother liquid, from which the base, koumine, had been separated, was evaporated to dryness. The residue was dissolved in ethyl alcohol and acidified with the desired amount of alcoholic hydrochloric acid. The solution was then allowed to stand for several days, whereupon the mixed hydrochlorides separated in the form of a crystalline pow-

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[1] The authors desire to express their thanks to Professor Treat B. Johnson of Yale University for his personal help in arranging this report for publication in THIS JOURNAL.

[2] Chou, *Chinese J. Physiol.*, **5**, 345–352 (1931).

[3] Chou, *ibid.*, **10**, 79–84 (1936).

TABLE I

PROPERTIES OF KOUMINE DERIVATIVES

Compound	Cryst. from	Crystal form	M. p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found		Hydrogen, % Calcd.	Hydrogen, % Found		Nitrogen, % Calcd.	Nitrogen, % Found
Hydrochloride	Alc.–ether	Cubes	258	$C_{20}H_{22}N_2O \cdot HCl$	70.04	69.40	69.43	6.77	7.20	6.97		
Hydrobromide	Alc.–ether	Cubes	268–269	$C_{20}H_{22}N_2O \cdot HBr$	62.00	62.56	62.22	5.99	6.29	6.03		
Sulfate			261–262									
Nitrate	Alcohol		249–250	$C_{20}H_{22}N_2O \cdot HNO_3$	65.00	65.56		6.28	6.19		11.38	10.62
Platinichloride	Dil. HCl	Brown ppt.	>310									
				$C_{20}H_{22}N_2O \cdot CH_3I$	56.23			5.62				
Methiodide	Dil. acetone	Needles,	230 dec.			54.21	54.24		5.79	5.92		
				$C_{20}H_{22}N_2O \cdot CH_3I \cdot H_2O$	54.06			5.84				

der. They were repeatedly purified by recrystallization from ethyl alcohol, and melted at 303°.

The free base was liberated from an aqueous solution of the crystallized mixed hydrochlorides by adding sodium carbonate just to neutrality. The resulting amorphous base was then filtered off and dried in a vacuum desiccator. It was soluble in most of the common organic solvents with the exception of petroleum ether and water, and refused to crystallize from any of the common solvents tried. This amorphous base, melting approximately at 108°, was extracted with hot benzine (b. p. 80–90°), and after filtering off the insoluble part and cooling, the benzine solution deposited a colorless amorphous solid. This amorphous base was then digested with petroleum ether (b. p. 40–60°) for twenty-four hours, whereupon the base gradually changed into a crystalline condition. It was then filtered and the base purified further by recrystallization from acetone. It separated in the form of long shining needles, melting at 176–178°. It contained acetone of crystallization. When 0.0735 g. of the substance was dried in a vacuum over phosphorus pentoxide at 117°, it was found that the weight lost was equal to 0.0111 g., where from the percentage of acetone of crystallization was 15.1, the calculated value for $C_{20}H_{22}O_2N_2 \cdot CH_3COCH_3$ being 15.27. A sample dried at room temperature was used for analysis.

Anal. Calcd. for $C_{20}H_{22}O_2N \cdot CH_3COCH_3$: C, 72.58; H, 7.42; N, 7.37. Found: C, 73.41, 73.10; H, 7.52, 7.67; N, 7.56.

Color Test.—A few crystals of the base were dissolved in a small quantity of concentrated sulfuric acid, to which a few crystals of potassium dichromate were then added. The solution first became violet, and then turned to a red color. On standing it changed to green.

Nitrate.—The pure base was dissolved in dilute nitric acid, and the solution evaporated to dryness in a vacuum desiccator. The residue was then recrystallized from ethyl alcohol and melted at 288°.

Anal. Calcd. for $C_{20}H_{22}O_2N_2 \cdot HNO_3$: C, 62.31; H, 6.02; N, 10.91. Found: C, 62.17, 62.70; H, 6.28, 6.17; N, 10.42.

Methiodide.—The pure base dissolved in warm acetone, to which an excess of methyl iodide was then added and the mixture heated for about one to two hours. The methiodide separated on cooling in colorless shining scales and melted at 284°.

Anal. Calcd. for $C_{20}H_{22}O_2N_2 \cdot CH_3I$: C, 54.29; H, 5.43. Found: C, 54.17, 53.91; H, 5.46, 5.59.

The alcoholic mother liquid, from which the crude gelsemine hydrochloride had been separated, was evaporated to dryness, and the residue dissolved in 1% hydrochloric acid. This acid solution was repeatedly washed with chloroform, and then made alkaline with sodium carbonate. The resulting solution was first extracted with ether to remove koumine and gelsemine, and then extracted with chloroform. When the solvent was distilled off an amorphous basic product was obtained and nothing crystalline could be isolated.

Isolation of Kouminidine.—The chloroform extract (B) was evaporated to dryness, and the crude base left over weighed 22 g. It dissolved in warm acetone, from which a small quantity of a neutral substance, melting at 62–64°, separated. The mother liquid was concentrated and allowed to stand for several days, whereupon a small quantity of a basic substance separated. This was then purified by recrystallization from a methyl alcohol–ethyl ether mixture and separated in colorless prisms, melting at 299° with decomposition. It was soluble in water and most organic solvents.

Anal. Calcd. for $C_{19}H_{25}N_2O_4$: C, 66.04; H, 7.30; N, 8.12. Found: C, 66.88, 66.42; H, 7.18, 7.29; N, 8.20.

Summary

1. The authors have repeated the work of Chou and have isolated from Kou Wen the alkaloid koumine, $C_{20}H_{22}N_2O$.

2. The alkaloid kouminine obtained from Kou Wen by Chou has been separated by the authors into gelsemine, $C_{20}H_{22}N_2O_2$, and other impure bases.

3. Gelsemine is also found in the plant Ta-Cha-Yeh.

WUCHOW, KWANGSI, CHINA

RECEIVED APRIL 7, 1938

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. XL. The Origin and Interrelationships of the Steroidal Hormones

BY RUSSELL E. MARKER

In the thirty-nine papers which have been reported from this Laboratory, we have described the progress made in our investigations of the steroid content of urines. Heretofore, our results have not been discussed from the broader standpoint of the origin and interrelationships of the steroidal hormones, but now sufficient information is at hand to make such a correlation desirable.

The isolation and synthesis of sex hormones, and more recent work on the isolation of steroids from the adrenal cortex, have led biochemists to the increasing realization of the important role played by steroids in the animal. It appears to be generally assumed that these various steroids arise from cholesterol.[1] This hypothesis has many more or less obvious difficulties. It is hard to understand how oxygen atoms such as occur at C-11 in cortical derivatives, or at C-12 in bile acids, could be introduced into the cholesterol molecule. Attempts to show that cholesterol may be converted by biochemical methods into sex hormones have been inconclusive.[2] Moreover, the assumption that sex hormones are derived from cholesterol through the intermediate formation of Δ^5-pregnenol-3β-one-20 and dehydroisoandrosterone leads to contradictions when the relative physiological activities of the hormones are considered. Thus it is not apparent, if progesterone is derived from Δ^5-pregnenol-3β-one-20, why the latter should show no progestational activity. The inactivity of this unsaturated hydroxy ketone suggests that it is a product of the utilization of progesterone and not a precursor. Moreover, the drastic conditions which must be employed in the laboratory to oxidize the cholesterol side chain to yield carbonyl and acetyl groups at C-17, and the fact that phytosterols are not utilized in the animal organism,[1] throw grave doubt on the possibility of a biochemical oxidation of the cholesterol side chain. Although Shimizu[3] has suggested that the isolation of trihydroxybufosterocholenic acid indicates a genetic relationship between sterols and bile acids, experiments by Schoenheimer and co-workers[4] on the deuterium content of bile acids of dogs injected with an emulsion of coprostanone-4,5d_2 show that the conversion of cholesterol to bile acids is extremely unlikely.

In the course of comprehensive studies in this Laboratory of the numerous steroids present in urine from various animals, a number of substances have been isolated which, we believe, cannot be accounted for satisfactorily on the assumption of an oxidative degradation of cholesterol in the animal. It now appears that sex hormones and the cortical substances may be derived from another precursor.

Before considering the nature of this precursor it seems desirable to attempt a correlation between the various urinary steroids that have been isolated. The isolation from urines of numerous reduction products of progesterone such as pregnanediol-3α,20α,[5,6] *allo*-pregnanediol-3α,20α,[6,7] *allo*-pregnanol-3α-one-20,[8] pregnanol-3α-one-20,[9] *allo*-pregnanedione.[10] pregnenediol-3β,20-α,[11] pregnanetriol-3α,4-β,20α,[12] pregnanedione,[10] *allo*-pregnanol-3β-one-20,[10] and *allo*-pregnanediol-3β-20α,[11] suggests that these are all formed by the biochemical reduction of progesterone, possibly according to the scheme of Fig. 1.

According to this hypothesis, most of the substances isolated are formed from progesterone either by initial reduction of the $\Delta^{4,5}$-double bond (Type I reduction), or by reduction of the carbonyl group at C-3 to a 3-β-OH with simultaneous migration of the double bond to the 5,6-position (Type II reduction). It is supposed that in the initial biochemical reduction of the double bond of progesterone according to Type I, both regular and *allo* series compounds are formed, in complete agreement with the course of reduction

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[1] Fieser, "Chemistry of Natural Products Related to Phenanthrene," 2nd ed., Reinhold Publishing Corp., New York, N. Y., pp. 251 ff., 1937.

[2] Rondoni, Carminati and Corbellini, *Z. physiol. Chem.*, **241**, 71 (1936); Rondoni, *ibid.*, **245**, 78 (1936); Voss and Rabald, *ibid.*, **245**, 76 (1936).

[3] Shimizu, "Chemie und Physiologie der Gallensäure."

[4] Schoenheimer, Rittenberg, Berg and Rousselot, *J. Biol. Chem.*, **115**, 635 (1936).

[5] Marrian, *Biochem. J.*, **23**, 1090 (1929); Butenandt, *Ber.*, **63**, 659 (1930).

[6] Marker, Kamm, Crooks, Oakwood, Lawson and Wittle, THIS JOURNAL, **59**, 2297 (1937).

[7] Hartmann and Locher, *Helv. Chim. Acta*, **18**, 160 (1935).

[8] Marker, Kamm and McGrew, THIS JOURNAL, **59**, 616 (1937).

[9] Marker and Kamm, *ibid.*, **59**, 1373 (1937).

[10] Marker, Lawson, Wittle and Crooks, *ibid.*, **60**, 1559 (1938).

[11] Marker and Rohrmann, *ibid.*, **60**, 1565 (1938).

[12] Haslewood, Marrian and Smith, *Biochem. J.*, **28**, 1316 (1934).

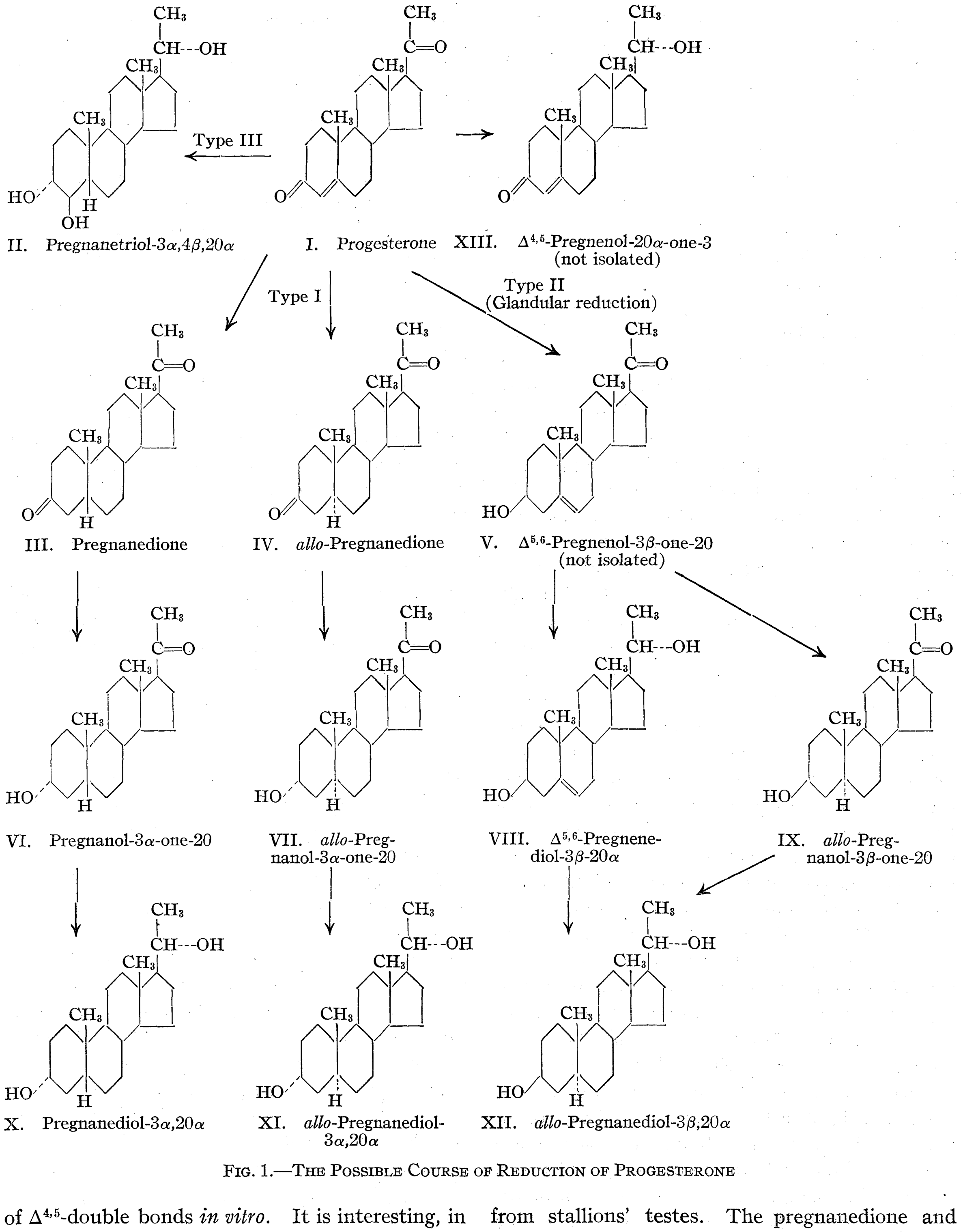

FIG. 1.—THE POSSIBLE COURSE OF REDUCTION OF PROGESTERONE

of $\Delta^{4,5}$-double bonds *in vitro*. It is interesting, in this connection, to note that Ercoli and Mamoli[13] have obtained aetiocholanedione-3,17, XVI, in 65% yield from Δ^{4}-androstenedione-3,17 by biochemical hydrogenation with an enzyme obtained from stallions' testes. The pregnanedione and *allo*-pregnanedione thus formed then probably suffer further reduction, first at the 3-carbonyl group, and then at the 20-carbonyl group. While the order of attack of these ketonic groups parallels the corresponding reactions under laboratory

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[13] Ercoli and Mamoli, *Ber.*, **71**, 156 (1938).

conditions,[14] the stereochemical relationships involved are entirely different *in vivo* from those *in vitro*. The steric arrangement of the 3-OH formed by *in vitro* reduction of steroids is determined by the Skita rule,[15] so that under like conditions of acidity or alkalinity pregnanedione and *allo*-pregnanedione yield 3-OH groups which have opposite configurations. The configuration of 20-OH groups formed on *in vitro* catalytic hydrogenation of 20-carbonyl groups under the most varied conditions is always found to be of the β-type.[16] In contrast to these rules, *in vivo* reduction of 3- and 20-keto-steroids appears always to give α-OH groups.

In the Type II reduction of progesterone steroids of the cholesterol type (3-βOH, $\Delta^{5,6}$) are assumed to be first formed. This reaction has not yet been performed in the laboratory. The suggestion that the reduction of cholestenone to cholesterol is unlikely since it has not yet been achieved in the laboratory, loses its force because, as Schoenheimer, Rittenberg and Graff[17] have suggested, cholestenone and cholesterol probably constitute a reversible biochemical oxidation–reduction system. These workers showed that the nature of the intestinal flora, which can be controlled by a suitable choice of diet, determines the nature of the sterols excreted in the feces of test dogs. When cholestenone was fed to a dog the sterol output in its feces was increased, and depending on whether the dog's basal diet was meat or dog biscuit, the major constituent of the excreted sterols was coprostanol or cholesterol, respectively. These results strongly suggest that cholestenone may be reduced biochemically to cholesterol.

The second stage of the Type II reduction may result in the formation of either VIII or IX. Judging from the products isolated, reduction of the double bond in the 5,6-position to form IX yields only substances of the *allo* series, in complete agreement with the results of the corresponding reaction in the laboratory; for example, the hydrogenation of cholesterol yields only β-cholestanol. (A careful search for carbinols of the 3-βOH type of the regular series from mares' pregnancy urine has revealed the presence of only uranediol-3β,11-β.[36]) Finally, the further reduction of either VIII or IX gives XII, *allo*-pregnanediol-3β,20α.

At least two other modes of reduction of progesterone seem possible. Pregnanetriol-3α,4β,20α (II), which was first isolated by Marrian,[12] and later studied by Marker,[18] may arise either by hydration of the double bond of progesterone followed by subsequent reduction of the pregnanedione-3,20-ol-4 thus formed, or by the hydration of the 3-enol form of pregnanedione. The latter mechanism, which is analogous to the mechanism by which oestriol is supposed to arise from oestrone, would suggest that *allo*-pregnanetriol-2,3,20 might also be found in mares' pregnancy urine. No other compounds which might throw light on this type of reduction have yet been found. By analogy with the formation of testosterone from androstenedione in the testes, we may expect the formation of XIII, $\Delta^{4,5}$-pregnenol-20α-one-3 from progesterone in the corpus luteum. This substance, however, probably can be found only in corpus luteum extracts, just as testosterone is found only in testicular extracts. The prolonged alkaline treatment which is necessary to hydrolyze urines probably destroys all α,β-unsaturated ketones so that, even if present originally, substances of this type cannot be isolated from urines. Further reduction of $\Delta^{4,5}$-pregnenol-20α-one-3, which has been prepared by Butenandt and Schmidt,[19] can proceed according to Type I or II, giving rise to pregnanediol-3α,-20α(X), *allo*-pregnanediol-3α,20α (XI), $\Delta^{5,6}$-pregnanediol-3β,20α, (VIII), and *allo*-pregnanediol-3β,20α (XII).

In contrast to the large number of reduction products of progesterone found in human and mares' pregnancy urine, relatively few reduction products of the corresponding parent male hormone, androstenedione (XIV), have been found, probably because of the very low steroid content of male urines. As would be expected, stallions' urine apparently contains no reduction products of progesterone,[20] and it is likely that none are present in human male urine. According to the present hypothesis the course of reduction of androstenedione (Fig. 2) is supposed to be similar to that of progesterone, so that most of the ex-

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[14] Marker, Kamm and Wittle, THIS JOURNAL, **59**, 1841 (1937).

[15] Ruzicka, Brungger, Eichenberger and J. Meyer, *Helv. Chim. Acta*, **17**, 1407 (1934).

[16] Marker, Kamm, Wittle, Oakwood, Lawson and Laucius, THIS JOURNAL, **59**, 2291 (1937).

[17] Schoenheimer, Rittenberg and Graff, *J. Biol. Chem.*, **111**, 183 (1935).

[18] Marker, Kamm, Wittle, Oakwood and Lawson, THIS JOURNAL, **60**, 1067 (1938).

[19] Butenandt and Schmidt, *Ber.*, **67**, 2092 (1934).

[20] Marker, Lawson, Rohrmann and Wittle, THIS JOURNAL, **60**, 1555 (1938).

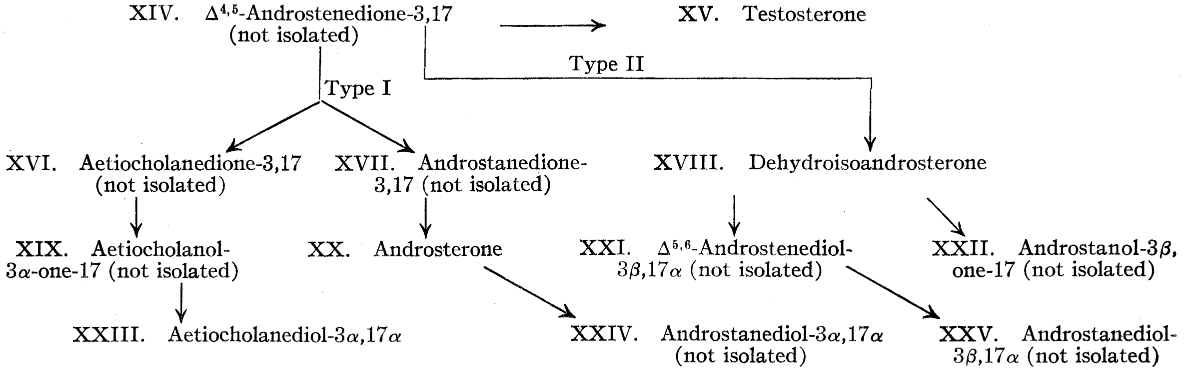

FIG. 2.—THE POSSIBLE COURSE OF REDUCTION OF ANDROSTENEDIONE

pected products would arise by Type I or Type II reduction, following the scheme indicated in Fig. 2. We have used the conventions of Ruzicka in regard to the stereochemistry of the 17-OH groups, except that we designate the configuration of the 17-OH group found naturally as α rather than *trans*. This is in agreement with the customary usage in regard to the configuration of hydroxyl groups at C-3 or C-20. Of the products listed in Fig. 2, only a few have been isolated. However, it should be noted that no C_{19} compounds have been isolated which are not predicted by the theory under discussion. The compounds isolated are androsterone,[21] dehydroisoandrosterone,[22] and aetiocholanediol-3α,17α[23] from human male urine, and testosterone[24] from testicular extracts.

In the foregoing discussion of the course of the reduction of progesterone and androstenedione to yield various steroids, most of the steroids mentioned have been found only in urines, although a few have been found only in the extracts from glands. Although our studies of the steroid content of various urines have not yet been completed, the large number of the possible reduction products of progesterone which have already been isolated suggests to us that all the reduction products possible according to the mechanism discussed in this paper occur in urine or glandular extracts.

At this point it may be profitable to compare briefly the types of compound which one may expect to isolate from urines and glandular extracts. It may be assumed that the parent hormones such as androstenedione and progesterone will exist as such in glandular extracts, but perhaps not in urines. However, it should be borne in mind that these parent substances are α,β-unsaturated ketones, and, even if present, may not survive the rigorous hydrolytic treatment to which the urines must be subjected, a treatment which is usually unnecessary to apply to glandular extracts. Besides the parent hormone such as androstenedione, progesterone, or cortin, the glandular extracts contain compounds which appear to be of only two types, corresponding in Rings A and B to cholestenone and β-cholestanol. Thus *allo*-pregnanol-3β-one-20 accompanies progesterone in corpus luteum extracts[25] and testastalone (*allo*-pregnanol-3β-one-20-al-21) accompanies testosterone in testicular extracts,[26] while numerous substances all of either the β-cholestanol or cholestenone type[27] have been found to accompany cortin in cortical extracts. The fact that only compounds of these two kinds are found in glandular extracts may indicate that glandular reduction occurs exclusively according to Type II. Although steroids of the cholesterol type have not yet been found in glandular extracts, they may be present; on the other hand, it may be that glandular reduction is so complete that no unsaturated sterols of the cholesterol type survive. The generalization that only substances of the cholestenone, β-cholestanol, and possibly of the cholesterol type, appear in glandular extracts, although it seems to be sound in view of the information now available, should of course be verified by a deliberate search

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(21) Butenandt and Tscherning, *Z. angew. Chem.*, **44**, 905 (1931); *Z. physiol. Chem.*, **229**, 167 (1934).

(22) Butenandt and Dannenbaum, *ibid.*, **229**, 192 (1934).

(23) Butenandt, Tscherning and Dannenberg, *ibid.*, **248**, 206 (1937).

(24) David, Dingemanse, Freud and Laqueur, *ibid.*, **233**, 218 (1935).

(25) Butenandt, Westphal and Hohlweg, *ibid.*, **227**, 84 (1934); Slotta, Ruschig and Fels, *Ber.*, **67**, 1270 (1934); Allen and Wintersteiner, *J. Biol. Chem.*, **107**, 321 (1934).

(26) Hirano, *J. Pharm. Soc. Japan*, **56**, 717 (1936).

(27) See Reichstein, "Chemie des Cortin und seiner Begleitstoffe (pp. 347ff.) (in Ruzicka and Stepp, "Ergebnisse der Vitamin und Hormonforschung," Akademische Verlagsgesellschaft, Leipzig, 1938) for a review of the isolation and properties of the cortical steroids.

for compounds of other types. It is perhaps to be expected that glandular extracts will contain few types of steroids, for primarily the glands are the sources of the hormones, which are then passed to other localities for utilization, with the formation of reduction products. These reduction products of varied types all will be excreted ultimately in the urine so that the latter must be expected to be a source of a much wider variety of steroid types than can be found in glandular extracts. Thus the reduction products of progesterone, androstenedione, and cortin which may be expected to occur in urine will conform, in the structure of rings A and B, to all of the types indicated in Fig. 1.

From these considerations it was suspected that cortical derivatives which we regard as reduction products of the as yet unknown cortical hormone, would be found to occur in urines, and, furthermore, it was anticipated that these reduced cortin derivatives would be found present in both male and female urines. During the last year the isolation from urines of a number of steroids containing oxygen atoms at C-11 has been reported from this Laboratory, and the presence of other such substances has been indicated. These new steroids proved to be derived not from pregnane or *allo*-pregnane, but from a new hydrocarbon, urane (9β-pregnane). While the inversion of the asymmetric center at C-9 might be expected to occur in the isolation of a pregnanone-11 derivative, no such inversion could be expected to have occurred with a pregnanol-11 derivative. Therefore the uranetriol-3,11,20 isolated from mares' pregnancy urine[28] must have been present originally as such in the urine. This occurrence of steroids inverted at C-9 (β-type), of which numerous other examples have been found since, would lead one to suspect that the cortical compounds isolated in the laboratories of Reichstein, Kendall, and Wintersteiner and Pfiffner may not possess the skeleton of *allo*-pregnane, as they assumed, but the skeleton of the corresponding hydrocarbon *allo*-urane, in which the hydrogen at C-9 is inverted (β-type).[28a]

The assignment of a cholestane configuration to the cortical steroids is due mainly to the splendid work of Reichstein, who obtained androstane and *allo*-pregnane by the reduction of cortical derivatives. Since experimental details of his conversion of corticosterone to *allo*-pregnane are not yet available,[28a] it is not possible to comment on this work, but it appears that his conversion of the saturated triketone, $C_{19}H_{26}O_3$, obtained from his compounds A, C, and D, to androstane may not give conclusive information in regard to the configuration at C-9 in the cortical steroids. When this triketone was reduced by the Clemmensen method, the hydrocarbon fraction obtained was highly unsaturated. Since the unsaturation would probably be at C-11, his subsequent hydrogenation may have yielded androstane even though the original triketone had a 9β-configuration. Such a conversion from a 9β to a 9α-configuration has been observed by Tschesche and Bohle[29] in the course of their investigations of the structure of sarmentogenin and digoxigenin (Fig. 3).

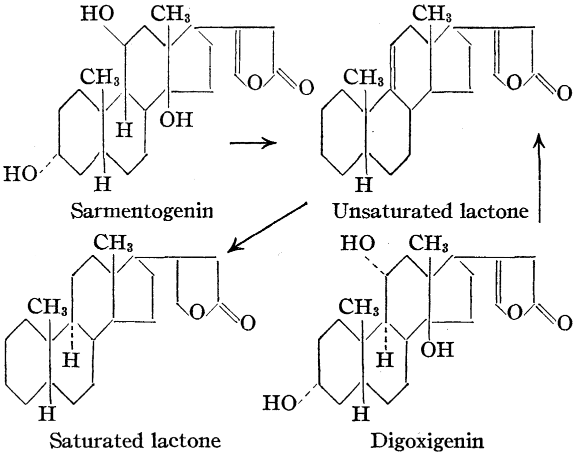

FIG. 3.—THE CORRELATION OF SARMENTOGENIN AND DIGOXIGENIN

Recent work in this Laboratory seems to support the idea that cortical steroids may be *allo*-urane derivatives. When uranetrione was reduced by the Clemmensen method in acetic acid and hydrochloric acid, the saturated hydrocarbon produced was urane. Yet when uranetrione was reduced by other means[30] with elimination of the carbonyl group at C-11 or C-20, pregnandione and uranedione were obtained. In the former case there was an inversion at C-9.

Another indication that cortical steroids may be of the *allo*-urane rather than of the *allo*-pregnane type is the apparently anomalous course of

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[28] Marker, Kamm, Crooks, Oakwood, Wittle and Lawson, THIS JOURNAL, **60**, 210 (1938).

[28a] Since submitting this paper for publication, Steiger and Reichstein, *Helv. Chim. Acta*, **21**, 164 (1938), have called attention to the possibility of an inverted configuration at C-9 in the cortical hormone series.

[29] Tschesche and Bohle, *Ber.*, **68**, 423 (1935); **69**, 793 (1936).

[30] Marker, Kamm, Wittle, Oakwood and Lawson, THIS JOURNAL, **60**, 1061 (1938).

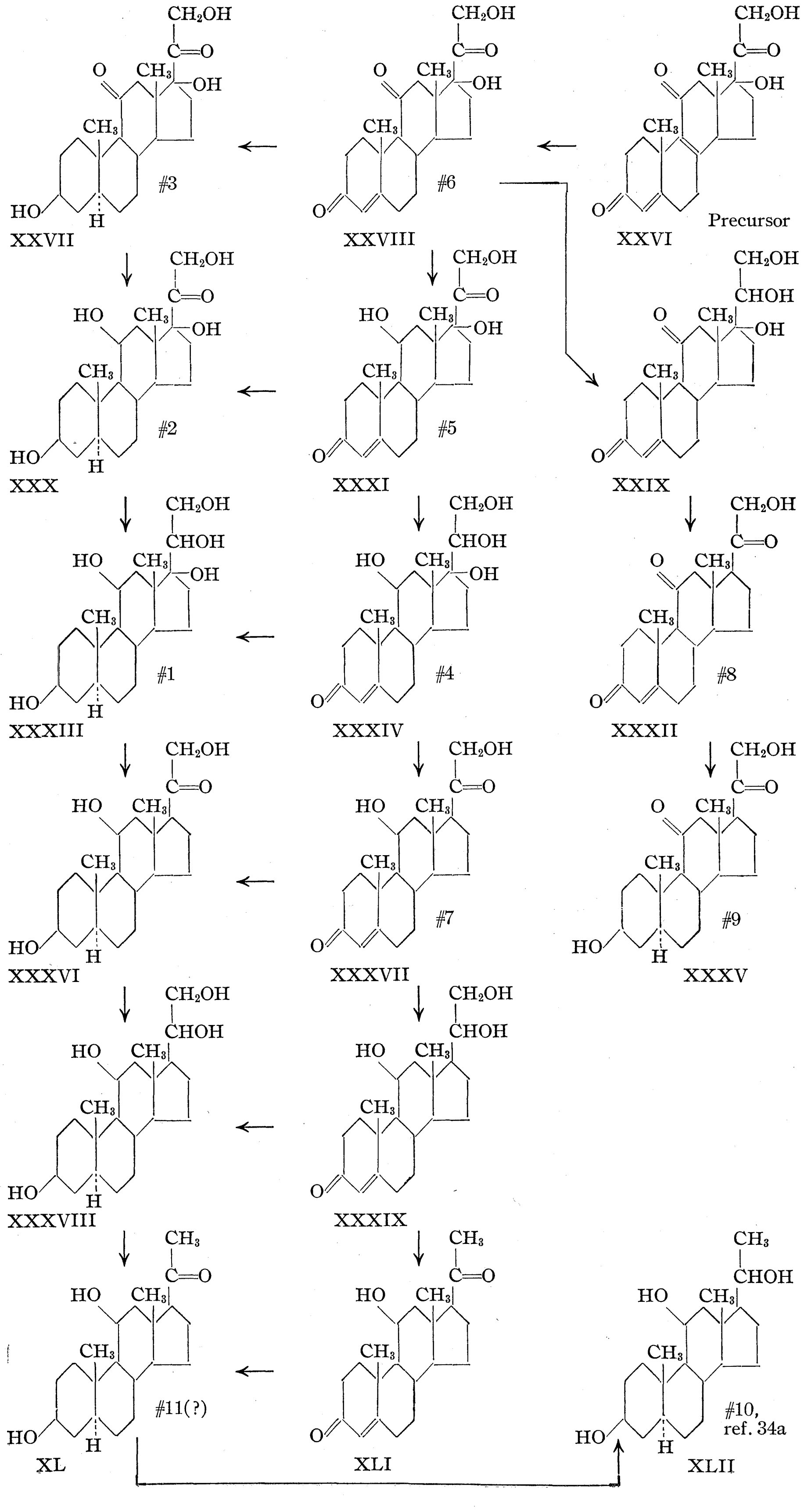

FIG. 4.—POSSIBLE COURSE OF REDUCTION (TYPES II AND III) OF PRECURSOR XXVI TO YIELD STEROIDS ISOLATED FROM CORTICAL EXTRACTS
The Arabic numbers given for the products isolated are those assigned by Reichstein in his Review Paper, Reference 27.

hydrogenation of compounds like corticosterone. While steroids having the cholestenone structure in Ring A usually give coprostane derivatives on catalytic hydrogenation,[31] the hydrogenation of the Δ^4-3-keto-cortical steroids yields only 3-β-hydroxy-*allo*-steroids. The presence of a 9β-configuration in Ring B may well account for the reduction of the Δ^4-double bond to give compounds of the *allo*-series rather than of the coprostane series, which are formed when cholestenone derivatives having a 9α-configuration are reduced.

While the suggestion that the cortical steroids may have a 9β-configuration cannot be proved definitely until diffraction and film measurements are made on cortical and urane derivatives, in this paper it will be assumed for consistency that the cortical steroids are *allo*-uranes. It is to be understood that the arguments for the theory of biogenesis of sex hormones presented in this paper are unaffected and remain valid regardless of the C-9 configuration of the cortical steroids.

In order to account for the inverted configuration at C-9 in urane and possibly in cortin derivatives, we assume that both types of substances are derived from the same hypothetical precursor, pregnadiene-4, 8-diol-17, 21-trione-3, 11, 20, (XXVI), or its hydrate at C-9, *which may be the as yet unisolated cortical hormone.* This substance would be expected to show the characteristic instability that cortin possesses, and upon reduction it could give rise to both C-9α and C-9β-compounds. This suggested precursor of the cortical and sex hormones can yield the compounds isolated from cortical extracts by an orderly scheme involving the application of definite rules in regard to the modes of reduction. Most of the compounds isolated from cortical extracts may be classified by the following statements: the structure of Ring A corresponds either to cholestenone or β-cholestanol; the asymmetric center C_9 probably has the β-configuration; the compounds possess carbonyl or β-OH groups at C-11, and have various oxygen-containing substituents at C-17 (as shown in Fig. 4). Figure 4 shows how these substances from cortical extracts may be formed in the course of the reduction of the hypothetical substance XXVI.

The first reduction product of the hypothetical parent hormone (XXVI) is assumed to be XXVIII a substance isolated by Wintersteiner and Pfiffner,[32] Kendall,[33] and Reichstein,[34] and designated respectively by them as compound F, E, and Fa. As has been mentioned previously, it is assumed that the asymmetric centers generated at C-8 and C-9 are of the normal (α) and *uro* (β) type, respectively.

The isolation of XXVII,[33,35] XXXI,[33,34] and XXXII[33] shows that further reduction of XXVIII to yield the other substances found in cortical extracts may follow at least three independent courses. According to the first mode of reduction a substance of the cholestenone type is reduced, in conformity with the rule of glandular reduction, to give the substances of the β-cholestanol type, while according to the second mode of reduction a C-11 carbonyl group is reduced to a 11-βOH-group. While this latter reaction proceeds with some difficulty in the laboratory, the large number of cortical derivatives with 11-OH groups indicate that *in vivo* the reaction proceeds readily. Alternatively, it is possible that the formation of 11-OH compounds occurs by a direct reduction of the hypothetical precursor XXVI, a reaction which might be expected to occur readily. According to the third mode of reduction the carbonyl group at C-20 is first reduced to a hydroxyl group. Although it is not possible yet to specify the configuration of the C-20-OH groups in cortical substances, it seems likely by analogy with the case of the reduction of progesterone that they will prove to be of the α-type. The substances of the glycerol type, XXXIII,[32,33,35] XXXIV,[34,35] and XXIX, are then assumed to be susceptible to ready biochemical dehydration, a reaction which may also be accomplished in the laboratory under not too vigorous conditions. The α-ketols XXXVI, XXXVII,[34,33] XXXII,[33] and XXXV[33] thus formed may be reduced further to the as yet unisolated α-glycols XXXVIII and XXXIX, which may suffer dehydration[34a] to yield the as yet unisolated ketone XLI, or the ketone XL which may be identical with Wintersteiner and Pfiffner's G.[32] Further reduction of the carbonyl group at C-20 will give rise to a 20-OH probably of the α-type.

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[31] Grasshof, *Z. physiol. Chem.*, **223**, 249 (1934); **225**, 197 (1934).

[32] Wintersteiner and Pfiffner, *J. Biol. Chem.*, **111**, 599 (1935); **116**, 291 (1935).

[33] Mason, Myers and Kendall, *ibid.*, **114**, 613 (1936); **116**, 267 (1936).

[34] Reichstein, *Helv. Chim. Acta*, **19**, 1107 (1936); **20**, 953, 978 (1937).

[34a] Steiger and Reichstein, *ibid*, **21**, 546 (1938).

[35] Reichstein, *ibid.*, **19**, 29 (1936).

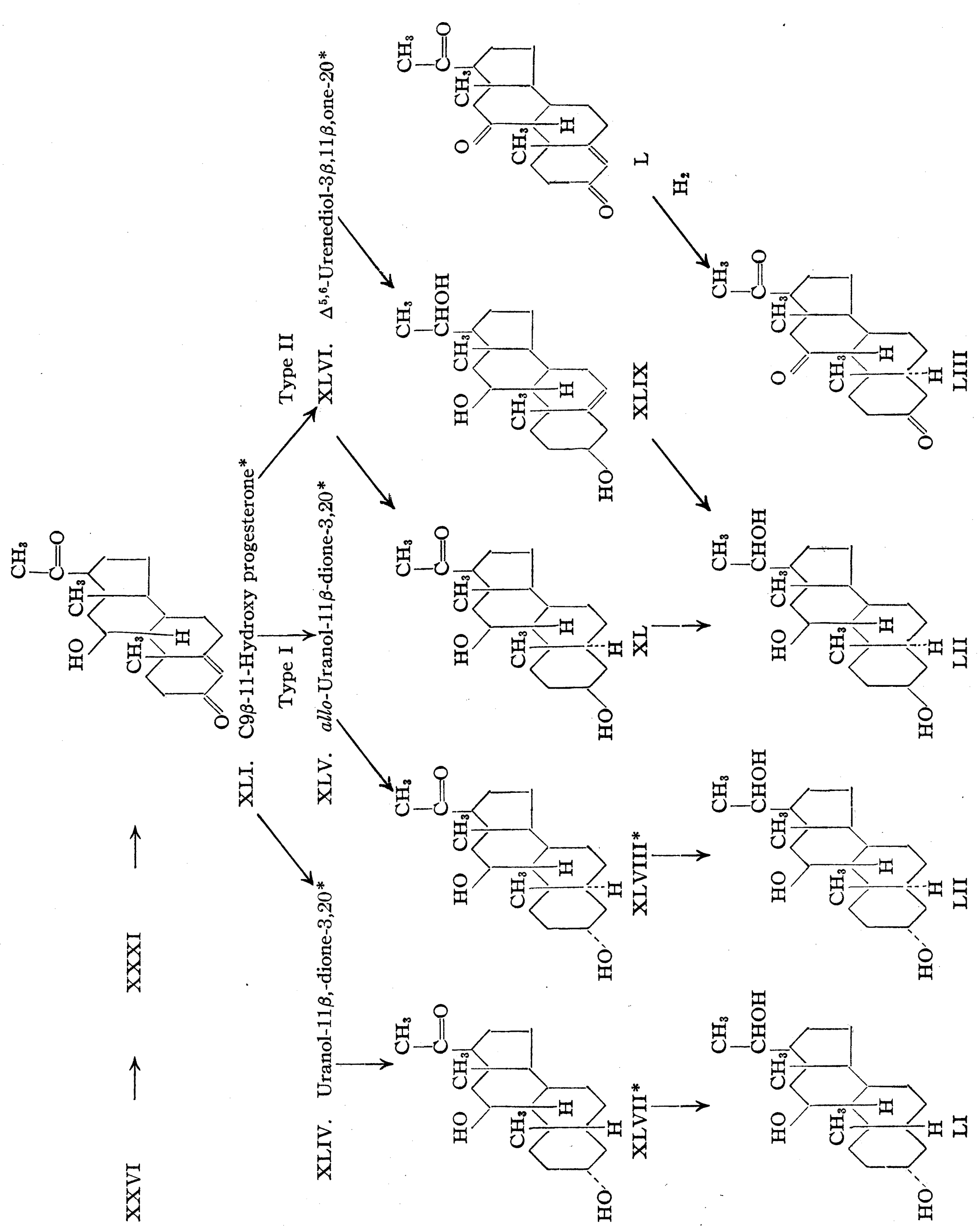

Fig. 5.—Possible Course of Reduction of Percursor XXVI to Yield Urane and *allo*-Urane Derivatives Compounds marked (*) have not been isolated as yet (L and LIII have been prepared synthetically).

The reduction of XXVI apparently proceeds further, for from urines there have been isolated a number of carbinols which appear to be derived from the cortical hormone, and evidence has been submitted of the occurrence of all other such compounds. Thus, from mares' pregnancy urine uranetriol-3α,11β,20α,[28] uranediol,[36] and uranolone[10] have been isolated and indications have been obtained of the occurrence of uranediol-3α,-11,[30] $\Delta^{5,6}$-urenetriol-3β,11,20 and of *allo*-uranetriol-3β,11,20.[37] Furthermore, it has been found that the carbinol fraction from mares' pregnancy urine yields ketones and acids on oxidation with periodic acid,[38] indicating the presence of the same characteristic glycol or glycerol residues that occur in the steroids from cortical extracts. Evidence has been obtained for the occurrence in stallions' urine of uranetriol-3α,11,20,[20] and *allo*-triol,[20] and an *allo*-tetrol.[20] These findings all

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[36] Marker, Rohrmann and Wittle, This Journal, **60**, 1561 (1938).

[37] Marker and Rohrmann, in press.

[38] Unpublished work of This Laboratory.

agree with the scheme given in Fig. 4. This seems to indicate that the cortical hormone, which may be identical with the hypothetical precursor XXVI, suffers the same type of biochemical reduction as progesterone and androstenedione. The formation of these urane and *allo*-urane derivatives from the hypothetical precursor XXVI may occur in the animal by several alternative or simultaneous processes. Thus the reduction of the conjugated system at 8, 9, 11 may yield either 11-keto-urane derivatives or 11-hydroxyurane derivatives, while at the same time the dihydroxyacetone residue may pass through the several stages of reduction and dehydration indicated in Fig. 4. The conjugated system at 3, 4, 5 at the same time may suffer reductions of Type I or Type II (Figs. 1 and 2).

In Fig. 5 a scheme is presented showing how all of the urane derivatives isolated to date may be formed by the reduction of the as yet unknown 11-hydroxy-9-β-progesterone XLI. It is to be understood, however, that several other intermediates, such as 11-keto-9β-progesterone, may, in accordance with the theory developed in this paper, also give rise to the urane derivatives found in urines. The reduction of 11β-hydroxy-9β-progesterone (XLI), if it proceeds according to Type I, will give rise, through the as yet unisolated compounds XLIV, XLV, XLVII and XLVIII, to uranetriol-3α,11β,20α (LI) and *allo*-uranetriol-3α,11β,20α (LII). The first of these compounds (LI) has been isolated from mares' pregnancy urine,[28] and its reactions and structure investigated.[30] Its presence in stallions' urine[20] has been demonstrated by the isolation of uranetrione-3,11,20 from the oxidation of an *epi*-carbinol fraction. *allo*-Uranetriol-3α,11β,20α (LII) may be identical with a triol whose presence has been demonstrated in stallions' urine.[20] If the reduction of 11β-hydroxy-9β-progesterone (XLI) proceeds according to Type II, it may give rise to either XL or XLIX. The first of these has not been isolated or demonstrated to exist in urines, but it may be identical with Wintersteiner and Pfiffner's compound G. Urenetriol-3β,11β,20α has not been isolated as such but its presence in mares' pregnancy urine has been demonstrated.[37] The digitonin precipitable carbinols from mares' pregnancy urine yielded an unsaturated fraction which on addition of bromine, oxidation, and debromination, yielded $\Delta^{4,5}$-urenetrione-3,11,20 (L), a substance which had been prepared previously from uranetrione.[30] The further biochemical reduction of either XL or XLIX would give *allo*-uranetriol-3β,11β,20α (XLII). The latter, which may be identical with the 3β-OH-*allo*-triol which was prepared as described above from stallions' urine, has been demonstrated to occur in mares' pregnancy urine.

From cortical extracts there is obtained,[35] besides the C_{21} compounds, a substance, adrenosterone (LIX) which has been shown to be androstenetrione-3,11,17. This compound shows androgenic activity, and may therefore be considered to be a connecting link between the cortical substances and the C_{19} and C_{18} sex hormones. It should be mentioned, however, that adrenosterone may have a *uro*-(β-type) configuration at C-9. The idea, suggested here, that cortical and sex hormones may be interrelated, is supported by numerous facts. The structures of the C_{21} cortical steroids and progesterone, on the one hand, and of adrenosterone and androstenedione on the other hand, indicate their close relationship. The influence of cortical disturbances on sexual characteristics is well known, and several instances can be cited where abnormal products related to sex hormones have been isolated from the urines of patients suffering from some disorder of the suprarenal gland. For example, Marrian and Butler[39] isolated pregnanetriol-3,17,20 from the urine of female patients with adrenal tumors, while Burrows, Cook and Warren[40] isolated $\Delta^{3,5}$-androstadienone-17, originating presumably from *epi*-dehydroandrosterone, from the urine of a man with an adrenal tumor.

This connection between cortical and sex hormones may be accounted for by the assumption that both types of hormones have a common precursor. We propose to show now how the hypothetical precursor (XXVI) of the adrenal steroids may be also the precursor of the sex hormones of the androgenic (C_{19}), progestational (C_{21}), and oestrogenic (C_{18}) types. In order to make the course of the conversions clear, it is necessary first to recount some recent work on the reduction of uranetrione in this Laboratory.[41]

When uranetrione (LIV) is reduced catalytically, there is formed (Fig. 6) in addition to uranetriol-3,11,20 (LV), uranediol-3,11 (LVI) and a

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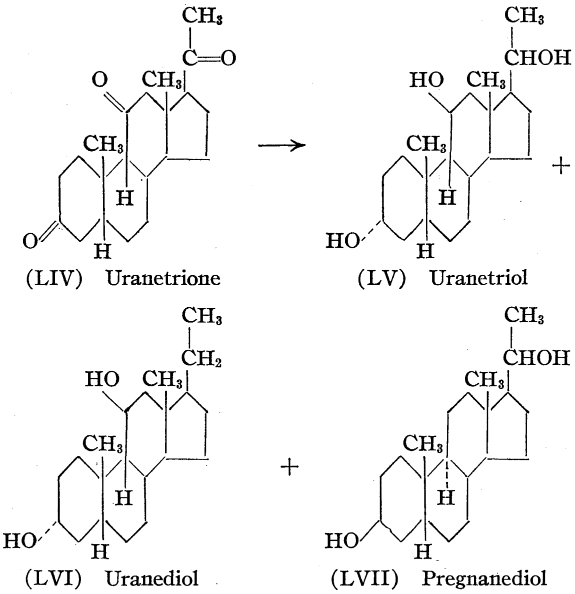
(39) Marrian and Butler, *J. Biol. Chem.*, **119**, lxvi (1937).

(40) Burrows, Cook and Warren, *J. Soc. Chem. Ind.*, **55**, 1031 (1936).

(41) Marker, Wittle and Oakwood, THIS JOURNAL, **60**, 1561 (1938).



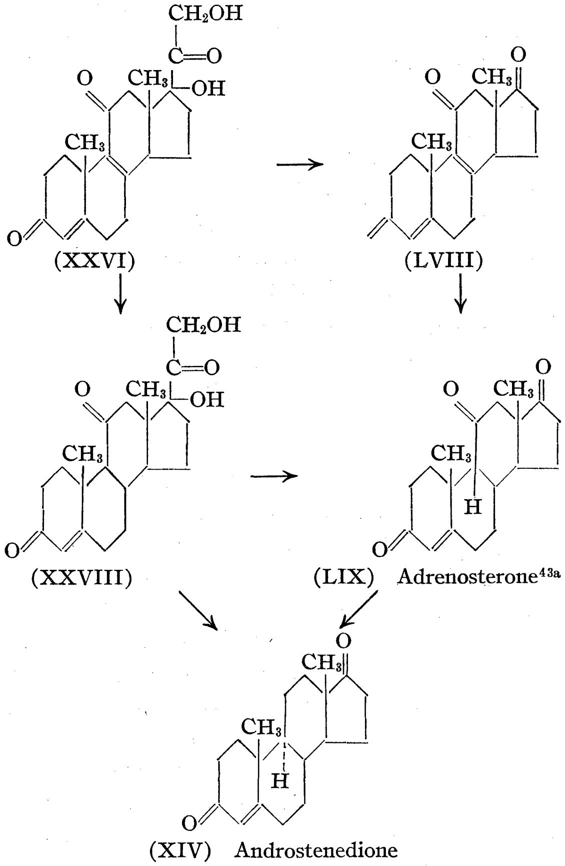
(LIV) Uranetrione (LV) Uranetriol

(LVI) Uranediol (LVII) Pregnanediol

FIG. 6.—PRODUCTS FROM THE CATALYTIC REDUCTION OF URANETRIONE

mixture of pregnanediols (LVII). This implies that the carbonyl groups at C-11 and C-20, which are adjacent to tertiary hydrogens, are to some extent completely reduced to methylene groups, and, furthermore, that when the C-11-carbonyl is completely reduced, the molecular skeleton suffers inversion from the *uro*- (β) to the normal (α) form, although, as would be expected in view of the much greater stability of the normal (α), as compared to the *iso*- (β) type at C-17,[42] no inversion occurs when the C-20 carbonyl group is completely reduced. While at first sight this reduction may appear anomalous, it is by no means without parallel. Thus, when 7-keto-cholesteryl chloride is hydrogenated catalytically, α-cholestyl chloride is the major product.[43] It is evident, in view of the isolation from mares' pregnancy urine of uranediol, uranolone, and uranediol-3α,11β (the latter as uranedione from an *epi*-carbinol fraction), that this reduction of a C-20 carbonyl group to a methylene group occurs in the animal. Therefore, it is also likely that the reduction of a 9β-11-CO-system to a 9α-11-CH_2-system may occur in the animal as well as in the laboratory.

We are now able to understand how sex hormones may be formed from the hypothetical substance XXVI. This substance and a number of its possible reduction products contain dihydroxyacetone residues which are readily susceptible to oxidation to yield carbonyl groups at C-17. In the laboratory this oxidation may be accomplished by the use of lead tetraacetate, periodic acid, or almost any of the common oxidizing agents such as chromic acid or potassium permanganate; the fact that adrenosterone accompanies the C-21 steroids from cortical extracts shows that a similar type of oxidation occurs in the animal. Figure 7 illustrates how adrenosterone (LIX) or a precursor such as (LVIII) may give rise by biochemical reductions, to androstenedione (XIV) and therefore to the other male hormones. It will be evident, in view of the previous discussion, that the application of this theory will predict the possible existence in urines or glandular extracts of other related steroids, such as Δ^4-androstenol-11β-dione-3,17, which might arise by the various modes of reduction which



(XXVI) (LVIII)

(XXVIII) (LIX) Adrenosterone[43a]

(XIV) Androstenedione

FIG. 7.—POSSIBLE FORMATION OF ADRENOSTERONE AND ANDROSTENEDIONE

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(42) Butenandt and Mamoli, *Ber.*, **68**, 1854 (1935); Butenandt and Fischer, *ibid.*, **70**, 96 (1937).

(43) Marker, Kamm, Fleming, Popkin and Wittle, THIS JOURNAL, **59**, 619 (1937).

(43a) Since sending this paper to press H. L. Mason, *Proc. Staff Meet. Mayo Clin.*, **13**, 235(1938), has converted XXVIII into adrenosterone (LIX) by treatment of the former with a solution of calcium hydroxide.

have been proposed, and, conversely, it should be noted that this theory predicts the *absence* in urines or glandular extracts of such a steroid as aetiocholanediol-3β,11β,-one-17. It should be emphasized that the reduction of the 11-carbonyl group to give an inversion from the 9β to the 9α-type is supposed to occur in the animal as well as during the catalytic hydrogenation *in vitro*.

The same type of simultaneous reduction and inversion of a 11-CO-9β system to a 11-CH$_2$-9α system in conjunction with the degradation of a dihydroxyacetone residue will account for the formation of progesterone and related steroids from XXVI. In Fig. 8, which shows how this may be accomplished, a number of the steps already shown in Fig. 7 are omitted, and it is to be understood that several alternate reduction schemes, which already have been discussed in similar instances, are omitted here for the sake of brevity.

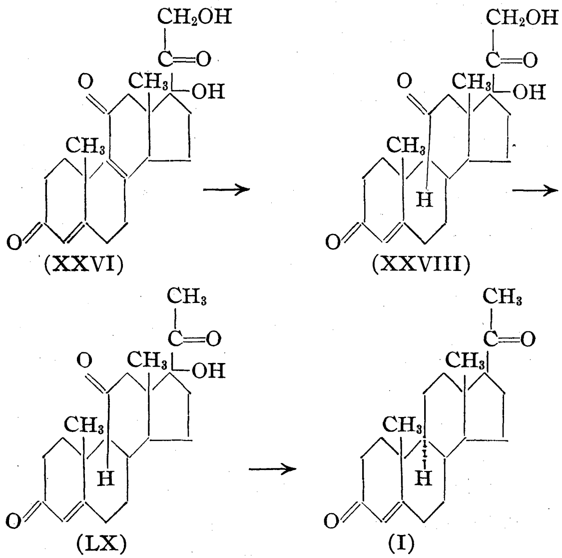

FIG. 8.—POSSIBLE FORMATION OF PROGESTERONE FROM (XXVI)

Not only is it possible to show how cortical steroids, male hormones, and progesterone derivatives may arise by orderly processes from XXVI, but it is also possible to show that the female hormones can be derived from the same parent compound. It is necessary to show first how the most characteristic feature of the female hormones, the occurrence of ring A, and sometimes B, in a benzenoid form, may arise. A number of examples are available to show that under drastic conditions, or because of the occurrence of an extended conjugated system, the methyl group at C-10 in many steroids may be lost as methane with the formation of benzenoid rings. One may cite the following examples: when apocholic acid is heated, methane is lost;[44] when ergopinacol is heated, neoergosterol is formed with the loss of methane;[45] when dianhydrostrophanthidin is treated with concentrated hydrochloric acid trianhydrostrophanthidin is formed;[46] when heptaacetyldesoxydihydroouabain is treated with hydrochloric acid and acetic acid the acetoxy lactone C$_{24}$H$_{30}$O$_4$, which contains a benzene ring, is obtained;[47] and finally when the debromination products of dibromoandrostanedione are heated, methane is evolved and phenolic compounds are formed.[48] These examples indicate that the elimination of methane with the formation of benzenoid rings is a type of reaction which may be expected to occur in the organism also if the parent molecule presents a sufficiently extended conjugated system, or some other structural feature which may be expected to facilitate the reaction. The hypothetical parent hormone (XXVI) has this type of molecular structure. In Fig. 9 a scheme is presented showing how the phenolic female hormones may be formed. It is not possible, of course, in view of the meager amount of data available, to state which of the several probably independent processes of dihydroxyacetone oxidation, loss of methane, and reduction of the 11-carbonyl group

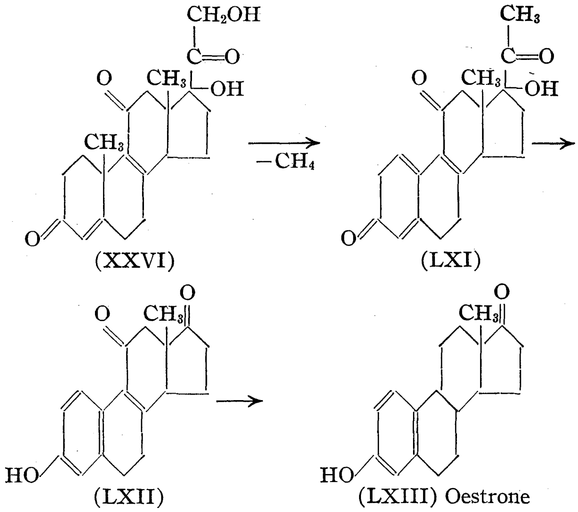

FIG. 9.—POSSIBLE FORMATION OF OESTRONE FROM XXVI

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(44) Wieland and Dane, *Z. physiol. Chem.*, **212**, 263 (1932).

(45) Windaus and Borgeaud, *Ann.*, **460**, 235 (1928).

(46) Jacobs and Collins, *J. Biol. Chem.*, **63**, 123 (1925); see Fieser, *op. cit.*, p. 274 for a discussion of this transformation.

(47) For references and a critical discussion, see Fieser, *op. cit.*, pp. 292 ff.

(48) Inhoffen, *Naturwissenschaften*, **25**, 125 (1937).

may be expected to occur first. It should be noted that the mechanism indicates how equilin, as well as oestrone, may be formed. The formation of equilin by a migration of the double bond from the 8,9- to the 7,8-positions may occur in the animal, or it may occur in the course of the prolonged alkaline treatment of the urine. This drift of a double bond near a benzene ring is a familiar process in the chemistry of allyl- and propenyl-benzene derivatives, although usually the tendency is toward the establishment of an equilibrium mixture containing predominantly the propenylbenzene derivative. The formation of equilenin by the loss of hydrogen is also readily understandable as a tendency of the second ring to become aromatic. In fact, so great is the tendency for equilin to yield equilenin that when attempts are made to hydrogenate the former catalytically, the latter is always formed instead.[49] It is possible, furthermore, that a compound like LXII might suffer further loss of methane to yield, ultimately, *ar*-dihydroxycyclopentanophenanthrene derivatives, none of which have so far been found. In support of the hypothesis that oestrone and related female hormones are derived from a common precursor which is primarily not a sex hormone itself, we may note that oestrone is found in stallions' urine[50] as well as in mare and human female urines.

A discussion of the mode of biogenesis of the precursor XXVI is beyond the scope of this paper. It seems likely that the precursor may be formed from sugar units[51] in the pituitary or some other master gland, and supplied to the suprarenals, ovaries, corpus luteum, or testes for the production of the specific hormones elaborated by these glands. The reactions by which these syntheses are effected may be enzymatic, or they may be a part of some intramolecular oxidation and reduction in the glands, but it is not the purpose of this paper to discuss their nature. Since ascorbic acid occurs in the suprarenal glands, it may be that its function is the reduction of a precursor like XXVI to give steroidal hormones.

The author wishes to thank Dr. Elmer J. Lawson for his suggestions and assistance in the preparation of this manuscript, and all the members of his sterol group, Drs. Eugene L. Wittle, Elmer J. Lawson, Thomas S. Oakwood, Ewald Rohrmann, Harry M. Crooks, Stephen B. Binkley and David M. Jones for the use of their unpublished work.

Summary

1. Arguments are advanced to indicate that the steroidal hormones and bile acids do not originate from cholesterol.

2. It is suggested instead that the steroidal hormones, including the C-18, C-19, and C-21 sex hormones and the cortical steroids, may come from another common precursor, pregnadiene-4,8-diol-17,21-trione-3,11,20 (XXVI) or its hydrate at C-9.

3. Considerations of the interrelationships among the many steroids from urines and from gland extracts make it possible to propose a definite structure (XXVI) for the precursor of the steroidal hormones.

4. It is shown how the various steroids isolated may arise from this precursor by orderly processes following definite rules and having with few exceptions, their counterpart in the laboratory.

STATE COLLEGE, PENNA. RECEIVED MARCH 22, 1938

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(49) Dirscherl and Hanusch, *Z. physiol. Chem.*, **233**, 13 (1935); **236**, 131 (1935).

(50) Zondek, *Nature*, **133**, 209, 494 (1934); Cortland, Meyer, Miller and Rutz, *J. Biol. Chem.*, **109**, 213 (1935).

(51) Reichstein, *op. cit.*, p. 368.

[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

The Polycondensation of α-Methylacrolein

BY EVERETT E. GILBERT[1] AND JOHN J. DONLEAVY

It was shown by von Pechmann and Röhm[2] that in the presence of sodium methylate, methyl acrylate polycondenses to give a 10% yield of α-methyleneglutaric ester together with an uninvestigated higher fraction. A similar dimerization also was observed[3] in the case of methyl crotonate when an ether solution of this compound was exposed to the action of sodium methylate. Michael[4] obtained the same dimer by the action of sodium upon an ether solution of the ester.

In a discussion of the probable mechanism of the reaction, von Pechmann suggests that a molecule of sodium methylate first adds to the heteroconjugate system of a molecule of acrylic ester, thus producing the sodium enolate of a saturated molecule containing an active methylene group. In the presence of the strongly alkaline catalyst, a Michael reaction was thought to occur between this saturated molecule and an acrylic ester molecule. Loss of sodium methylate led to the formation of α-methyleneglutaric ester as the final product.

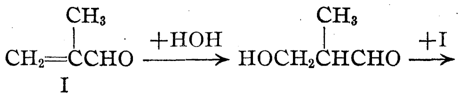
The purpose of this article is to record a similar type of polycondensation for α-methylacrolein. This investigation was conducted in connection with a study of the Michael polycondensation of various alpha, beta-unsaturated compounds being undertaken in this Laboratory. In this case the reaction occurred easily in the presence of dilute aqueous alkali. This extreme ease of reaction may be explained in part by the greater activation of the aldehyde group as compared to the ester grouping of ethyl acrylate. In addition, the final molecules produced from the methylacrolein contained no olefinic bonds, the addendum (water) being incapable of removal except by ring formation when stage II has been reached. A parallel is found in the dimerization of methyl vinyl ketone in the presence of dilute aqueous alkalies to produce octanol-8-dione-2,6.[5] A similar reaction, to be reported subsequently, has been observed in the case of acrolein.

Three polymers were isolated and identified—a trimer, a tetramer, and a pentamer. All three contained a molecule of water introduced during the polycondensation. They gave an immediate precipitate with Tollens' reagent, a delayed but positive test with Schiff's reagent, and an immediate precipitate of manganese dioxide when treated at room temperature with neutral aqueous permanganate. All three fractions yielded yellow 2,4-dinitrophenylhydrazones. As may be seen from Table I, the increases in refractive index and density from the trimer through the pentamer are approximately linear. A similar gradation was observed in the colors—the lowest fraction being colorless, the middle slightly yellow, and the top fraction a deeper shade of yellow. The three fractions were viscous oils, the viscosity increasing through the pentamer. All fractions possessed a mild and slightly spicy odor.

TABLE I

Fraction		Low	Middle	High
B. p.	°C.	113–118	159–164	175–180
	Mm.	12	12	9
	Bath., °C.	135–140	195–210	200–210
d^{20}_{20}		1.017	1.062	1.096
$n^{20}\mathrm{D}$		1.4441	1.4657	1.4867
$Mk\mathrm{D}$	Calcd.	59.41	78.01	96.61
	Found	59.61	77.73	96.60
Mol. wt.	Calcd.	228	298	368
	Found	237	288	371
Carbon, %	Calcd.	63.12	64.43	65.18
	Found	62.80	64.64	65.55
Hydrogen, %	Calcd.	8.77	8.73	8.70
	Found	8.94	8.86	9.00

The mechanism of the polycondensation is probably as follows. A molecule of water is first added to a molecule of α-methylacrolein, thus forming a β-hydroxyaldehyde containing the necessary active hydrogen. A series of Michael reactions then occurs, leading to the formation of the products isolated. Both of these processes are of a type known to occur with remarkable ease in the presence of alkalies. These reactions may be expressed as follows



$$\underset{\text{I}}{CH_2{=}\overset{CH_3}{\overset{|}{C}}CHO} \xrightarrow{+HOH} HOCH_2\overset{CH_3}{\overset{|}{C}}HCHO \xrightarrow{+I}$$

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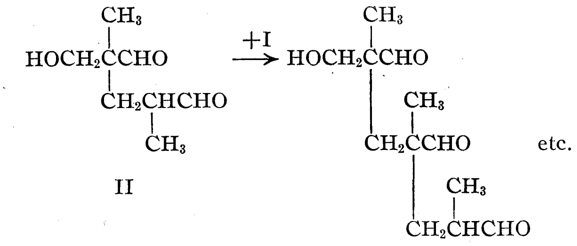
[1] This communication describes work done by Everett E. Gilbert in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry.

[2] H. von Pechmann and O. Röhm, *Ber.*, **34**, 427 (1901).

[3] H. von Pechmann, *ibid.*, **33**, 3323 (1900).

[4] A. Michael, *ibid.*, **33**, 3766 (1900).

[5] Farbenfabriken vorm Freidr. Bayer and Co. in Elberfeld, German patent, 227,177 (1910).



II

Experimental

The α-methylacrolein was purchased from the Shell Development Co. It was of about 98% purity and contained 0.05% hydroquinone as an antioxidant. Since it was desired to avoid polymerization produced by peroxides, and since the hydroquinone did not appear to inhibit the polycondensation, it was used as received without further purification.

Thirty-three grams of methylacrolein was mixed with 200 cc. of distilled water. About 50 cc. of ethyl alcohol was added to promote solution and ten cc. of 4% aqueous sodium hydroxide. A brown flash of color appeared which disappeared upon shaking. In about ten minutes turbidity appeared and a yellow oil began to settle. Heat was evolved; the flask was cooled by bathing in cold running water. After allowing the flask to stand for one hour (during which time it was shaken frequently), the solution was extracted three times with ether, and the extract was dried over sodium sulfate. The ether was removed and the oil was fractionated under reduced pressure. In the preliminary distillation three fractions were collected as follows:

(1)	Bath 165–170° (15 mm.)	141.1 g.
(2)	Bath 195–210° (10 mm.)	3.6 g.
(3)	Bath 225–250° (10 mm.)	7.6 g.

The total yield of crude oils was 71.3% of the theoretical Other experiments gave similar results.

Upon redistillation the above fractions were found to consist almost entirely of the pure polymers. The properties were determined from these purified fractions. The molecular weights were determined in freezing benzene. These and other data are listed in Table I.

Preparation of the Tri-2,4-dinitrophenylhydrazones of the Polymers.—The method employed was essentially that suggested by Shriner and Fuson.[6] An equivalent of dinitrophenylhydrazine for each aldehyde group was employed. Yellow tridinitrophenylhydrazones were obtained in each case. The derivative of the trimer separated from the reaction mixture even when boiling. Cooling was resorted to in the other cases to obtain crystallization of the derivatives. They were then recrystallized from benzene. The tridinitrophenylhydrazone of the trimer decomposed to a red liquid at 173–174° (uncorr.), but the other two derivatives decomposed indefinitely as the temperature was raised above 100°.

Anal. Trimer. Calcd. for $C_{30}H_{32}N_{12}O_{13}$: N, 21.8. Found: N (Dumas), 21.4. Tetramer. Calcd. for $C_{34}H_{38}N_{12}O_{14}$: C, 48.65; H, 4.53; N, 20.0. Found: C, 48.60; H, 4.82; N, 20.4. Pentamer. Calcd. for $C_{38}H_{44}N_{12}O_{15}$: N, 18.5. Found: N, 18.5.

Summary

α-Methylacrolein polycondenses by the Michael reaction in the presence of dilute aqueous alkali. A trimer, a tetramer, and a pentamer were isolated and characterized.

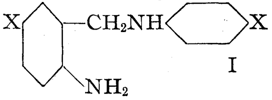
(6) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1935, p. 148.

New Haven, Conn. Received May 23, 1938

[Contribution from the Department of Chemistry and Chemical Engineering of the University of Pennsylvania]

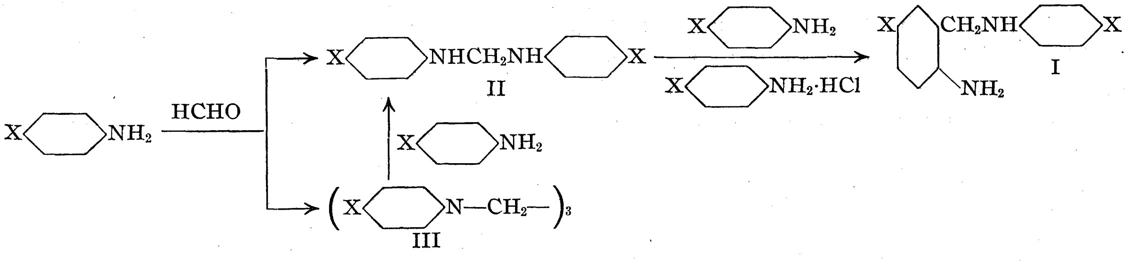
A Study of the Conversion of Para-substituted Methylene-bis-arylamines and Trimeric Methylene-arylamines to Substituted 2-Aminobenzylarylamines

By T. R. Miller and E. C. Wagner



I

Aminobenzylarylamines of type I may be prepared from para-substituted amines through the reactions



The only published procedure[1] is cumbersome, as it requires mechanical stirring of a mixture of methylene-*p*-toluidine, *p*-toluidine and *p*-toluidine hydrochloride for forty-eight hours at 20°, in the presence of enough nitrobenzene to yield a mass which is finally liquid. The mild conditions specified (which greatly prolong the reaction period) are clearly intended to exclude or minimize

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(1) German Patent 105,797; *Friedl.*, **5**, 84; v. Walther and Bamberg, *J. prakt. Chem.*, [2] **71**, 153 (1905).

the further reaction by which I is converted to the diphenylmethane base. With diimines (II) and trimeric Schiff bases (III) obtained from amines with open para-position this reaction occurs readily on warming in the presence of amine salt (or free acid),[2] and can be excluded only by operating at or below 20°, at which temperatures aminobenzylarylamines of the type  are obtainable.[3] It is now known[4] that aminobenzylarylamines of type I (from para-substituted amines) are less readily converted to diphenylmethane bases: at 100° the conversion of *o*-amino-*m*-xylyl-*p*-toluidine (I) to 2,2′-diamino-5,5′-dimethyldiphenylmethane is slight,[5] and at 125° the conversion is only 50% complete.[6] These facts suggested the possibility of converting II or III more rapidly to I by use of temperatures well above 20°. As is shown in the experimental part the reaction goes well at 80–100°, and normal yields are obtained in a few hours, the nitrobenzene and (in small runs) mechanical stirring being dispensable.

The proportions of diimine (II) or Schiff base (III), free amine and amine salt hitherto used in these reactions appear to be based upon no published experimental work. As a result of Simons' study[7] of the reactions of diimines (II) with amines and amine salts it is established that II with amine salt yields as the normal end-product the corresponding dihydroquinazoline (*e. g.*, 6-methyl-3-*p*-tolyl-3,4-dihydroquinazoline), with I formed as an intermediate, but that presence of free amine tends to exclude the later steps of the complete transformation and thus favors survival of I. With 25 molar equivalents of amine to one equivalent each of II and amine hydrochloride an 82.5% yield of I was obtained. This amount of free amine is inconveniently large, for the excess, together with amine taken as hydrochloride, must be removed subsequently by steam distillation or otherwise, in the isolation of I. Experimental trials, reported below, showed that satisfactory practical molar ratios for preparation of I are diimine:amine:amine hydrochloride = 1:10–12:0.5. When the trimeric Schiff base is used, three equivalents of amine are consumed in the initial reaction[2b] requiring for the

$$(\mathrm{ArNCH_2}\!-\!)_3 + 3\mathrm{ArNH_2} \longrightarrow 3\mathrm{ArNHCH_2NHAr}$$

Schiff base the molar proportions trimer (III): amine : amine hydrochloride = 1 : 33–39 : 1.5. The proportions previously specified[1] for the cold reaction are III: amine: amine hydrochloride = 1 : 16.7 : 5.8, *i. e.*, more than the necessary amine salt (shown by Simons[7] to be 0.5–1.0 equivalent referred to the diimine), and an amount of amine less than adequate for the hot reaction. The most satisfactory combination of conditions includes the ratio of reactants stated, a temperature of 80–90°, and, for 0.01–0.1 molar quantities, a reaction period of two hours. With larger quantities the time should be extended to three to five hours and the mixture should be stirred mechanically.

The applicability of the procedure for preparative purposes appears to be limited. Satisfactory results were obtained in the preparation of the aminobenzylarylamines from *p*-toluidine, *p*-chloroaniline and *p*-bromoaniline. Attempts to prepare those from *p*-anisidine and *p*-phenetidine were unsuccessful, owing apparently to isolation difficulties, which it is safe to say would be greater with para-substituted amines not volatile with steam.

The conversion of II to I by substitutive ortho-coupling (rather than by rearrangement) suggests the possibility of making 2-aminobenzylarylamines of mixed type by warming diimines or Schiff bases with different amines and their hydrochlorides. The analogous process has been used for preparation of diphenylmethane bases of mixed type from simple aminobenzylarylamines.[8] Preliminary trials[9] yielded unpromising viscous liquids from which no well-defined product could be isolated.

Experimental

Chemicals.—Methylene-*bis*-*p*-toluidine (m. p. 95°), methylene-*bis*-*p*-chloroaniline (m. p. 59–60°) and methylene-*bis*-*p*-bromoaniline[10] (m. p. 92°) were made by the method of Eberhardt and Welter[2b] and Bischoff and Reinfeld.[11] The trimeric Schiff bases (melting respectively at 127, 151 and 166°[12]) were prepared by the procedure of J. G. Miller.[13]

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[2] (a) German Patents 53,937, 58,072, 70,402, 107,718; *Friedl.*, **2**, 53; **3**, 79, 80; **5**, 78; (b) Eberhardt and Welter, *Ber.*, **27**, 1804 (1894); (c) Rivier and Farine, *Helv. Chim. Acta*, **12**, 865 (1929).

[3] German Patents 87,934, 104,230; *Friedl.*, **4**, 66; **5**, 83.

[4] Wagner, THIS JOURNAL, **56**, 1944 (1934).

[5] *Cf.* Eberhardt and Welter, ref. 2b, p. 1812.

[6] At higher temperatures (200–220°) diphenylmethane bases of this type, in presence of amine and amine salt, split out ammonia and yield dihydroacridines [Ullmann, *Ber.*, **36**, 1017 (1903)].

[7] Simons, THIS JOURNAL, **59**, 518 (1937).

[8] German Patent 108,064; *Friedl.*, **5**, 85; Cohn and Fischer, *Ber.*, **33**, 2586 (1900).

[9] These experiments were performed by J. R. Feldman.

[10] Wagner, *J. Org. Chem.*, **2**, 162 (1937).

[11] Bischoff and Reinfeld, *Ber.*, **36**, 41 (1903).

[12] Wagner and Eisner, THIS JOURNAL, **59**, 881 (1937).

[13] Miller and Wagner, *ibid.*, **54**, 3698 (1932).

Procedure.—The mixture of diimine or Schiff base (0.01 mole), amine and amine hydrochloride in a flask was heated in an oil-bath at the desired temperature (thermometer in the bath), and was then treated with enough sodium hydroxide solution to neutralize the acid taken as amine salt and was submitted to rapid steam distillation. When all steam-volatile material was removed the residual mixture was cooled to solidify the crude product, which was separated by filtration, washed once with water and then without drying was crystallized as follows. The moist product, in a 200-cc. flask, was heated on a water-bath, and ligroin (70–90°) was added gradually until a solution nearly saturated at the boiling point was obtained. Anhydrous potassium carbonate sufficient to "fix" the separated water was added, and the mixture was digested with about 0.5 g. of charcoal and then filtered rapidly using a heated filter. The liquid was chilled in ice, and the separated crystals were removed by filtration, washed with cold ligroin and dried in a vacuum desiccator. The yields stated represent nearly pure product but do not indicate quite the maximum yields obtainable, as the ligroin mother liquors were not worked up to recover the small amount of product still present though not readily isolable owing to presence of resinous impurities. In several experiments the mother liquors were found to contain small amounts of the dihydroquinazolines, isolated and identified as their picrates.

In the first series of experiments reported below the product was isolated and weighed as the benzal derivative.[7] This procedure indicated higher but less reproducible yields than the procedure described above.

Series 1: Effect of Temperature.—Conditions: methylene-*bis*-*p*-toluidine (II), 0.01 mole (2.26 g.), *p*-toluidine, 0.05 mole (5.5 g.), *p*-toluidine hydrochloride, 0.005 mole (0.70 g.); time one hour. Product isolated as benzal derivative.

Temperature, °C.	50	60	70	80	90	100
Yield of I, %	63.7	65.3	64.7	66.0	66.9	66.6

Series 2: Effect of Variation in Proportions of Reactants (and Time).—In experiments using the diimine (II) the above ratio of II to *p*-toluidine hydrochloride was held constant (being within the optimum limits reported by Simons[7]), and the ratio of *p*-toluidine to II was varied. In the experiments using the Schiff base trimer (III) the ratio of III to *p*-toluidine hydrochloride was 1:1.5, and the proportions of *p*-toluidine were varied. In the table the values for the ratio of *p*-toluidine to Schiff base refer to moles of *p*-toluidine available as "regulator," calculated in terms of equivalent moles of diimine, *viz.*, $(x - 3y)/3y$, in which x = moles of *p*-toluidine and y = moles of Schiff base; temperature, 80°.

Starting comp.	Ratio *p*-toluidine: II or III[a]	Yield of I, %	
	A, Time 0.5 hour		
III	10	50.1	51.6
III	15	57.4	
II	25	59.3	
	B, Time 1 hour		
II	5	48.7	
III	5	48.7	
III	8	50.2	
II	10	51.2	
III	10	50.0	
II	12	51.5	51.0[b]
III	12	52.0	
III	15	56.0	59.1
II	20	58.5	
III	20	60.4	
II	25	61.2	
III	25	62.0	

[a] Calculated in terms of equivalent II, as explained above. [b] Temperature 100°.

Series 3: Effect of Time.—In experiments with diimine the proportions of reactants were as in Series 1, *i. e.*, 1:10:0.5. In experiments using the Schiff base trimer the proportions were 1:33:1.5 (or 1:10:0.5 calculated to equivalent diimine); temperature 80°.

Starting compound	III	II	II	II
Time, hrs.	0.5	1	2	3
Yield, %	51.6	54.7	63.3	62.7
	50.1	54.0	60.0	

Preparative Trials

Cold Procedure.[1]—The starting compound was in all cases III, the amounts ranging from 53 to 73.5 g. The molar proportions, in terms of equivalent diimine, were 1:4.6:1.9, with nitrobenzene 1.7 cc. per gram of III. The reaction mixtures were stirred mechanically during forty-eight to fifty-three hours, at temperatures which ranged from 15 to 24° and which were for the most part not above 20°. The best yields obtained were 61.4 and 56.3%.

Hot Procedure.—The starting compound was II, the time two hours, and the temperature 80–90°. For ratio 1:12:0.5 the yield was 61.5%; for ratio 1:21:1.6 the yield was 64.5%.

The foregoing results, and those of series 1, 2 and 3 show the conversion of II or III to I to be fairly rapid at 80–90°, the yields increasing as the molar ratio of available free amine is increased. For preparative purposes a molar ratio of about 10:1 when the starting compound is II, or of 33:1 when the starting compound is III, is recommended. The yields are then satisfactory and the amount of amine to be removed during the isolation is not excessive. The diimine or the Schiff base may be used equally well as starting material.

Conversion of Diimines and Schiff Bases from *p*-Chloroaniline and *p*-Bromoaniline to Corresponding 2-Aminobenzylarylamines. Conditions.—Molar ratio for diimine 1:12:0.5, and equivalent ratio for Schiff base; temperature 80°; time two hours.

Starting compound	II	III
Yield of I, %		
Cl compound	45.3	46.3[14]
Br compound	50.2	47.3[14]

Grateful acknowledgment is made to the Faculty Research Committee of the University of Pennsylvania for a grant to assist this study.

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(14) Some results by a closely similar procedure were mentioned in an earlier paper (Ref. 12, p. 879).

Summary

1. A study of the effects of variations in temperature, time and molar ratios of reactants upon the conversion of methylene-*bis-p*-toluidine or trimeric methylene-*p*-toluidine to N-(5-methyl-2-aminobenzyl)-*p*-toluidine, in the presence of *p*-toluidine and *p*-toluidine hydrochloride, showed: (a) at 80–100° the reaction is rapid and does not proceed beyond the aminobenzylarylamine stage. The conditions previously specified, *viz.*, a temperature of 20° and a reaction time of forty-eight hours, were based on a misconception. (b) The extent of the conversion increases with increase in the molar ratio of free amine to diimine or Schiff base. Highest yields require an inconveniently large excess of free amine. Satisfactory practical ratios, which give good yields and do not too greatly prolong the isolation procedure, are diimine : amine : amine hydrochloride = 1:10:0.5, or trimeric Schiff base : amine : amine hydrochloride = 1:33:1.5.

2. The procedure based upon the above conditions has been used for the preparation of the aminobenzylarylamines obtainable from *p*-toluidine, *p*-chloroaniline and *p*-bromoaniline. It failed in the cases of *p*-anisidine and *p*-phenetidine and its usefulness apparently is impaired by the limitations of the isolation method now available.

THE JOHN HARRISON LABORATORY OF CHEMISTRY
PHILADELPHIA, PENNA.
RECEIVED MAY 11, 1938

The Structure of Beta and Gamma Tocopherols

BY OLIVER H. EMERSON

To date there have been described in the literature three tocopherols, which we designated provisionally as alpha, beta and gamma.[1,2] Alpha was obtained from wheat germ oil, cottonseed oil, palm oil, and lettuce leaves. Beta was first obtained by us from wheat germ oil, and later by Todd, Bergel, Waldmann and Work, who obtained it in addition from rice bran oil.[3,4] It was obtained subsequently from wheat germ oil by Drummond and Hoover,[5] John,[6] who suggested the name cumo-tocopherol for it, and Karrer, Salomon and Fritsche,[7] who proposed the name neo-tocopherol. Dr. John[8] kindly compared a sample of our β-tocopherol allophanate with his cumo-tocopherol allophanate and found them identical. It is interesting that the European workers found that in their preparations of wheat germ oil, β-tocopherol predominated to such an extent that the suggestion was put forward that alpha might be an artifact,[9] whereas from the Californian wheat germ oil we have regularly obtained at least twice as much alpha as beta. γ-Tocopherol has been obtained from cottonseed oil and palm oil. In our experience at the University of California and in the Research Laboratories of Merck & Co., Inc., where several hundred pounds of cottonseed oil have been worked up, the ratio of alpha to gamma varies within wide limits. Sometimes there is as much gamma as alpha but usually much less. Other oils beside wheat germ and cotton seed, notably grape seed oil, are known to vary greatly in their chemical constituents, depending not only on the locality, but also on the year of the crop.

On pyrolysis Fernholz[10] showed that α-tocopherol yields durohydroquinone. Under similar conditions, from β-tocopherol John[6] obtained trimethylhydroquinone, and Bergel, Todd and Work[9] reported a mixture of trimethylhydroquinone and durohydroquinone.

Fernholz's original view that α-tocopherol is a simple mono-ether of durohydroquinone was modified by the results of the chromic acid oxidation,[11] whereby he obtained dimethylmaleic anhydride; a lactone $C_{21}H_{40}O_2$, the hydroxy acid of which forms a characteristic benzylthiuronium salt; and an acid $C_{16}H_{32}O_2$ which on vigorous oxidation yielded two moles of acetic acid. From this evidence Fernholz proposed formula I for α-tocopherol

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(1) H. M. Evans, O. H. Emerson and G. A. Emerson, *J. Biol. Chem.*, **113**, 319 (1936).

(2) O. H. Emerson, G. A. Emerson, A. Mohammad and H. M Evans, *ibid.*, **122**, 99 (1937).

(3) A. R. Todd, F. Bergel, H. Waldmann and T. S. Work, *Nature*, **140**, 361–2 (1937).

(4) A. R. Todd, F. Bergel and T. S. Work, *Biochem. J.*, **31**, 2257 (1937).

(5) J. C. Drummond and A. A. Hoover, *ibid.*, **31**, 1852 (1937).

(6) W. John, *Z. physiol. Chem.*, **250**, 11 (1937).

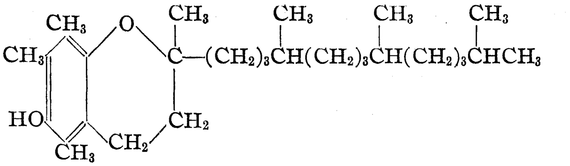
(7) P. Karrer, H. Salomon and H. Fritsche, *Helv. Chim. Acta*, **20**, 1422 (1937).

(8) W. John, *Z. physiol. Chem.*, **252**, 201 (1938).

(9) F. Bergel, A. R. Todd and T. S. Work, *J. Chem. Soc.*, 253 (1938).

(10) E. Fernholz, THIS JOURNAL, **59**, 1154 (1937).

(11) E. Fernholz, *ibid.*, **60**, 700 (1938).



I

We have oxidized β- and γ-tocopherol under the conditions described by Fernholz and have obtained from both the same lactone that had been obtained from α-tocopherol. We failed to obtain dimethylmaleic anhydride, but the amount of material used by us was much smaller than that employed by Fernholz so that dimethylmaleic anhydride, if formed, might have escaped our attention.

We have also pyrolyzed γ-tocopherol at 360°, and obtained trimethylhydroquinone. From these facts, it is evident that β- and γ-tocopherol differ from alpha only in the absence of one of the three methyl groups attached to the benzene ring. This had been suspected by John[6] and Karrer, Salomon and Fritzsche.[12]

Oxidation of β-Tocopherol.—Eight hundred and nine milligrams of β-tocopherol was oxidized as described by Fernholz.[11] A lactone was obtained which was purified by distillation in high vacuum (yield 351 mg.). This yielded a benzylthiuronium salt which, after several recrystallizations from acetone, melted at 116–117°. A sample of the corresponding benzylthiuronium salt, prepared by Fernholz from α-tocopherol, melted at 116–117.5°; mixed m. p. 116–117°. *Anal.* Calcd. for $C_{29}H_{52}O_3N_2S$: C, 68.45; H, 10.30; N, 5.50. Found: C, 68.22, 68.51, 68.15; H, 10.23, 10.44, 10.23; N, 5.42, 5.54.

Oxidation of γ-Tocopherol.—Three hundred and seventy four milligrams of γ-tocopherol, oxidized as above, yielded 90 mg. of lactone after purification by high vacuum distillation. This gave a benzylthiuronium salt melting at 116–117° which showed no depression on admixture with a sample of the corresponding benzylthiuronium salt of the same melting point from α-tocopherol. *Anal.* Calcd. for $C_{29}H_{52}O_3N_2S$: C, 68.45; H, 10.30; N, 5.50. Found: C, 68.59, 68.65; H, 10.35, 10.26; N, 5.48.

Pyrolysis of γ-Tocopherol.—Five hundred milligrams of γ-tocopherol was heated at 360° in an atmosphere of carbon dioxide. This gave 30 mg. of a crystalline sublimate, which appeared to be a mixture of trimethylhydroquinone with a little durohydroquinone. By careful recrystallization from benzene there was obtained a fraction melting at 167–170° which gave no depression with authentic trimethylhydroquinone. A benzoate was also obtained melting at 175–178° which gave no depression when mixed with an authentic sample of trimethylhydroquinone dibenzoate melting at 178–180°.

The trimethylhydroquinone and its dibenzoate were supplied by Professor Lee Irvin Smith to whom we wish to express our thanks.

Summary

Oxidation of β- and γ-tocopherols yielded the same $C_{21}H_{40}O_2$ lactone that had been obtained by Fernholz from α-tocopherol.

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[12] P. Karrer, H. Salomon, and H. Fritzsche, *Helv. Chim. Acta.*, **21**, 302 (1938).

[CONTRIBUTION NO. 180 FROM THE EXPERIMENTAL STATION OF E. I. DU PONT DE NEMOURS & COMPANY]

Carbamic Esters from Urea

BY RALPH A. JACOBSON

Esters of carbamic acid are usually prepared either by treating an alcohol with phosgene and adding ammonia to the chloroformic ester thus formed, or by treating the alcohol with cyanic acid. The reaction of urea with an alcohol has also been utilized[1] but the method has not been applied widely, probably because the lower alcohols, *e. g.*, methyl and ethyl, require pressure. Butanol, however, reacts with urea at atmospheric pressure[2] to give butyl carbamate in 75% yield. This suggests wider application of the method for the preparation of carbamic esters of alcohols having boiling points higher than that of butanol. In the present paper, we have adapted this method to the synthesis of octyl carbamate, *n*-dodecyl carbamate, and several other esters of carbamic acid.

The optimum temperature range for carbamate formation appears to be 175–190°. At this temperature, aliphatic monohydric alcohols react smoothly with urea with the evolution of ammonia and the formation of carbamates. While the reaction is usually over within a few hours at this temperature, a reaction period of twelve to twenty-four hours or longer is required for al-

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[1] Hoffmann, *Ber.*, **4**, 268 (1871); Bunte, *Ann.*, **151**, 181 (1869); Cahours, *Chem. Zentr.*, **4**, 482 (1873); *Compt. rend.*, **76**, 1387 (1873); Werner, *J. Chem. Soc.*, **113**, 626 (1918).

[2] Davis and Lane, *Org. Syntheses*, **9**, 24 (1929).

cohols having boiling points considerably lower than the optimum temperature. In such cases the reaction is usually very slow initially, but as the concentration of carbamate in the mixture increases and the boiling point of the mixture approaches the optimum temperature, the reaction rate increases markedly. The products are isolated by filtering the mixture to remove the small amount of cyanuric acid usually formed, and distilling the filtrate. After removal of the alcohol, the less volatile carbamates are purified by distillation or by crystallization.

The formation of butyl carbamate from urea and *n*-butanol is expressed by Davis and Lane as follows

$$NH_2CONH_2 \longrightarrow NH_3 + HNCO \quad (1)$$
$$HNCO + C_4H_9OH \longrightarrow NH_2COOC_4H_9 \quad (2)$$

If these reactions correctly express the mechanism, the formation of carbonates by the reaction of urea with two molecules of the alcohol as shown in equation (3) is unlikely.

$$NH_2CONH_2 + 2ROH \longrightarrow R_2CO_3 + 2NH_3 \quad (3)$$

Since phosgene, however, reacts with two molecules of an alcohol to yield the carbonate, it seems at least theoretically possible that urea—the diamide from phosgene—could react similarly. In other words, the reaction expressed by equation (3) might take place in either direction depending upon the conditions. Indeed the reaction from right to left does go readily in the case of diphenyl carbonate which can be converted into urea and phenol in 70% yields by treatment with aqueous ammonia[3]

$$2C_6H_5CO_3 + 2NH_3 \longrightarrow NH_2CONH_2 + 2C_6H_5OH \quad (4)$$

Our attempts to force the reaction (3) from left to right, however, were unsuccessful since none of the experiments yielded carbonates. In one instance, sulfuric acid was added to a mixture of urea and *n*-dodecyl alcohol to remove the ammonia immediately upon formation, but quantitative dehydration of the *n*-dodecyl alcohol to *n*-dodecyl ether resulted.

The reaction of urea with polyhydric alcohols also was examined briefly. Ethylene glycol, sorbitol, and triethylene glycol reacted readily with urea to give viscous water-soluble sirups. Upon standing, the sirup from triethylene glycol deposited crystals of the diurethan (m. p. 108°). In general, however, the reaction of urea with polyhydric alcohols appears unpromising for the preparation of pure carbamates of polyhydric alcohols.

Experimental Part

***n*-Dodecyl Carbamate.**—A mixture of 120 g. of urea, 372 g. of *n*-dodecyl alcohol, and 12 g. of glycerol was heated at 170° for two hours and finally at 190° for three hours. The reaction mixture was distilled in a vacuum and 150 g. of *n*-dodecyl alcohol boiling at 135° under 12 mm. was recovered. The liquid in the distilling flask solidified on cooling. The crystalline product was washed with petroleum ether and melted at 81–82°[4]; yield 138 g. (60%). The product was soluble upon heating in toluene, alcohol, ethyl acetate, ether, carbon tetrachloride, and acetic acid.

Anal. Calcd. for $C_{13}H_{27}O_2N$: C, 68.12; H, 11.79. Found: C, 67.68; H, 11.14.

***n*-Octyl Carbamate.**—This compound was prepared as above except that purification was effected by distillation, followed by crystallization from benzene. The compound boiled at 136° under 4 mm. pressure and melted at 67°.[5] The yield was 55% of the theoretical.

Isobutyl Carbamate.—A mixture of 270 g. of urea, and 1813 g. of isobutanol was refluxed for seventy-two hours. The excess isobutanol was distilled and the residue extracted three times with ligroin, b. p. 90–100°. Urea amounting to 101 g. was recovered. After removal of the ligroin the isobutyl carbamate was collected at 117° under 25 mm. pressure, the product m. p. 65–66° weighing 225 g. (42.8% conversion or 65% based on the urea consumed).

An attempt was made to reduce the time of reaction by utilizing isobutyl phthalate to increase the initial boiling point of the mixture. Under these conditions isobutyl allophanate was obtained as a by-product.

A mixture of 120 g. of urea, 148 g. of isobutanol, 250 g. of isobutyl phthalate, and 12 g. of glycerol was heated on the hot-plate for nineteen hours. During the first twelve hours, the boiling point of the mixture increased from 123 to 137° and during the next seven hours from 137 to 170°. The solution upon cooling deposited crystals (15 g.) of isobutyl allophanate which on purification from acetone melted at 174°. The liquid portion was distilled and the fraction boiling at 95–110° under 12 mm. was collected. Upon cooling, the liquid solidified to a white crystalline solid which, after being washed with petroleum ether, melted at 65–66°.[6]

Anal. of isobutyl allophanate m. p. 174°. Calcd. for $C_6H_{12}O_3N_2$: C, 45.00; H, 7.50; N, 17.50. Found: C, 44.92; H, 7.10; N, 17.32.

Anal. of isobutyl carbamate m. p. 65–66°. Calcd. for $C_5H_{11}O_2N$: C, 51.28; H, 9.40. Found: C, 51.77; H, 8.96.

Mixed Carbamates from the Higher Alcohol Mixture Obtained in the Synthetic Methanol Process.—A mixture of 90 g. of urea, 9 g. of glycerol, and 308 g. of the fraction

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[3] Kirkhgof and Astrova, *Khim. Farm. Prom.*, 281 (1933); *C. A.*, **28**, 3718 (1934).

[4] Béhal, *Bull. soc. chim.*, **25**, 480 (1919), prepared dodecyl carbamate by passing cyanic acid into the alcohol but gave 77° as the melting point.

[5] Béhal[4] reported 67° as the melting point.

[6] Béhal[4] gives 180.5° for the allophanate and 59.5° for the carbamate.

of higher alcohols boiling at 135–150° obtained from the synthetic methanol process,[7] was refluxed for twelve hours. The liquid was decanted from a small amount of solid material (4.5 g.) and distilled. After removal of the excess alcohols, the carbamate was obtained at 110–125° under 4 mm. pressure. The product was slightly yellow and remained liquid at room temperature. The yield was 137 g. or about 60% of the theoretical.

Ethylene Glycol and Urea.—A mixture of 240 g. of urea, 124 g. of ethylene glycol, and 12 g. of glycerol yielded a transparent water-soluble sirup after a heating period of six hours at 160–165° and four hours at 170–175°.

Triethylene Glycol and Urea.—A mixture of 60 g. of urea, 6 g. of glycerol, and 150 g. of triethylene glycol was heated at 140–150° for one and one-half hours and slowly increased during eight hours to 175°. The excess triethylene glycol was removed by distillation and 115 g. (57.8%) of a non-volatile water soluble sirup obtained. Upon standing for two weeks, a small amount of crystalline material separated which, upon crystallization from acetone, melted at 108° and proved to be the diurethan.

Anal. Calcd. for $C_8H_{16}O_6N_2$: C, 40.67; H, 6.77; N, 11.86. Found: C, 40.87; H, 6.65; N, 11.32.

Sorbitol and Urea.—Resins of varying viscosity were obtained depending upon the ratio of urea to sorbitol. Pure compounds could not be isolated.

Summary

n-Dodecyl carbamate, octyl carbamate, isobutyl carbamate, and the mixed carbamates from one fraction (b. p. 135–150°) of the higher alcohols obtained in the methanol synthesis have been prepared by the reaction of urea with the corresponding alcohols at atmospheric pressure. Attempts to obtain alkyl carbonates by the same procedure were unsuccessful.

Polyhydric alcohols reacted with urea under the same conditions to yield sirups from which pure compounds could not be isolated except in the case of triethylene glycol. The latter yielded a sirup from which a small amount of the diurethan of m. p. 108° was obtained.

WILMINGTON, DELAWARE RECEIVED MAY 19, 1938

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[7] The following compounds have been identified in this fraction by Graves, *Ind. Eng. Chem.*, **23**, 1381 (1931): 2-methyl-1-pentanol, 2,4-dimethyl-3-pentanol and 2,4-dimethyl-1-pentanol.

[CONTRIBUTION FROM THE LABORATORY OF BIOLOGICAL CHEMISTRY, SCHOOL OF MEDICINE, UNIVERSITY OF BUFFALO]

A Critical Examination of the Reaction of Iodine Monobromide with Cholestenone and β-Cholestanone

BY J. O. RALLS

In a previous study,[1] it was shown that cholestenone was one of the products of the reaction of iodine monobromide with cholesterol. It was also shown that cholestenone behaved toward halogen in a manner that was then considered "abnormal." In addition, Copping[2] had stated that cholestenone did not yield analytically correct iodine numbers when Dam's[3] suggested application of the Rosenmund and Kuhnhenn[4] method was used. We were interested, therefore, in attempting to ascertain the causes of this peculiarity.

Inasmuch as $\Delta^{4,5}$-cholestenone, commonly called cholestenone (suggested name, coprostenone),[5] contains a double bond and a ketone group (in a conjugated system), the problem was one of attempting to evaluate the role of each in the reaction of cholestenone with iodine monobromide. Cholestanone, which contains no double bond, and cholestanoxime, which contains neither the double bond nor the ketone group, served to evaluate the effect of the carbonyl group; while cholestenoxime, which does not contain the ketone group but still possesses the double bond, was used in attempting to evaluate the role of the latter group.

In the course of the experimentation, hydrogen bromide catalysis of halogenation was investigated, as was, also, the effect of the oximino hydroxyl upon the halogenation of the ethylene group in cholestenoxime. In the latter work, the factors of solvent nature, of air (oxygen) inhibition, and of the configuration of the oxime were considered. In these studies, *syn*-styrylphenylketoxime, 3,5-diphenylisoxazol, and 3,5-diphenylisoxazoline were also used.

Discussion and Results

The peculiarities of the reaction of cholestenone with iodine monobromide (Curves 1, Fig. 1) are especially evident in the graph of the organic

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[1] Ralls, THIS JOURNAL, **55**, 2083 (1933).

[2] Copping, *Biochem. J.*, **22**, 1142 (1928).

[3] Dam, *Biochem. Z.*, **152**, 101 (1924).

[4] K. W. Rosenmund and W. Kuhnhenn, *Z. Untersuch. Nahr. u. Genussm.*, **46**, 154–9 (1923).

[5] O. Rosenheim and H. King, *Ann. Rev. Biochem.*, **3**, 90 (1934).

halogen. There appears to be some autocatalysis, but it is not simple. Inasmuch as cholestenone contains both a double bond and a ketone group, the complexity might well have been due to the influence of these two groups. Because it contained the ketone group only, β-cholestanone was allowed to react with iodine monobromide. It was surprising to find that it consumed halogen more rapidly (Curves 2, Fig. 1) than did cholestenone. (Of course, it has long been known that it did react with halogen.[6,7]) Examination of the curves showed that, while the reaction of cholestanone lacked the aforementioned complexity, it did possess an autocatalytic nature. Doreé[6] has remarked on the initial lag followed by a rapid consumption of halogen accompanied by a marked evolution of halogen acid when cholestanone reacted with bromine. The above author suggested that substitution had occurred. In the work reported here, the ratios between the total halogen consumed and the halogen organically bound were two to one, which fact is indicative of substitution. But β-cholestanol, from which β-cholestanone is derived, did not undergo substitution under similar conditions.[1] Furthermore, substitution, in the common sense, would not be expected to display signs of autocatalysis. But a substitution preceded by an enolization or activation of a ketone group could do so. It is generally conceded that enolization or activation of a saturated ketone precedes its bromination.

The specific evidence that β-cholestanone also undergoes enolization or activation in its reaction with iodine monobromide is the following. First: when cholestanoxime was allowed to react with iodine monobromide, no appreciable reaction occurred (broken Curve 2, Fig. 1). Of course, this is not absolute evidence that the bromination of cholestanone is via enolization, because the presence of the oximino group in cholestanoxime might have changed the activity of nearby hydrogen. Second: determinations of the order of the reaction of cholestanone with iodine monobromide disclosed that it was monomolecular. (Table I is presented as an example of the results—other initial concentrations were also used.) This finding paralleled those of Meyer,[8] who studied the order of the bromination of malonic acid, and of Cohen,[9] who studied the bromination of acetone in organic solvents. Third: the initial speed of the reaction of cholestanone with iodine monobromide was increased when hydrogen bromide was added to the halogenating agent. These results were similar to those obtained in a like study of cholestenone (Figs. 2 and 3). On the basis of the work of Lapworth,[10] Meyer,[8] Dawson,[11] Cohen,[9] Hanson and Williams,[12] and of Kröhnke,[13] it is generally conceded that mineral acids catalyze the enolization or activation which precedes the bromination of ketones. Further, it is evident that such workers as Butenandt and Wolff[7] and Ruzicka, *et al.*,[14] tacitly assume that cholestanone enolizes during its bromination. Fourth: photographic records of the ultraviolet absorption spectra of cholestanone in chloroform, in chloroform–glacial acetic acid, and in chloroform–glacial acetic acid–hydrogen bromide (Plate 1) and of the enol ethyl ether of cholestanone (Plate 2) in chloroform were made. That of the cholestanone in the presence of hydrogen

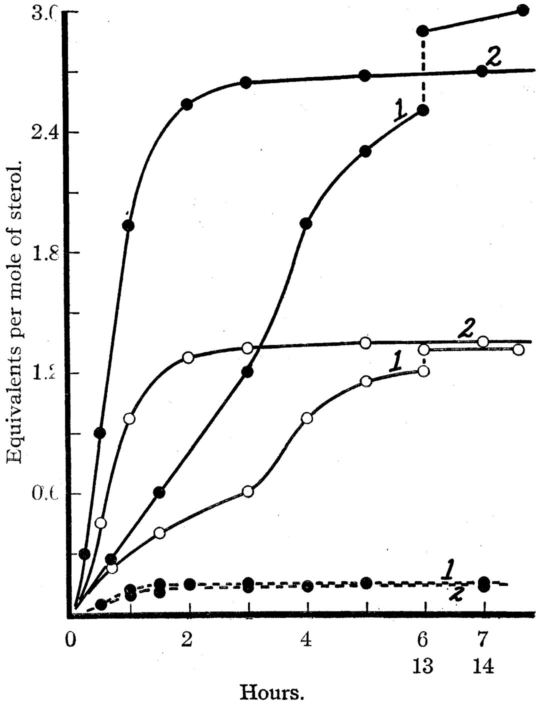

Fig. 1.—The reaction of iodine monobromide with cholestenone, cholestanone, and their oximes: 1, cholestenone; 2, cholestanone; —●—, oximes; ●, total halogen consumed; ○, organic halogen.

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(6) Doreé, *J. Chem. Soc.*, **95**, 648 (1909).

(7) Butenandt and Wolff, *Ber.*, **68**, 2091–2094 (1935).

(8) Meyer, *Ann.*, **380**, 212 (1911); *Ber.*, **44**, 218 (1911).

(9) Cohen, THIS JOURNAL, **52**, 2827–2835 (1930).

(10) Lapworth, *J. Chem. Soc.*, **85**, 30 (1904).

(11) Dawson, *ibid.*, **95**, 1860 (1909); **101**, 1503 (1912); **105**, 532 (1914).

(12) Hanson and Williams, *ibid.*, 1059–63 (1930).

(13) Kröhnke, *Ber.*, **69B**, 921–935 (1936).

(14) L. Ruzicka, Bosshard, Fischer and Wirz, *Helv. Chim. Acta*, **19**, 1147 (1936).

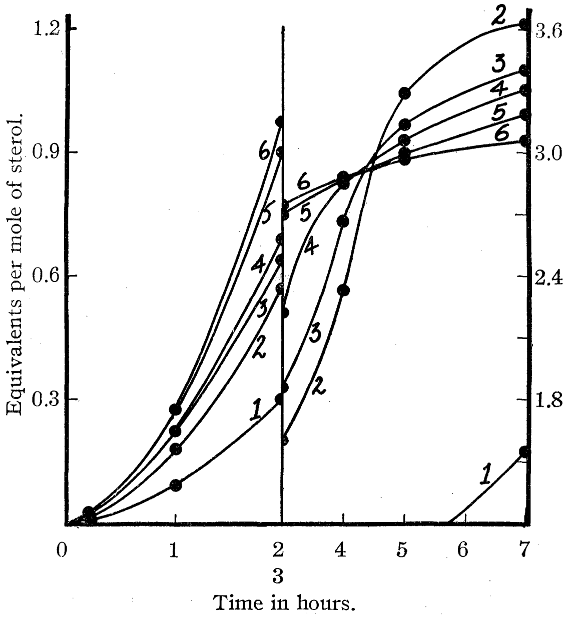

Fig. 2.—The influence of aqueous hydrogen bromide upon the consumption of halogen by cholestenone. Initial hydrogen bromide concentrations mμ 6 cc.: 1, 0.000; 2, 0.020; 3, 0.042; 4, 0.059; 5, 0.079; 6, 0.099.

bromide was similar to that of the enol ethyl ether in chloroform.

Table I

The Order of Reaction of Cholestanone with IBr

Cholestanone in CCl_4, IBr in CH_3COOH

	C = 0.082 mM			C = 0.041 mM		
Reaction time, min.	Milliequivalents Residual	Consumed	Equiv. per mole	Milliequivalents Residual	Consumed	Equiv. per mole
Blank	0.1648	0.0000	0.000	0.0824	0.0000	0.000
2	.1408	.0240	.300	.0704	.0120	.300
4	.1243	.0405	.493	.0624	.0200	.488

Order is apparently monomolecular, since $t_2/t_1 = 1 = 2^\circ = 2^{n-1}$.

Cholestanone in CCl_4, IBr in CCl_4

	C = 0.0764 mM			C = 0.0382 mM		
Reaction time, min.	Milliequivalents Residual	Consumed	Equiv. per mole	Milliequivalents Residual	Consumed	Equiv. per mole
Blank	0.1528	0.0000	0.000	0.0764	0.0000	0.000
2	.1457	.0071	.093	...	...	..
4	.1075	.0453	.594	.0536	.0228	.597
8	.0960	.0568	.743	.0480	.0284	.743
16	...	...	...	.0440	.0324	.849

Order is apparently monomolecular.

An error of 0.010 cc. in titration produces a minimum error of 0.010 in equivalents per mole when C = 0.080 mM, and one of 0.020 when C = 0.040 mM.

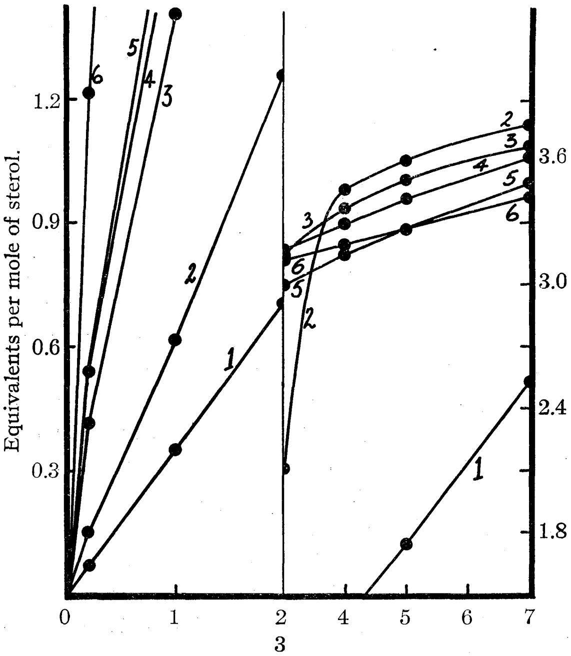

Fig. 3.—The influence of anhydrous hydrogen bromide upon the consumption of halogen by cholestenone. Initial hydrogen bromide concentrations, mμ in 6 cc.: 1, 0.000; 2, 0.020; 3, 0.042; 4, 0.059; 5, 0.079; 6, 0.099.

While our experiments were being carried on, Inhoffen[15] reported that cholestenone enolizes during its bromination and that hydrogen bromide stimulates the enolization. We, also, had noted that hydrogen bromide catalyzed the reaction of cholestenone with iodine monobromide (Figs. 2 and 3). Further, the reaction of cholestenone with iodine monobromide in carbon tetrachloride–glacial acetic acid, and in carbon tetrachloride alone, was found to be monomolecular. These results are similar to those obtained using cholestanone. Cholestenone reacted similarly to cholestanone in one other respect. Cholestenoxime, like cholestanoxime, resisted halogenation in the presence of glacial acetic acid (Fig. 1 and Table II). (Added hydrogen bromide did not

Table II

Equivalents of Halogen Consumed per Mole of Substance Reacting with Iodine Monobromide for Ninety Minutes

	In CCl_4 + CH_3COOH		In CCl_4	
Substance	In air	In H_2	In air	In H_2
Cholestanone	2.37	2.49	3.49	4.10
Cholestanoxime	0.11	0.13	0.57	0.63
Cholestenone	.43	.45	0.60	0.80
Cholestenoxime	.15	.15	1.17	1.24
Cholestenoxime[a]	...	...	0.80	...
Cholestenoxime[b]	...	...	1.20	...
Benzalacetophenone	...	...	1.70	...
syn-Styrylphenylketoxime		...	1.42	1.42
3,5-Diphenylisoxazol		...	1.35	1.37
3,5-Diphenylisoxazoline		...	0.11	0.11

[a] Cholestenoxime, recrystallized from glacial acetic acid. [b] Cholestenoxime, recrystallized from glacial acetic acid and then heated to 120°.

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(15) Inhoffen, *Ber.*, **69B**, 2141–7 (1936).

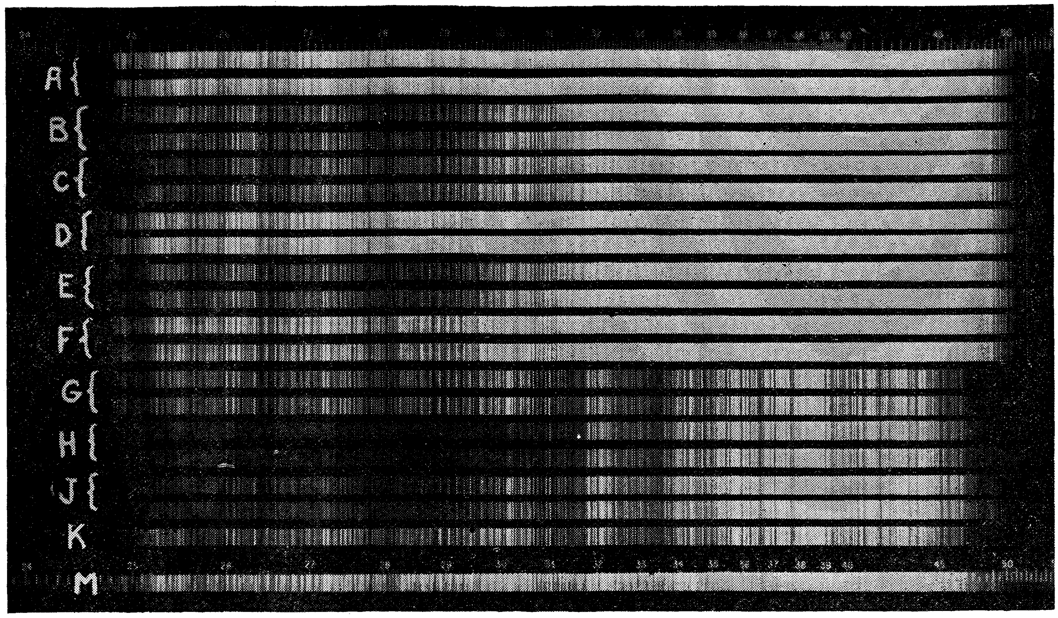

Plate 1.—Ultraviolet absorption spectra of cholestanone in various solvents: A, chloroform control; B, 0.02 *M* cholestanone in chloroform; C, 0.01 *M* cholestanone in chloroform; D, chloroform in 0.04 *M* glacial acetic acid; E, 0.02 *M* cholestanone in chloroform—0.04 *M* glacial acetic acid; F, 0.01 *M* cholestanone in chloroform—0.04 *M* glacial acetic acid; G, chloroform—0.04 *M* glacial acetic acid—0.01 *M* anhydrous hydrogen bromide; H, 0.02 *M* cholestanone in same solvent; J, 0.01 *M* cholestanone in same solvent; K, like J but with 2 × exposure; M, chloroform control.

induce any greater reaction.) This fact was further circumstantial, but not absolute, evidence that cholestenone enolizes during halogenation.

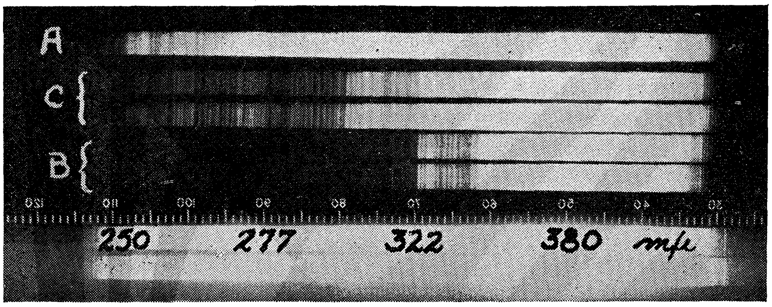

Plate 2.—Ultraviolet absorption spectra of enol ethyl ether of cholestanone: A, chloroform control; B, 0.02 *M* enol ethyl ether of cholestanone (based on the molecular weight of cholestanone) in chloroform; C, 0.01 *M* enol ethyl ether of cholestanone in chloroform.

The lack of appreciable reaction between cholestenoxime and iodine monobromide in glacial acetic acid–carbon tetrachloride indicated that, at least in that medium, the double bond of cholestenoxime was not "active." Inhoffen[15] has shown that the ethylene linkage of cholestenone resists bromination and exerts only a directive influence. It seemed to us that the simple statement, *the double bond is not active*, was not sufficient in the case of cholestenoxime. Accordingly, other factors were investigated. Our cholestenoxime was real, or normal, and was not the by-product described by Diels and Abderhalden,[16] for it melted at 151° and did not reduce Fehling's reagent. Air (oxygen) inhibition[17] was not involved (Table II). The nature of the reaction medium was found to affect the extent of reaction (at the end of the arbitrarily selected ninety minutes) of cholestanone, of cholestanoxime, of cholestenone, and of cholestenoxime. The effect was most marked in the case of the last substance and was paralleled by the effect upon the reactions of styryl phenyl ketone and *syn*-styryl phenyl ketoxime with iodine monobromide (Table II). There were five (at least) possible explanations for this marked difference: first, only the rates of reaction in the two media dif-

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[16] Diels and Abderhalden, *Ber.*, **37**, 3101 (1904).

[17] Bauer and Daniels, THIS JOURNAL, **56**, 2014 (1934).

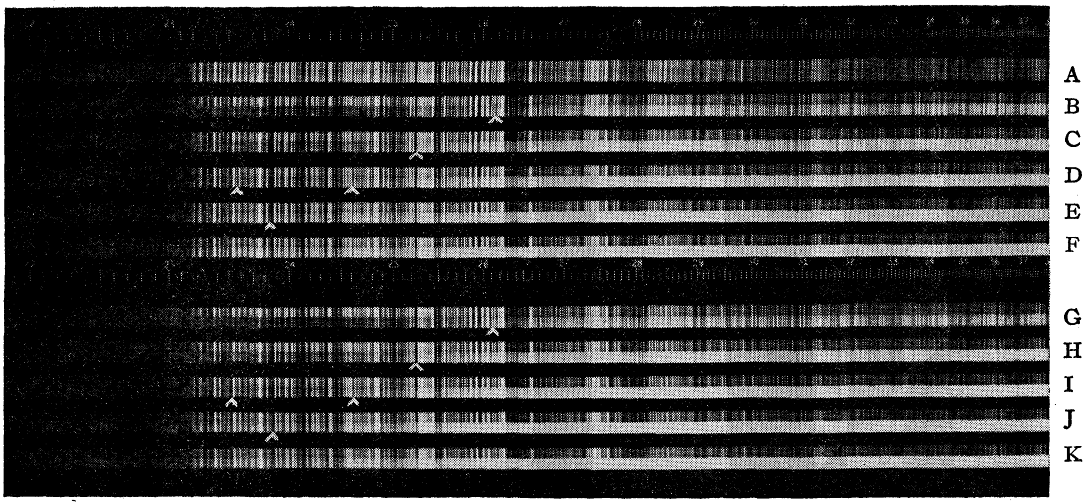
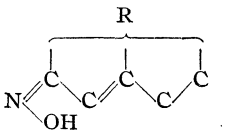
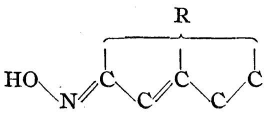


Plate 3.—Ultraviolet absorption spectra of "cholestenoxime" (after crystallization from glacial acetic acid) and of cholestenoxime: solvent, absolute alcohol; tube length 1 cm.; concn., 0.002% or 5 × 10^{-5} molar. Upper half of each spectrograph is that of the controlled or measured light; lower half is that of experimental substance. "Cholestenoxime:" A, control at $d = 0$; B, $d = 0.6$; C, $d = 1.0$; D, $d = 1.2$; E, $d = 1.40$; F, $d = 1.5$. Cholestenoxime: G, $d = 0.6$; H, $d = 1.0$; I, $d = 1.2$; J, $d = 1.4$; K, $d = 1.5$.

fered;[18] second, in the presence of glacial acetic acid, cholestenoxime might have rearranged to Diels and Abderhalden's by-product,[16] but this was not likely; third, glacial acetic acid might have added to the double bond—not at all probable; fourth, in glacial acetic–carbon tetrachloride, cholestenoxime might have undergone cyclization to produce an isoxazoline,[19,20] which cyclization would not occur in carbon tetrachloride alone; fifth, in glacial acetic–carbon tetrachloride, the stereoisomeric cholestenoxime A might have existed, whereas in carbon tetrachloride, B might have existed.


A


B

In A, due to the proximity of the two groups, coördination between the oximino hydroxyl and the ethylene linkage might have retarded halogenation. In B, the relations would not favor such action.

When cholestenoxime was dissolved in glacial acetic–carbon tetrachloride and recrystallized from that medium, crystals were obtained which differed in form from those of the original oxime and melted at 60°, resolidified around 90°, and remelted at 151.8° (m. p. of cholestenoxime). The new compound lost weight when it was heated to 90° or more, but this loss was too small for it to have been due to loss of solvent of crystallization. Since the nitrogen content of the compound was the same as that of cholestenoxime, the substance was not an addition product of acetic acid and cholestenoxime. It did not reduce Fehling's reagent, and so was not Diels and Abderhalden's[16] by-product. Its ultraviolet absorption spectrum appeared to be the same as that of the original cholestenoxime (Plate 3). Therefore, it was probably not an isoxazoline (the absorption spectrum of an isoxazoline should differ markedly from that of an α,β-unsaturated ketoxime). The apparent identity of the ultraviolet absorptions of the new compound and the cholestenoxime, together with the evident ease of converting the one into the other (after being heated to 120°, the new compound did not depress the melting point of cholestenoxime), indicated that the two were probably stereoisomeric ketoximes. When the new compound was allowed to react with iodine monobromide in carbon tetrachloride, it did so more slowly than did either the heat transformed substance or the original cholestenoxime (Table II). Unfortunately, in the only case on record where two stereoisomeric ketoximes have been halogenated, no statement concerning the relative speeds of the halogenations was made.[21] Moreover, the same product (*syn*-

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[18] Böeseken and Gelber, *Rec. trav. chim.*, **46**, 158 (1927).

[19] Blatt, This Journal, **53**, 1137 (1931).

[20] Auwers and Seyfried, *Ann.*, **484**, 201–2 (1930).

[21] Blatt and Stone, This Journal, **53**, 4137 (1931).

dibromostyryl *p*-bromophenyl ketoxime) resulted from the action on both isomers.

Although increased initial concentrations of hydrogen bromide increased the initial rate of halogenation, these greater concentrations depressed the total amount of halogen consumed by cholestenone and by cholestanone (Fig. 2). Such phenomena, at least in other reactions,[22] are usually due to not less than two opposing forces. In these studies, the increased rates were due to the usual catalyzation of enolization. The repression of the halogenation observed at the longer reaction times (four or more hours) was due to the action of the hydrogen bromide but not to that of water, although water did repress the halogenation over its entire course[9] (Figs. 2 and 3). There appeared to be no differences between the general nature of the reactions at low and that at high hydrogen bromide concentrations: monomolecular at 2.5 and at 12.5 millimol. of hydrogen bromide per liter of reaction mixture. A clue as to the probable nature of the repressing action was seen in the fact that, at the lower hydrogen bromide concentration, only 45% of the reacted halogen was organically bound, whereas, at the higher concentration, 55% was so bound. According to Inhoffen,[15] the mechanism of the bromination of cholestenone is: 1, enolization; 2, bromine addition; 3, cleavage of halogen acid; 4, allylation; 5, enolization; 6, bromine addition; 7, halogen acid cleavage; 8, etc. Up to step 3, the product is an unstable dibromide. A stable dibromide results from the whole process. If the hydrogen bromide had partially inhibited step 3, the result would have been a diminished consumption of halogen but a larger proportion of that consumed would have been organically bound. On the other hand, direct addition of hydrogen bromide to the cholestenone in stage 1 could have produced the same observed relations. However, no halogenated steroid was obtained when, in the absence of iodine monobromide, cholestenone was treated with an extremely high concentration of hydrogen bromide.

It is well known that hydrogen bromide, iodine, and bromine interact to form complexes such as I_2Br^-, IBr_2^-, IBr_3, Br_3^-, and others. Of these I_2Br^- forms the least readily.[23,24] Transmission measurements (Fig. 4) showed that, in the medium we employed in our studies, a relatively low concentration of hydrogen bromide produced evidence of complex formation with iodine monobromide and with bromine, but that there was little evidence of iodine–Br^- complexes unless the hydrogen bromide concentration was relatively large. Furthermore, by other means, it was found that bromine was the active agent in iodine monobromide, a fact recently reported by Militzer also[25] (Fig. 5). Thus it was evident that an increase in the initial concentration of hydrogen bromide, while stimulating enolization, was also decreasing the concentration of the active halogenating agent. This latter action could have caused the diminished consumption of halogen.

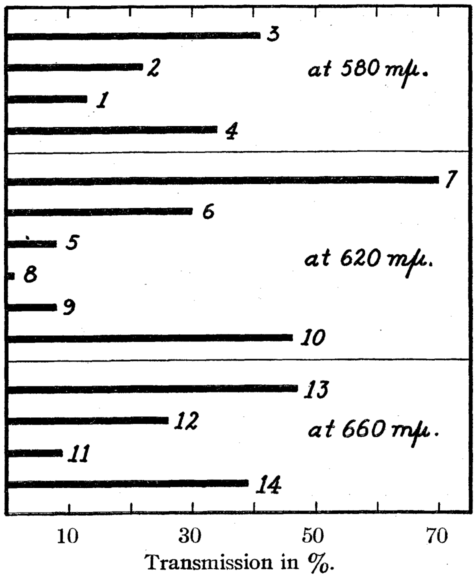

Fig. 4.—Light transmission through bromine, iodine, and iodine monobromide solutions with and without hydrogen bromide: solvent, glacial acetic acid; 1, 0.04 *N* bromine; 2, 0.03 *N* bromine; 3, 0.02 *N* bromine; 4, 0.04 *N* bromine–0.0232 *M* HBr; 5, 0.005 *N* iodine; 6, 0.0025 *N* iodine; 7, 0.0013 *N* iodine; 8, 0.01 *N* iodine–0.0058 *M* HBr; 9, 0.005 *N* iodine–0.0029 *M* HBr; 10, 0.005 *N* iodine–0.0261 *M* HBr; 11, 0.04 *M* iodine monobromide; 12, 0.02 *M* iodine monobromide; 13, 0.01 *M* iodine monobromide; 14, 0.04 *M* iodine monobromide–0.0232 *M* HBr.

Reaction Products

We did not isolate any of the products of the reaction of iodine monobromide with cholestenone, but, inasmuch as bromination resulted from the treatment with iodine monobromide, they, undoubtedly, would have been the same as those

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[22] Nicholson and Holly, Jr., *Ind. Eng. Chem.*, **30**, 114 (1938).

[23] Forbes and Faull, Jr., THIS JOURNAL, **55**, 1820 (1933).

[24] Faull, Jr., *ibid.*, **56**, 522 (1934).

[25] Militzer, *ibid.*, **60**, 256 (1938).

described by Inhoffen[15] and by Butenandt, *et al.*[26,27]

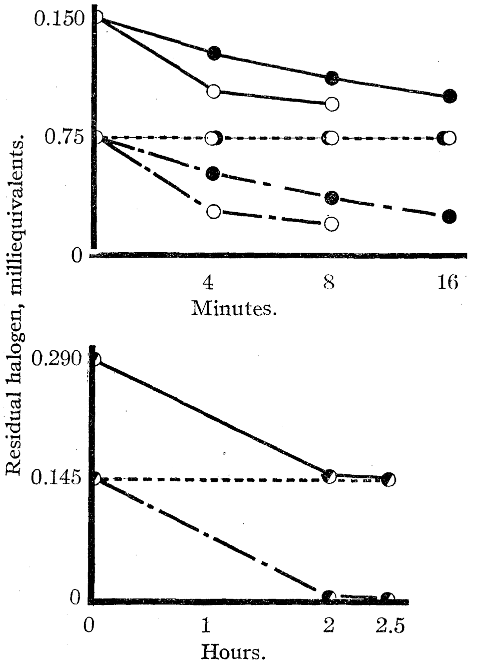
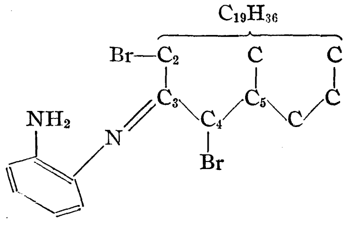


Fig. 5.—Residual total halogen, iodine, and bromine at certain periods in the reaction of iodine monobromide with cholestanone, with 2-bromocholestanone, and with cholestenone (solvent, carbon tetrachloride): ○, cholestanone; ●,2-monobromocholestanone; ◐,cholestenone; - - - - - - -, iodine; — - —, bromine; ———, total halogen.

From β-cholestanone–iodine monobromide reaction mixtures, three compounds were isolated: a monobromide, m. p. 171.5°; and two dibromides, m. p. 147 and 194°, respectively. The monobromide proved to be 2-monobromocholestanone.[7] Although the one dibromide (m. p. 147°) has not, as yet, been identified, it must contain at least one bromine atom at position 2 of the steroid structure, for it was a product of the reaction of iodine monobromide with 2-monobromocholestanone also.

The other dibromo compound (m. p. 194°) has been the subject of much debate. Ruzicka, *et al.*,[14] maintained that it was 2,2-dibromocholestanone, while Butenandt, *et al.*,[26] identified it as 2,4-dibromocholestanone. Lately, the latters' findings have been confirmed.[28] Although we firmly believe that the compound is 2,4-dibromocholestanone, we must admit that we were unable to get a diosphenol by treating it with potassium acetate.[26] On the other hand, the compound did yield a derivative with *o*-phenylenediamine, but this derivative was not the quinoxaline described by Ruzicka,[14] although it did have the same melting point (184°). It still contained halogen. Inasmuch as one bromine in the dibromo compound is known to be at position 2, and in view of the fact that the nitrogen and the halogen content of the *o*-phenylenediamine derivative were such as to indicate the presence of two atoms of each, it is believed that this *o*-phenylenediamine derivative was 3-*o*-aminoanilido-2,4-dibromocholestane, m. p. 184°, $C_{33}H_{50}N_2Br_2$, or



Materials

Cholestenone, $\Delta^{4,5}$, m. p. 81°, prepared according to Windaus[29] and Schoenheimer.[30]

Cholestanone, m. p. 129.5°, according to Doreé.[6]

Cholestenoxime, m. p. 151°; and *cholestanoxime,* m. p. 199°, according to Diels and Abderhalden.[16]

2-Monobromocholestanone, m. p. 171.5°.[7]

Benzalacetophenone, m. p. 57–58°, a recrystallized Eastman Kodak Co. product.

syn-**Styryl phenyl ketoxime,** m. p. 116°,[19,21] prepared as described by Henrich.[31]

3,5-Diphenylisoxazol, m. p. 140°,[32,33] prepared according to Goldschmidt.[34]

3,5-Diphenylisoxazoline, m. p. 75°,[19,20,33] prepared as described by Henrich.[31]

Experimental

The Reaction of Iodine Monobromide with Cholestenone, with Cholestanone, with Cholestenoxime, and with Cholestanoxime.—Twenty cc. of 0.0167 *M* steroid in carbon tetrachloride was pipetted into one arm of a T-tube (turned on its side), while 40 cc. of approximately 0.08 *N* iodine monobromide in glacial acetic acid was measured accurately into the foot of the T-tube. After the two solutions had come to temperature (25°), they were mixed quickly. At the end of definite intervals of time, 6-cc. aliquot portions were removed for analysis. Residual or

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(26) Butenandt, Schramm, Wolff and Kudzus, *Ber.*, **69B**, 2779–2783 (1936).

(27) Butenandt, Schramm and Kudzus, *Ann.*, **531**, 176–208 (1937).

(28) Inhoffen, *Ber.*, **70**, 1695 (1937).

(29) Windaus, *ibid.*, **39**, 518 (1906).

(30) Schoenheimer, *J. Biol. Chem.*, **110**, 461 (1935).

(31) Henrich, *Ann.*, **351**, 172 (1907).

(32) Fleck, Dissertation, Leipzig, 1903.

(33) Auwers and Muller, *J. prakt. Chem.*, **137**, 57, 81 (1933).

(34) Goldschmidt, *Ber.*, **28**, 986 (1895).

unreacted halogen, halogen acid, and organic halogen were determined as previously described.[1] The total halogen consumed and the organically bound halogen are plotted in Fig. 1, as equivalents of halogen per mole of sterol, against reaction time in hours.

The Order of the Reaction of Cholestenone, of Cholestanone, and of 2-Monobromocholestanone with Iodine Monobromide.—In determining the order of reaction, we employed the method described by Lewis[35] in which the time required for any fraction of the initial concentration (the initial concentrations of all reacting components are made equal) of a substance to react is compared with the time required for the same fraction to react when the initial concentration is different from the first. By this method, $n = 1 + \frac{\log t_2/t_1}{\log a_1/a_2}$, where n is the order of the reaction, t_1 and t_2 are the respective reaction times, and a_1 and a_2 are the respective initial concentrations. If a_1 is made equal to $2a_2$, then $n = 1 + \frac{\log t_2/t_1}{\log 2}$, or $2^{n-1} = t_2/t_1$.

In actually making the determinations, the steroid solution was measured into a 200 × 25 mm. test-tube and the iodine monobromide was measured from a microburet into a thin-walled glass bulb. The bulb was carefully slid into the tube and then quickly broken by means of a glass rod passed through the stopper used to close the tube. At the expiration of one or two or four or eight, etc., minutes, 3 cc. of 0.05 *M* potassium iodide was added and the unreacted halogen was titrated with standard sodium thiosulfate. As an example of the results, a sample of those for cholestanone are given in Table I. (The notation $C = 0.082$ *mM* means that there were that many milliequivalents of each reactant in the mixture.) The reaction was first order for each of the substances tested.

The Effect of Hydrogen Bromide upon the Reaction of Iodine Monobromide with Cholestenone, with Cholestanone, and with 2-Monobromocholestanone.—These reactions were run and the results obtained in a manner similar to that used for the study of the reaction of iodine monobromide with cholestenone and cholestanone, except that varying initial concentrations of hydrogen bromide were secured by adding definite quantities of aqueous 48% hydrogen bromide, or anhydrous hydrogen bromide in glacial acetic acid, to the iodine monobromide solutions. The results of the studies on cholestenone are plotted as equivalents of halogen consumed per mole of steroid (Figs. 2 and 3). The effect upon the reactions with cholestanone and 2-monobromocholestanone was the same except for slight differences in degree.

The Ultraviolet Absorption Spectrum of Cholestanone as Affected by Hydrogen Bromide.—Two hundredths molar (0.02 *M*) solutions of cholestanone in chloroform, in 0.04 *M* glacial acetic acid in chloroform, and in 0.04 *M* glacial acetic acid and 0.01 *M* anhydrous hydrogen bromide in chloroform were prepared. Diluting solutions like those above, but not containing the steroid, were also prepared. Using a 25-mm. absorption cell, photographs were made of the spectra of each solvent and of 0.02 and of 0.01 *M* cholestanone (Plate 1). Photographs were made of the spectra of chloroform and of 0.02 and 0.01 *M* enol ethyl ether of cholestanone in chloroform[36] (Plate 2). Unfortunately, the instrument used in the first part was not available for this second work.

The Reaction of Iodine Monobromide with Certain Substances as Affected by: (a) Nature of Solvent, (b) Air (Oxygen) and Hydrogen.—Cholestenone, cholestenoxime, cholestanone, cholestanoxime, benzalacetophenone, *syn*-styryl phenyl ketoxime, 3,5-diphenylisoxazol, 3,5-diphenylisoxazoline, and a product derived from cholestenoxime, by treatment with glacial acetic acid, were the materials used in these experiments. In each case, 0.033 mmol. of the substance was weighed accurately and transferred to a 200 × 32 mm. test-tube. Two cc. of carbon tetrachloride was added. The tube was closed with a two-holed rubber stopper carrying a glass stopcock and a glass tube closed by means of pinch-clamp on a rubber tube. The test-tube was evacuated and filled with hydrogen three times. Then 4 cc. of 0.04 *M* iodine monobromide in glacial acetic acid or in carbon tetrachloride was admitted. After ninety minutes, the unreacted halogen was titrated with standard thiosulfate. These experiments, but with the omission of the evacuation and filling with hydrogen, were repeated (see Table II).

The Effect of Glacial Acetic Acid upon Cholestenoxime.—Two hundred milligrams of cholestenoxime was dissolved in 12 cc. of carbon tetrachloride and 24 cc. of glacial acetic acid. After one hour, the solution was concentrated *in vacuo* at a low temperature. Upon chilling the concentrate, crystals separated which were filtered, washed with cold alcohol and cold water, and dried by suction. These crystals melted at 60°, resolidified at 90°, and then remelted at 151.8° (the latter is the melting point of cholestenoxime). When weighed samples were heated to 120° and then reweighed, they were found to have lost 1.85% of their weight. The calculated loss of weight for solvent of crystallization would have been: for 1 CH_3COOH, 13.0%; for 1 C_2H_5OH, 10.3%; for 1 H_2O, 4.2%; and for ½ H_2O, 2.2%.

Anal. Calcd. for $C_{27}H_{45}ON$ (oxime or isoxazoline): N, 3.5. Found: N, 3.5, 3.52.

The absorption spectrographs of 0.002% solutions of cholestenoxime and of the above product from glacial acetic acid displayed the same maximum at 238 mμ ($\log \epsilon = 4.4$) (Plate 3).

Two samples of crystals, described above (the one sample was heated to 120° and cooled, while the other was not so treated), were allowed to react with iodine monobromide. The untreated material consumed less halogen than did the other (Table II).

The Effect of Small and of Large Initial Hydrogen Bromide Concentrations upon the Order of the Reaction of Iodine Monobromide with Cholestenone.—These experiments were carried out in the same way as the others preceding these, except two different iodine monobromide solutions were used. The one was made 0.005 *M* and the other 0.025 *M*, with respect to hydrogen bromide. The reaction was first order in both solutions.

The Relation between the Halogen Combined with and the Total Consumed by Cholestenone Reacting with Iodine

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[35] Lewis, "A System of Physical Chemistry," Vol. I, Longmans, Green and Company, New York, N. Y., 1918, pp. 397–8, B.

[36] The author wishes to thank Dr. G. H. Cartledge, of the University of Buffalo, Chemistry Department, for his aid and suggestions in the spectrophotometric work.

Monobromide Solutions Containing Small and Large Initial Amounts of Hydrogen Bromide.—The solutions of cholestenone and iodine monobromide were 0.035 *M*. The iodine monobromide solutions were made 0.005 and 0.025 *M*, with respect to hydrogen bromide. At the end of seven hours, total halogen consumed and organically bound halogen were determined as in the first "experimental" section. At seven hours, in the lower concentration of hydrogen bromide, cholestenone had reacted with 0.9 equivalent of halogen per mole of steroid. Of this 0.4 equivalent, or 45%, was organically bound. At the higher concentration of hydrogen bromide, the results were: 0.8 reacted and 0.46, or 55%, bound.

Attempt to Find Products of the Addition of Hydrogen Bromide to Cholestenone and to Cholestanone.—Solutions of 0.2 g. of cholestenone and of 0.2 g. of cholestanone in 20 cc. of carbon tetrachloride were prepared. Each solution was "loaded" with 2.5 cc. of 4.27 *N* anhydrous hydrogen bromide in glacial acetic acid. After four hours, the solutions were brought to dryness *in vacuo*. The residues from each were recrystallized from alcohol. No halogen containing products were found.

The Effect of Added Hydrogen Bromide upon Bromine, upon Iodine, and upon Iodine Monobromide in Glacial Acetic Acid.—Solutions of bromine, of iodine, and of iodine monobromide in glacial acetic acid were prepared. To portions of each, definite quantities of 4.27 *N* hydrogen bromide in glacial acetic acid were added. (For concentrations, please see the key to Fig. 4.) The transmission of light of various wave lengths was measured through 1 dm. of each solution. The results are shown as a barogram in Fig. 4. Only a few wave lengths are shown in order to avoid complexity.

Evidence that the Bromine of Iodine Monobromide, and Not the Iodine, nor Iodine Monobromide, Reacts with the Steroid in the Reactions under Investigation.—Into each of several large test-tubes were pipetted 2 cc. of 0.0167 molar solutions of steroid (cholestanone and 2-monobromocholestanone) in carbon tetrachloride and 2 cc. of 0.0373 *M* iodine monobromide in carbon tetrachloride. In the case of cholestenone, double the indicated volumes were used. At the end of definite intervals of time, total residual halogen was determined in the usual way, while the residual iodine was determined by means of a modification of a procedure for the determination of iodine and bromine in the presence of one another as described by Spitzer.[37] Our procedure was: to the reaction mixture, at the expiration of the reaction period selected, 3 cc. of 3% potassium bromide in water and 0.75 cc. of 5% sodium formate (made from redistilled formic acid) were added and the mixture was shaken moderately for three minutes. This treatment reduced the residual bromine but left the iodine untouched (glacial acetic acid must be absent). Then 3–5 cc. of 0.05 *M* potassium iodide was added and the iodine was titrated in the usual manner. Residual bromine was taken as the difference between the total residual halogen and the residual iodine. The results are plotted as milliequivalents of residual halogen against the time of reaction (Fig. 5). Iodine did not react.

The Isolation of the Products of the Reaction of Iodine Monobromide with Cholestanone.—A solution of 4.95 g. of cholestanone in 660 cc. of carbon tetrachloride was mixed with 1320 cc. of 0.04 *M* iodine monobromide in glacial acetic acid. A 6-cc. aliquot of this mixture required 4.37 cc. of 0.0737 *N* thiosulfate for the complete reduction of the halogen. When the titer had fallen to and remained constant at 2.95 cc. (2.7 equivalents of consumed halogen per mole of steroid), water, potassium iodide, and thiosulfate were added to remove the excess halogen. The carbon tetrachloride layer was washed free of acid with plenty of water and sodium bicarbonate. It was then dried and distilled *in vacuo*. The residue was leached with warm alcohol, from which, upon being cooled, crystals separated. Fractionation of these, with methyl alcohol–acetone, yielded three products: A, 3.60 g., m. p. 171.5°; B, 0.08 g., m. p. 147°; and C, 0.15 g., m. p. 194°.

Determination of the halogen content of each of these products was effected by means of the Willard–Thompson method.[38]

Anal. Subst. A. Calcd. for $C_{27}H_{45}OBr$: Br, 17.2. Found: Br, 17.9. Subst. B. Calcd. for $C_{27}H_{44}OBr_2$: Br, 29.4. Found: Br, 30.1. Subst. C. Calcd. for $C_{27}H_{44}OBr_2$: Br, 29.4. Found: Br, 30.4.

A is, therefore, monobromo, and B and C are dibromo compounds. It is noteworthy that a small amount of B and a larger amount of C were obtained when A reacted with iodine monobromide under the same conditions that produced A, B, and C from cholestanone.

The Action of Potassium Acetate upon Compound A (m. p. 171.5°).—Two-tenths gram of A and 19 cc. of 21% fused potassium acetate were mixed and heated at 200° for five hours. The mixture was then diluted with water and extracted several times with small portions of ether. The combined extracts were washed free of acid, dried, and distilled *in vacuo*. The residue, recrystallized from dilute alcohol, yielded a small amount of fine plates which melted at 111°. This melting point corresponds to that given for $\Delta^{1,2}$-cholestenone which is obtainable by the action of potassium acetate upon 2-monobromocholestanone.[7]

The Action of Dry Pyridine upon Compound A (m. p. 171.5°).—Two-tenths gram of A was dissolved in 8 cc. of dry pyridine and refluxed for fifteen hours. When the solution had cooled, 30 cc. of ether was added. The pyridine was washed out with water. The ether was dried and then distilled *in vacuo*. The residue, when recrystallized, proved to be the original starting material. The bromine of A was, therefore, not in position 4 or 5, but rather in position 1 or 2. This is further evidence that A is 2-monobromocholestanone.

The Action of Fused Potassium Acetate upon Compound B (m. p. 147°).—One-tenth gram of compound B was dissolved in 3 cc. of benzene and 7 cc. of absolute alcohol. Powdered fused potassium acetate was added and the mixture was allowed to stand at room temperature for forty-eight hours. Ether and water were then added. The ether layer was washed, dried, and distilled *in vacuo*. The residue crystallized from acetone as fine needles (m. p. 119°). The crystals contained no halogen. For want of material, no further work was done on compound B.

The Action of Fused Potassium Acetate and of Dry Pyridine upon Compound C (m. p. 194°).—Although compound C was treated with fused potassium acetate and

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[37] Spitzer, *Ind. Eng. Chem., Anal. Ed.*, **8**, 465 (1936).

[38] Willard and Thompson, THIS JOURNAL, **52**, 1893 (1930).

with dry pyridine exactly as was A, no definitely crystalline product was obtained. Nor was a definitely pure crystalline product obtained when 650 mg. of compound C was refluxed with 60 cc. of butyl alcohol containing 3 g. of potassium acetate. The impure products, in each case, did not give a typical positive diosphenol reaction with ferric chloride. It did give a dirty brownish-red color, which, possibly, could be called positive.[26]

The Action of *o*-Phenylenediamine upon Compound C (m. p. 194°).—A solution of 0.5 g. of C and 0.2 g. of *o*-phenylenediamine in 170 cc. absolute alcohol was refluxed for five hours. The alcohol was then carefully distilled at low temperature *in vacuo*. The residue was dissolved in ether and the excess phenylenediamine was extracted with dilute hydrochloric acid. The ether, after being washed thoroughly, was dried and distilled *in vacuo*. The residue, dissolved in alcohol, yielded crystals which melted at 184°. This was the same as the melting point given for the compound said to be the quinoxaline derived from the purported 2,2-dibromocholestanone.[14] But our derivative still contained halogen.

Anal. Calcd. for $C_{33}H_{50}N_2Br_2$: N, 4.41; Br, 25.2. Found: N, 4.34; Br, 25.6.

Summary

1. The reactions of cholestenone and of cholestanone with iodine monobromide possess autocatalytic characteristics.

2. The reaction of iodine monobromide with cholestenone, with cholestanone, and with 2-monobromocholestanone is first order.

3. The oximes of cholestenone and cholestanone do not react readily with iodine monobromide in glacial acetic acid.

4. As in the case of the action of bromine upon cholestenone, evidence indicates that enolization is the first step in the reaction of cholestenone with iodine monobromide.

5. Hydrogen bromide speeds the action of iodine monobromide upon cholestenone, cholestanone, and 2-monobromocholestanone, but it has no detectable influence on the reaction with the oxime of either cholestenone or cholestanone.

6. The double bond in cholestenoxime is resistant to halogenation in a glacial acetic acid containing medium.

7. There is some evidence that cholestenoxime undergoes a rearrangement in glacial acetic acid.

8. In concentrations of hydrogen bromide greater than a small amount, the total halogen consumed by cholestenone, by cholestanone, and by 2-monobromocholestanone is decreased, but the proportion of organically bound halogen is increased.

9. The inhibiting influence of the larger concentrations of hydrogen bromide may be due to its effect on intermediate steps in the reactions, or to its formation of complexes with bromine or with iodine monobromide.

10. Bromine is the active ingredient of iodine monobromide.

11. 2-Monobromocholestanone, m. p. 171.5°, is a product of the reaction of cholestanone with iodine momobromide.

12. An unidentified dibromo derivative of cholestanone was isolated (m. p. 147°).

13. Further evidence that the dibromocholestanone, melting at 194°, is 2,4-dibromocholestanone, and not 2,2-dibromocholestanone, is given.

BUFFALO, N. Y. RECEIVED MARCH 30, 1938

[CONTRIBUTION FROM THE BELL TELEPHONE LABORATORIES]

An Electron Diffraction Examination of Some Linear High Polymers

BY K. H. STORKS

Because of the general structural similarities between synthetic linear polyesters and many natural fibers, fundamental studies of the simpler compounds are of obvious importance. Several members of a series of these esters have been made the subject of X-ray study by Fuller and Erickson.[1] It is possible to prepare many of these in the form of films suitable for examination by electron diffraction. The experiments to be described here have two purposes: to demonstrate the utility of the electron diffraction method for studies of the structure of highly polymerized materials, and to discover the behavior of macromolecules in extremely thin layers. The methods are shown to be equally applicable to the natural polymer gutta-percha.

The fact that these materials can be cold drawn to a considerable extension without breakage is well known,[2] a high degree of orientation

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[1] C. S. Fuller and C. L. Erickson, THIS JOURNAL, **59**, 344 (1937).

[2] W. H. Carothers and J. W. Hill, *ibid.*, **54**, 1579 (1932).

being produced in the samples by this "stretching." Electron diffraction data for stretched polymers are directly comparable with many of the available X-ray data, and such a comparison will serve to demonstrate the utility of the method. In order to make this comparison polyethylene succinate, polyethylene adipate, polyethylene sebacate and two specimens of unvulcanized gutta-percha[3] (containing a small amount of antioxidant) have been examined in the stretched condition.

The second aim of this paper is accomplished by examinations of the conditions existing in unstretched films. Unstretched films of polyethylene sebacate and the two grades of gutta-percha have been studied.

Experimental

The transmission method is used exclusively in the experiments to be described here, the materials to be examined being prepared in the form of films 10^{-5} cm. or less in thickness. A film to be examined is placed in the path of a well-defined beam of electrons of homogeneous velocity and the resulting diffraction pattern recorded on a photographic plate. The camera employed has been described by Germer.[4]

Preparation of Stretched Films.—Specimens for examination in the stretched condition are prepared from relatively thick preliminary films. Such a preliminary film, approximately 10^{-4} cm. thick, is deposited on a conditioned microscope slide[5] by evaporation of a solution (approximately 2%) of the polymer in chloroform. If the slide is held at an angle of approximately 30° to the horizontal a long narrow strip of film with one end relatively thick is deposited when a drop of this solution is allowed to flow freely along the length of the slide.

The preliminary film prepared in this way on a glass slide may be stretched by one or both of two different methods, the choice of method being determined by ability of the film to resist change on contact with water. Films of polyethylene adipate and polyethylene sebacate are transferred from the slide to a water surface[6] and thence to a pair of jaws that can be separated by a screw. When all trapped water has evaporated the film is stretched by turning the screw. The stretched film is refloated and transferred to a slit type foil holder.[7] The orientation of the stretching direction is carefully noted. After all water has evaporated the film is found to be mounted firmly but without tension.

Films of stretched polymers also can be prepared and mounted without contact with liquid water. After the preliminary film is deposited, the thick end is loosened from the glass with a razor blade and the free end wound up on a round jeweler's file. The film can now be separated from the glass and stretched in the same operation. Best results are accomplished if the film leaves the slide at an angle of approximately 30° and if the stretching is continuous and rather rapid. If the stretched film is held under tension and laid across the foil holder the natural tackiness of the material will hold it in place and maintain the tension. This technique is found to be necessary when preparing polyethylene succinate films, and to be the simplest method of preparing stretched specimens of gutta-percha.

A double purpose is accomplished by each method of stretching; the films are thinned sufficiently for examination, and a high degree of fibrous orientation is produced.

Preparation of Unstretched Films.—If the pattern of an unstretched specimen is to be obtained, the proper thickness for examination must be deposited upon the glass slide. The thinner film is deposited from a more dilute solution (approximately 0.4%). These chloroform solutions do not spread well on monolayers of grease and mechanical spreading is found to be necessary. An efficient mechanical spreader has been made by clamping a new and freshly cleaned razor blade, edge down, above and parallel to a smooth level surface. A microscope slide, beneath which lies a thin sheet of paper, is placed under the blade which is lowered to a position of uniform and light contact. After removal of the paper spacer and after conditioning the slide, the latter is replaced and a drop of solution, in position near one end, is uniformly distributed over the conditioned surface by a single translation of the slide under the blade. After evaporation of the solvent the film is transferred to a water surface and finally to a foil holder. No indications have been found that a film is stretched by this manipulation.

Film Thickness Measurements.—Since knowledge of film thickness is of importance in interpretation of some of the following results, the method of obtaining this value will be indicated. A film of the polymer is prepared and mounted, from water, on a clean polished chromium surface. A known number of layers of barium stearate are now added to the polymer film by the Blodgett technique.[8] The interference color of the composite film is compared with colors of known numbers of barium stearate layers on a reference slide, and the barium stearate equivalent thickness is easily and accurately determined.

Extra Precautions.—All films are prepared at room temperature and, in most cases, under normal illumination from tungsten filament lamps. The early experiments upon the "Br-4" grade of gutta-percha have been repeated with the "Pure White" product[9] under low intensity

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(3) These specimens were the "Br-4" and the "Pure White" grades of gutta-percha from "The Netherlands East Indies Government Rubber and Gutta-Percha Plantations, Buitenzorg, Java."

(4) L. H. Germer, *Rev. Sci. Instruments*, **6**, 138 (1935).

(5) A conditioned microscope slide is a slide coated with a monomolecular layer of grease. This layer is of considerable importance if thin films are to be easily separated from glass. The monolayer can be deposited from clean dry cheesecloth if a freshly cleaned slide is vigorously rubbed with this material.

(6) The transfer, microscope slide to water surface, is easily accomplished if the slide is held, film side up, at an angle of approximately 15° to the horizontal and lowered slowly through a clean water surface. The film is separated from the glass by this procedure and is left floating. The floating film is transferred to a holder by raising the holder under the film. The film is mounted more smoothly if the holder is uniformly wet by water.

(7) See Fig. 4, L. H. Germer and K. H. Storks, *Proc. Nat. Acad. Sci.*, **23**, 390 (1937).

(8) K. B. Blodgett, THIS JOURNAL, **56**, 495 (1934).

(9) This material had been removed from the sealed shipping container and stored in a refrigerator away from light for about six months. The stock solution was made up from material from the inside of a massive block.

illumination from a 10-watt Mazda red lamp. Rate of oxidation should be decreased considerably by this precaution. In addition, the stretching properties of a preliminary film have always been tested immediately prior to preparation of a film for examination in the unstretched condition; satisfactory stretching characteristics are taken as sufficient evidence that oxidation in solution has not been serious.

Experimental Results

Data from Stretched Polymers.—Figures 1–5[10] are electron diffraction patterns from stretched samples of polyethylene succinate, polyethylene adipate, polyethylene sebacate, gutta-percha "Br-4" and gutta-percha "Pure White." The vertical axis of each of these patterns is parallel to the direction along which the material was stretched. In each case the primary beam was normal to the foil surface. No additional reflections are found when a foil is rotated around the stretching direction.

Table I contains representative data from patterns of this sort. Columns headed (D) contain the diametral separation of symmetrical spots in mm.; estimated intensities of these reflections are given in the columns headed (Int.), the higher numbers being assigned to the stronger reflections; the small letter (d) indicates interplanar spacings, in one column X-ray values, and in the other, values calculated in these experiments from measured separations (D) by means of the formula

$$d = 2L\lambda/D \qquad (1)$$

(In Eq. (1) λ is the electron wave length and L the plate specimen separation; the constant $L\lambda$ is determined by calibration against a foil of metallic silver.) The X-ray values of (d) are those given by Fuller and Erickson[1] and the customary designation of reflections, which they use, are given in the first columns.

TABLE I

Ref.	D, mm.	Int.	d, Å. (These expts.)	d, Å. (X-rays)
Polyethylene succinate $L\lambda = 2.00_{(0)} \times 10^{-6}$ mm.^{2}				
A_1	7.45	0.5	5.37	5.37
A_2	8.95	10	4.47	4.41
A_3	10.5	12	3.81	3.85
A_4	12.9	2	3.10	3.12
A_5	14.9	2	2.68	2.70
A_6	17.2	1	2.33	2.29
A_7	21.0	2	1.90	1.92
A	30.0	0.5	1.33	
I_2	8.0	1	5.00	5.02
I_3	10.4	10	3.85	3.91
I_4	12.1	4	3.31	3.31
I	13.0	3	3.08	
I_5	13.5	3	2.96	2.94
II_2	13.0	4	3.08	3.04
II_4	15.55	1	2.57	2.52
II_5	17.45	2	2.29	2.26
II_6	18.4	1	2.17	2.18
II	20.4	2	1.96	
II	21.4	1	1.87	
II	23.3	1	1.72	
II	24.0	1	1.67	
III?	15.0	3	2.67	
III?	16.0	1	2.50	
III_1	17.9	4	2.23	2.20
III_2	18.9	4	2.12	2.09
IV_0	19.0	20	2.11	
IV_1	20.0	1	2.00	1.98
IV	21.0	1	1.90	
IV	21.7	2	1.84	
V	24.5	1	1.63	
V	25.4	2	1.57	
VI	29.6	1	1.35	
VI	32.3	3	1.24	
VI	33.6	1	1.19	
VII	34.2	1	1.17	
$VIII_0$	38.1	2	1.05	
Polyethylene adipate $L\lambda = 2.01_{(5)} \times 10^{-6}$ mm.^{2}				
A_2	9.6	14	4.20	4.15
A_3	11.3	13	3.57	3.63
A_5	13.8	4	2.92	2.95
A_6	16.0	5	2.52	2.52
A_8	18.4	5	2.19	2.17
A_9	19.5	5	2.07	2.08
A	20.9	1	1.93	
A	22.3	1	1.81	
A	24.6	2	1.64	
II_1	7.4	1	5.45	5.46
II_2	14.1	3	2.86	2.88
IV_1	14.9	3	2.70	2.72
IV_2	17.0	1	2.37	2.37
V_1	18.1	2	2.23	2.23
V_2	19.1	8	2.11	2.12
V	20.4	1	1.98	
V	22.8	1	1.77	
V	24.3	2	1.66	
VI	21.6	1	1.87	
IX_0	30.5	2	$1.32_{(1)}$	
X_0	33.9	5	$1.18_{(9)}$	
XI_0	37.1	1	$1.08_{(6)}$	
Polyethylene sebacate $L\lambda = 2.01_{(8)} \times 10^{-6}$ mm.^{2}				
A_2	9.6	15	4.20	4.17
A_3	11.2	14	3.60	3.67
A_5	13.6	4	2.97	2.96
A_6	16.0	8	2.52	2.51
A_8	18.2	5	2.22	2.18
A_9	19.3	7	2.09	2.08
A	20.7	2	1.95	
A	21.8	2	1.85	
A	23.0	2	1.75	

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[10] The extra expense for the illustration insert was borne by the Bell Telephone Laboratories.

TABLE I (*Concluded*)

Ref.	*D*, mm.	Int.	*d*, Å. (These expts.)	*d*, Å. (X-rays)
A	24.5	3	1.65	
A	28.8	1	1.40	
A	31.6	1	1.28	
III_1	7.8	1	5.17	5.14
III_3	13.95	1	2.89	2.88
V?	13.0	5	3.10	
V_2	15.9	2	2.54	2.54
VI_1	15.8	5	2.56	2.56
VI_2	17.05	3	2.37	2.35
VII_2	18.6	12	2.17	2.16
VII_3	19.8	3	2.04	2.01
VII_4	21.5	4	1.88	1.89
VII	23.6	3	1.71	
VII	25.6	2	1.58	
VII	28.5	2	1.42	
VII	29.5	2	1.37	
VII	31.5	1	1.28	
VII	32.7	1	1.23	
VII	36.6	1	1.10	
$VIII_1$	20.5	4	1.97	1.97
IX	22.6	2	1.79	
X	24.5	1	1.65	
XI	26.4	2	1.53	
$XIII_0$	31.0	5	$1.30_{(2)}$	
XIII	32.0	3	1.26	
XIV_0	33.4	6	$1.20_{(8)}$	
XIV	34.5	3	1.17	
XV_0	35.8	3	$1.12_{(8)}$	
XV	36.7	2	1.10	
XVI_0	38.15	2	$1.05_{(8)}$	
"Pure White" Gutta-percha[a]				
$L\lambda = 2.70_{(9)} \times 10^{-6}$ mm.^{2}				
A_4	9.2	0.5	5.89	5.95
A_7	11.5	10	4.71	4.73
A_8	14.0	10	3.87	3.91
A_{11}	18.4	3	2.94	2.98
A_{12}	19.7	4	2.75	2.78
A_{13}	23.0	8	2.36	2.37
A_{16}	28.0	1	1.94	1.95
A	28.5	3	1.90	
A	31.1	1	1.74	
A	34.5	1	1.57	
II_1	12.25	2	4.42	4.45
II_2	14.1	1	3.84	3.87
II_4	17.9	1	3.03	3.08
II_5	18.55	2	2.92	2.93
II_6	22.8	1	2.38	2.42
II_7	24.2	1	2.24	2.25
II	30.5	1	1.78	
II	43.3	1	1.25	
IV_0	22.9	8	$2.36_{(6)}$	2.36
IV_1	26.5	4	2.04	2.02
VI	35.8	3	1.51	
$VIII_0$	45.9	5	$1.18_{(0)}$	
XII_0	68.8	1	0.788	

[a] The plates for the two grades of gutta-percha are identical and only data from the "Pure White" grade are listed.

Values of the fiber periods obtained from the data of Table I are written down in the second column of Table II, together with the X-ray values of Fuller and Erickson in the third column.

TABLE II

	Fiber periods, Å. (Storks)	(Fuller and Erickson)
Polyethylene succinate	8.42	8.32
Polyethylene adipate	11.91	11.71
Polyethylene sebacate	16.92	16.67
Gutta-percha (β modification)	9.46	9.54

Data from Unstretched Polyethylene Sebacate.—Electron diffraction patterns from an unstretched specimen of polyethylene sebacate are reproduced in Figs. 6 and 7. The former was obtained with the electron beam incident normally upon the film, and the latter at 45° incidence, the film having been rotated about a horizontal axis as the pattern is reproduced here. The film which produced these patterns had a thickness of 200 ± 25 Å.

In order to describe data obtained from Fig. 7, Cartesian coördinates have been chosen on the photographic plate, with their origin at the primary beam position and the x-axis parallel to the axis about which the film was rotated when Fig. 7 was produced. These coördinates, and other useful quantities, are designated on Fig. 10. In this figure P represents the photographic plate and S the specimen film. O′O is the primary beam direction, O′X′ the axis of rotation in the specimen (parallel to OX), and O′N the normal to the film surface. The angle α defines the rotation of the specimen from the position normal to the beam, and the angles ϕ_1 and ϕ_2 the angular limits measured from the x-axis of a particular diffraction arc AB recorded on the photographic plate.

Numerical data obtained from the patterns of Figs. 6 and 7 are given in Table III. Except for the angles ϕ_1 and ϕ_2 which refer to arcs in Fig. 7, the quantities described in this table are the same as those of Table I. (X-Ray values of d have not been tabulated again.) For those arcs in Fig. 7 which are continuous across the x-axis no values of ϕ_1 can be recorded, and for arcs across the y-axis no values of ϕ_2.

Data from Unstretched Gutta-percha.—Patterns from unstretched gutta-percha, at normal and at 45° incidence, are reproduced in Figs. 8 and 9; data obtained from these patterns are given in Table IV. The angles ϕ referring to the pattern of Fig. 9 are values of $(\phi_1 + \phi_2)/2$.

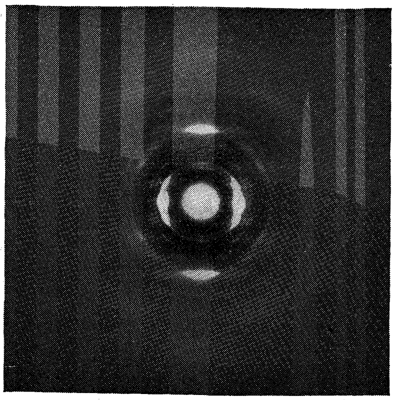

Fig. 1.—Electron diffraction pattern from stretched polyethylene succinate.
($L\lambda = 2.00_{(0)} \times 10^{-6}$ mm.^{2}.)

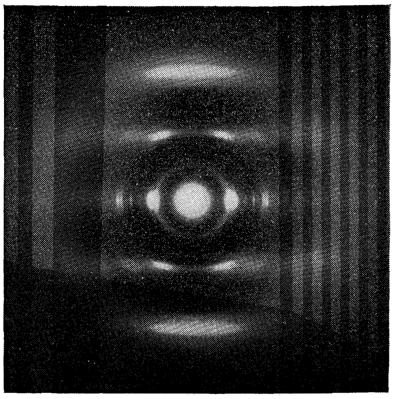

Fig. 2.—Electron diffraction pattern from stretched polyethylene adipate.
($L\lambda = 2.01_{(5)} \times 10^{-6}$ mm.^{2}.)

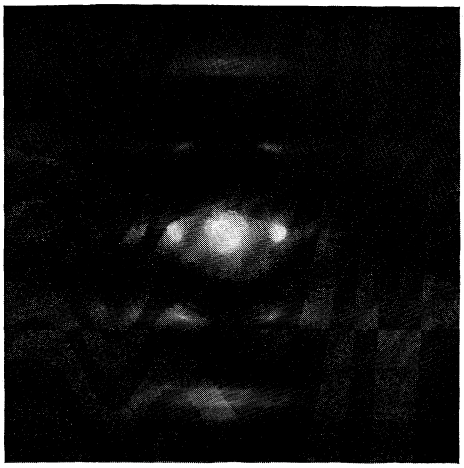

Fig. 3.—Electron diffraction pattern from stretched polyethylene sebacate.
($L\lambda = 2.74_{(4)} \times 10^{-6}$ mm.^{2}.)

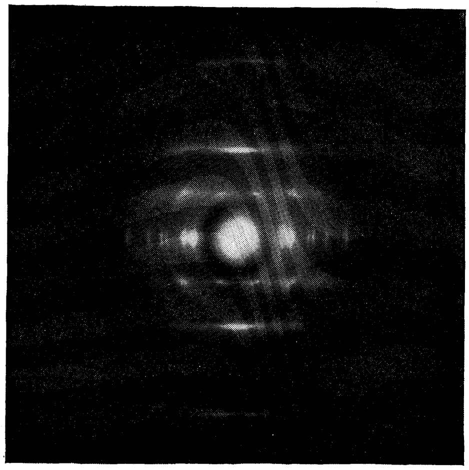

Fig. 4.—Electron diffraction pattern from stretched "Br-4" grade gutta-percha.
($L\lambda = 2.73_{(0)} \times 10^{-6}$ mm.^{2}.)

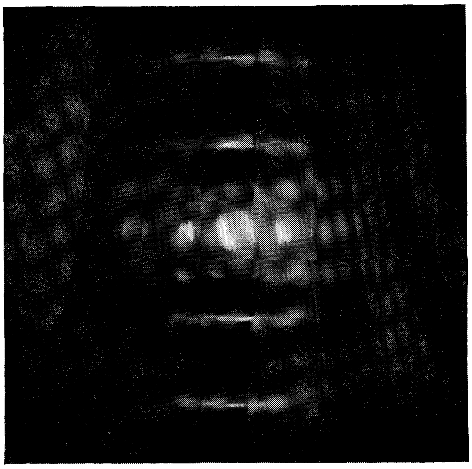

Fig. 5.—Electron diffraction pattern from stretched "white" gutta-percha.
($L\lambda = 2.70_{(9)} \times 10^{-6}$ mm.^{2}.)

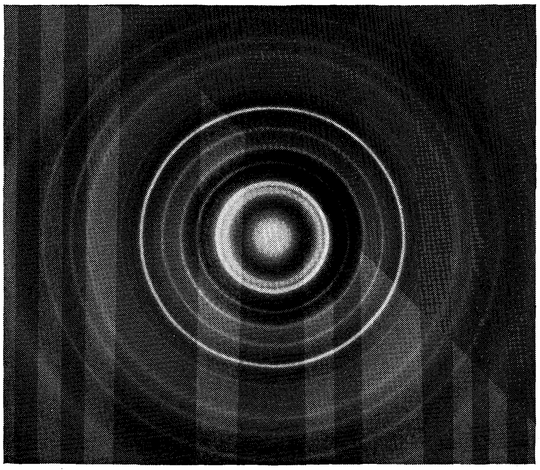

Fig. 6.—Electron diffraction pattern from unstretched polyethylene sebacate at normal incidence. ($L\lambda = 2.74_{(4)} \times 10^{-6}$ mm.^{2}.)

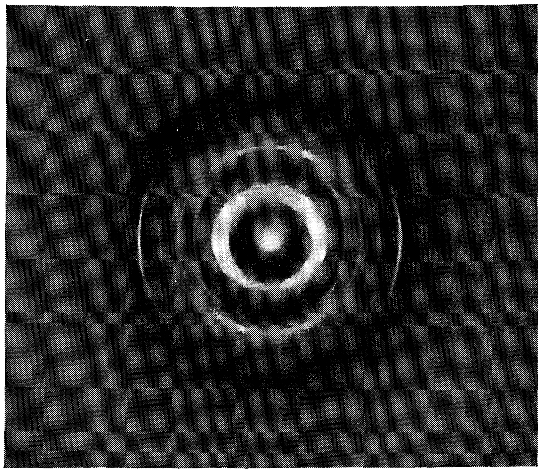

Fig. 7.—Electron diffraction pattern from unstretched polyethylene sebacate at 45° incidence. ($L\lambda = 2.74_{(4)} \times 10^{-6}$ mm.^{2}.)

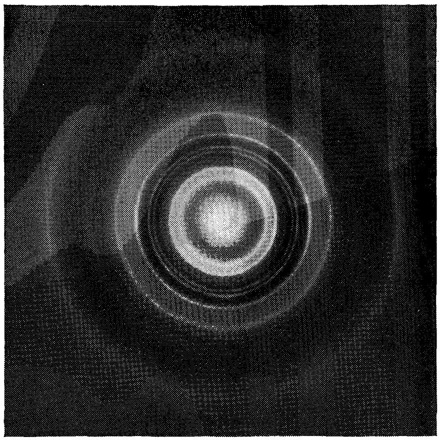

Fig. 8.—Electron diffraction pattern from unstretched "white" gutta-percha at normal incidence. ($L\lambda = 2.70_{(9)} \times 10^{-6}$ mm.^{2}.)

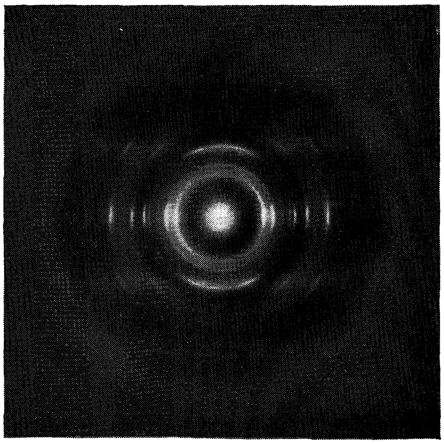

Fig. 9.—Electron diffraction pattern from unstretched "white" gutta-percha at 45° incidence. ($L\lambda = 2.70_{(9)} \times 10^{-6}$ mm.^{2}.)

TABLE III

UNSTRETCHED POLYETHYLENE SEBACATE

$L\lambda = 2.74_{(4)} \times 10^{-6}$ mm.^{2}

Ref.	Fig. 6 Normal incidence D, mm.	Int.	d, Å.
A_2	13.0	5	4.22
A_3	14.9	15	3.68
V_1, A_5	18.05	1	3.04
[a]	20.45	7	2.68
A_8, VII_2	24.7	7	2.22
A_9, VII_3	26.45	0.5	2.07
A, VII_4	29.65	7	1.85
VII, A, IX	31.55	1	1.74
X, A	33.05	0.5	1.66
[a]	35.3	12	1.55
VII, A	38.8	1	1.41
[a]	40.8	3	1.35
XIII_0, VII, A	42.45	1	1.29
XIV_0, XIV	46.0	0.5	1.19
XV_0, VII, XV	49.8	4	1.10
[a]	54.0	4	1.02
	61.2	4	0.897
	70.9	2	.774
	73.9	1	.743

Ref.	Fig. 7 45° Incidence D, mm.	Int.	d, Å.	ϕ_1	ϕ_2
A_2	13.0	15	4.22	13°	52°
A_3	15.0	13	3.66		19
V_1	18.0	3	3.05	12	52
[a]	20.4	6	2.69		39
A_6	21.5	6	2.55	18	49
VI_2	23.2	1	2.37	32	58
A_8	24.8	6	2.21	2	38
VII_2	24.8	8	2.21	41	
A_9	26.5	5	2.07	17	46
A	27.5	1	2.00	71	
A	29.2	4	1.88	37	72
A, VII_4	29.8	4	1.84		17
A	31.2	2	1.76	14	38
VII	32.5	3	1.69	18	45
A	33.5	2	1.64	30	52
[a]	35.4	10	1.55		45
?	37.2	0.5	1.48	36	
[a]	40.8	2	1.35		16
XIII_0, VII, A	42.4	1	1.29		16
XIV_0, XIV	45.0	0.5	1.22		10
XV_0, VII, XV	49.6	2	1.11		23
[a]	53.6	2	1.02		29
	61.0	2	0.90		30

[a] These reflections arise from an impurity that is occasionally found associated with organic films. Reflections which are designated without subscripts are assigned to layer lines only. Two designations are given to the same reflection if the spacing is too close for resolution.

These diffraction patterns were obtained from a film of "Pure White" gutta-percha about 200° Å. thick. Patterns also have been obtained from the "Br-4" grade of gutta-percha. These are found to be similar to those of Figs. 8 and 9 except for greater "spottiness" of diffraction features, indicating that the crystallites are considerably larger in films made from the "Br-4" grade than in films made from the "Pure White" grade.

TABLE IV

GUTTA-PERCHA UNSTRETCHED

$L\lambda = 2.70_{(9)} \times 10^{-6}$ mm.^{2}

	Fig. 8 Normal incidence			Fig. 9 45° incidence				
Ref.	D, mm.	Int.	d, Å.	D, mm.	Int.	d, Å.	ϕ (obsd.)	ϕ (calcd.)
A_7	11.5	10	4.71	11.3	10	4.79	0	0
A_8	14.0	10	3.87	13.8	9	3.93	0	0
[a]	16.3	3	3.32	16.2	2	3.34	0	0
A_{11}	18.3	4	2.96	18.2	4	2.98	0	0
A_{12}	19.7	5	2.75	19.5	8	2.78	0	0
A_{13}	22.8	8	2.38	22.5	7	2.41	0	0
A_{14}	25.0	0.3	2.17					0
A_{15}	26.5	0.3	2.04					0
A_{16}	27.5	3	1.97	27.5	3	1.97	0	0
A	28.4	4	1.91	28.0	6	1.94	0	0
A	30.8	1	1.76	30.5	1	1.78	0	0
A				34.0	1	1.59	0	0
A				35.5	0.3	1.53	0	0
A	45.5	2	1.18	45.5	1	1.18	0	0
II_4				17.5	2	3.10		
II_5				18.5	7	2.93		
II_6				22.5	2	2.41	51	46
II_7				24.0	4	2.26	47	42
II				30.2	0.3	1.79		
II				34.6	0.3	1.57		
II				36.3	1	1.49	29	26
II				42.9	1	1.26	22	22

[a] Reflection from the alpha modification.

Discussion of Results

Stretched Polymers.—In the introduction it was stated that the experiments to be described in this paper have two purposes, to demonstrate the utility of the electron diffraction method in the field of polymeric compounds, and to obtain new information regarding the structure of macromolecules in extremely thin layers—which cannot be studied by X-rays. The first of these purposes has been accomplished by the direct comparisons of X-ray and electron diffraction results upon stretched polymers. These comparisons are given in Table I and Table II. A few additional remarks regarding these data seem to be necessary, before passing on to the second part of the paper, which is concerned with the data of Table III and Table IV.

It has been pointed out that no additional reflections are found when a stretched foil is rotated around the stretching direction. This fact proves that individual crystallites are oriented with all degrees of rotation around this direction. Crystallites of small cross sectional areas in the planes normal to their fiber directions seem to be required to account for random rotation in foils as thin as those of these experiments, (400–1000 Å.).

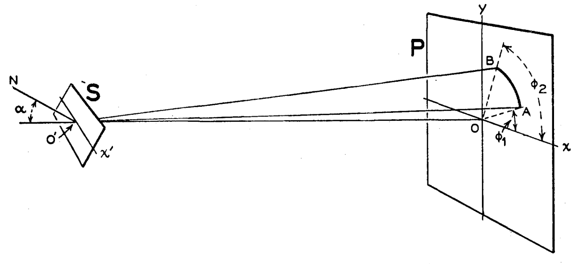

Fig. 10.

Fiber period reflections have not been observed in X-ray experiments upon polyethylene adipate or polyethylene sebacate, values of the fiber period spacings having been determined indirectly.[1] Such reflections are, however, shown clearly in Figs. 2 and 3[11] and are tabulated in Table I. The orders which appear are the 9th, 10th and 11th for the former and the 13th, 14th, 15th and 16th for the latter polymer. The occurrence of these particular high orders only seems rather curious. An approximate calculation of relative intensities has been carried out in order to understand why only these high orders are found. Assuming a macromolecular type of lattice[12,13] and macromolecules that are straight for distances greater than the length of a single chemical repeating unit, it is not difficult to show that, on account of the comparable sizes of the C–C and the C–O spacings, the geometrical structure factor for fiber period reflections has appreciable magnitude at a few orders only. These orders are multiples of the nth, and one or two successive orders above and below, where n represents the number of chain atoms in a chemical repeating unit. To obtain this result one assumes that any lengthwise displacement of neighboring chains is an integral multiple of the fundamental atomic spacing along the axis of the chain. Since there are 10 chain atoms in the repeating unit of polyethylene adipate and 14 in that of polyethylene sebacate, the observation of only the 9th, 10th and 11th orders of the fiber period reflection from the former and only the 13th, 14th, 15th and 16th orders from the latter seems to be adequately accounted for.

Unstretched Gutta-percha.—From the continuous but spotty rings of Fig. 8 one concludes that the individual crystals in a thin unstretched film of gutta-percha are relatively large and randomly oriented about the normal to the film surface. Inspection of Figs. 8 and 9 reveals at once, however, that these crystals are highly oriented. The nature of the orientation is immediately clear from the fact that the first four columns of Table IV (obtained from Fig. 8) contain only equatorial reflections ($hk0$); with the exception of five described by Fuller[13a] as very weak (VW), all equatorial reflections observed by him are obtained in the present studies and written down in the first four columns of Table IV. Thus in the unstretched film of gutta-percha the crystallites are oriented with their fiber axes approximately normal to the film surface. Furthermore, it seems possible to conclude that no appreciable number of crystallites have fiber axis directions that deviate by more than 15° from parallelism with this normal. Greater deviation would allow the occurrence of the layer line reflection for which $d = 1.25$ Å.

Figure 9 and the data of the last five columns of Table IV confirm these conclusions and enable one to calculate the precision of orientation of the fiber axis directions of the crystallites. From the orientation just described it is evident that for $\alpha \neq 0$ the equatorial reflections must occur as arcs across the x-axis of the plate, and some layer line reflections will in general appear as arcs on displaced layer lines. The first twelve reflections indicated on the right-hand side of Table IV, which are equatorial reflections occurring along the horizontal center line in Fig. 9, are in excellent agreement with the reflections observed at normal incidence.

The extreme half angle width of equatorial reflections in Fig. 9 is measured to be about $\Phi_A = 8°$. This is related to the largest angle (δ') between the normal to the specimen surface and an appreciable number of fiber axis directions by the equation

$$\sin \delta' = \sin \alpha \sin \Phi_A \qquad (2)$$

For $\alpha = 45°$ (Fig. 9) this yields $\delta' = 6°$ as a quantitative measure of the precision of orientation in the unstretched "Pure White" gutta-percha foil. Corresponding diffraction patterns and measurements upon an unstretched film of "Br-4"

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[11] See reflections lying across the vertical axes.

[12] W. H. Carothers, *Chem. Rev.*, **8**, 416 (1931).

[13] H. Staudinger and R. Signer, *Z. Krist.*, **70**, 193, 202 (1929).

[13a] C. S. Fuller, *Ind. Eng. Chem.*, **28**, 907 (1936).

grade gutta-percha have yielded $\delta' = 4°$ for this particular foil. It is clear that in general the orientation in thin unstretched films of gutta-percha is nearly perfect.

As a further check it is interesting to compare calculated with observed angular positions of the layer line reflections which appear in Fig. 9; this comparison is given in the last two columns of Table IV. The quantity ϕ represents here the mean value of ϕ_1 and ϕ_2 (see Fig. 10). Measured values of ϕ are taken directly from Fig. 9, and calculated values are obtained from the relation

$$\sin \phi \approx \cos \Theta/\sin \alpha, \quad (3)$$

in which Θ is the inclination of the crystallographic plane giving rise to the particular layer line reflection to the plane normal to the fiber axis. Values of Θ, necessary to calculate ϕ, have been obtained by direct angular measurement upon a diffraction pattern from a stretched film, Fig. 5. It is obvious that only those fiber period reflections can occur for which $(\Theta + \delta') > \alpha$, and that reflections for which α lies between $(\Theta + \delta')$ and $(\Theta - \delta')$ will lie across the vertical axis in Fig. 9.

In Table IV is listed a single reflection attributed to the alpha crystallographic modification, suggesting that the foil is a mixture of two polymorphic forms of gutta-percha. One concludes that the film is a mixture of the beta modification and a very small quantity of the alpha modification. No reflections attributable to the alpha modification have been observed in experiments on stretched specimens.

It is surprising that most of the crystallites are oriented with their fiber axis directions normal to the plane of a film the thickness of which is much less than the total length of a macromolecule. There is considerable evidence that the material has not oxidized sufficiently to cause serious depolymerization for some time after all but possible traces of "absorbed" solvent have evaporated. The possibility of crystallite rearrangement in the solid film after subsequent oxidation has shortened the chains appears to be doubtful. It therefore seems necessary that the macromolecular configuration of gutta-percha is not generally linear in these thin films. The gutta-percha macromolecule may possibly fold by a mechanism of rotation around single bonds. The chemical repeating unit of this polymer is short and relatively few folds per macromolecule are required in a film 200° Å. thick. It is conceivable that such infrequent folding would not affect the crystal structure.

Unstretched Polyethylene Sebacate.—From the continuous rings of Fig. 6 one concludes that the individual crystals in a thin unstretched film of polyethylene sebacate are relatively small and, as in the case of unstretched gutta-percha films, are randomly oriented about the normal to the film surface. The marked difference between Figs. 7 and 9 suggests at once that the type of orientation in the unstretched polyethylene sebacate film is, however, entirely different from that in gutta-percha. The nature of the orientation in thin unstretched films of polyethylene sebacate is not established so readily as is that in gutta-percha films. The difficulty arises from the low intensity of many of the reflections, and from the fact that in many instances layer line and equatorial reflections are found to correspond to nearly equal interplanar spacings.

The absence of the A_6 reflection in the data of Table III rules out the possibility of an orientation like that in gutta-percha. An indication of a possible orientation is found in the weak reflections corresponding to the spacings 1.29 and 1.19 Å. From the polyethylene sebacate data of Table I we find that the first of these could be a weak equatorial reflection, a weak seventh layer line reflection or the strong fiber period reflection ($XIII_0$); the second must be one or both of the strong reflections (XIV_0) or (XIV). The stronger reflection for which $d = 1.10$ could possibly be a weak seventh layer line reflection or the medium reflections (XV_0) and/or (XV). The occurrence of these reflections can be explained if the fiber axis directions lie approximately in the plane of the foil. If this is the case, the evidence of missing and abnormally weak reflections does not allow the crystallites of the foil to have all degrees of rotation around the fiber axis directions.

It is possible that confirmation of these ideas can be found in the pattern from the same foil with the primary beam incident at 45° from the surface normal. (A pattern at near grazing incidence could be interpreted more easily, but it is not possible to obtain such patterns from foils mounted for study by the transmission method.) The 45° incidence pattern is shown in Fig. 7, and numerical data obtained from it are recorded in the last six columns of Table III. Several facts are immediately apparent. All reflections which are observed with normal intensity in the normal incidence pattern occur as continuous arcs across the x-axis of the plate while those of abnormally low intensity have strengthened, on the average, to normal with extremely low intensity across x. Many reflections not observed in Fig. 6 are found as arcs lying in a single quadrant of the pattern. These observations confirm the existence of crystallite orientation and give assurance that the foil is actually scattering as a three dimensional grating. It is still impossible to identify positively all reflections and hence to establish the orientation unequivocally; but, with the designations assigned in column five of Table III, the results are in good agreement if the fiber axes of the crystallites lie approximately in the plane of the foil with a small degree of rotational freedom around the directions of these axes. Such orientation is probably due in part to the presence of carbonyl groups along the chain. The minimum value for the angle between chain axis directions and foil surface normal is estimated, from the angular positions of the arcs listed in Table III, to be of the order of 79°. The freedom of crystallite rotation around the fiber axis directions is estimated to be ±10°.

The angular limits of the arc positions are given by the equations

$$\sin \phi_1 = \frac{\sin \Theta \cos \delta \cos A - \cos \Theta \sin \delta}{\sin \alpha} \qquad (4)$$

$$\sin \phi_2 = \frac{\sin \Theta \cos \delta \cos B + \cos \Theta \sin \delta}{\sin \alpha} \qquad (5)$$

In these, $(90 - \delta)$ = the minimum angle between fiber axis directions and the specimen surface normal, $A = (\psi + \gamma_1)$, $B = (\psi - \gamma_1)$ or *vice versa*, while Θ and α have their former significance. The angle δ can be determined from the half angle width (Φ_F) of fiber period reflections and the equation

$$\sin \delta = \sin \alpha \sin \Phi_F \qquad (6)$$

The angle ψ is most clearly visualized by consideration of an average crystallite having the average rotation around the fiber axis and lying with this axis in the plane determined by the specimen surface normal and the rotation axis. ψ is the angle between this plane and the plane containing the fiber axis direction and the reciprocal lattice point corresponding to any reflection. γ_1 is the limit of crystallite rotation around the fiber axis directions, and is measured from the mean position.

A value of $\sin \phi_2 > 1$ indicates that the rotation of the foil around the surface normal cannot bring all planes of the particular set under consideration into diffracting positions. This condition produces an arc across the y-axis of the plate. Such an arc shows a relative intensity somewhat below normal.

A weakness of this interpretation lies in the low relative intensity of the several high order reflections previously mentioned as well as in the uncertainty of identification of a number of general reflections. Dr. Fuller has suggested that the perfection of chain arrangement may be greatly increased by the stretching process; if this is the case, a difference in intensity of fiber period reflections in patterns of stretched and unstretched material is understandable.

The electron diffraction method should supply an easy means of studying conditions in films of this and similar materials from the oriented unstretched state through a series of controlled degrees of stretching. Diffraction patterns obtained from the same film after varying amounts of stretching should not only definitely establish the orientation in the unstretched condition, but should supply considerable information concerning the mechanism of stretching. It is proposed to conduct such experiments in the near future.

It seems of further interest to consider briefly an estimate of the angle δ made by assuming thin rod-like crystallites of a length comparable to the average length of the polyester chain. The sample of polyethylene sebacate used in these experiments has an average chain length of approximately 1400 Å. If rod-like crystallites of this length are arranged at random between two surfaces 200 Å. apart, $(90 - \delta)$ is found to be of the order of 82°. The agreement of this value with the value of 79° previously estimated from the experiments suggests that the polyethylene sebacate chain configuration is generally linear.

Additional experiments with films of various thicknesses indicate that both δ and γ_1 increase as the film thickness increases. Combining this observation with the observation of Fuller and Erickson[1] that thick unstretched polyethylene sebacate specimens give complete Debye–Scherrer ring patterns, it seems likely that films of such esters will show a preferred orientation until the film thickness exceeds the average chain length. It is proposed that a systematic study of orientation, film thickness, and molecular weight distribution may provide interesting and useful information concerning the molecular structure and film behavior of various polymeric type compounds.

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Summary

1. Electron diffraction experiments have been carried out upon very thin films of several synthetic polyesters and natural gutta-percha.

2. *Stretched films* show diffraction patterns characteristic of sharply oriented crystals. Measurements upon these patterns are in excellent agreement with existing X-ray data upon the same materials. The utility of the electron diffraction method for structural studies of polymerized substances is thus demonstrated.

3. *Unstretched films of gutta-percha* are found to be composed of relatively large crystallites which are precisely oriented with their fiber axis directions normal to the film surface. It is presumed that the macromolecules are folded back and forth upon themselves in such a way that adjacent sections remain parallel.

4. *Unstretched films of polyethylene sebacate* consist of relatively small crystals which are believed to be oriented with their fiber axis directions approximately in the plane of the film, but with limited rotation around the fiber axis directions.

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Note on a Corresponding-States Equation of Practical Interest for General Physicochemical Computations

BY FREDERICK G. KEYES

During the last few years the desire to compute equilibrium physicochemical quantities under conditions removed from the range of validity of the ideal gas laws has led to a renewed interest in the search for an empirical relation of the corresponding-states character.

One form of this effort has been to test the relation of the fugacity–pressure ratio, γ, to the pressure–critical pressure ratio, π, using the existing p–v–T data for gases, to form a graph of constant temperature–critical temperature, θ, lines. The iso-reduced temperature lines of necessity start from $\gamma = 1$ on the vertical axis[1] and are approximately linear in π for θ large, but become increasingly convex relative to the horizontal, or π, axis for θ small. A chart of this sort for hydrocarbons was prepared and its uses discussed by J. D. Cope, W. K. Lewis and H. C. Weber; W. K. Lewis and C. D. Luke and others.[2] Recently[3] R. H. Newton brought together the data for twenty-four substances and found that within a range of 4%, with some exceptions, the data for the substances in the form $(\gamma)_\theta$ *versus* π fell together. A ficticious critical temperature and pressure, however, had to be selected for H_2 and He to bring the data for these substances into line with other substances.

The existence of an exact, universal correspondence in terms of a relation between θ, π, and φ has, however, good reason to be doubted. The cases of H_2 and He at higher temperatures are well-known examples of how badly the concept works out at ordinary temperatures when the form of the equation of state is based on the van der Waals concept of the molecular field.[4] There does exist, however, a range of temperature for all substances, perhaps, where the van der Waals concept leads to a fair approximation in representing the behavior of individual gases.

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[1] See G. Tunnel's article, *J. Phys. Chem.*, **35**, 2885 (1931), for a comprehensive discussion of the definition and evaluation of the fugacity [G. N. Lewis, *Proc. Am. Acad. Arts Sci.*, **37**, 95 (1901)]. Also, L. H. Adams, *Chem. Rev.*, **19**, 1 (1936).

[2] J. D. Cope, W. K. Lewis and H. C. Weber, *Ind. Eng. Chem.*, **23**, 887 (1931); W. K. Lewis and C. D. Luke, *Trans. Am. Soc. Mech. Eng.*, **54**, 55 (1932); and *Ind. Eng. Chem.*, **25**, 725 (1933); C. W. Selheimer, M. Souders, Jr., R. L. Smith and G. G. Brown, *ibid.*, **24**, 515 (1932); G. G. Brown, W. K. Lewis and H. C. Weber, *ibid.*, **26**, 325 (1936); W. K. Lewis and W. C. Kay, *Oil Gas J.*, **32**, 40, 45 (1934).

[3] R. H. Newton, *Ind. Eng. Chem.*, **27**, 1 (1935). See also, R. H. Newton and B. F. Dodge, THIS JOURNAL, **56**, 1 (1934).

[4] F. G. Keyes, *Chem. Rev.*, **6**, 175 (1929).

The van der Waals concept is equivalent to the assumption that molecules may be represented in their physical interaction by the existence of a positive potential which becomes infinite on contact of the supposedly rigid spherical molecules of invariable diameter σ, but zero for all distances of separation of molecular centers greater than σ when a spherically symmetrical negative potential appears. The latter may be represented in the simplest cases by the expression cr^{-m} where m is an integer not smaller than 4. If w represents the potential we may write for the van der Waals field the following relation

$$w = \begin{pmatrix} +\ \infty;\ r = \sigma \\ 0;\ r > \sigma \end{pmatrix} - cr^{-m}$$

The equation of state for low pressures may then be shown to be, for pure gases

$$p = \frac{RT}{v - B_0}$$

where

$$B_0 = \beta - A/RT \sum_{\nu=0}^{\nu=\infty} \frac{(m-3)^{\nu+1}}{(1+\nu)!\cdot 3^{\nu}\,[(1+\nu)\,m - 3]} \left(\frac{A}{RT\beta}\right)^{\nu} \tag{1}$$

For mixtures of gases we may write quite generally (p small)

$$p = \frac{RT\Sigma n_1}{V - [B_0]} \tag{1A}$$

$$[B_0] = \frac{1}{\Sigma n_1}\,[\Sigma B_{0\ 11}\, n_1^2 + 2\Sigma B_{0\ 12}\, n_1\, n_2] \tag{1B}$$

In the van der Waals form for B_0, β is four times the volume of the spheres contained in the volume v and A is proportional to the constant of the negative potential and an inverse power of σ depending on the exponent m. For $m = 6$ we find the following expression

$$B_0 = \beta - \frac{A}{RT}\left[\left(1 + {}^1\!/_6\,\frac{A}{RT\beta} + {}^1\!/_{30}\left(\frac{A}{RT\beta}\right)^2 \ldots\right]\right. \tag{2}$$

The chart produced by Roger H. Newton was based on the computation of γ by the equation

$$\gamma = f/p = \exp.\left[(RT)^{-1}\int_0^p (RT/p - v)\,\mathrm{d}p\right] \tag{3}$$

where p, v and T represent the experimental data for the substances. The integrand has been shown repeatedly not to vanish for $p \longrightarrow 0$ but on the contrary to reduce to a pure temperature function and this well-established fact accords with the prediction of the statistical theory of gases using for example the specialized concept of the intramolecular potential of van der Waals. Thus we find using equation (1)

$$\gamma = \exp.\ [(RT)^{-1}\,(-B_0)p] \tag{4}$$

Now taking the γ, π chart quite literally we would be justified in assuming that whatever the functional relation between γ and π for constant θ, provided only that it is finite and continuous, γ will be linear for π small. We may proceed to write as follows

$$\gamma = 1 + \mathrm{f}(\theta)\pi \text{ : for } \pi \text{ small} \tag{5}$$

Expanding γ we obtain further

$$1 - \frac{B_0 p}{RT} = 1 + \mathrm{f}(\theta)\pi \tag{5A}$$

or

$$\frac{B_0 p_c}{T_c} = -R\theta\mathrm{f}(\theta) \tag{6}$$

where the right-hand member is a universal function, the same for every substance in the gaseous state.

In the present state of our knowledge of the molecular field and the available data, no decisive opinion can be formed regarding the degree of exactness of relation (6). We observe, however, that it bears a close relation to Daniel Berthelot's expression for the effect of intramolecular potential in the equation of state.

Some years ago Beattie and Bridgeman[5] formulated the greater part of the existing data for gases using a correlative equation which employs for B_0 the expression

$$B_0 = \beta - \frac{A}{RT} - \frac{c}{T^3} \tag{7}$$

This is equivalent to a van der Waals expression in which the contribution of the series part or coefficient of A/RT of B_0 in equation (1) is represented by $1 + (CR/AT^2)$. I propose to designate this for reasons of convenience by the expression $1 + (\alpha_2)\ [A^2/(RT)^2\beta^2]$ where (α_2) is a quantity which may vary from substance to substance. What is here proposed for later use is the same thing as setting C equal to $(\alpha_2)\ (A^3/R^3\beta^2)$ and we write for B_0 the following equation

$$B_0 = \beta - A/RT - (\alpha_2)\,\frac{A^3}{(RT)^3\beta^2} \tag{7A}$$

We now obtain however using equations (6) and (7) the relation

$$B_{0\theta} = \beta(p/T)_c - \frac{A}{R\theta T_c}\,(p/T)_c - \frac{C}{\theta^3 T_0^3}\left(\frac{p}{T}\right)_c = -R\theta\mathrm{f}(\theta) \tag{6A}$$

or

$$B_{0\theta} = \beta_\theta - A_\theta/\theta - C_\theta/\theta^3$$

where the expectation derived from the γ, π chart is that β_θ, A_θ and C_θ will each turn out to be the same number regardless of the substance. Using

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[5] J. A. Beattie and O. C. Bridgeman, *Proc. Am. Acad. Arts Sci.*, **63**, 229 (1928).

Beattie and Bridgeman's constants,[6] Table I has been compiled.

TABLE I

EQUATION OF STATE CONSTANTS IN REDUCED UNITS (π, φ, θ)

Substance	β	$A_0/R = A'\cdot 10^{-3}$	$C \times 10^{-6}$	β_θ	A'_θ	C_θ
He	14.00	0.2632	0.4	6.08	21.74	1196.0
Ne	20.60	2.590	1.01	12.48	35.34	6.99
A	39.31	15.73	59.9	12.52	33.24	5.57
H_2	20.96	2.41	0.50	8.08	27.95	5.31
N_2	50.46	16.38	42.0	13.42	34.57	5.58
O_2	46.24	18.17	48.0	14.89	37.93	4.21
Air	46.11	15.86	43.4	12.96	33.65	5.24
CO_2	104.8	61.01	660.0	25.14	48.13	5.63
CH_4	55.9	27.75	128.3	13.39	34.82	4.41
C_2H_4	121.56	74.97	226.8	21.88	47.72	1.80
C_2H_6	94.00	71.60	900.0	15.04	37.54	5.07
$(C_2H_5)_2O$	454.46	381.16	333.3	34.54	62.04	0.25

Non-polar gases $B_0\theta = 13.29 - \dfrac{34.9}{\theta} - \dfrac{5.47}{\theta^3}$

Substance	β	$A_0/R = A'\cdot 10^{-3}$	$C \times 10^{-6}$	β_θ	A'_θ	C_θ
NH_3	40.86	39.43	3053.0	11.24	26.74	12.59
H_2O	34.05	47.59	8842.0	11.48	24.80	10.99

Polar gases $B_0\theta = 11.36 - \dfrac{25.77}{\theta} - \dfrac{11.8}{\theta^3}$

Non-polar gas $C_\theta = 0.0227 \dfrac{(A_\theta)^3}{(\beta_\theta)^2}$

Polar gas $C_\theta = 0.089 \dfrac{(A'_\theta)^3}{(\beta_\theta)^2}$

The units are cc. per mole, atm. °K.

A somewhat astonishing accord of the numbers β_θ, A_θ, and C_θ for the different substances is evident. The case of helium is not significant since helium is the worst known example of a van der Waals molecule even at 100°K. Ether is really a polar gas and moreover the data are neither very exact nor sufficiently extensive in temperature range. The "universal equation" selected to represent the non-polar class of molecules is given at the foot of the table along with a similar one for the polar case. The latter equation is of course based on only two examples, but I have no knowledge of sufficiently precise data for other examples of polar gases. The reason for calling attention to the relation (6A) is solely because it has been found that certain important types of calculations may be facilitated using the "universal" functions B_0 with a combination rule for the constants of mixtures.

The combination rule whereby the constants for a mixture may be computed from the constants (β and A for example) for the pure substances is in a primitive stage. Data for the favorable case of nitrogen–methane mixtures[7] were obtained some years ago for the purpose of investigating the combination rule where the van der Waals form is a reasonable approximation in representing the behavior of the components. It was found that the rule

$$\beta_{12} = {}^1/_2(\beta_1 + \beta_2)\ ;\ A_{12} = (A_1A_2)^{1/2}$$

was suitable for this binary mixture of non-polar molecules. The result accords with quantum theory indications in the case of N_2 and CH_4 molecules as far as the A_{12} rule is concerned but if the van der Waals concept for the positive potential were exact the rule $\sigma_{12} = {}^1/_2(\sigma_1 + \sigma_2)$ would be justified. In the case of polar substances there are definite indications from current quantum theory that the A_{12} rule just given is over simplified. However, even in this case at high temperatures the rule should be a fair approximation.

Accepting the combination rule as stated and extending it to serve for the general case we have the following relationship which may be deduced from (1B)

$$[B_0] = \Sigma\beta_1n_1 - \frac{(\Sigma A_1{}^{1/2}n_1)^2}{RT\Sigma n_1} - \frac{1}{(RT)^3}\left[\Sigma(\alpha_2)_1 \frac{A_1{}^3}{\beta_1{}^2}\frac{n_1{}^2}{\Sigma n_1} + 2\Sigma(\alpha_2)_{12}\frac{A_{12}^3}{\beta_{12}^2}\frac{n_1n_2}{\Sigma n_1}\right] \quad (7B)$$

As examples of the practical applications of the "universal" functions, $B_{0\theta}$, and the equation (7), the Haber equilibrium constants ratio K_p/K^* will be computed and also the ratio px_1/p_1 for Gillespie's experiment[8] where ($BaCl_2 \cdot 8NH_3$) was used effectively as a semi-permeable membrane. Here K_p is the equilibrium constant for any pressure p and K^* is the same quantity for pressures approaching zero. For Gillespie's experiment px_1 is the Dalton's law pressure for NH_3 in a mixture of NH_3 and N_2 at total pressure p, while p_1 is the equilibrium pressure of the $BaCl_2 \cdot 8NH_3$ in contact with the gaseous $NH_3 : N_2$ mixture. Of course, every sort of calculation for gases may be made subject to the limitations of the $B_{0\theta}$ equations.

The general equation for the equilibrium constant ratio is

$$\ln K_p/K^* = -(RT)^{-1}\,\Sigma\nu \int_0^p \left[\frac{\partial V}{\partial n_1} - \frac{RT}{p}\right] \mathrm{d}p \quad (8)$$

For Gillespie's experiment we find the following equation from the relation $(\mu_{NH_3})_{p1} = [\mu_{NH_3}]_p$ where

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[6] The constants for NH_3 and H_2O are taken from the author's formulations for these substances. The complete expressions are

$$(B_0)_{NH_3} = 2.4 - 2316\tau \times \text{exp. } 7.744 \times 10^4\tau^2$$

and

$$(B_0)_{H_2O} = 1.89 - 2641.6\tau \times \text{exp. } 1.858 \times 10^5\tau^2$$

where the units are in cc./g. The first two terms of the expanded exponential were assumed the equivalent of $(1 + CR/AT^2)$. This procedure is satisfactory provided the temperature is high enough.

[7] F. G. Keyes and H. G. Burks, THIS JOURNAL, **50**, 1100 (1928). The case is favorable from the point of view of interpretation because chemical action is excluded and the molecules are non-polar.

[8] E. Lurie and L. J. Gillespie, *ibid.*, **49**, 1146 (1927).

$(\mu_{NH_3})_{p1}$ is the chemical potential of the pure gas in equilibrium with the same gas in the mixture the chemical potential of which is $(\mu_{NH_3})_p$.

$$\ln \frac{px_1}{p_1} = (RT)^{-1} \left[\int_0^p \left(\frac{\partial V_1}{\partial n_1} - \frac{RT}{p} \right) dp_1 - \int_0^p \left(\frac{\partial V}{\partial n_1} - \frac{RT}{p} \right) dp \right] \quad (9)$$

where p_1 is the $BaCl_2 \cdot 8NH_3$ equilibrium pressure of pure ammonia and p the total pressure.

Using the relations (7) there results

$$\ln K_p/K^* = -(RT)^{-1} \left(\Sigma\nu_1 \frac{\partial [B_0]}{\partial n_1} \right) p \quad (8A)$$

$$\ln px_1/p_1 = (RT)^{-1} \, [B_{01}p_1 - \partial/\partial n_1 [B_{01}]p] \quad (9A)$$

where in (9A) B_{01} refers to pure ammonia in equilibrium through a semi-permeable membrane with the ammonia in the gaseous mixture $[B_{01}]$. In detail we find using (7) the following equations

$$\ln K_p/K^* = (RT)^{-1} \, [-\Sigma\beta_1\nu_1 + (RT)^{-1} (A) + (RT)^{-3} (B + C)] \quad (8B)$$

$$(A) = 2(\Sigma A_1{}^{1/2}x_1)(\Sigma A_1{}^{1/2}\nu_1) - (\Sigma A_1{}^{1/2}x_1)\Sigma\nu_1$$

$$(B) = \Sigma \mathbf{A}_1 x_1 \, (2 - x_1)\nu_1$$

$$(C)^9 = 2 \left\{ \begin{array}{l} [\mathbf{A}_{12}x_2(1 - x_1) + \mathbf{A}_{13}x_3(1 - x_1) - \mathbf{A}_{23}x_2x_3]\nu_1 \\ [\mathbf{A}_{12}x_1(1 - x_2) + \mathbf{A}_{23}x_3(1 - x_2) - \mathbf{A}_{13}x_1x_3]\nu_2 \\ [\mathbf{A}_{13}x_1(1 - x_3) + \mathbf{A}_{23}x_2(1 - x_3) - \mathbf{A}_{12}x_1x_2]\nu_3 \end{array} \right\} \text{for 3 components}$$

$$\ln \frac{px_1}{p} = (RT)^{-1}[-\beta_1(p - p_1) + (RT)^{-1} (Q) + (RT)^{-3} (S)] \quad (9B)$$

$$(Q) = [2(\Sigma A_1{}^{1/2}x_1)A_1{}^{1/2} - (\Sigma A_1{}^{1/2}x_1)^2]p - A_1p_1$$

$$(S) = \{\mathbf{A}_1(2 - x_1)x_1 - [\mathbf{A}_2x_2 - 2\mathbf{A}_{12}(1 - x_1)]x_2\}p - \mathbf{A}_1p_1$$

where $\mathbf{A} = (\alpha_2) \dfrac{A^3}{\beta^2}$; $(\alpha_2)_{12} = [(\alpha_2)_1(\alpha_2)_2]^{1/2}$; $\mathbf{A}_{12} = (\alpha_2)_{12} \dfrac{A_{12}^3}{B_{12}^2}$

Summary

It is shown that the recent fugacity–pressure ratio charts for constant reduced temperatures *versus* reduced pressure, taken literally, lead at low pressures to a simple reduced equation of state. The constants of this equation are deduced from the values of the van der Waals constants deduced for thirteen substances by Beattie and Bridgeman. It appears that there is a distinguishable difference in the reduced-constants values for non-polar compared with polar gases. A test of the usefulness of the reduced equation is made by computing the equilibrium constants for the Haber equilibrium for high pressures and for Gillespie's experiment. In applying the equation to mixtures of gases use was made of a "constants" combination rule previously found valid for nitrogen–methane mixtures. The results indicate that the reduced equation is useful for making approximate physico-chemical calculations involving gases under pressure. The present reduced equations suffer from the assumption that a van der Waals type of molecular field is assumed valid, and more precise data for gases and gas mixtures at low pressures are needed before the implications deducible from the existing fugacity–pressure ratio charts can be explored satisfactorily.

CAMBRIDGE, MASS. RECEIVED MAY 18, 1938

TABLE II

AMMONIA SYNTHESIS

450 °C.

p	Obsd.[a] (K_p/K^*)	Calcd.[b] (K_p/K^*)	Calcd.[c] (K_p/K^*)	Calcd.[c] mol % NH_3	Obsd. mol % NH_3
100	1.093	1.105	1.110		
300	1.351	1.419	1.454		
600	1.966	2.240	2.384	56.2	53.3
1000	3.483	4.407	4.969	73.1	68.6

[a] L. J. Gillespie, *J. Math. Phys., M. I. T.*, **4**, 84 (1925); L. J. Gillespie and J. A. Beattie, *Phys. Rev.*, **36**, 743 (1930). I have the pleasure of thanking Professor Gillespie for providing me with the ratios in the second column.

[b] Computed using the first two terms of (8B). No consideration has been given the fact that 0.3 mol per cent. of argon was present.

[c] Computed using all three terms of (8B).

TABLE III

GILLESPIE'S EXPERIMENT[a]

$BaCl_2 \cdot 8NH_3 : N_2$ at 45°

p total	p_1 $BaCl_2 \cdot 8NH_3$	x_1	(px_1/p_1) obsd.	(px_1/p_1) calcd.
60.86	7.44	0.1484	1.214	1.228

[a] E. Lurie and L. J. Gillespie, THIS JOURNAL, **49**, 1146 (1927).

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(9) This term is written out for the case of these constituents only.

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY AND PHARMACOLOGY, NEW YORK UNIVERSITY]

Thioesters of Choline and β-Methylcholine and their Physiological Activity. Onium Compounds. XIX

BY R. R. RENSHAW, P. F. DREISBACH,[1] M. ZIFF AND D. GREEN

The work described in the present paper is a continuation of an investigation of compounds in which sulfur was introduced into the structure of choline derivatives and into analogous compounds. Previous papers have described substances in which the onium element, nitrogen, has been replaced by sulfur to form sulfonium derivatives as well as to replace the oxygen of the hydroxyl group to form thiol derivatives, thioethers and sulfones. Certain acyl derivatives of "thiol-choline" are described here. In papers to be presented later, work on derivatives of sulfinic and sulfonic acids will be described.

Thiol-choline bromide, β-thiolethyltrimethylammonium bromide, was prepared in this Laboratory a number of years ago by the use of thiomethyluracil for replacing the halogen in bromocholine bromide by the thiol group.[2] Recently,[3] the introduction of the sulfur atom into the choline structure has been accomplished more readily by replacing the halogen in chloroethyldimethylammonium chloride by hydrolyzing the thiourea addition product of this compound. The same procedure was used in the present work and extended to the preparation of the β-thiolpropyldimethylamine.

The thiourea addition complexes of these halogen amines can be obtained in practically theoretical yield by heating the reactants in various alcoholic solutions. The thiolamines are obtained readily in good yield from the thiourea complex by hydrolyzing the latter with dilute bases. When the quantity of base used is sufficient to give marked alkalinity to the final reaction mixture, notable quantities of the disulfide are formed due to the ready oxidation of the thiol. For the preparation of certain derivatives, it is more convenient to oxidize the thiol at this stage and isolate the product as the disulfide.

The tertiary aminothiols acylate readily with acyl chlorides. The resulting thiol esters undergo hydrolysis and alcoholysis surprisingly easily considering the relative stability of compounds of similar structure (thiocaine) described by Hansen and Fosdick.[4] These tertiary amino thiol esters are readily converted into the quaternary compounds with alkyl halides. The resulting esters are more stable to alcoholysis and hydrolysis in acid solutions than the esters of the tertiary amines.

The addition of alkyl halides to the tertiary aminothiols to form the quaternary compounds does not take place in a clear-cut manner due to a simultaneous alkylation of the thiol group with the formation of tertiary amino thioethers. The latter may then be alkylated either on the nitrogen or sulfur atom or both.

By the action of the methyl iodide on β-thiolpropyldimethylamine a mixture of products was obtained from which two substances were isolated. The analysis of one product indicated a composition corresponding to the β-methyl thioether of propyltrimethylammonium iodide. This product melted nearly 40° higher than a product obtained by Mylius[5] by the action of methyl iodide on the methyl thioether of the corresponding primary amine. It has not been determined which of these products is the ammonium and which the sulfonium derivative. The second product isolated in small quantity showed, upon analysis, the composition of the expected β-methylthiolcholine. While it contained one active hydrogen, it did not show a thiol test and was probably the hydroiodide of the methyl thioether of the tertiary amine.

The quaternary thiols are best prepared by reduction of the *bis*-quaternary disulfide which may be obtained in nearly quantitative yields from the disulfides of the tertiary amines. They are also readily obtained by hydrolysis of the thioacyl derivative of the quaternary compounds.

Preliminary experiments carried out in this Laboratory in August, 1936, on the activities of acetylthiocholine and β-methyl-acetylthiocholine showed a remarkable variation in one of the ac-

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[1] The chemical part of this paper has been constructed from a thesis presented by P. F. Dreisbach, December, 1936, for the degree of Doctor of Philosophy at New York University.

[2] Harada, *Bull. Chem. Soc., Japan*, **4**, 171 (1929); see also, *ibid.*, **6**, 25 (1931).

[3] Williams, Doctoral Dissertation, New York University, June, 1933.

[4] Hansen and Fosdick, THIS JOURNAL, **55**, 2873 (1933).

[5] Mylius, *Ber.*, **49**, 1100 (1916).

tions of these compounds from what one would expect from the properties of other choline derivatives. It has been shown previously[6] that when the hydroxyl group of choline is replaced by the thiol group there is only a slight weakening of the typical depressor acetylcholine action. On the other hand, the stimulating nicotine action was diminished markedly and the paralyzing nicotine and curare actions augmented largely. In a more recent study of the acetyl derivatives of these thiols, the earlier results have been confirmed and extended.

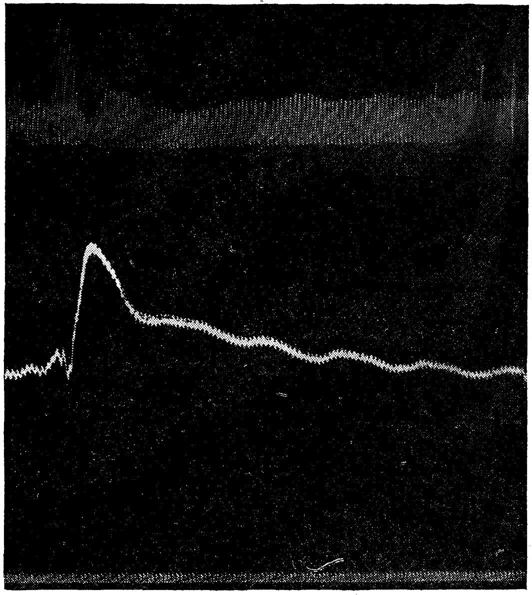

Fig. 1.—0.1 Mg. of thioacetyl-β-methylcholine iodide after atropine.

The acetylation of the thiocholine brings about a reversal of the effect of introducing the sulfur atom and produces a marked augmentation of the stimulating nicotine action. After atropine, 0.1 mg. of this product caused a rise of blood pressure from 128 to 166 mm. More remarkable is the fact that the acetyl derivative of the β-methyl-thiocholine produces a greater augmentation of the stimulating nicotine action. After atropine, 0.1 mg. of this substance caused the blood pressure to rise from 130 to 210 mm. The intensity of the activity of this compound was not greatly affected by the removal of the adrenals although the blood pressure returned to normal much more quickly after adrenalectomy. When one recalls that the introduction of the β-methyl group into acetylcholine nullifies the stimulating nicotine action of the latter, one is amazed at the extraordinary pressor activity of this sulfur β-methyl derivative. In large doses, both of these products have marked paralyzing nicotine and curare actions.

Chemical Experimental Part

With P. F. Dreisbach

β-(Chlorido-thiourea)-propyldimethylammonium Chloride.—A mixture of 50 g. of β-methyl-β-chloroethyldimethylammonium chloride and 25 g. of thiourea, dissolved in just enough *n*-propyl alcohol to effect solution when hot, was refluxed for nine hours and then allowed to stand at ice-box temperature for two days. The product formed was recrystallized from propyl alcohol, from which it separates in clusters of fine needles. These are slightly soluble in acetone and insoluble in ether; additional material obtained from the mother liquor gave a total yield of 92%, m. p. 201–202°.

Anal. Calcd. for $C_6H_{17}Cl_2N_3S$: Cl, 30.29. Found: Cl, 30.38, 30.37.

β-Thiol-propyldimethylamine.—A solution of 47 g. of β-chlorido-thiourea-propyldimethylammonium chloride and 22.5 g. of potassium hydroxide in 234 cc. of water was allowed to stand overnight at room temperature. The solution was then continuously extracted with ether for several days, a small amount of dicyandiamide separating out in the ether extract. From the dried ether extract, there was obtained by distillation 14.4 g. (61%) of a product boiling from 153 to 154° at 762 mm. and 46 to 51° at 14 to 18 mm. The amino thiol is soluble in water and the common organic solvents. With sodium nitroprusside it gives a positive test for the thiol group. It is relatively stable in air and in acid solution, but oxidation to the disulfide takes place rapidly in alkaline solution.

Anal. Calcd. for $C_5H_{13}NS$: H, 10.99; C, 50.34. Found: H, 11.39; C, 50.20.

The picrate crystallizes from glacial acetic acid in the form of needles melting with decomposition from 159 to 166° (sinters before melting).

Anal. Calcd. for $C_5H_{13}NS{\cdot}C_6H_3N_3O_7$: N, 16.09. Found: N, 15.99.

The cyano-mercury salt was obtained by treating the product with a saturated aqueous solution of mercuric cyanide. This salt crystallizes from water in the form of needle crystals which, when heated, gradually decompose from 125° upward.

Anal. Calcd. for $C_6H_{12}N_2SHg$: Hg, 58.18. Found: Hg, 57.93.

β,β′-Dithio-*bis*-(propyldimethylamine).—The hydrolysis of 48 g. of crude thiourea complex was carried out as above excepting that a small excess of potassium hydroxide was used so that the reaction solution acquired a decidedly alkaline reaction. Distillation of the ether extract gave 4 g. of pure thiol and, as the main product, 11 g. of the disulfide which boils at 151–154° at 14 mm. It is insoluble in water and alkali and soluble in dilute mineral acid, alcohol and ether. The disulfide was readily reduced to the thiol.

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[6] Hunt and Renshaw, *J. Pharmacol.*, **44**, 151 (1932).

Anal. Calcd. for $C_{10}H_{24}N_2S_2$: H, 10.24; C, 50.77; mol. wt., 236.3. Found: H, 9.90; C, 50.55; mol. wt., 240.

β,β′-Dithio-*bis*-(propyltrimethylammonium Iodide).—Treatment of β,β′-dithio-*bis*-(propyldimethylamine) with excess methyl iodide in ethyl alcohol gave this product in almost theoretical yield. It crystallizes from ethyl alcohol as spheres of feather-like crystals which are soluble in water, slightly soluble in propyl alcohol and insoluble in acetone and ether; m. p. 207–208° (dec.).

Anal. Calcd. for $C_{12}H_{30}I_2N_2S_2$: H, 5.81; C, 27.69; N, 5.39; I, 48.79; active hydrogen, 0. Found: H, 5.91; C, 27.33; N, 5.53; I, 48.92; active hydrogen, 0.

Treatment of β-Thiol-propyldimethylamine with Methyl Iodide.—The addition of excess methyl iodide to an ether, benzene or toluene solution of β-thiol-propyldimethylamine gave, after three days of standing at room temperature, a precipitate consisting of a mixture of compounds from which there was isolated, by a series of fractional recrystallizations, a pure compound which turned brown at 189–195° and decomposed at 197–200°. The analysis of this is in agreement with the theoretical for β-(methyl-thio)-propyltrimethylammonium iodide, but the melting point does not agree with that of the product described by Mylius[5] as β-(methyl-thio)-propyltrimethylammonium iodide which he obtained by the action of methyl iodide on the thioether of isopropylamine. His product melted at 162–163°. Evidently, either his product or ours is the sulfonium iodide rather than the ammonium iodide. We did not attempt to prove the structure of this substance, but, due to the fact that our product is the higher melting, we suspect that it is the quaternary ammonium compound.

Anal. Calcd. for $C_7H_{18}INS$: C, 30.55; H, 6.59; I, 46.11. Found: C, 30.40; H, 6.87; I, 46.31, 46.17.

β-(Acet-thio)-propyldimethylammonium Chloride.—This product was obtained in almost theoretical yield by the slow addition of 4.4 g. of β-thiol-propyldimethylamine in 20 cc. of dry ether to 8 g. of acetyl chloride in 10 cc. of dry ether with vigorous agitation, while cooling the mixture in ice. When purified from an ether–amyl alcohol mixture, it forms hard, clear needles which are very hygroscopic and soluble in the common alcohols and esters; m. p. 91–92°. This ester is hydrolyzed rapidly in alkaline solution. Attempts to liberate the free base with sodium carbonate or sodium bicarbonate caused considerable hydrolysis. The free base also readily undergoes alcoholysis in alcohol solution.

Anal. Calcd. for $C_7H_{16}ClNOS$: Cl, 17.94. Found: Cl, 18.07, 18.28.

β-(Acet-thio)-propyltrimethylammonium Iodide.—A water solution of 7.5 g. of β-(acet-thio)-propyldimethylammonium chloride was shaken with excess silver oxide and the mixture then immediately extracted with ether. Addition of excess methyl iodide to the dried ether extract gave a product as a precipitate after standing at room temperature for five days. Recrystallized from butyl alcohol, it forms fine prisms which are very soluble in water and ethyl alcohol; yield 64%; m. p. 144–145°.

Anal. Calcd. for $C_8H_{18}NOSI$: I, 41.86. Found: I, 41.90, 41.78.

β-(Benz-thio)-propyldimethylammonium Chloride.—To 10 g. of benzoyl chloride in 10 cc. of dry ether there was added, slowly and with cooling, an ether solution of 5 g. of β-thiol-propyldimethylamine. The product began to precipitate immediately and the solution was then warmed on the steam-bath for one hour to complete the reaction. The product was obtained as clusters of fine, white needles by dropwise addition of ether to an ethyl alcohol solution. They are soluble in ethyl alcohol, slightly soluble in benzene and insoluble in ether and acetone; yield 90%; m. p. 122.5°.

The free base, which may be liberated from the hydrochloride by sodium bicarbonate, slowly undergoes alcoholysis on standing in ethyl alcohol.

Anal. Calcd. for $C_{12}H_{18}ClNOS$: Cl, 13.65. Found: Cl, 13.79, 13.74.

β-(Benz-thio)-propyltrimethylammonium Iodide.—An ether solution of β-(benz-thio)-propyldimethylamine was prepared by treating 5 g. of its hydrochloride in water with excess dilute sodium bicarbonate solution and immediately extracting with ether. The free base precipitated in the water solution as an emulsion. Excess methyl iodide was added to the dried ether extract and, after standing for several days at room temperature, the product had precipitated completely. It crystallizes from ethyl alcohol and from concentrated aqueous solution in the form of rosets of needles which are soluble in water and ethyl alcohol and slightly soluble in the higher alcohols; yield 85%; m. p. 185–186°. The substance is fairly stable in acid solution.

Anal. Calcd. for $C_{13}H_{20}INOS$: H, 5.52; C, 42.72; I, 34.75. Found: H, 5.55; C, 42.39; I, 34.53, 34.71.

β-(*p*-Nitrobenz-thio)-propyldimethylammonium Chloride.—A solution of 5.2 g. of β-thiol-propyldimethylamine in 25 cc. of benzene was added dropwise to 8 g. of *p*-nitrobenzoyl chloride in 20 cc. of benzene with cooling and shaking. The mixture was then refluxed for half an hour, after which precipitation of the product was complete. The product was purified by several recrystallizations from an absolute alcohol solution, m. p. 199–200°.

Anal. Calcd. for $C\ _2H_{17}ClN_2O_3S$: H, 5.62; C, 47.26; Cl, 11.64. Found: H, 5.77; C, 46.93; Cl, 11.77, 11.85.

The free base of this compound, prepared from its hydrochloride by dilute sodium bicarbonate solution, crystallizes from ligroin as orange-yellow plates, m. p. 85°. It is soluble in ether and insoluble in water. This product undergoes some hydrolysis even on standing in moist air. In alcohol solution, it alcoholizes almost immediately as is shown by the precipitation of ethyl *p*-nitrobenzoate from a freshly prepared alcoholic solution upon the addition of water.

Anal. Calcd. for $C_{12}H_{16}N_2O_3S$: N, 10.44. Found: N, 10.20, 10.35.

β-(*p*-Nitrobenz-thio)-propyltrimethylammonium Iodide.—An ether solution of the free base from 1 g. of β-(*p*-nitrobenz-thio)-propyldimethylamine hydrochloride was treated with excess methyl iodide and allowed to stand for two days at room temperature when precipitation of the product was complete. Recrystallized from a relatively small amount of water, it forms clear, orange-yellow needles; yield, 59%. It is moderately soluble in water and alcohol and insoluble in ether. In boiling alcohol, decomposition takes place; m. p. 190–191°.

Anal. Calcd. for $C_{13}H_{19}IN_2O_3S$: I, 30.94. Found: I, 30.91, 30.74.

β-(Chlorido-thiourea)-ethyldimethylammonium Chloride (With J. H. Williams[3]).—This product was obtained in practically theoretical yield when 55 g. of β-chloroethyldimethylammonium chloride and 30 g. of thiourea were refluxed for four and one-half hours in 60 cc. of absolute ethanol. Recrystallization from an acetone–ethanol mixture gave fine, colorless needles; m. p. 181–182°.

Anal. Calcd. for $C_5H_{15}N_3SCl_2$: Cl, 32.22. Found: Cl, 32.24, 32.19.

β,β'-Dithio-*bis*-(ethyltrimethylammonium Iodide).—Air was aspirated slowly for twenty minutes through a solution of 1 g. of β-thiol-ethyldimethylamine in 10 cc. of dilute potassium hydroxide solution kept at 80°. A layer of water insoluble liquid formed on the top surface and the whole was extracted with ether. Excess methyl iodide was added to the dried ether solution and, after six hours of standing, 1.1 g. of material had precipitated. This crystallizes from methyl alcohol solution as needles which turn brown at 220° and decompose at 230° when heated at the rate of 6° per minute, or at 235° heated at the rate of 12° per minute.

From the melting points and mixed melting point, this product was shown to be identical with a product isolated by Williams[3] in this Laboratory from the action of methyl iodide on β-thiol-ethyldimethylamine.

Anal. Calcd. for $C_{10}H_{26}N_2S_2I_2$: I, 51.56. Found: I, 51.35, 51.28.

β-(Acet-thio)-ethyldimethylammonium Chloride.—This product was prepared from β-thio-ethyldimethylamine and acetyl chloride according to the method outlined above for the corresponding β-methyl substituted compound in a yield of 78%. It recrystallized in needles from an ether–amyl alcohol mixture. The product is very hygroscopic; m. p. 95°.

Anal. Calcd. for $C_6H_{14}ClNOS$: Cl, 19.31. Found: Cl, 19.21, 19.24.

β-(Acet-thio)-ethyltrimethylammonium Iodide.—This was obtained from β-(acet-thio)-ethyldimethylammonium chloride, using silver oxide to liberate the free base, and methyl iodide by a method similar to that outlined for the preparation of the corresponding β-methyl substituted compounds; yield 77%. Recrystallized from propyl alcohol, it forms glistening plates which are soluble in water and the alcohols and insoluble in acetone and ether; m. p. 203–204°.

Anal. Calcd. for $C_7H_{16}INOS$: I, 43.90. Found: I, 43.70, 43.69.

β-(Benz-thio)-ethyldimethylammonium Chloride.—This compound was obtained from the tertiary amino thiol and benzoyl chloride; yield, almost the theoretical. Recrystallized from amyl alcohol, it forms colorless plates soluble in water and alcohols; m. p. 164.5–165°.

Anal. Calcd. for $C_{11}H_{16}ClNOS$: Cl, 14.44. Found: Cl, 14.61, 14.74.

β-(Benz-thio)-ethyltrimethylammonium Iodide.—This product was obtained from the corresponding amino-thiol hydrochloride, using dilute sodium bicarbonate solution to liberate the free base, and methyl iodide. Recrystallized from water, it forms glistening plates decomposing at 257° dependent on rate of heating; yield 84%. The product is soluble in water, slightly soluble in ethyl alcohol and insoluble in ether.

Anal. Calcd. for $C_{12}H_{18}INOS$: I, 36.15. Found: I, 36.12, 35.98.

β-(*p*-Nitrobenz-thio)-ethyldimethylammonium Chloride.—This *p*-nitrobenzoyl derivative was obtained in practically theoretical yield by a procedure analogous to the preceding. Recrystallized from isoamyl alcohol, it forms fine plates. It is soluble in water, ethyl alcohol and hot propyl and amyl alcohols; insoluble in ether and benzene; m. p. 187° (dec.).

Anal. Calcd. for $C_{11}H_{15}ClN_2O_3S$: Cl, 12.20. Found: Cl, 12.29, 12.31.

β-(*p*-Nitrobenz-thio)-ethyltrimethylammonium Iodide.—This quaternary ammonium compound was obtained from β-(*p*-nitrobenz-thio)-ethyldimethylammonium chloride, using dilute sodium bicarbonate solution to liberate the free base, and methyl iodide according to the method described above for the preparation of the corresponding β-methyl compound; yield 81%. The compound is moderately soluble in water, slightly soluble in the alcohols and insoluble in ether. Recrystallized from water, it forms yellow-orange plates which darken at 195° and melt at 212–216° to a red melt.

Anal. Calcd. for $C_{12}H_{17}IN_2O_3S$: I, 32.05. Found: I, 32.08, 32.05.

Pharmacological Experimental Part

With D. Green and M. Ziff

The experiments were performed upon cats anesthetized by means of nembutal. The following effects were noted:

1. Acetylcholine or "muscarine" action: a fall in blood pressure of vascular origin and prevented by atropine.
2. "Stimulating nicotine" action: a rise in pressure due to stimulation of sympathetic ganglia cells.
3. "Paralyzing nicotine" action: abolition of effects on the eye upon electrical stimulation of the cervical sympathetic; abolition of the rise in pressure caused by small doses of nicotine.
4. "Curare" action: abolition of response to electrical stimulation of motor nerves (femoral).

β-Acet-thio-ethyltrimethylammonium iodide had a moderate acetylcholine effect, being in the order of one hundredth as active as acetylcholine. In one experiment, 0.1 mg. of the drug caused a fall of 48 mm. as compared with a fall of 64 mm. produced by 0.001 mg. of acetylcholine. This effect was most marked in doses of the order of 0.1 mg. In larger doses, the "stimulating nicotine" effect was so great—even without previous administration of atropine—as to partially neutralize the fall in pressure by the production of a secondary rise. After atropine, the pressure rose abruptly and then fell rather slowly to normal. A curious feature of this return, after atropine, was the occcurrence of marked Traube–Hering waves.

After adrenalectomy, the "stimulating nicotine" effect was somewhat diminished, but still pronounced. The return of pressure to normal was much more rapid, however. The relationship of the acetylcholine to the "stimulating nicotine" effect, under various conditions, is shown in Table I.

TABLE I

Dose (mg./kg.)	Initial pressure	Fall to	2° Rise to
Acet-thiocholine iodide			
0.0277	158	110	164
.057	150	134	178
.33	136	98	194
.57	136	112	190
.75	122	76	120
2.2	144	40	74
After atropine			
0.0277	128	...	162
After atropine and adrenalectomy			
0.0277	144	...	164
.055	148	...	184
β-Methyl-acet-thiocholine iodide			
0.0277	158	136	190
.057	120	...	214
.50	114	96	148
.75	106	76	104
After atropine			
0.0277	130	...	208
After atropine and adrenalectomy			
0.0277	142	...	208
.055	154	...	236
Methyl-thiocholine iodide			
0.0455	138	104	150
.091	110	66	126
.435	128	84	132

The "paralytic nicotine" and "curare" effects of this compound became evident rather abruptly as one increased the dosage. Thus, evidences of these effects were lacking in doses of 0.285 and 0.33 mg. per kilogram; whereas, in doses of 0.75, 0.90 and 2.2 mg. per kilogram, both effects were not only strong but the curariform paralysis of respiration was ultimately sufficient to produce death.

β-(Acet-thio)-propyltrimethylammonium iodide had an acetylcholine action somewhat weaker than the acet-thiocholine. In one experiment 0.1 mg. caused a fall of 32 mm. as compared with a fall of 48 mm. produced by the same amount of the latter. The acetylcholine action of the compound was obscured to a far greater extent, however, by the "stimulating nicotine" effect, which was very pronounced, in some cases so great that the only observable blood pressure effect was a rise. The effect of the β-methyl group of this substance, which caused more than a two-fold increase in the pressor activity over that of the parent substance, seems remarkable. After atropine, the pressor effect was enhanced, and Traube–Hering waves observed. Adrenalectomy again diminished, somewhat, the "stimulating nicotine" action and markedly shortened its duration. "Curare" and "paralytic nicotine" effects were observed in doses of 0.5 to 0.75 mg. per kilogram, but unlike the effects with corresponding doses of acet-thiocholine they were transient and did not cause death of the animal.

β-Methylthio-ethyltrimethylammonium iodide was investigated briefly. It exhibited a moderately strong and consistent acetylcholine action, being in that respect about equal to that of the acetyl-thio derivative. There was in this compound (as in the others of the series) a definite rise in pressure observable even without the administration of atropine, as seen in Table I. "Curare" and "paralytic nicotine" effects were observed in doses of 0.435 mg. per kilogram. Respiratory paralysis was transient, however, and did not cause death.

PROTOCOL

Cat No. 11; 3.6 kg.; Nembutal 2.8 grains; blood pressure from the carotid artery; injections into femoral vein. AcC = acetylcholine bromide; PD-1 = acet-thiocholine iodide; PD-2 = β-methyl-acet-thiocholine iodide.

9:32 AcC, 0.001 mg. Blood pressure fell 64 mm. (160 to 96).

9:51 PD-1, 0.1 mg. Blood pressure fell from 158 to 110 mm. and then rose to 164. Respiratory stimulation.

9:54 PD-2, 0.01 mg. Practically no effect.

9:57 PD-2, 0.1 mg. Blood pressure fell from 158 to 136 mm. and then rose to 190 mm. Respiratory stimulation.

10:10 Atropine sulfate, 4 mg.

10:18 AcC, 0.001 mg. Blood pressure rose from 108 to 118 mm.

10:26 PD-1, 0.1 mg. Blood pressure rose from 128 to 162 mm. Traube–Hering waves noted.

10:30 PD-2, 0.1 mg. Blood pressure rose from 130 to 208 mm. and slowly returned to 136 mm.

10:40 Adrenalectomy bilaterally.

11:29 AcC, 0.001 mg. Little effect.
11:32 PD-2, 0.1 mg. Blood pressure rose from 142 to 208 mm. Rapid return to normal.
11:35 PD-1, 0.1 mg. Blood pressure rose from 144 to 164 mm. Traube–Hering waves. Transitory respiratory stimulation.
11:38 PD-2, 0.2 mg. Blood pressure rose from 154 to 236 mm. Traube–Hering waves. Transitory respiratory stimulation.
11:43 PD-1, 0.2 mg. Blood pressure rose from 148 to 184 mm. Traube–Hering waves. Transitory respiratory stimulation.

The authors wish to express their appreciation and thanks to Professor George B. Wallace, in whose laboratory most of the experiments were performed.

Summary

1. Methods of preparation of tertiary amino alkyl thiols are described.

2. Thioethyldimethylamine and its β-methyl derivative have been acylated and the resulting thioesters converted into quaternary ammonium derivatives yielding thioesters of choline and β-methylcholine.

3. The acetyl derivatives of thiocholine and the acetyl derivative and methyl thioether of β-methylthiocholine have been tested pharmacologically for their acetylcholine, "stimulating" and "paralytic nicotine" and "curare" actions.

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[A COMMUNICATION FROM THE LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Effects of Solvents on Polarographic Wave Heights

BY EDMOND S. PERACCHIO[1] AND VILLIERS W. MELOCHE

Since the discovery of the polarograph by Heyrovsky, many contributions have been made to the literature involving the use of the instrument. Aside from describing the process at the dropping mercury capillary electrode and developing equations for the polarographic curve, most papers were concerned with proof of reduction or qualitative detection of a great variety of substances. Actual applications of the method to quantitative analysis were few in number and often the procedures were poorly defined. Heyrovsky, Ilkovic and others have mentioned variables which affect wave height and its relationship to concentration of a given ion. In this connection they have included the mobility of the reducible ion as an important consideration. When one examines several papers which have appeared in the literature,[2] it may seem that a given amount of one reducible substance will give a wave height equal to that of an equivalent amount of another reducible substance or that differences between the wave for equivalent amounts of two different ions are not significant in quantitative analysis. From our studies it became evident that this was not necessarily true. At the same time it is true that the order of magnitude of these differences could be changed by the addition of various reagents to the solution of the sample.

Since in a preliminary investigation we found that the wave for lithium chloride was defined better in a solution containing ethyl alcohol than it was in water, it was decided to extend the study of the polarographic wave heights to systems containing high concentrations of non-aqueous solvents.

The purpose of this investigation is to illustrate the differences in wave heights which exist for equivalent weights of the alkali metals in certain aqueous solutions and to show how these differences are affected by the introduction of certain organic solvents.

Apparatus.—The usual Heyrovsky[3] polarographic system was used. A few changes were made in the manipulation and construction of the dropping mercury cathode. In the usual construction of the cathode, a mercury reservoir is suspended about 15 inches (38 cm.) above the capillary tip and is connected to the tip by means of gum rubber tube. This arrangement was not satisfactory even when the tube received special treatment. For our experiments, a 100-ml. dropping funnel was used as the reservoir, Fig. 1. The glass tube below the stopcock was long enough so that the distance from the surface of the mercury in the reservoir to the capillary tip afforded a mercury pressure of about 15 to 20 inches (38–51 cm.). The capillary was attached to the glass tube from the reservoir by a short piece of rubber tube which had been conditioned by

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[1] This paper is offered in partial fulfilment of the requirements for the degree of Doctor of Philosophy. The work was supported by a grant from the Wisconsin Alumni Research Foundation.

[2] References on wave height discrepancies: Heyrovsky and Nejedly, *Coll. Czech. Chem. Comm.*, **3**, 126 (1931); Suchy, *ibid.*, **3**, 358 (1931); Prajzler, *ibid.*, **3**, 408 (1930); Ilkovic and Semerano, *ibid.*, **4**, 176 (1932); Tokuoka, *ibid.*, **4**, 452 (1935); Rylich, *ibid.*, **7**, 290 (1935).

[3] Hohn, *Z. Elektrochem.*, **43**, 127 (1937); Winkle and Proske, *Angew. Chem.*, **50**, 18 (1937).

boiling in dilute sodium hydroxide, washing with hydrochloric acid and finally with water. Thermometer tube, 5.0 mm. o. d. and 0.5 mm. i. d., was used for the capillary tips, the tubes being drawn in such a manner that they had a long gradual taper. To prepare a tip for use, it was attached to the reservoir as described and immersed in water. Successive small portions were broken off until the mercury droplet barely formed. Using a solution 0.1 *N* in tetramethylammonium hydroxide and 0.001 *N* potassium chloride, the necessary connections were made preparatory to electrolysis and the trolley was set for a voltage nearly equal to the reduction potential for the potassium. Successive small portions were again broken from the tip until the oscillations of the galvanometer were at a minimum for a given voltage. Such a tip produces a smooth curve when used in the analysis of the alkali metals. The drop rate is usually about 1 drop every two seconds.

A straight-walled vessel was used instead of the usual Erlenmeyer type used by Heyrovsky and others (Fig. 2). The rubber stopper in the vessel had two holes. In one there was a glass tube which was slightly larger than the capillary tip and through which the tip could move freely as through a sleeve. The other hole provided for a tube through which hydrogen could be passed over the surface of the solution. The whole cathode, Fig. 1, was supported on a ring stand in such a manner that it could be raised or lowered by adjustment of a screw. In ordinary cases the hydrogen used for removing the dissolved oxygen from the solution of the sample was purified by passing it through alkaline pyrogallol and then through sulfuric acid. When the solution to be examined contained a highly volatile substance, the hydrogen was saturated by passing it through a portion of the solution before it passed through the sample in the vessel. This minimized the change of concentration caused by loss of the volatile substance.

Materials.—Tetramethylammonium hydroxide was used as the supporting electrolyte for all of the work with the alkali salts. It was prepared as follows: 17 g. of silver nitrate was dissolved in about 150 ml. of water. Four grams of sodium hydroxide was dissolved in about 150 ml. of water and poured with vigorous stirring into the silver nitrate solution. The precipitated silver oxide was washed 12 to 15 times by decantation using about 300 ml. of distilled water, mixing thoroughly each time and draining as completely as possible. Fifteen and six-tenths grams of tetramethylammonium bromide was dissolved in about 100 ml. of water and the solution poured with vigorous stirring into the washed silver oxide. After mixing, the solution was decanted and allowed to stand for several days. During this time most of the very fine particles of silver bromide settled. The solution was filtered through hard paper, diluted to 200 ml. and was ready for standardization.

Sodium chloride was prepared from a sample of fused sodium chloride by saturating a solution of the fused salt with hydrogen chloride, forcing the sodium chloride out of solution. The sodium chloride thus obtained was recrystallized from water.

Potassium chloride was prepared by treatment of analytical reagent potassium carbonate with hydrochloric acid and subsequent recrystallization of the potassium chloride.

Rubidium and cesium chlorides were prepared from analytical reagent quality materials. The chlorides were further purified according to the method of Wells and Stevens[4] for the separation of the alkali metals.

Lithium chloride was prepared from lithium metal and freshly prepared hydrochloric acid. The lithium chloride was extracted with pyridine to separate it from any of the other alkalies. Finally it was recrystallized from water.

Rochelle salt used as the supporting electrolyte in the cadmium and lead systems was reagent quality.

The alcohols used, methyl, ethyl, and propyl, were dried over calcium oxide and then fractionated. The fraction collected boiled over a 1° range. Ethylene glycol, trimethylene glycol, and glycerol were treated in a similar manner.

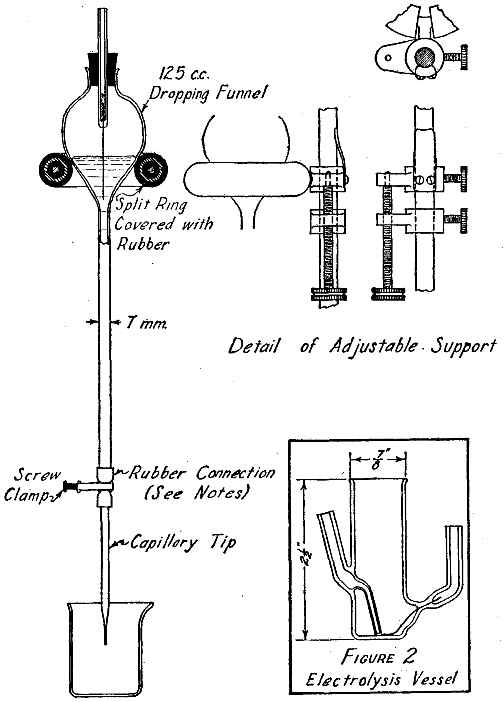

Fig. 1. Fig. 2.

1,4-Dioxane was dried over sodium metal and fractionated. Only freshly distilled product could be used. Apparently, on standing, the dioxane tends to form peroxides and these react with the mercury in the polarographic vessel. Freshly distilled dioxane did not do this.

Water was redistilled in a copper still and only the middle third collected for use.

The mercury used for the cathode and anode was aerated under a solution of sodium hydroxide, washed in a tower with 3% nitric acid, and finally with water. The dry mercury was distilled under reduced pressure.

Method.—Fairly concentrated stock solutions were prepared so that by taking a definite aliquot of each reagent and mixing them together the resulting solution contained each constituent in the desired concentration. The solutions used for electrolysis were made 0.001 *N* to the reducible ion, *i. e.*, sodium, potassium, etc., and 0.1 *N* to

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[4] Wells and Stevens, *Ind. Eng. Chem., Anal. Ed.*, **6**, 439 (1934).

the supporting electrolyte, tetramethylammonium hydroxide.

The concentration of the organic solvent was generally 80% except in a few cases where the concentration is specified. A sufficient quantity of the solution was prepared so that a portion of it could be placed in the saturation vessel and a portion in the cell used for electrolysis. Oxygen-free hydrogen was passed through the two solutions until the oxygen was removed from the solutions. This operation required three to five minutes. The solution was then ready for electrolysis. Wave heights were measured according to the method described as A_4B_4 by Borcherdt, Meloche and Adkins.[5] There was a slight exception in that the slope of the base of the curves was more nearly horizontal than illustrated. Therefore an application of the method A_1B_1 would not alter the results very much.

Wave Heights in Aqueous Systems.—In the course of our polarographic investigations, it was observed that the wave heights for equivalent weights of sodium and potassium were not equal. An illustration of this difference appears in Fig. 3. The first four curves represent 0.001 *N* sodium chloride, the second four 0.001 *N* potassium chloride, and the last two represent a 1–1 mixture of sodium chloride and potassium chloride, the total concentration of the mixture being 0.001 *N*. The average wave height for sodium is 0.755″ (19.1 mm.) and the average for potassium is 0.858″ (21.8 mm.). An average value for the 1–1 mixture of sodium and potassium as represented in the last two curves of Fig. 3 is 0.823″ (20.9 mm.) and this is 0.068″ (1.7 mm.) more than the equivalent wave height for sodium. Since the reduction potentials for the alkali metals are close to each other, the polarograph does not register them separately. One might expect that the wave height for a 1–1 mixture of 0.0005 *N* sodium and potassium would give a wave height half-way between the equivalent height for 0.001 *N* sodium and 0.001 *N* potassium. The curves which illustrate this point actually show a difference of 0.103″ (2.6 mm.) between sodium and potassium, and the wave height for the mixture is 0.068″ (1.7 mm.) greater than the sodium, showing that the wave height for the mixture did not fall half-way between the height for the sodium and the potassium but nearly so. It did not seem that these differences were small enough to be ignored; hence this study was extended to include rubidium and cesium.

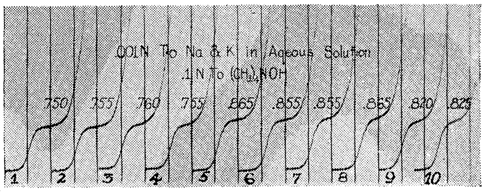

Fig. 3.—Curves 1, 2, 3, 4 for 0.001 *N* NaCl; curves 5, 6, 7, 8 for 0.001 *N* KCl; curves 9 and 10 for 0.0005 *N* NaCl and 0.0005 *N* KCl.

Solutions of equivalent weights of sodium, potassium, rubidium, and cesium chlorides were prepared and electrolyzed under conditions identical to those illustrated by the polarograms in Fig. 3. A representative set of curves for such a series is shown in Fig. 4. Direct comparison of the magnitude of the wave heights in Figs. 3 and 4 cannot be made because the sensitivity was different for each series and the tip also was different. By comparing the average wave heights in Fig. 4 one observes that the difference between sodium and potassium is 0.127″ (3.2 mm.), between potassium and rubidium 0.042″ (1.1 mm.), and between rubidium and cesium 0.067″ (1.7 mm.). The order of magnitude of the wave heights increases in the order sodium, potassium, rubidium, and cesium.

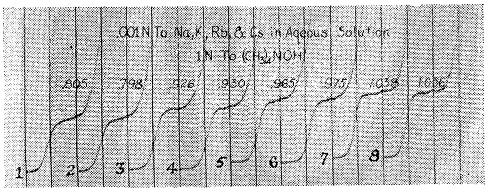

Fig. 4.—Curves 1 and 2 for 0.001 *N* NaCl; curves 3 and 4 for 0.001 *N* KCl; curves 5 and 6 for 0.001 *N* RbCl; curves 7 and 8 for 0.001 *N* CsCl.

Curves for lithium are not included in Fig. 4. This is due to the fact that the saturation wave for lithium is imperfectly, if at all, defined in aqueous systems.

In comparing the differences in wave heights for equivalent weights of elements of the alkali group, there is a variation in atomic weight from sodium to cesium. It is desirable to examine other elements not only to provide an element having a higher atomic weight but to provide two elements which are reduced at different potentials. Cadmium and lead were chosen for the purpose. For an electrolysis, it was found that 0.06 *N* Rochelle salt was satisfactory. The reducible ions, cadmium and lead, were 0.001 *N*. Representative results from this study are shown in Fig. 5. It can be seen that a difference does exist between the wave heights for equivalent weights of cadmium and lead. For a 1–1 mixture of the salts, the total equivalent weight being equal to that of the previous curves, the two waves did not appear in a ratio of 1–1 but appeared in heights nearly proportional to the differences shown in the two previous curves.

In the introduction we mention articles[2] that seem to indicate that equivalent amounts of cadmium, lead, and bismuth gave wave heights which were practically identical. While we will show that it is possible to change the environment in such a manner that the wave heights for equivalent amounts of different elements are the same, it did not seem that equal normal solutions necessarily should give equal wave heights for cadmium, lead, and bismuth when lithium nitrate and nitric acid were used as the supporting electrolyte in an aqueous system. Heyrovsky and Suchy[2] used lithium nitrate and nitric acid as supporting electrolytes when they studied the polarographic behavior of cadmium, lead, and bismuth. Since we had not used this particular supporting electrolyte, we repeated our experiments on cadmium, lead, and bismuth, duplicating as nearly as possible the conditions described by the above authors in their papers. Our results are shown in Fig. 6. It is observed that the differences in wave heights for cad-

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(5) Borcherdt, Meloche and Adkins, THIS JOURNAL, **59**, 2171 (1937).

mium and lead in this system are even greater than they appeared in Fig. 5 when Rochelle salt was used as the electrolyte. The second curve in Fig. 6 illustrates the addition of bismuth to the mixture. So far as the sensitivity of this system is concerned, the addition of bismuth did not seem to alter the differences which were previously observed between cadmium and lead.

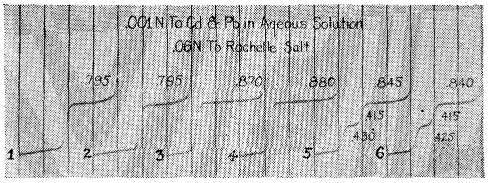

Fig. 5.—Curves 1 and 2 for 0.001 *N* $Cd(NO_3)_2$; curves 3 and 4 for 0.001 *N* $Pb(NO_3)_2$; curves 5 and 6 for 0.0005 *N* $Cd(NO_3)_2$ with 0.0005 *N* $Pb(NO_3)_2$.

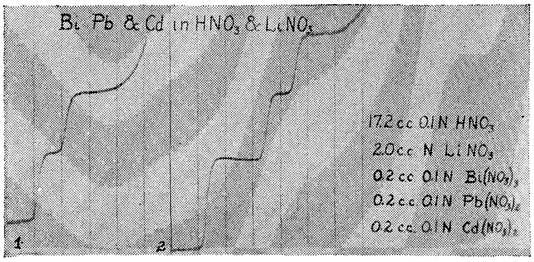

Fig. 6.—Curve 1 for 0.001 *M* $Cd(NO_3)_2$ with 0.001 *M* $Pb(NO_3)_2$; curve 2 for 0.001 *M* $Cd(NO_3)_2$; curve 2 for 0.001 *M* $Cd(NO_3)_2$, 0.001 *M* $Pb(NO_3)_2$ and 0.001 *M* $Bi(NO_3)_3$.

This information further substantiates the differences found for the elements of the alkali group, and indicates that when dealing with more than one element in solution, one cannot assume that equal wave heights of different elements mean equivalent concentration.

Wave Heights in Water–Alcohol Systems.—We know that aside from such factors as the capillary tip and temperature, we can alter the wave height for a given substance by changing the chemical environment. In the following experiments the effect of organic solvents on polarographic wave heights is described. A concentration of alcohol was selected which would easily change the character of the solution and yet not cause too great a difficulty in dissolving the salts of the alkali metals. Figure 7 represents the electrolysis of solutions containing the alkali chlorides 0.001 *N*, ethyl alcohol 80%, and tetramethylammonium hydroxide 0.1 *N* Several important differences can be noticed. In the water–alcohol system lithium now shows a reproducible saturation wave. The order of the differences in wave height is lithium, sodium, potassium, rubidium, and cesium. Differences in wave height for equivalent amounts of these elements are less in alcohol–water than in pure water.

Table I gives the order of magnitude of decrease in wave height for sodium or potassium in various concentrations of alcohol as well as the relative wave heights for equivalent weights of sodium or potassium in different alcohols. A graph of percentage alcohol against wave height reveals that, in general, wave height decreases as the concentration of the alcohol increases. An equivalent weight of sodium or potassium in 70% ethyl or methyl alcohol gives wave heights of about the same magnitude. For a solution of propyl alcohol, the wave heights are decidedly lower.

TABLE I

Conversion factor inches to mm. = 25.4

Curve	% alcohol	Wave height, inches		
		Methyl alc.	Ethyl alc.	Propyl alc.
		Sodium Chloride		
1	0	1.38	1.40	1.37
2	10	1.27	1.33	1.14
3	20	1.18	1.21	0.99
4	30	1.17	1.16	.89
5	40	1.10	1.09	.81
6	50	1.13	1.00	.78
7	60	1.01	0.99	.68
8	70	1.08	1.00	.56
		Potassium Chloride		
1	0	1.165	1.175	1.185
2	10	1.08	1.110	1.075
3	20	1.045	1.065	1.00
4	30	0.995	1.03	0.92
5	40	.915	1.03	.90
6	50	.945	1.02	.765
7	60	.92	0.975	.70
8	70	.935	.99	.68

Since we know that the differences in wave heights for sodium and potassium are greater in the water system than in the water–alcohol system, it seemed desirable to extend this study to certain other organic solvents. We therefore included ethylene glycol, trimethylene glycol, and glycerol.

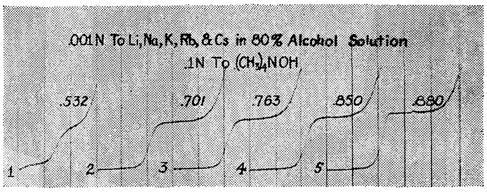

Fig. 7.—Curve 1 for 0.001 *N* LiCl; curve 2 for 0.001 *N* NaCl; curve 3 for 0.001 *N* KCl; curve 4 for 0.001 *N* RbCl; curve 5 for 0.001 *N* CsCl.

Polarograms for equivalent weights of sodium and potassium chlorides in ethylene glycol, trimethylene glycol, and glycerol are shown in Fig. 8. In curve 1 of Fig. 8, we have shown an equivalent weight of sodium chloride in water as a reference. Curve 2 shows sodium chloride in 80% ethyl alcohol; curve 3, sodium chloride in 80% ethylene glycol; curve 4, sodium chloride in 80% trimethylene glycol; curve 5, sodium chloride in 80% glycerol. Figure 9 represents a similar series for potassium. It will be noted that the wave heights for both sodium and potassium in these solvents decrease in the order mentioned, namely, water, ethyl alcohol, ethylene glycol, trimethylene glycol, and glycerol. As previously mentioned, in the water system, a given concentration of potassium gives a higher wave than an equivalent concentration of sodium. Equivalent concentrations of sodium and potassium give lower wave heights in 80% alcohol than in the water system, and the differences in height for sodium and potassium are less in the alcohol–water system than they are in pure water. While the wave height in 80% ethylene glycol is less than that in 80% ethyl alcohol, there is still a perceptible difference shown for equivalent weights of sodium and potassium. Wave heights in trimethylene glycol are only slightly smaller than those in ethylene glycol, and the differences shown for equivalent weights of sodium and potassium are almost imperceptible.

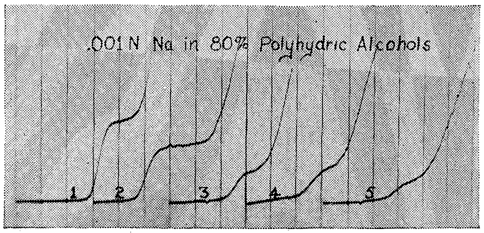

Fig. 8.—Curve 1 for 0.001 *N* NaCl in water; curve 2, same in ethyl alcohol; 3, in ethylene glycol; 4, in trimethylene glycol; 5, in glycerol.

The wave heights for equivalent weights of sodium and potassium in a solution containing glycerol are lowest of all, and there is no perceptible difference in the two wave heights. However, it will be noticed that while the shape of the curves for samples containing alcohol was almost ideal for quantitative measurements, the waves for the last three curves in Fig. 8 and Fig. 9 are successively less well defined. In this connection it may be observed that the viscosities of the last three media are relatively high.

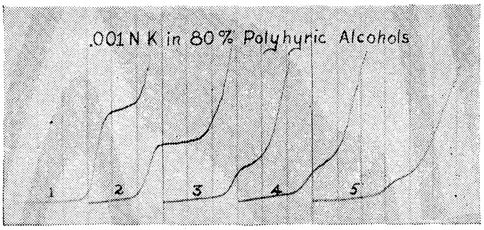

Fig. 9.—Curve 1 for 0.001 *N* KCl in water; 2, same in ethyl alcohol; 3, in ethylene glycol; 4, in trimethylene glycol; 5, in glycerol.

Wave Heights in Dioxane–Water System.—Figure 10 shows four curves, the first two of which represent equivalent weights of sodium and potassium in water and the second two represent the same weights of sodium and potassium in 70% dioxane. While the waves are less well defined in the dioxane system, it is important to note that the waves for sodium and potassium are practically identical. Figure 11 shows curves for equivalent weights of sodium, potassium, rubidium, and cesium in 80% dioxane. In this system the curves, so far as measurement is concerned, are identical. Since the curves in Fig. 10 are made with a different tip, they cannot be compared with curves in Figs. 8, 9, and 11. However, it may be mentioned that an equivalent weight of sodium or potassium in 80% dioxane gives a smaller wave height than it does in either water or alcohol systems.

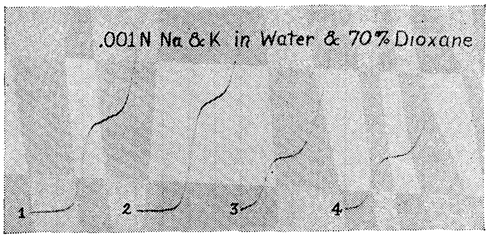

Fig. 10.—Curve 1 for 0.001 *N* NaCl in water; 2, 0.001 *N* KCl in water; 3, 0.001 *N* NaCl in dioxane; 4, 0.001 *N* KCl in dioxane.

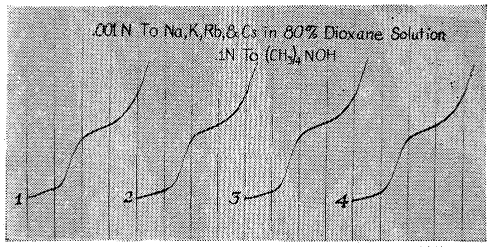

Fig. 11.—Curve 1 for 0.001 *N* NaCl in dioxane; 2, for 0.001 *N* KCl; 3, for 0.001 *N* RbCl; 4, 0.001 *N* CsCl.

Conclusion

In a preliminary paper before the Wisconsin Academy of Science[6] we reported that when solutions of sodium chloride and potassium chloride which are 0.001 *N* to chloride and 0.1 *N* to tetramethylammonium hydroxide are examined by means of the polarograph, the wave heights are not the same. In the present paper we have shown that the wave heights are different not only for equivalent concentrations of sodium and potassium chloride but also for all of the alkali chlorides. The wave heights increase in magnitude from sodium to cesium. These differences are not small enough to be ignored and therefore interfere with the application of the polarograph to quantitative analysis. In the usual procedure for the estimation of one element in an unknown an internal standard is used. The unknown is prepared in a suitable solution with a supporting electrolyte and a polarogram is recorded. Then a known amount of the element to be determined is added and another curve is recorded. The increase in wave height caused by the added standard is measured and from this the relationship

[6] Peracchio and Meloche, *Wisconsin Acad. Sci.*, April 17, 1936.

between wave height and concentration of the element is calculated. By this procedure a reasonably precise value is obtained.

When there is more than one reducible ion in solution, one cannot presume that if the relationship between wave height and concentration is established for one, it will also hold for the others. In the precise application of the polarograph to chemical analysis, one is faced therefore, with the necessity of correcting for the discrepancies which exist or eliminating them.

In reporting the effect of the addition of certain non-aqueous solvents to solutions used in polarographic analysis we have shown that the wave heights for equivalent concentrations of alkali chlorides were lowered and that the differences between the wave heights for the alkalies were lessened. We also indicated that in solutions which contained 80% dioxane the wave heights for equivalent weights of alkali chlorides were the same. From these data one might assume that in cases where more than one element is to be determined one should use dioxane in the solution. This is by no means the case. Certainly, at present there is no one set of conditions which satisfy all samples. Information must be collected for the case at hand.

Ilkovic, Heyrovsky, Kemula, and Maas[7] have reported studies on the limiting current and have suggested the dependence on the diffusion constant, on the rate of dropping and the size of the drops at the dropping mercury cathode. Little emphasis has been placed on the importance of mobility in the application of the polarographic method to quantitative analysis. The few papers in this field have ignored the existence of differences in mobility and consequent differences in wave heights. This would be permissible if the highest degree of precision is not attempted. However, wave height differences cannot be ignored if the application of the technique is to be precise.

Summary

Polarograms are shown for sodium, potassium, rubidium, and cesium chloride in aqueous solutions and differences in wave height are shown to exist for equivalent concentrations of the chlorides.

Contrary to indications in the literature, it is shown that equivalent concentrations of cadmium, bismuth and lead chlorides do not give equal wave heights.

It is shown that the presence of various alcohols lowers the wave heights exhibited in aqueous solutions. Differences between the wave heights for equivalent concentrations of alkali chlorides are lessened.

Addition of certain polyhydric alcohols to the aqueous solutions of the alkali chlorides also lowered the wave heights but in cases of the more viscous solutions the curves were poorly defined.

When dioxane was added to aqueous solutions of the alkali chlorides, the wave heights for equivalent concentrations of the salts were the same. Although the shape of the curves was not ideal, the wave heights could be measured and the curves were suitable for quantitative analysis.

While the universal use of organic solvents in solutions prepared for the polarograph is not recommended, there are many cases where the use of such systems is desirable and in some cases even mandatory.

MADISON, WISCONSIN

RECEIVED APRIL 4, 1938

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[7] Information on limiting current: Ilkovic, *Coll. Czech. Chem. Comm.*, **6**, 498 (1934); Heyrovsky, *ibid.*, *loc. cit.*; Kemula, Congress Pure and Applied Chemistry, Madrid, 1934; Maas, *Coll. Czech. Chem. Comm.*, **10**, 42 (1938).

[CONTRIBUTION FROM THE RESEARCH LABORATORY, GENERAL ELECTRIC COMPANY]

The Hydroxyanthraquinones as Analytical Reagents. The Colorimetric Determination of Zirconium or Hafnium

BY HERMAN A. LIEBHAFSKY AND EARL H. WINSLOW

The use of the hydroxyanthraquinones in analytical chemistry has grown steadily since Atack[1] discovered that aluminum could be detected with alizarin red S,[2] the sodium salt of alizarin sulfonic acid. Their value as colorimetric reagents for precise quantitative work, however, has not been appreciated widely partly because the compounds (lakes) which these dyes form with all or nearly all metallic cations[3] are sparingly soluble, and partly because the dyes themselves are so intensely colored that the quantitative estimation by simple visual comparison of a small amount of lake in the presence of excess dye is practically impossible. In working with zirconium and hafnium, we have minimized the first difficulty by maintaining the lakes at great dilution in 95% ethyl alcohol. Color interference, the second difficulty, does not exist when a spectrophotometer[4] is used. This investigation is an attempt to establish the hydroxyanthraquinones as colorimetric reagents upon a systematic quantitative basis through accurate measurements of the light absorbed by these dyes and their lakes.

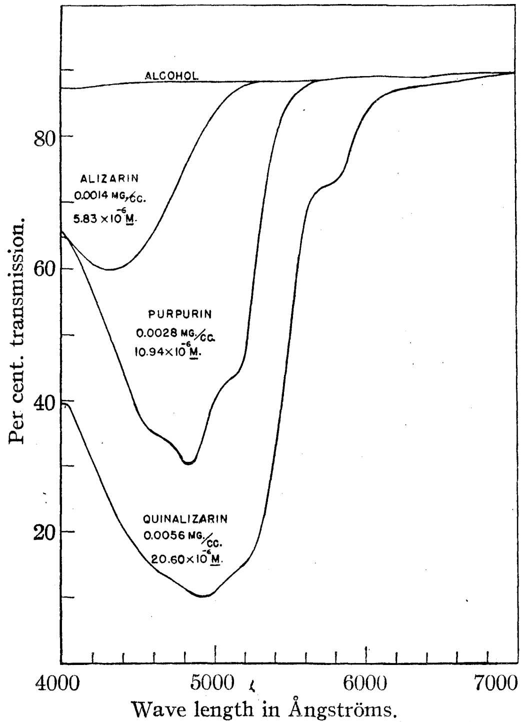

Fig. 1.—Transmission curves for each of the three hydroxyanthraquinones in dilute alcoholic solution.

The lakes formed by alizarin with most metallic cations, including aluminum, do not persist when an excess of a strong acid is added. The extraordinary stability of the alizarin–zirconium lake under these conditions was discovered by deBoer[5] as he attempted to use Atack's reaction to detect aluminum in the presence of zirconium. His work afforded us a welcome point of departure in the development of the colorimetric methods given below, with which it is possible to determine even a few micrograms of zirconium or hafnium with reasonable accuracy.

The absorption of visible light by acid alcoholic solutions of alizarin (1,2-dihydroxyanthraquinone), purpurin (1,2,4-trihydroxyanthraquinone) and quinalizarin (1,2,5,8-tetrahydroxyanthraquinone) is shown in Fig. 1. Each of these curves belongs to a family that was obtained to establish the molar extinction coefficients of the dyes, to be subsequently reported. Occasionally small decreases in transmission were observed near 6000 Å. with concentrated dye solutions; these were probably due to slight impurities not present in the stock solutions and introduced haphazardly in preparing the specimens for the transmission measurements; because of their infrequent, random occurrence, they were not investigated further.

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(1) Atack, *J. Soc. Chem. Ind.*, **34**, 936 (1915).

(2) *Cf.* Feigl, "Qualitative Analyse mit Hilfe von Tüpfelreaktionen," Akademische Verlagsgesellschaft, Leipzig, 1938, for an excellent discussion of and reference to the use of the hydroxyanthraquinones in analytical chemistry.

(3) *Cf.* Beilstein, "Handbuch der organischen Chemie," 4th Ed., Erstes Ergänzungswerk, Vol. VIII, Verlag von Julius Springer, 1931, pp. 711, *et seq.*

(4) Michaelson and Liebhafsky, *Gen. Elec. Rev.*, **39**, 445 (1936), give a description of the General Electric Company recording photoelectric spectrophotometer, which plots accurately the absorption spectrum of a solution for the visible range as a function of wave length in two and one-half minutes.

(5) (a) DeBoer, *Chem. Weekbl.*, **21**, 404 (1924). The work was extended to include the detection of hafnium and fluorine with alizarin and other hydroxyanthraquinones by (b) deBoer, *Rec. trav. chim.*, **44**, 1071 (1925); (c) deBoer and Basart, *Z. anorg. Chem.*, **152**, 203 (1926), who give a method for the titration of fluoride in which the zirconium-alizarin lake serves as indicator. The zirconium–purpurin lake is utilized similarly by (d) Kolthoff and Stansby, *Ind. Eng. Chem.*, *Anal. Ed.*, **6**, 118 (1934).

General Experimental Details.—All transmission measurements were made with the General Electric Company recording photoelectric spectrophotometer.[4] The alcoholic solutions (or suspensions) were usually contained in a cylindrical quartz cell (inside length, 5.15 cm., inside diameter, 2.40 cm.) with nearly plane ends, which was always inserted into the instrument in the same way.

The standard zirconium solution, containing 1 mg. of zirconium per cc., was prepared by dissolving C. P. $ZrOCl_2 \cdot 8H_2O$ in strong hydrochloric acid at room temperature and diluting until the acid concentration was about 2 *N;* the strength of this solution, determined by igniting and weighing the precipitate obtained from a known volume with ammonium hydroxide, showed this salt to be over 99% pure. The standard hafnium solution was prepared by dissolving a known weight of hafnium dioxide (Deutsche Auer Gesellschaft, Berlin) in mixed concentrated hydrofluoric and nitric acids, fuming three times with sulfuric acid, diluting, repeatedly precipitating the hydroxide with ammonium hydroxide until the washings from the precipitate gave no test for sulfate, and finally dissolving this hafnium hydroxide in strong hydrochloric acid and diluting the resulting solution until the acid concentration was about 3 *N*. The hafnium content of this solution was determined by igniting the precipitated hydroxide. A large excess of acid is necessary to make certain that no hydrolysis beyond MO^{++} occurs; such hydrolysis interferes with the colorimetric methods given below.

The dyes, of good quality, were not purified further. They were dissolved by warming them in contact with 95% ethyl alcohol; the resulting solutions were cooled, filtered, and diluted with additional solvent. Solutions thus prepared precipitated the solute even after weeks or months of standing in the laboratory; this annoying behavior, which is in accord with Hüttig's[6] observations on aqueous solutions of alizarin, is probably due to the formation of unstable colloidal suspensions during the heating. (That the tendency to form suspensions of this sort is even more pronounced with the lakes formed by these dyes will appear subsequently.) The stable solutions finally employed contained: alizarin, 1.250 mg./cc.; purpurin, 0.754 mg./cc., quinalizarin, 0.328 mg./cc. Presumably solutions of these concentrations would have been stable initially.

The Colorimetric Method.—The following detailed instructions gradually evolved as zirconium determinations were carried out over a period of several months. Reasona[illegible] adherence to them is advisable if precise results are [illegible].

The [illegible]e formed in clean glass-stoppered graduated cylinders [illegible]ve been rinsed with alcohol. The proper volume (sat[illegible]ory volumes of our solutions: alizarin, 0.5 cc.; purp[illegible] 1 cc.; quinalizarin, 1.5 cc.) of the stable dye solution is added to a small amount (up to, say, 120 micrograms—the maximum amount permissible varies with the dye employed) of the zirconyl ion contained in 1 cc. or less of about 2 *N* hydrochloric acid solution. Strong ammonium hydroxide is now added drop by drop until the color change of the dye reveals that the solution is slightly alkaline. The mixture is then allowed to stand for two minutes, neutralized with 1 *N* hydrochloric acid, and 0.1 cc. of 7 *N* hydrochloric acid finally added. When this mixture has been diluted with alcohol to the proper volume (in our case 27 cc.), its absorption from 4000 to 8000 Å. is measured on the spectrophotometer.

The rate at which the lake forms when no ammonium hydroxide is used decreases as the acidity increases; the addition of ammonium hydroxide eliminates this difficulty. When, in subsequent work, the lakes were formed differently, the differences are described.

Analytical Results.—The transmission curves obtained for a series of zirconium–alizarin determinations are given in Fig. 2, those for a zirconium–purpurin series in Fig. 3. The curves for the zirconium–quinalizarin families resemble those of Fig. 3 closely enough so that it is unnecessary to reproduce them. The absorption due to the dye alone occurs mainly at the shorter wave lengths as the curve for the first colored solution in each series shows; at wave lengths beyond 5600 Å. (alizarin) or 5800 Å. (purpurin) this absorption is so small that the transmission of the dye solution can be taken as I_0 in evaluating the results according to Beer's law

$$\log_{10} \frac{I_0}{I} = \epsilon_2 \, l \, (L) = k\epsilon_2 \, l \, (\mathrm{ZrO}^{++}) \qquad (1)$$

I is the light transmitted at a longer wave length by the sample containing dye and lake; ϵ_2 is the molar absorption coefficient of the lake; *l* is the length of the cell in cm.; (ZrO^{++}) is the "concentration" (moles/liter) of this ion calculated from the micrograms of zirconium added to 27 cc.; *k* is a proportionality constant introduced because the combining ratio of zirconium to dye is unknown; (*L*) is the "concentration" (moles/liter) of the lake in the final solution. The data of Figs. 2 and 3 evaluated in this way for several wave lengths are shown in Figs. 4 and 5; a quinalizarin series is evaluated in Fig. 6; the product $k\epsilon_2$ is given in parentheses for each line beside the corresponding wave length. Examination of these figures reveals that: (1) alizarin gives precise results over the entire range of abscissa explored; (2) quinalizarin is the most sensitive reagent (largest value of $k\epsilon_2$), purpurin being intermediate; (3) as increasing amounts of the zirconium–purpurin lake are formed, *I* becomes too small, leading to positive deviations from Beer's law, which *increase* with the wave length; (4) under the same conditions, *I* for the quinalizarin lakes becomes too large, leading to negative deviations that tend to *decrease* with the wave length. The positive deviations will be discussed below; the negative in a subsequent article. We have found it convenient to use the following

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(6) Hüttig, *Z. physik. Chem.*, **87**, 129 (1914).

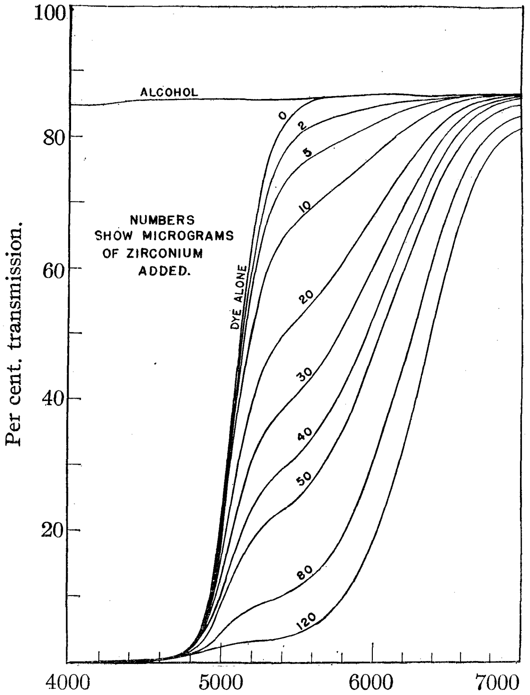

Fig. 2.—Standard transmission curves for the estimation of zirconium with alizarin.

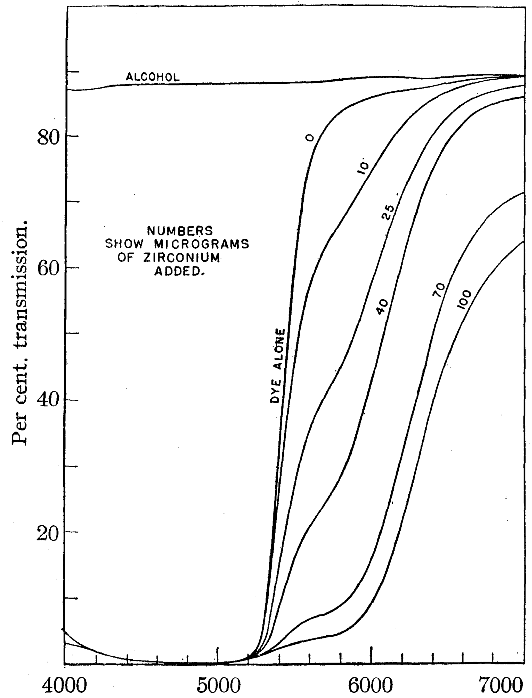

Fig. 3.—Standard transmission curves for the estimation of zirconium with purpurin.

wave lengths (at which absorption by the dye is negligible) in analytical work: alizarin, 5600 Å.; purpurin, 5800 Å.; quinalizarin, 6200 Å.

Effect of Added Substances.—Since the problem of removing interference by most other metallic cations often can be solved by increasing the acid concentration until interfering lakes will not form, the effect of added acid on lake formation was investigated. As 12 *N* hydrochloric or perchloric acid was added before dilution with alcohol to the lake formed from 50 micrograms of zirconium, a minimum in the transmission for 5600 Å. was observed with 0.05 cc. of excess acid. The other transmissions corresponded to the following decreases in micrograms of zirconium: 4.2 (no excess acid); 4.2 (0.5 cc. excess); 11.6 (1 cc. excess). The large transmission at 7000 Å. increased continuously with added excess of acid and the change expressed in micrograms of zirconium was much more pronounced at this wave length.

Sulfate and fluoride ions unite with zirconyl ion to form complex ions so stable that lake formation in the presence of sulfuric or hydrofluoric acid is decreased or prevented.[7] Preliminary experiments indicate that our colorimetric method is adapted to estimating small amounts of either of these interfering anions. Sulfate ion has been studied more thoroughly, and with the following results. When the alizarin lake is formed in the usual manner, and sulfuric acid is added before dilution, the color due to the lake disappears at a measurable rate which increases with greater amounts of added acid. When the acid is added after dilution, the change is similar but less rapid; the transmissions in such experiments increased markedly at first, more slowly afterward: whe[illegible] 0.05 cc. of 12 *N* acid was added to the final [illegible] cc.) volume, the transmissions at 56[illegible]r different times were 55.1% (one-h[illegible]our); 68.6% (fifteen hours); 70.4% ([illegible]y-three hours); 71.2% (forty-seven hours[illegible] The transmission without added sulfuric a[illegible] was 13.6% at 5600 Å. and increased only a few per cent. in forty-eight hours.) When the sulfuric acid is present initially, much less lake is formed; if ammonium hydroxide is used, lake formation is less than when the sulfuric acid is not neutralized;

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(7) Feigl (ref. 3, p. 254) mentions that fluorides, sulfates, phosphates, organic hydroxy acids, molybdates and tungstates interfere with or modify the formation of the zirconium-alizarin lake. The literature on complex zirconium ions containing fluoride and sulfate is extensive; *cf.* (a) Venable, "Zirconium and its Compounds," Chemical Catalog Co., New York, 1922; (b) Ruer and Levin, *Z. anorg. Chem.*, **46**, 449 (1905); (c) Chauvenet, *Ann. chim.*, [9] **13**, 59 (1920).

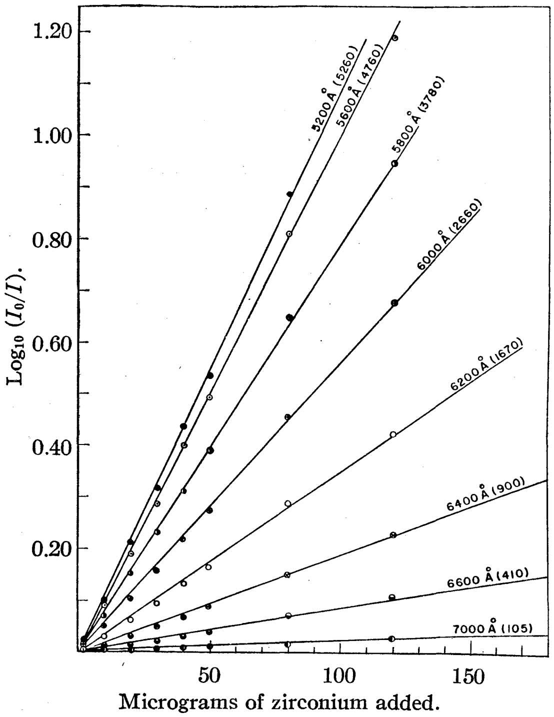

Fig. 4.—Beer's law curves for Fig. 2.

in the 0.05 cc. sulfuric acid experiment soon after mixing, the transmissions at 5600 Å. were 64.8% in the former case and 61.0% in the latter. (It is strange that these transmissions should be smaller than the limiting value, near 70% observed above.) Since the presence of 30 mg. of sulfuric acid increases the transmission due to the zirconium lake from 14 to 65%, it is obvious (since the transmission values are accurate to 0.1 or 0.2%) that this colorimetric method could be used for a rapid estimation of sulfate as well as for studying the formation of zirconyl–sulfate complex ions. A parallel investigation for fluoride ion ought to present no serious difficulty.

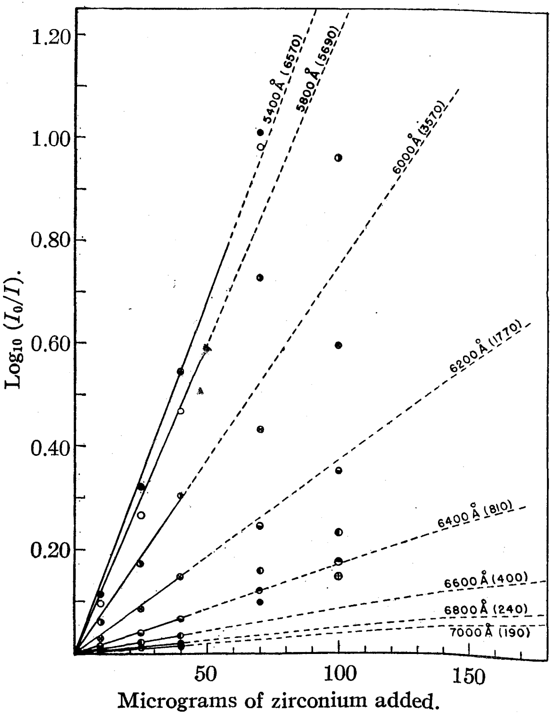

Fig. 5.—Beer's law curves for Fig. 3.

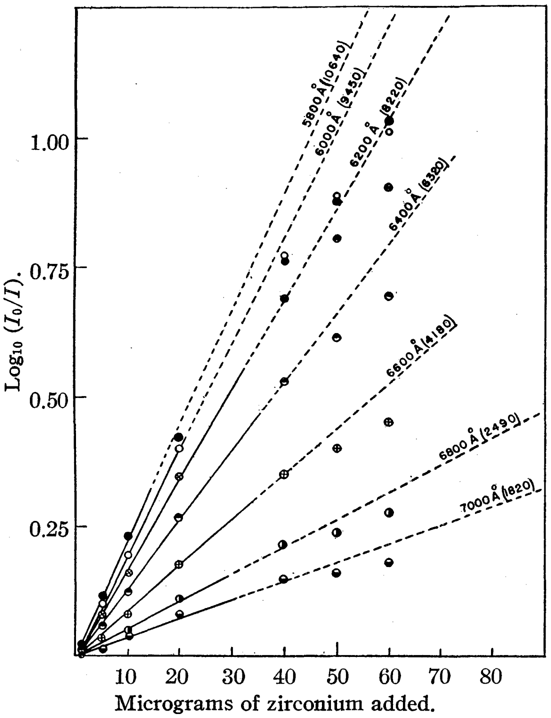

Fig. 6.—Beer's law curves for zirconium-quinalizarin experiments like the alizarin experiments of Fig. 2.

The interference of representative metallic cations not in the same periodic table group with zirconium was studied by adding 1 mg. of these ions to 10 micrograms of zirconium and then forming the lakes in the usual manner, that is, using 0.1 cc. of 7 N hydrochloric acid in excess. Under these conditions, the amount of zirconium cannot be determined accurately from data like those in Fig. 4; but the discrepancy in most cases will not exceed 50%, and may be positive or negative. Fe^{III}, Cr^{III} and Co^{II} decrease the transmission most markedly, without changing greatly the shape of the curve; W^{VI} and Mo^{VI} give curves much steeper than those for zirconium in the 5600 Å. region; many cations (Cd^{++}, Cu^{++}, Pb^{++}, Al^{+++}), when added in the presence of hydrochloric acid, increase the transmission, indicating that here, as with sulfate and fluoride, lake formation is decreased. In order to discover whether this decrease persists when chloride ion (which readily forms complexes) is absent, the experiments described in Fig. 7 were performed.

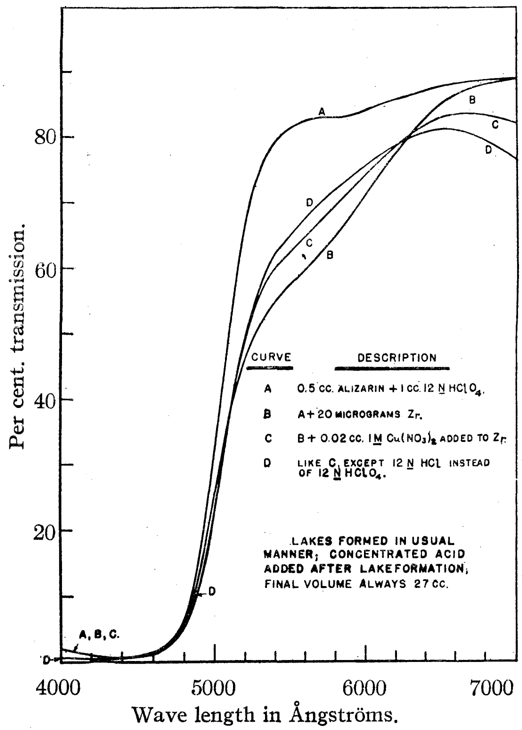

Fig. 7.—Interference of cupric ion with the determination of zirconium.

The curves show that lake formation is decreased even with perchloric acid, although to a smaller extent than with hydrochloric. (It was proved in experiments not given that the absorption near 7000 Å. persists when no dye is used; *i. e.*, it is the absorption due to the blue, solvated cupric ion.) The simplest explanation for the decreasing lake formation encountered when cations like Cu^{++} are added assumes that complex ions (*e. g.*, $CuCl_4^{=}$) derived from them unite with the zirconyl ion. If this explanation is correct, it is surprising to discover that a similar union can occur when perchlorate is the principal anion present: if ZrO^{++} can involve perchlorate in complex ion formation, it probably can react similarly with any other anion.

Experiments have shown that positive errors encountered with ions like Fe^{+++} can be reduced by increasing the amount of excess hydrochloric acid added; under these conditions, of course, the absorption due to the zirconium lake is also decreased.

To summarize: When present in hundred-fold excess, many cations interfere with the colorimetric estimation of zirconium because they either form lakes themselves or because they involve the zirconyl ion in complex formation. The former interference can be mitigated at the expense of sensitivity by increasing the excess of added acid; the latter, by working with perchlorates; either type of error can be compensated obtaining data like those in Fig. 4 with the interfering ion present; the shape of the spectrophotometric curves often reveals whether interference is occurring. There is no reason to believe that these cations will influence appreciably the colorimetric determination of a comparable amount of zirconium.

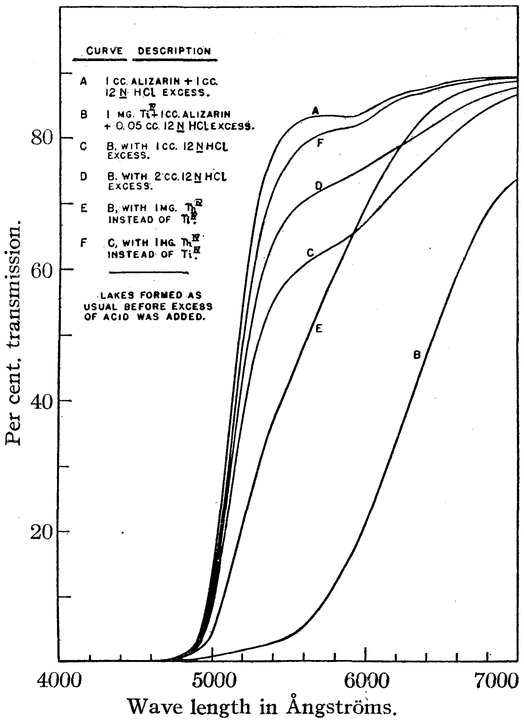

Fig. 8.—Interference of $Ti^{(IV)}$ and $Th^{(IV)}$ with the determination of zirconium.

Other Elements of Group IV.—Figure 8 shows the transmission curves obtained when varying excesses of concentrated hydrochloric acid were added to alizarin lakes formed in the usual manner with hydrochloric acid solutions containing Ti^{IV} and Th^{IV}. The curve from the thorium experiment with 1 cc. of excess acid is not greatly different from the curve for the dye alone; in other words, under our conditions interference by thorium is less serious than interference by titanium. Also, the absorption spectrum of the thorium lake differs markedly from those of the titanium and zirconium lakes, which resemble each other. This difference probably can be traced to the much smaller tendency of thorium to hydrolyze.

Although the close chemical similarity of hafnium to zirconium militates against the existence of any marked difference in their reactions with the hydroxyanthraquinones, there was some hope of finding a difference detectable by the spectrophotometer. Curves analogous to those of Fig. 2 were obtained for each of the three lakes, but they are not reproduced because each is qualitatively identical with the curve for the corresponding zirconium lake. The Beer's law data for the hafnium–alizarin family are given in Fig. 9. Comparison of these $k\epsilon_2$ values with those of Fig. 4 shows the latter to be, on the average, 1.30 times larger; in other words, a gram atom of zirconium combined as the alizarin lake behaves toward the spectrophotometer like 1.3 gram atoms of hafnium similarly combined. It follows that 1 g. of zirconium is spectrophotometrically equivalent to 2.55 g. of hafnium, and that the two elements can be determined in a known weight of sample provided other metallic cations can be removed if they are present. Experiments on hafnium lake formation with varying excesses of perchloric or sulfuric acid gave results similar to those obtained with zirconium.

The Lakes as Suspensions.—The general behavior of the lakes formed in this colorimetric work proves that they form suspensions, not true solutions. No matter what dye is used, the lakes eventually will settle out provided excess dye is present; the settling occurs more rapidly with purpurin and quinalizarin; the purpurin lakes are the most turbid initially, while those of alizarin seem at first to be in solution; the quinalizarin lakes form the most voluminous precipitate. The alizarin and purpurin lakes are red, with the latter darker; the quinalizarin lakes are purple. Having once settled out, the lakes can be re-dispersed easily by shaking; the transmission curve of the re-dispersed lake is very little different from that of the lake freshly prepared.

Crude sedimentation experiments[8] gave 1 micron as the order of magnitude of the average particle diameter in these lakes. Microscopic examination revealed that the diameters ranged, say, from 0.5 to 5 microns; the larger particles appeared to be clusters of smaller ones. It appears, therefore, that we are dealing with particles, near 1 micron in diameter, suspended in an alcoholic dye solution, from which they precipitate as coagulation occurs.

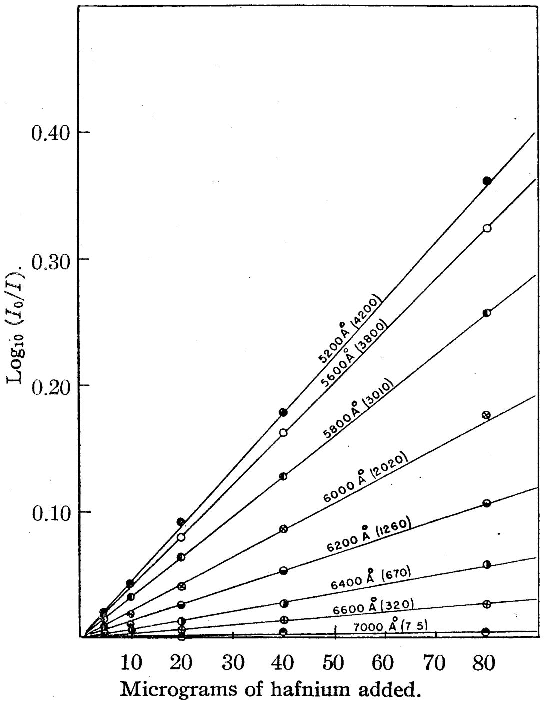

Fig. 9.—Beer's law curves for hafnium–alizarin experiments like the zirconium experiments of Fig. 2.

The rates at which these particles form and dissociate are of interest. Variation, by addition of alcohol, of the volume in which the zirconium–alizarin lake was formed gave the following transmissions for 5600 Å.: 10.0% (usual volume, *ca.* 0.5 cc.); 16.7% (10 cc.); 19.6% (25 cc.). Eight hours later these transmissions were: 10.0, 14.9 and 17.4%; obviously, lake formation, complete in the first experiment, was proceeding very slowly in the other two. To test the reverse reaction, 0.2 mg. of zirconium was converted to the lake with 1 cc. of dye solution and diluted to 50 cc. with alcohol. Aliquot parts of the resulting suspension were diluted 5 and 25 times; the following transmissions were measured at 5600 Å. (the transmission of alcohol was taken as I_0):

Relative dilution	1	5	25
Log (I_0/I) after 1 hr.	1.01	0.179	0.028
Log (I_0/I) after 24 hrs.	0.94	.181	.013

With no change whatever occurring, the values of log (I_0/I) should be inversely proportional to the relative dilution; this is nearly true, not only im-

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[8] *Cf.* Freundlich, "Kapillarchemie," Vol. I, Akademische Verlagsgesellschaft, Leipzig, 1930, p. 491.

mediately after preparation but also after one day's standing. (An increase in transmission from 83.6 to only 84.3 caused the large change in log (I_0/I) for the most dilute experiment.) Since no appreciable dissociation of the lake was observed in these experiments, more extreme conditions were sought. A zirconium–quinalizarin lake was centrifuged out of the dye solution and redispersed in alcohol: no quinalizarin absorption was detected in this suspension even after several days of standing, after violent shaking (the lake precipitated from alcohol also), or after boiling for five minutes on the steam-bath; the transmission curve of the lake was virtually unaltered by this treatment. The conclusion from these experiments is either that an infinitesimal concentration of the dye or zirconium prevents the dissociation of the lake, or (what is much more probable) that this reaction is very slow. The latter explanation is more easily reconciled with the observation, already mentioned, that sulfuric acid will react with a small amount of lake even when the total volume is 27 cc.

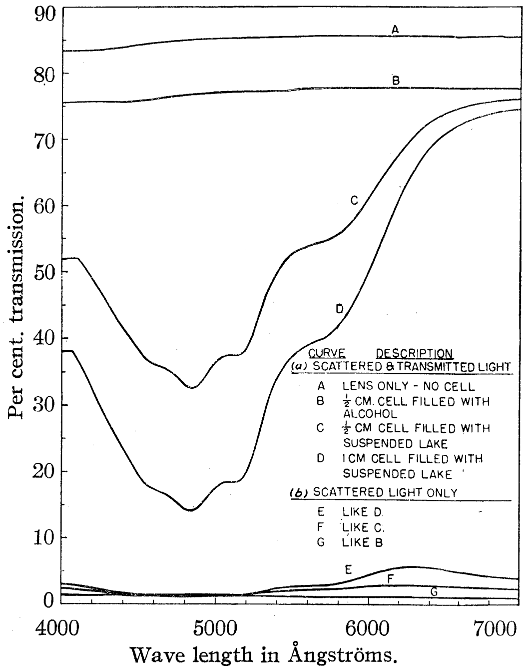

Fig. 10.—Direct measurement of light scattered by a suspended zirconium–purpurin lake.

Scattering of Light.—Particles approximately 1 micron in average diameter will scatter visible light of all wave lengths. Since this diameter does not greatly exceed the average wave length of visible light, the scattering is intermediate between scattering according to Rayleigh's law (amount of scattered light proportional to $1/\lambda^4$) and scattering by white fog (amount of scattered light independent of wave length).[9] It would not be surprising, therefore, to find that the amount of light scattered by the suspended lakes decreased slightly with the wave length.

Two methods of utilizing the spectrophotometer for measuring scattered light were employed. (1) A lens was inserted in the path of the transmission beam so that this beam, normally almost an ellipse (1″ × $^{13}/_{16}$″ or 2.54 × 2.06 cm.) at the entrance to the integrating sphere, converged to an approximate rectangle ($^1/_{16}$″ × $^3/_{16}$″ or 1.58 × 4.75 mm.) at that point. A removable piece of black tape just large enough to block out the beam could be placed on the cell to permit separate measurement of the scattered, and of the scattered plus transmitted light (Fig. 10). (2) Transmission measurements were made with a 1-cm. cell in two positions: against the integrating sphere ("near" position) and 5.5 cm. removed ("far" position). The proportion of scattered light entering the sphere obviously would be much less in the second position (Fig. 11). Glass cells were used for this work; reference to a description of the instrument[4] will aid in showing how the measurements were carried out.

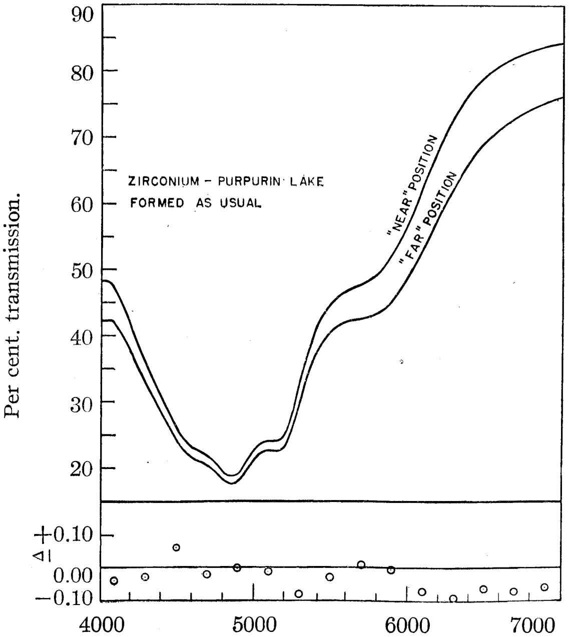

Fig. 11.—Indirect measurement of light scattered by a suspended zirconium–purpurin lake.

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[9] Langmuir and Westendorp, *Physics*, **1**, 273 (1931).

In connection with Fig. 11, assume (1) that a narrow transmitted beam I^t decreases in intensity from I_0^t to I_l^t as it passes through a 1-cm. cell; (2) that the scattering and the spatial distribution of scattered light are independent of wave length; (3) that the scattered light I_l^s entering the sphere results from a narrow beam I_m^s, whose intensity is proportional to that of the transmitted beam, from which it deviates at a point[10] m, where the intensity, the "mean" intensity, of the latter is I_m^t. I_m^s will travel through the cell along a path a, which is greater than l-m, and will have decreased in intensity to I_l^s when it reaches l. In the "near" position, the light entering the sphere will be $I_l^t + I_l^s$; in the "far" position, the entering light will be assumed equal to I_l^t, although it will be slightly greater since this position is not at infinite distance from the sphere. Under these simplified conditions, if second-order effects are neglected, it can be shown that

$$-\mathrm{d}\log\left(\frac{I_l^s}{I_l^t}\right)\bigg/\mathrm{d}\lambda = [(m + a) - l]\mathrm{d}\epsilon/\mathrm{d}\lambda \quad (2)$$

This treatment is so approximate that $[(m + a) - l]$ will be taken as unity, thus anticipating the results to some extent. Then

$$\Delta = \mathrm{d}\log\left(\frac{I_l^s}{I_l^t}\right)\bigg/\mathrm{d}\lambda + \mathrm{d}\epsilon/\mathrm{d}\lambda = 0 \quad (2a)$$

For Fig. 11, I_l^s/I_l^t at every wave length was calculated as the difference of the two transmission curves divided by the transmission, I_l^t, for the "far" position; ϵ was deduced according to Beer's law from I_0^t, the transmission of alcohol, and I_l^t; the results obtained by applying Eq. 2 to the curves in Fig. 11 are given in the lower part of the figure. (An increase of 0.1% in I_l^t at 4800 Å. produces, other things equal, a decrease of 0.15% in the absolute value of I_l^s, and a decrease at 4700 Å. in Δ from -0.02 to -0.06. This extreme example illustrated the precision required of the spectrophotometer for these measurements.) At the longer wave lengths, Δ is consistently negative, which means, since ϵ is decreasing continuously in this region, that I^s is not increasing rapidly enough. Beyond 5800 Å., log I_l^s/I_l^t actually decreases; only in this region do both quotients in Eq. 2 have the same sign. The simplest explanation of this behavior is that here the second assumption made above is no longer valid—probably because the wave length is large enough relative to the diameter of the particles to decrease their scattering power. Similar calculations have not been carried out for Fig. 10 because the scattering background (near 1% at all wave lengths as shown by the Curve G) is so large that I_l^s cannot be estimated for all wave lengths. Qualitatively Figs. 10 and 11 are in agreement; the decrease in I_l^s is particularly noticeable in the former.

This simplified analysis of scattering by the suspended lakes shows such scattering to be the cause of the positive deviations in Fig. 5; these deviations are greater at longer wave lengths because the ratio of scattered to absorbed light increases with the wave length. Scattering by the lakes (and hence their average particle size) decreases in the order purpurin, quinalizarin, alizarin; scattering by the dilute dye solutions is too small to be measured on the spectrophotometer. The increase in transmission at 7000 Å. observed when excess acid was used (see above) probably results from decrease in the amount of scattered light, indicating that the particle size is smaller with excess acid.

Applicability of the Methods.—Because lake formation by the hydroxyanthraquinones appears to occur with all metallic cations if the hydrogen ion concentration is properly adjusted, there is reason to believe that these dyes can be used for the accurate colorimetric estimation of, say, 10 micrograms of any isolated metallic cation. In other words, their value as *general* reagents for the estimation of any cation may well offset their failure to act as *specific* reagents in all cases. Perhaps the simplest way to carry out the estimation of any isolated metallic cation is by precipitating the lake in ammoniacal solution, washing it free of excess dye, and re-dispersing it in basic or acid alcohol for the transmission measurements. (Preliminary work on the estimation of small amounts of barium has shown the feasibility of this method.) When more than one metallic cation is present, specificity, to a limited degree at least, may be sought by adjusting the hydrogen ion concentration, or by adding ammonium salts to form complexes with the interfering cations.

The scope of the hydroxyanthraquinones as colorimetric reagents thus corresponds roughly with that of dithizone (diphenylthiocarbazone),

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(10) The point m should lie in the half of the cell nearest the integrating sphere for two reasons. (1) Scattered light originating in the other half of the cell must travel a longer path before reaching the sphere and hence will be more strongly absorbed. (2) Because of geometrical considerations, light from this half of the cell has a smaller chance of finding the opening in the sphere.

which Fischer[11] has so thoroughly investigated. Our experience indicates that dithizone is a good deal more sensitive than the hydroxyanthraquinones (thus ϵ_2 for copper dithizonate is about 35,000[11a]; ϵ_2 for the zirconium–quinalizarin lake is only 10,000); that the former reagent is much more difficult to prepare and to keep unchanged; that procedures involving it are likely to be more tedious, and that precise results are more difficult to obtain when it is used.

Summary

With the aid of a photoelectric recording spectrophotometer, precise colorimetric methods for the determination of zirconium or hafnium in small amounts have been developed. The methods involve lake formation with the hydroxyanthraquinone dyes.

Hafnium and zirconium, while qualitatively indistinguishable, can be estimated in a known weight of sample provided other cations can be removed if they are present.

The effect on lake formation of varying the acid concentration has been studied.

Interference by other cations is negligible unless these are present in larger excess.

The decrease in lake formation caused by complex formation between zirconyl and sulfate ions has been investigated. This decrease is pronounced enough to warrant the belief that the colorimetric methods could be used for the estimation of the various anions, particularly fluoride, that form complexes of this kind.

The scattering of light by the lakes, which are present as suspensions in the alcoholic dye solutions, has been briefly investigated and discussed.

A comparison of the hydroxyanthraquinones with dithizone, another colorimetric reagent that reacts with many cations, shows the latter to be several times more sensitive while the former are simpler to prepare and keep, and are capable of giving accurate results with the expenditure of less time and effort.

Schenectady, N. Y. Received June 9, 1938

[11] References to Fischer's valuable work are given by (a) Liebhafsky and Winslow, This Journal, **59**, 1966 (1937), who used the spectrophotometer to study dithizone as a colorimetric reagent.

[Contribution from the Department of Chemistry, and Radiation Laboratory, Department of Physics, University of California]

Artificial Radioactivity as a Test for Minute Traces of Elements

By G. T. Seaborg and J. J. Livingood

The high voltage and large current of the Berkeley cyclotron[1] have made it possible to obtain radioactive isotopes with activities of extremely high intensities, especially when deuterons are used as the bombarding particles. It is the purpose of this note to show how this circumstance has made it possible to identify extremely small amounts of impurities by means of their characteristic half-lives, after the substance containing the impurities has been bombarded with deuterons in the cyclotron. A quantitative estimation of the amount of the impurity can be made in those cases where the yield of the reaction involving the impurity has been previously determined. In the cases where this yield is not known an estimate can be made by means of a comparison with the known yield of some reaction of the same type. As an example the detection of extremely small amounts of gallium in iron is described. Other examples are given more briefly.

When a sample of iron was bombarded with deuterons it was found that two of the radioactivities produced could be ascribed to an extremely small amount of gallium impurity in the iron (~ six parts in one million, as will be shown later). This was established by the fact that the half-lives of the two activities, 22 min. and 14 hr. (electron emitters), were identical with the known half-lives of electron emitting Ga^{70} and Ga^{72}, respectively.[2,3] A chemical separation according to the methods of Noyes and Bray was performed upon a sample of bombarded iron to which a small amount of "carrier" gallium had been added after the bombardment. The 22 min. and 14 hr. periods appeared only in the gallium fraction.

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[1] Lawrence and Livingston, *Phys. Rev.*, **45**, 608 (1934); Lawrence and Cooksey, *ibid.*, **50**, 1131 (1936).

[2] Amaldi, D'Agostini, Fermi, Pontecorvo, Rasetti and Segre, *Proc. Roy. Soc.* (London), **A149**, 522 (1935).

[3] Sagane, *Phys. Rev.*, **53**, 212 (1937).

The radioactive isotopes are formed according to the reactions

$$Ga^{69} + H^2 \longrightarrow Ga^{70} + H^1 \quad (1)$$
$$Ga^{71} + H^2 \longrightarrow Ga^{72} + H^1 \quad (2)$$

and decay as follows

$$Ga^{70} \longrightarrow Ge^{70} + e^- \; (T_{1/2} = 22 \text{ min.}) \quad (3)$$
$$Ga^{72} \longrightarrow Ge^{72} + e^- \; (T_{1/2} = 14 \text{ hr.}) \quad (4)$$

It would be possible to make an accurate estimate of the amount of gallium impurity in the iron if the cross section of reaction (1) or (2) were known, but the yield of these reactions has not been determined. However, an approximate estimate of the amount can be made by comparing the initial intensity of Ga^{70} or Ga^{72} with the initial intensity of another radioactive isotope formed by the same type of reaction under the same conditions from an isotope of known concentration. It has been established[4] by chemical separations that one radio-iron isotope is produced when iron is bombarded with deuterons (in addition to several radio-cobalt and radio-manganese isotopes), and that this radio-iron activity is due to Fe^{59} produced according to the reaction

$$Fe^{58} + H^2 \longrightarrow Fe^{59} + H^1 \quad (5)$$

The Fe^{59} emits electrons and decays with a half-life of 47 days

$$Fe^{59} \longrightarrow Co^{59} + e^- \quad (6)$$

Iron and gallium were separated together by an ether extraction from a sample of iron which had been bombarded in the cyclotron for forty-five minutes with 50 microamperes of deuterons with 6.4 million electron volts of energy. The initial measured activities of the 22 min. Ga^{70}, 14 hr. Ga^{72} and 47 day Fe^{59}, as measured with a Lauritsen type quartz fiber electroscope, were 0.12, 0.0033 and 0.10 divisions/sec., respectively. After correction to infinite bombardment time (through the relation $N_0 = N_\infty\,(1-e^{-0.693\,t/T_{1/2}})$), these initial activities become 0.16, 0.091 and 217 divisions/sec., and these corrected initial activities should be proportional to the concentrations of Ga^{69}, Ga^{71} and Fe^{58} in the bombarded iron. (This assumes that the cross sections of reactions (1), (2) and (5) are equal; they should be nearly equal for elements of nearly the same atomic weight.) It is known that the concentration of Fe^{58} in iron[5] is 0.5% and that gallium[5] is composed of 61.2% Ga^{69} and 38.8% Ga^{71}. Therefore the corrected initial intensities of Fe^{59} and either Ga^{70} or Ga^{72}, together with these abundance ratios, lead to a concentration of six parts per million of gallium in the bombarded iron. One-tenth this much could readily have been detected.

The half-life of an activity can be established quite well (unless it is very short) if it has an initial measured intensity of several times the background (natural leak) of the electroscope. Radioactive isotopes with initial measured activities of ten million times the electroscope background can be formed in many elements (*e. g.*, manganese, nickel, copper) by deuteron bombardments of the order of 100 microampere-hours at 6 to 8 million electron volts. Thus when these elements are present as impurities to as small an extent as one part in a million they can be detected after a deuteron bombardment has been made. The radioactive atoms formed from such minute impurities often must be chemically separated (after the addition of inactive material to act as "carrier") in order that their weak activities may not be buried in the much stronger radiation of the main activity.

On the other hand, larger amounts of impurities (0.01–0.1%) often can be detected by measuring the composite decay curve of a bombarded sample which has not been subjected to a chemical separation. Upon the analysis of the decay curve extraneous periods appear which can be attributed to known radioactive isotopes and hence can be used to identify some of the impurities in the bombarded sample. This method has the advantage that the material is not used up or disturbed in any way. In this manner the presence of a small amount of copper in nickel was established as the result of a neutron bombardment of the nickel. (The neutrons were produced by the reaction of deuterons with beryllium.) The well-known 6 min. electron emitting activity[2] of Cu^{66} and the 12.5 hr. positron and electron emitting activity[6] of Cu^{64} appeared. These were formed according to the reactions

$$Cu^{63} + n \longrightarrow Cu^{64} + \gamma \quad (7)$$
$$Cu^{65} + n \longrightarrow Cu^{66} + \gamma \quad (8)$$

The presence of a small amount of iron in a sample of cobalt oxide was established by a deuteron bombardment of the oxide. The analysis of the composite decay curve revealed an 18-hr. positron emitting activity. It has been shown that this activity is due to a radio-cobalt which can be formed only by the bombardment of iron.[4]

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(4) Livingood, Seaborg and Fairbrother, *Phys. Rev.*, **52**, 135 (1937).

(5) Livingston and Bethe, *Rev. Modern Phys.*, **9**, 380 (1937).

(6) Van Voorhis, *Phys. Rev.*, **49**, 876 (1936).

In other experiments it has been possible to establish the presence of extremely small amounts of phosphorus and sulfur as a result of the appearance of the 14-day electron emitting activity of P^{32}. The P^{32} was formed according to the reactions

$$P^{31} + H^2 \longrightarrow P^{32} + H^1 \qquad (9)$$
$$P^{31} + n \longrightarrow P^{32} + \gamma \qquad (10)$$
$$S^{32} + n \longrightarrow P^{32} + H^1 \qquad (11)$$

For example, a neutron bombardment of a sheet of paper revealed the presence of the sulfur as the result of reaction (11).

This research has been made possible through the generous coöperation of the Research Corporation, the Chemical Foundation and the Josiah Macy, Jr., Foundation.

Summary

It is shown how it is possible to detect and identify very small amounts of impurities by means of their characteristic half-lives, after the substance containing the impurities has been rendered radioactive by bombardment with charged particles of high energy or with neutrons. With the help of a chemical separation after the bombardment, impurities present to the order of one part in a million can sometimes be detected. For example, a gallium impurity of six parts per million was found in a sample of iron. Impurities to the extent of one part in one thousand to ten thousand can often be detected without subjecting the sample to chemical analysis.

BERKELEY, CALIFORNIA RECEIVED MAY 16, 1938

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY OF THE CALIFORNIA INSTITUTE OF TECHNOLOGY, NO. 642]

The Magnetic Properties and Structure of Manganous and Cobaltous Dipyridine Chlorides

BY DAVID P. MELLOR AND CHARLES D. CORYELL

It has been reported by Cox, Shorter, Wardlaw, and Way[1] on the basis of a determination of unit cell dimensions that manganous dipyridine chloride and the α-form of cobaltous dipyridine chloride have square *trans*-coördination of pyridine and chlorine about the metal atoms. Complexes of atoms with square bonds have been the object of much interest since this type of structure was first proposed by Werner to explain the existence of certain isomeric platinum compounds.[2] With the extension of our knowledge about the nature of chemical bonds there has been formulated[3] a reliable magnetic criterion by which the existence of square covalent structures for manganous, ferric, ferrous, cobaltic, cobaltous, and nickelous atoms may be determined. It is concluded in this paper that the results of magnetic measurements on the manganous and α-cobaltous dipyridine chlorides are not compatible with the square coördinated structure proposed by Cox and coworkers, but that they are compatible with an octahedral ionic type of structure.

Magnetic measurements were carried out on the manganese compound by the Gouy method. The forces in mg. (Δw corrected for blank) for a cylindrical tube with water in the upper compartment and air in the lower compartment were for two different field strengths -2.03 and -3.39. The forces with manganous dipyridine chloride, twice crystallized from ethanol and packed to a density of 0.99_5 g./ml., were $+135$ and $+234$, respectively, at 22° against air. With use of an estimated value of -160×10^{-6} for the molecular diamagnetism of the compound and with the assumption of the validity of Curie's law, the calculated values of the magnetic moment are 5.94 and 6.00 Bohr magnetons, the average being 5.97. The expected value of the moment for the manganous atom forming four dsp^2 bonds, essentially covalent and directed toward the corners of a square, is 3.88 plus a small orbital contribution; the expected value for the atom with tetrahedral sp^3 bonds or for the ion is 5.92 magnetons with no orbital contribution (normal state $^6S_{5/2}$). The measurements are in good agreement with the second of these values.

Barkworth and Sugden[4] have shown that the α-form (violet modification) of cobaltous dipyridine chloride has a moment of 5.34 Bohr magnetons, and that the β-form (blue modification) has

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[1] E. G. Cox, A. J. Shorter, W. Wardlaw, and W. J. R. Way, *J. Chem. Soc.*, 1556 (1937).

[2] A. Werner, *Z. anorg. allgem. Chem.*, **3**, 267 (1893).

[3] L. Pauling, THIS JOURNAL, **53**, 1367 (1931).

[4] E. D. P. Barkworth and S. Sugden, *Nature*, **139**, 374 (1937).

a moment of 4.60 magnetons. The expected moment for the cobaltous atom forming dsp^2 bonds is 1.73 plus orbital contribution, and that for the atom forming sp^3 bonds or for the ion is 3.88 plus orbital contribution. We accordingly conclude that the bonds to the cobalt atom are essentially ionic, with an unexpectedly large orbital contribution in the case of the α-form.

A tetrahedral configuration is not compatible with the small dimensions of the c-axes (3.73 and 3.65 Å., respectively) of the manganous and cobaltous compounds, as pointed out by Cox and his co-workers. This configuration is not, however, the only alternative to a square configuration. A reasonable structure for the complexes, one not considered by these workers, can be formulated with each metal ion sharing four coplanar chloride ions in pairs and holding two pyridine molecules at right angles to the plane of the chloride ions. The proposed structure thus contains an ionic octahedral complex with two shared edges. The metal-metal distances in the metal-dichloride chains are calculated[5] to be 3.7 and 3.6 Å., respectively. The pyridine rings lie in planes the same distance apart. The calculated distances agree with the observed c values to within the accuracy of the ionic radii.

Both the α- and β-forms of the cobalt compound give in organic solvents[6] identical blue solutions, which have been shown[1,6] to contain monomeric solute molecules in bromoform, chloroform, and phenol. It is probable that the configuration about the cobalt ion is tetrahedral in these solutions. The fact that the colors of the solutions are nearly the same as that of the solid β-modification suggests that there is tetrahedral coördination around the metal ions in this solid.

Compounds with a coplanar configuration containing ionic bonds are to be expected only if the electronegative groups are part of a rigid plane structure, as for example in ferriheme chloride (hemin) and ferroheme, in both of which the iron atoms were shown[7] to be held as ions. It seems very likely that the bonds to beryllium in beryllium phthalocyanin and the bonds to magnesium in chlorophyll are predominantly ionic. The existence of these compounds accordingly is not proof that the metals form square covalent bonds; whereas square coördination with groups which are free to rearrange is an indication of the predominant covalent character of the bonds.[3,8] Square bonds have not as yet been found in any manganous compound; it has been reported that impure cobalt phthalocyanin[9] and an impure cobaltous phenanthroline cyanide[10] show magnetic evidence for square bonds, but these observations have not been verified with pure substances.

Summary

The magnetic criterion for bond type indicates that manganese and cobalt atoms in the dipyridine dichloride compounds form ionic bonds rather than covalent dsp^2 bonds. It is suggested that an octahedral ionic type of structure occurs in the manganese and α-cobalt compound and a tetrahedral ionic type occurs in the β-cobalt compound.

PASADENA, CALIF. RECEIVED APRIL 4, 1938

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[5] With the use of the crystal radii of L. Pauling, THIS JOURNAL, **49**, 765 (1927), not corrected for the effect of structure.

[6] D. P. Mellor and B. S. Morris, article in press, *Proc. Roy. Soc., New S. Wales* (1938).

[7] L. Pauling and C. D. Coryell, *Proc. Nat. Acad. Sci.*, **22**, 159 (1936).

[8] For a discussion of ionic and covalent character in bonds, see L. Pauling, THIS JOURNAL, **54**, 988 (1932).

[9] L. Klemm and W. Klemm, *J. prakt. Chem.*, **143**, 82 (1935).

[10] L. Cambi and A. Cagnasso, *Rend. ist. lombardo sci.*, **67**, 741 (1934).

[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY, UNIVERSITY OF NEBRASKA]

The Preparation of Fully Acetylated Amides of Aldonic Acids

BY GORDON B. ROBBINS AND FRED W. UPSON

Acetylgluconic acid was prepared by Upson and Bartz[1] by direct acetylation of δ-gluconic lactone. Tetraacetylgluconic acid monohydrate which results on acetylation of δ-gluconic lactone was reported in the journal article but the 2,3,4,5,6-pentaacetylgluconic acid was also prepared by further acetylation of the 2,3,4,6-product and is reported in the thesis of Bartz. More recently Major and Cook[2] report the pentaacetyl derivative prepared by the same method. This method, however, has not proved to be a general one for the preparation of fully acetylated acids since all other lactones with which we have worked have yielded acetylated lactones. It is necessary to start with a derivative such as the amide or ester which is not lactone in character.[2,3]

Major and Cook have made, from completely acetylated aldonic acids, the corresponding acid chlorides which offer a number of possibilities for the synthesis in the sugar series.

A method for the preparation of fully acetylated sugar acids has been reported by Hurd and Sowden[4] using the following sequence of reactions: aldose ⟶ aldose oxime ⟶ acetylated nitrile ⟶ acetylated amide ⟶ acetylated acid.

Acetylated amides of the aldonic acids have been prepared in this Laboratory by a method which is general in its application and is less complicated than that of Hurd and Sowden. The aldonic acid lactone is converted to the amide by solution in liquid ammonia followed by spontaneous evaporation of the excess ammonia.[5]

The amide results in pure condition and the yield is excellent. The amide is then subjected to direct acetylation using either sulfuric acid or zinc chloride as the catalyst. We have been able to explain a discrepancy between the work of Miksic[6] and that of Zemplén and Kiss.[7] Miksic reported the preparation of acetyl derivatives in which both the amide group and the hydroxyl groups are acetylated whereas the latter authors have obtained an acetyl derivative of an unacetylated amide group. Zemplén and Kiss used zinc chloride as the catalyst whereas Miksic used sulfuric acid. The work here reported indicates that the use of zinc chloride causes acetylation of the hydroxyl groups only whereas acetylation occurs in the amide group as well when sulfuric acid is the catalyst. This is illustrated in the acetylation of gluconamide and galactonamide using the two substances as catalysts.

The acetyl amides are readily converted to the corresponding acids by the method of Hurd and Sowden[4] through the action of nitrous acid in glacial acetic acid solution. We have shown that it is not necessary to isolate the acetyl amide. The acetylating mixture containing the amide may be treated directly with nitrous oxide giving excellent yields of the acetyl aldonic acid. Experiments with these acetyl aldonic acids will be reported in a later paper.

Experimental

Below is described the acetylation of the amides of several aldonic acids together with the properties of the resulting products. In all cases the rotatory power of the compounds was determined by means of a Bates saccharimeter using white light and a dichromate solution as a filter.

Pentaacetyl-*d*-gluconamide.—Fused zinc chloride (5 g.) was dissolved in acetic anhydride (50 cc.) and the mixture was cooled to 0°. Gluconamide (7.5 g.) was added with shaking, and the mixture was kept in an ice-bath for an hour. The reaction mixture stood at room temperature for twenty-four hours (or until all amide was dissolved).

The mixture was poured out into 200 cc. of ice and water, and stirred vigorously for forty-five minutes, giving a crystalline powder. The solid was filtered and washed with water. It was recrystallized from 95% alcohol: m. p. 184–185°; $[\alpha]^{25}\text{D}$ +23.6° (*c*, 0.9 in $CHCl_3$)[1,4,7].

Pentaacetyl-*d*-galactonamide.—Galactonamide was acetylated as described above. No solid separated upon stirring. Extraction with chloroform was followed by evaporation of solvent. Addition of ether gave a solid product which was filtered. Recrystallization from benzene yielded pure pentaacetyl-*d*-galactonamide: m. p. 165–166°; $[\alpha]^{25}\text{D}$ +26.7° (*c*, 1.8 in $CHCl_3$).[4]

Anal. Calcd. for $C_{16}H_{23}O_{11}N$: C, 47.38; H, 5.73. Found: C, 47.36; H, 5.74.

Pentaacetyl-*d*-mannonamide.—Mannonamide was acetylated as described above and the chloroform extract was evaporated to a gum which crystallized on standing. Recrystallization was accomplished from butyl ethyl ether

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[1] Upson and Bartz, THIS JOURNAL, **53**, 4226 (1931).

[2] Major and Cook, *ibid.*, **58**, 2477 (1936).

[3] Major and Cook, *ibid.*, **58**, 2410 (1936).

[4] Hurd and Sowden, *ibid.*, **60**, 235 (1938).

[5] Glattfeld and McMillan, *ibid.*, **56**, 2481 (1934).

[6] Miksic, Ves Kral-Ces. Spal-Nauk Cl. 11 (1929).

[7] Zemplén and Kiss, *Ber.*, **60**, 165 (1927).

of ethylene glycol; m. p. 110°; $[\alpha]^{25}D$ +38.7° (*c*, 1.8 in $CHCl_3$).

Anal. Calcd. for $C_{16}H_{23}O_{11}N$: C, 47.38; H, 5.73. Found: C, 47.30; H, 5.75.

Pentaacetyl-*d*-gulonamide.—This compound was prepared from a sample of *d*-gulonic lactone ($[\alpha]^{20}D$ −54.4°), using the method described in the preparation of the galactonic derivative. Recrystallization several times from absolute alcohol gave crystals melting at 162–164°; $[\alpha]^{25}D$ +22.7° (*c*, 1.6 in $CHCl_3$).

Anal. Calcd. for $C_{16}H_{23}O_{11}N$: C, 47.38; H, 5.73. Found: C, 47.19; H, 5.68.

Hexaacetyl-*d*-gluconamide.—Acetic anhydride (50 cc.) and concentrated sulfuric acid (3 cc.) were mixed and cooled to 0°. Gluconamide (6 g.) was added and the reaction was completed as in the case of the pentaacetyl derivatives. The solution was poured into ice water and sodium bicarbonate (10 g.) was added. Chloroform extraction yielded a sirup which crystallized upon standing. Ether was added and it was filtered. Recrystallization from alcohol gave the hexaacetyl-*d*-gluconamide: m. p. 110°; $[\alpha]^{25}D$ +25.8° (*c*, 1.8 in $CHCl_3$).

Anal. Calcd. for $C_{18}H_{25}O_{12}N$: C, 48.31; H, 5.64. Found: C, 48.14; H, 5.70.

Hexaacetyl-*d*-galactonamide.—Galactonamide was acetylated in the same manner as for preparation of the hexaacetyl-*d*-gluconamide. A solid separated upon stirring with ice water and sodium bicarbonate. The material was filtered and recrystallized from benzene: m. p. 149.5–150°; $[\alpha]^{25}D$ +19.0° (*c*, 1.8 in $CHCl_3$).

Anal. Calcd. for $C_{18}H_{25}O_{12}N$: C, 48.31; H, 5.64. Found: C, 48.08; H, 5.71.

Summary

1. A general preparation of acetylated sugar acid amides has been indicated. This offers an easier route to obtain the fully acetylated sugar acids.

2. The product of acetylation of amides of sugar acids is governed by the catalyst used. Concentrated sulfuric acid gives a product in which both hydroxyl groups and amide nitrogen are acetylated. Zinc chloride gives a product in which only hydroxyls are acetylated.

3. The above methods have been applied to the preparation of several acetylated amides, of which four are new compounds.

LINCOLN, NEBRASKA RECEIVED MAY 16, 1938

[CONTRIBUTION FROM THE BURROUGHS WELLCOME & CO., U. S. A. EXPERIMENTAL RESEARCH LABORATORIES]

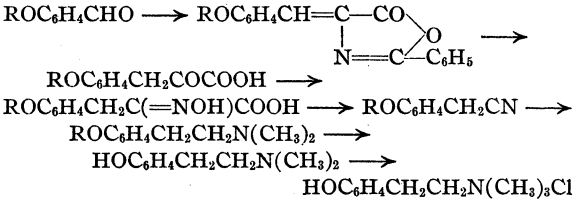
β-Phenylethylamine Derivatives.[1] Tertiary and Quaternary Salts

BY JOHANNES S. BUCK, RICHARD BALTZLY AND WALTER S. IDE

The present paper describes the preparation and properties of tertiary amine salts and quaternary salts containing the phenylethyl group. One series consists of alkoxy- and hydroxy-β-phenylethyldimethylamine hydrochlorides, of the type of hordenine, the other of the quaternary derivatives of these compounds.

Hordenine has received considerable attention in the literature, and a few related compounds also have been dealt with. For the most part the syntheses are unsatisfactory and not capable of being applied generally. The authors therefore worked out a series of reactions, a composite of various literature methods, which is generally applicable and which gives good yields at each stage. Starting with a substituted benzaldehyde, this is converted successively into the azlactone, the phenylpyruvic acid, the pyruvic acid oxime, and the phenylacetonitrile. This latter is then reduced, in one step, to the alkoxy-β-phenylethyldimethylamine, by catalytic reduction in the presence of excess dimethylamine. The tertiary amine may be converted readily into the quaternary salt, or O-dealkylated to give the hydroxy compound, which, in turn, easily forms the quaternary compound.

The series of reactions used is as follows



$$ROC_6H_4CHO \longrightarrow ROC_6H_4CH{=}\underset{\displaystyle N{=}C{<}C_6H_5}{C{-}CO{>}O} \longrightarrow ROC_6H_4CH_2COCOOH \longrightarrow ROC_6H_4CH_2C({=}NOH)COOH \longrightarrow ROC_6H_4CH_2CN \longrightarrow ROC_6H_4CH_2CH_2N(CH_3)_2 \longrightarrow HOC_6H_4CH_2CH_2N(CH_3)_2 \longrightarrow HOC_6H_4CH_2CH_2N(CH_3)_3Cl$$

Experimental

The intermediates required were all prepared by the methods given below. A number of them have been described previously in the literature (many prepared by other methods). Only the ones not previously recorded are given (Table I).

Azlactones (2-Phenyl-4-(alkoxybenzal)-oxazolones).—These compounds were prepared in the conventional way from the appropriate benzaldehyde and hippuric acid,[2] and

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[1] This work is part of a joint research being carried out in collaboration with a pharmacological group at the above laboratories.

[2] Kropp and Decker, *Ber.*, **42**, 1184 (1909); *Org. Syntheses*, **13**, 8 (1933).

TABLE I

NEW INTERMEDIATES

Substituent	Appearance	M. p. or b. p., °C. (corr.)	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
	Azlactones (2-Phenyl-4-(alkoxybenzal)-oxazolones)						
2-Ethoxy	Lemon-yellow glittering flakes	186	$C_{18}H_{15}O_3N$	73.69	5.16	73.64	5.12
3-Ethoxy	Pale yellow felted slender prisms	123	$C_{18}H_{15}O_3N$	73.69	5.16	73.60	5.23
4-Ethoxy	Golden-yellow crystalline crusts	168	$C_{18}H_{15}O_3N$	73.69	5.16	73.92	5.32
2-Ethoxy-3-methoxy	Large deep yellow flaky prisms	140	$C_{19}H_{17}O_4N$	70.57	5.30	70.68	5.21
3,4-Diethoxy	Orange-yellow tiny glittering needles	161	$C_{20}H_{19}O_4N$	71.19	5.68	71.06	5.83
	Alkoxyphenylpyruvic Acids						
2-Methoxy	Small flat pointed prisms	161	$C_{10}H_{10}O_4$	61.83	5.19	62.08	5.28
2-Ethoxy	Felted tiny prisms	164	$C_{11}H_{12}O_4$	63.43	5.81	63.67	6.16
3-Ethoxy	Meshed small flat needles	132	$C_{11}H_{12}O_4$	63.43	5.81	63.67	5.93
4-Ethoxy	Flat chalky thin needles	182	$C_{11}H_{12}O_4$	63.43	5.81	63.38	5.78
2-Ethoxy-3-methoxy	Not crystallized	..	$C_{12}H_{14}O_5$	60.48	5.93	....	...
3,4-Diethoxy	Pearly thin felted plates	164	$C_{13}H_{16}O_5$	61.87	6.39	61.86	6.51
	Alkoxyphenylacetonitriles						
3-Ethoxy	Viscous colorless refractile liquid	141 (8 mm.)	$C_{10}H_{11}ON$	74.49	6.88	74.36	6.98
2-Ethoxy-3-methoxy	Faint yellow refractile liquid	133 (2.0 mm.)	$C_{11}H_{13}O_2N$	69.07	6.85	68.82	6.95
3-Ethoxy-4-methoxy	White crystalline solid m. p. 61.5°	151 (2.5 mm.)	$C_{11}H_{13}O_2N$	69.07	6.85	68.74	6.81

were recrystallized from acetic acid, in which they are rather sparingly soluble, until pure. The unrecrystallized material is usually satisfactory for the subsequent hydrolysis. With most aldehydes the yield is from 60 to 70%.

Alkoxyphenylpyruvic Acids.—The azlactones were hydrolyzed by sodium hydroxide and the phenylpyruvic acid separated from benzoic acid by means of sulfur dioxide, followed by washing with ether where the solubility permitted.[3] For analysis they were recrystallized until pure, from aqueous acetic acid, aqueous alcohol, or ether–pentane. Ordinarily, the reaction product was used directly for the next step (oximation). Melting points are usually unsharp. The yields vary widely with different acids, from 55 to 90%.

Alkoxyphenylpyruvic Acid Oximes.—The method of Baker and Robinson[4] was found to be quite satisfactory for the preparation of these compounds. However, attempts at rigid purification were in general unsuccessful, dehydration and decarboxylation gradually taking place, the corresponding phenylacetonitrile being obtained ultimately. For this reason, the unpurified oxime, after drying, was used directly for the next step, a procedure for which there is ample precedent.[5] The yields of the oximes are high, usually well over 80%.

Alkoxyphenylacetonitriles.—Decarboxylation and dehydration of the oximes were carried out simultaneously by means of acetic anhydride, using not more than 20 g. of oxime for a preparation.[4] Acetic anhydride is retained persistently by the nitriles so that, after isolation, washing and distillation, they were again washed and redistilled or recrystallized from hexane. The liquid nitriles have only a faint nitrile-type odor. The yields vary according to the oxime used, but usually are considerably over 80%.

Alkoxyphenylethyldimethylamine Hydrochlorides.—The alkoxyphenylacetonitrile, in methanol solution, with excess (2.5 mol) of dimethylamine (33% in methanol) was reduced catalytically with a palladium catalyst. This reaction, first used by Kindler and Hesse,[6] gave excellent results. After reduction was complete the catalyst was removed, excess dimethylamine and methanol distilled off, and the residual oil dissolved in dilute hydrochloric acid. Non-basic material was extracted with ether, and the aqueous solution then cooled in ice and treated with sodium nitrite solution (40 g. nitrite per mole of base). After thorough extraction with ether, the acid solution was made strongly alkaline and the base extracted with ether. After drying the extract over solid potassium hydroxide, the hydrochloride was obtained by passing hydrogen chloride into the ether solution. The crude hydrochlorides were recrystallized twice or more from methyl or ethyl alcohol, with ethyl acetate and/or ether, and were so obtained as well crystallized white salts, readily soluble in alcohol, water and hydrochloric acid and practically insoluble in ether, ethyl acetate, etc. Some of them are hygroscopic.

The palladium catalyst was either the commercial "palladium mohr" or material prepared by the Willstätter–Waldschmidt-Leitz method. The optimum speed of reduction appears to be about 1 g. nitrile per hour (Burgess–Parr apparatus, at room temperature and 3 atm. pressure) and relatively large amounts of catalyst, one-quarter upward of the weight of nitrile, were used to obtain this speed. The nitrile must be very pure.

Hydroxyphenylethyldimethylamine Hydrochlorides.—These compounds were obtained by demethylating the corresponding methoxy hydrochlorides with hydrochloric acid (two hours at 160° in carbon dioxide atmosphere). The acid solution was then evaporated to dryness under reduced pressure and the residue recrystallized as with the

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(3) (a) *Org. Syntheses*, **15**, 31 (1935); (b) Buck and Perkin, *J. Chem. Soc.*, **125**, 1675 (1924); (c) Pfeiffer, Quehl and Tappermann, *Ber.*, **63**, 1301 (1930).

(4) (a) Baker and Robinson, *J. Chem. Soc.*, 152 (1929); (b) *cf.* Edwards, *ibid.*, 740 (1926); (c) *cf.* Haworth and Richardson, *ibid.*, 120 (1935).

(5) *Cf.* ref. 3c; Julian and Sturgis, THIS JOURNAL, **57**, 1126 (1935); ref. 4c.

(6) Kindler and Hesse, *Arch. Pharm.*, **271**, 439 (1933).

TABLE II

PHENYLETHYLDIMETHYLAMINE HYDROCHLORIDES

Substituent	Appearance	M. p., °C. (corr.)	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
None[7]	Large silky leaves	165	$C_{10}H_{16}NCl$	64.66	8.69	64.74	8.75
2-Methoxy	Glittering silky leaves	159.5	$C_{11}H_{18}ONCl$	61.22	8.41	61.45	8.33
3-Methoxy	Felted silky leaves	135	$C_{11}H_{18}ONCl$	61.22	8.41	61.32	8.56
4-Methoxy[8]	Small glittering rectangular prisms	176.5	$C_{11}H_{18}ONCl$	61.22	8.41	61.11	8.34
2,3-Dimethoxy	Dull tiny nodules of prisms	140	$C_{12}H_{20}O_2NCl$	58.63	8.21	58.79	8.22
3,4-Dimethoxy[8]	Chalk-white tiny meshed prisms	197	$C_{12}H_{20}O_2NCl$	58.63	8.21	58.76	8.33
2-Ethoxy	Felted slender silky needles	143	$C_{12}H_{20}ONCl$	62.71	8.78	62.78	8.74
3-Ethoxy[9]	Clumps of small stout prisms	137	$C_{12}H_{20}ONCl$	62.71	8.78	62.89	9.00
4-Ethoxy[10]	Glittering tiny flat prisms	175	$C_{12}H_{20}ONCl$	62.71	8.78	62.67	8.69
2-Ethoxy-3-methoxy	Slender meshed needles	145	$C_{13}H_{22}O_2NCl$	60.08	8.54	60.41	8.73
3-Methoxy-4-ethoxy	Small pearly leaves	151	$C_{13}H_{22}O_2NCl$	60.08	8.54	59.94	8.79
3-Ethoxy-4-methoxy	Small glittering irregular plates	161.5	$C_{13}H_{22}O_2NCl$	60.08	8.54	60.26	8.65
3,4-Diethoxy	Tiny meshed flat prisms	138	$C_{14}H_{24}O_2NCl$	61.39	8.84	61.46	8.84
2-Hydroxy[11]	Leaves	108	$C_{10}H_{16}ONCl$	59.53	8.00	59.68	8.05
3-Hydroxy[9]	Small glittering stout prisms	164	$C_{10}H_{16}ONCl$	59.53	8.00	59.71	8.23
4-Hydroxy[12]	Silky tiny leaves	181	$C_{10}H_{16}ONCl$	59.53	8.00	59.53	8.02
2,3-Dihydroxy	Small grayish nodules	96	$C_{10}H_{16}O_2NCl$	55.15	7.41	55.23	7.55
3,4-Dihydroxy[8]	Small grayish glittering leaves	127	$C_{10}H_{16}O_2NCl$	55.15	7.41	55.25	7.57

TABLE III

PHENYLETHYLTRIMETHYLAMINE CHLORIDES

Substituent	Appearance	M. p., °C. (corr.)	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
None[13]	Masses of minute plates	192	$C_{11}H_{18}NCl$	66.13	9.09	66.34	9.28
2-Methoxy	Glittering stout leaves	221	$C_{12}H_{20}ONCl$	62.71	8.78	62.80	9.01
3-Methoxy	Small powdery prisms	158	$C_{12}H_{20}ONCl$	62.71	8.78	62.92	9.01
4-Methoxy[14]	Chalky tiny meshed needles	206	$C_{12}H_{20}ONCl$	62.71	8.78	62.62	8.74
2,3-Dimethoxy	Stout prisms	180	$C_{13}H_{22}O_2NCl$	60.08	8.54	60.15	8.57
3,4-Dimethoxy	Tiny glittering flat prisms	206	$C_{13}H_{22}O_2NCl$	60.08	8.54	59.99	8.64
2-Ethoxy	Small glittering leaves	211	$C_{13}H_{22}ONCl$	64.03	9.10	64.13	9.15
3-Ethoxy[15]	Dull powdery plates	160	$C_{13}H_{22}ONCl$	64.03	9.10	64.10	8.99
4-Ethoxy	Powder of small prisms	193	$C_{13}H_{22}ONCl$	64.03	9.10	64.16	9.24
2-Ethoxy-3-methoxy	Glittering irregular plates	182	$C_{14}H_{24}O_2NCl$	61.39	8.84	61.64	9.16
3-Methoxy-4-ethoxy	Glittering prism clusters	173	$C_{14}H_{24}O_2NCl$	61.39	8.84	61.59	9.02
3-Ethoxy-4-methoxy	Obscure prisms	162	$C_{14}H_{24}O_2NCl$	61.39	8.84	61.59	9.10
3,4-Diethoxy	Tiny glittering needle prisms	125	$C_{15}H_{26}O_2NCl$	62.57	9.11	62.55	9.30
2-Hydroxy[16]	Clumps of tiny prisms	254 dec.	$C_{11}H_{18}ONCl$	61.22	8.41	61.35	8.59
3-Hydroxy	Nodules of small spindles	220	$C_{11}H_{18}ONCl$	61.22	8.41	61.25	8.35
4-Hydroxy[15]	Glittering small leaves	287 dec.	$C_{11}H_{18}ONCl$	61.22	8.41	61.09	8.42
2,3-Dihydroxy	Clumps of small prisms	225	$C_{11}H_{18}O_2NCl$	56.99	7.82	57.09	7.75
3,4-Dihydroxy[17]	Small stout obscure prisms	263 dec.	$C_{11}H_{18}O_2NCl$	56.99	7.82	56.93	7.83

alkoxy hydrochlorides. The *p*-hydroxy compound was identical with authentic hordenine. The properties of the compounds (hydroxy and alkoxy) are given in Table II.

Alkoxy- and Hydroxyphenylethyltrimethylamine Chlorides.—The quaternary salts were prepared from the tertiary amines, this method being preferable to using the primary amine. The starting hydrochloride was dissolved in water and the base liberated by potassium carbonate solution, extracted with (or, if solid, dissolved in) benzene, and dried with solid potassium hydroxide (for the alkoxy bases) or sodium sulfate (for the hydroxy bases). A considerable excess of methyl iodide was added, when the quaternary iodide rapidly separated out. After some hours ether was added to the usually gelatinous mass, and the solid filtered off, washed with ether, dissolved in water, and converted into the chloride by silver chloride. The aqueous solution was evaporated to dryness under reduced pressure and the residue recrystallized from alcohol–ether.

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(7) Johnson and Guest, THIS JOURNAL, **32**, 761 (1910); Tiffeneau and Fuhrer, *Bull. soc. chim.*, [4] **15**, 162 (1914).

(8) Kindler and Hesse, *Arch. Pharm.*, **271**, 439 (1933). No hydrochloride.

(9) German Patent 233,069. Base only.

(10) German Patent 234,795. Base mentioned.

(11) *Cf.* v. Braun and Bayer, *Ber.*, **57**, 913 (1924).

(12) Léger, *Bull. soc. chim.*, [3] **35**, 235 (1906). German Patent 233,069.

(13) *Cf.* Beilstein's "Handbuch," **12***, 473. No chloride.

(14) *Cf.* Rosenmund, *Ber.*, **43**, 306 (1910). Iodide.

(15) German Patent 233,069.

(16) *Cf.* Pschorr and Einbeck, *Ber.*, **38**, 2067 (1905). Iodide.

(17) *Cf.* Barger and Ewins, *J. Chem. Soc.*, **97**, 2253 (1910).

The chlorides form well-crystallized compounds, soluble in water, alcohol and hydrochloric acid, and practically insoluble in ether, ethyl acetate, etc. They are unusually difficult to analyze. Their properties are described in Table III.

Summary

A series of hydroxy- and alkoxyphenylethyldimethylamine hydrochlorides (18 compounds) and a series of hydroxy- and alkoxyphenylethyltrimethylamine chlorides (18 compounds) have been prepared, all by the same sequence of reactions, which appears to be general. The preparation of the intermediates also is described.

TUCKAHOE, NEW YORK RECEIVED MAY 20, 1938

[CONTRIBUTION FROM THE BIOCHEMISTRY LABORATORY OF THE UNIVERSITY OF OKLAHOMA MEDICAL SCHOOL]

Relations of *cis-trans* Isomerism to Asymmetric Oxidation of Sugars[1]

BY M. R. EVERETT AND FAY SHEPPARD

Richtmyer and Hudson[2] recently reported the interesting phenomenon of unequal quantitative reduction of alkaline copper reagents by *d*- and *l*-forms of aldoses, when *d*- or *l*-tartaric acids were used in Shaffer–Hartman–Somogyi reagents. We have now completed similar experiments with *d*-, *l*- and *meso*-tartrate Folin–Wu reagents.[3] The *l*-tartaric acid employed was prepared by the method described by Richtmyer and Hudson, and had the correct $[\alpha]^{20}\text{D}$ $-14°$. The *d*- and *meso*-tartaric acids were Central Scientific Co. and Eastman Kodak Co. products with $[\alpha]^{20}\text{D}$ $+14$ and $+0.05°$, respectively. The sugar solutions and special reagents[4] were freshly prepared, immediately before analysis. Several concentrations of each sugar were investigated and compared with suitable *d*-glucose standards. Determinations were made under strictly comparable conditions.

The results reported in Table I are the reducing equivalents relative to *d*-glucose and *d*-tartrate reagent taken as 1.00 and are averages of four or more determinations. Corrections for moisture content of sugars and proportionality of the analytical method have been applied. The reagents employed by us appear to be somewhat more sensitive to spacial configuration than the copper reagents used by Richtmyer and Hudson, but both investigations show that *d*-forms of arabinose, fructose and mannose and *l*-forms of fucose and rhamnose select the *l*-tartrate reagent; *d*-forms of galactose, lactose and mannoketoheptose and *l*-arabinose select the *d*-tartrate reagent; and *d*-forms of glucose and xylose show little selectivity. For sugars not investigated by Richtmyer and Hudson, we find that *d*-forms of maltose, melibiose and ribose select the *l*-tartrate reagent; *d*-forms of galacturonic and glycuronic acids, mannoheptose and sorbose select the *d*-reagent; *d*-forms of cellobiose, gentiobiose, glucosamine and lyxose and *l*-forms of ascorbic acid, sorbose and xylose are not very selective. Our *meso*-tartrate reagent is reduced more than either of the *trans* reagents by *d*-forms of cellobiose, gentiobiose, glycuronic acid, lactose, maltose, α-mannoheptose, mannoketoheptose and mannose.

It is evident from these results that asymmetric oxidation of sugars bears no simple relation to ordinary optical or planar isomerism, and is influenced by extraplanar molecular relations (group substitution, *cis–trans* relations, etc.). The reducing values of Table I are definitely related to the *cis–trans* classification of sugars suggested by the authors.[6,7] This arrangement of sugars in eight *cis–trans* groups, corresponding to the eight aldopentoses, is reproduced in Table II.

Oxidation in alkaline solution is complicated by mutarotation and epimerization, and recently Isbell[8] has shown that mutarotation is correlated with *cis–trans* configuration. The behavior of

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[1] Aided by a grant from the Research Fund of the University of Oklahoma Medical School. The authors also wish to acknowledge the following gifts: α-*d*-mannoheptose and *d*-mannoketoheptose from Dr. C. S. Hudson and *d*-galacturonic acid from Dr. Karl Link.

[2] Richtmyer and Hudson, THIS JOURNAL, **58**, 2540 (1936).

[3] Folin and Wu, *J. Biol. Chem.*, **67**, 357 (1926).

[4] For each 20 cc. of alkaline tartrate reagent we used 0.1696 g. of tartaric acid (*d*-, *l*- or *meso*-), 3 cc. of distilled water, 2 cc. of 1.125 *N* sodium hydroxide and 15 cc. of buffer solution (containing 4.667% sodium carbonate and 1.467% sodium bicarbonate); 18 cc. of this solution was then mixed with 2 cc. of 5% cupric sulfate solution. The time of heating was uniformly seven and one-half minutes on the boiling water-bath. The Folin[5] acid reagent was used for color development.

[5] Folin, *J. Biol. Chem.*, **82**, 83 (1929).

[6] Everett and Sheppard, *Proc. Okla. Acad. Sci.*, November, 1936.

[7] Everett and Sheppard, "The Oxidation of Carbohydrates in Acid Solution," University of Oklahoma Medical School Monograph, 1936.

[8] Isbell, *J. Research Natl. Bur. Standards*, **18**, 505 (1937).

TABLE I

RELATIVE REDUCING EQUIVALENTS OF SUGARS (*d*-GLUCOSE = 1.00)

Sugars	Folin–Wu tartrate reagents mg./cc.	*d*-	*l*-	*meso*	Sumner reagent (0.5 mg./cc.)
d-Xylose	0.1	0.97	1.02	0.91	1.14
d-Xylose	.2	.985	.995	.94	
l-Xylose	.1	.965	1.05	.955	1.18
l-Xylose	.2	.99	1.05	.955	
d-Lyxose	.1	.96	0.94	.855	1.16
d-Lyxose	.2	.96	.935	.88	
d-Arabinose	.1		.92	.76	1.13
d-Arabinose	.2	.69	.88	.78	
d-Arabinose	.4	.685			
l-Arabinose	.1	.86		.765	1.14
l-Arabinose	.2	.87	.73	.77	
l-Arabinose	.4		.69		
d-Ribose	.1		.84		1.08
d-Ribose	.2	.62	.83	.70	
d-Ribose	.4	.655		.73	
d-Glucose	.1	1.00	.98	1.00	1.00
d-Glucose	.2	1.00	.975	1.00	
d-Mannose	.2	0.45	.56	0.70	0.97
d-Mannose	.4	.57	.63	.68	
d-Galactose	.1	.78			.97
d-Galactose	.2	.79	.64	.755	
d-Galactose	.4		.63	.72	
d-Glucosamine·HCl	.1	.77	.79	.73	.33[a]
d-Glucosamine·HCl	.2	.81	.80	.755	
d-Glycuronic acid	.1			.95	.91
d-Glycuronic acid	.2	.71	.65	.945	
d-Glycuronic acid	.4	.80	.715		
d-Galacturonic acid·H_2O	.2	.655	.45	.58	.87
d-Galacturonic acid·H_2O	.4	.65	.46	.565	
d-Sorbose	.1	.76	.70	.745	.99
d-Sorbose	.2	.80	.71	.785	
l-Sorbose	.1	.80	.795	.785	.95
l-Sorbose	.2	.85	.83	.83	
d-Fructose	.1	.89	.965	.94	.99
d-Fructose	.2	.93	.975	.98	
l-Rhamnose·H_2O	.3	.315	.40	.385	.98
l-Rhamnose·H_2O	.6	.375	.41	.44	
l-Fucose	.3	.45	.53	.475	1.00
l-Fucose	.6	.42	.48	.45	
α-*d*-Mannoheptose	.2	.60	.515	.67	0.83
α-*d*-Mannoheptose	.4	.63	.51	.66	
d-Mannoketoheptose	.2	.68	.605	.75	1.00
d-Mannoketoheptose	.4	.70	.60	.73	
l-Ascorbic acid	.1	.55	.55	.55	0.44
l-Ascorbic acid	.4	.925	.90	.945	
Gentiobiose	.2	.54	.54	.57	.66
Gentiobiose	.4	.535	.535	.57	
Cellobiose	.2	.535	.53	.655	.83
Cellobiose	.4	.52	.51	.645	
Maltose·H_2O	.2	.415	.46	.51	.76
Maltose·H_2O	.4	.425	.44	.51	
Melibiose·$2H_2O$	.2	.495	.52	.50	.63
Melibiose·$2H_2O$	.4	.49	.50	.50	
Lactose·H_2O	.2	.475	.45	.535	.77
Lactose·H_2O	.4	.475	.445	.53	

[a] Used 1 mg./cc.

TABLE II

CLASSIFICATION OF PENTOSES, METHYLPENTOSES AND HEXOSES ACCORDING TO *cis-trans* ISOMERISM OF PYRANOID FORMS

trans Forms

d-Xylose group	*l*-Xylose group
d-Isorhamnose	*l*-Isorhamnose
d-Sorbose	*l*-Sorbose
d-Glucose	*l*-Glucose
l-Idose	*d*-Idose

2,3-*cis* Forms

d-Lyxose group	*l*-Lyxose group
d-Rhamnose	*l*-Rhamnose
d-Tagatose	*l*-Tagatose
d-Mannose	*l*-Mannose
l-Gulose	*d*-Gulose

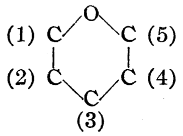
3,4-*cis* Forms

d-Arabinose group	*l*-Arabinose group
l-Fucose	*d*-Fucose
d-Fructose	*l*-Fructose
d-Altrose	*l*-Altrose
l-Galactose	*d*-Galactose

2,3,4-*cis* Forms

d-Ribose group	*l*-Ribose group
Epifucose	Epirhodeose
d-Psicose	*l*-Psicose
d-Allose	*l*-Allose
l-Talose	*d*-Talose

Type formula



Carbon 1 is the characteristic potential carbonyl.

pentoses with alkaline reagents (Table I) follows epimeric relations; thus, xylose and lyxose (epimeric *trans* types) react almost equally with *d*- and *l*-tartrate reagents, whereas ribose and arabinose (epimeric *cis* types) select opposite enantiomorphs of reagents. Six and seven carbon sugars behave qualitatively like related epimeric pentose types, but deviate quantitatively. Additional carbon at pyranoid positions 1 or 5 (Table II) limits mobility of the cyclic oxygen, allowing opposite planar arrangements of cyclic oxygen in aldohexoses of each *cis–trans* group and the resultant alteration of *cis–trans* influences at pyranoid position 5.

In our experiments *cis* sugars with opposite extraplanar relationships showed opposing selectivity for asymmetric oxidizing agents. *d*-Mannose and *l*-rhamnose, with 2,3-*cis* hydroxyls *trans* to cyclic oxygen, selected *l*-tartrate reagent, and *d*-galactose, an extraplanar opposite as far as positions 2, 3 and 4 are concerned, selected the *d*-reagent (Table I). The oxidation of sugars is thus influenced by spacial configuration in three dimensions.

In Table III we have listed molar reducing equivalents of sugars and their percentage deviations from the *d*-glucose standard. The molar equivalents have been calculated as percentages

TABLE III

MOLAR REDUCING EQUIVALENTS AND PERCENTAGE DEVIATIONS OF SUGARS RELATIVE TO *d*-GLUCOSE

Sugars	Folin–Wu equivalents				Deviation, %			Sumner equivalent[a]	Deviation, %
	mg./cc.	*d*-Reag.	*l*-Reag.	*m*-Reag.	X	Y	Z		
d-Xylose	0.1	0.81	0.85	0.76	− 4	−15	−24	0.95	− 5
d-Xylose	.2	.82	.83	.78	− 1	−17	−22		
l-Xylose	.1	.805	.875	.795	− 7	−12.5	−20.5	.98	− 2
l-Xylose	.2	.825	.875	.795	− 5	−12.5	−20.5		
d-Glucose	.1	1.00	.98	1.00	+ 2	0	0	1.00	0
d-Glucose	.2	1.00	.975	1.00	+ 2.5	0	0		
d-Glucosamine	.1	0.92	.95	0.875	− 3	− 5	−12.5	0.395	−60.5
d-Glucosamine	.2	.97	.96	.905	+ 1	− 4	− 9.5		
d-Glycuronic acid	.1			1.025			+ 2.5	.98	− 2
d-Glycuronic acid	.2	.765	.70	1.02	+ 6.5	−23.5	+ 2		
d-Glycuronic acid	.4	.86	.77		+ 9	−14			
d-Sorbose	.1	.76	.70	0.745	+ 6	−24	−25.5	.99	− 1
d-Sorbose	.2	.80	.71	.785	+ 9	−20	−21.5		
l-Sorbose	.1	.80	.795	.785	+ 0.5	−20	−21.5	.95	− 5
l-Sorbose	.2	.85	.83	.83	+ 2	−15	−17		
d-Lyxose	.1	.80	.78	.71	+ 2	−20	−29	.965	− 3.5
d-Lyxose	.2	.80	.78	.73	+ 2	−20	−27		
d-Mannose	.2	.45	.56	.70	−11	−44	−30	.97	− 3
d-Mannose	.4	.57	.63	.68	− 6	−37	−32		
l-Rhamnose	.3	.32	.405	.39	− 8.5	−59.5	−61	.99	− 1
l-Rhamnose	.6	.38	.415	.445	− 3.5	−58.5	−55.5		
d-Mannoketoheptose	.2	.79	.71	.875	+ 8	−21	−12.5	1.16	+16
d-Mannoketoheptose	.4	.82	.70	.85	+12	−18	−15		
d-Arabinose	.1		.77	.63		−23	−37	0.94	− 6
d-Arabinose	.2	.575	.73	.65	−15.5	−27	−35		
d-Arabinose	.4	.57							
l-Arabinose	.1	.72		.64		−28	−36	.95	− 5
l-Arabinose	.2	.725	.61	.64	+11.5	−27.5	−36		
l-Arabinose	.4		.575						
d-Galactose	.1	.78				−22		.97	− 3
d-Galactose	.2	.79	.64	.755	+15	−21	−24.5		
d-Galactose	.4		.63	.72			−28		
d-Galacturonic acid	.2	.77	.53	.68	+24	−23	−32	1.025	+ 2.5
d-Galacturonic acid	.4	.765	.54	.665	+22.5	−23.5	−33.5		
d-Fructose	.1	.89	.965	.94	− 7.5	− 3.5	− 6	0.99	− 1
d-Fructose	.2	.93	.975	.98	− 4.5	− 2.5	− 2		
l-Fucose	.3	.41	.48	.43	− 7	−52	−57	.91	− 9
l-Fucose	.6	.38	.44	.41	− 6	−56	−59		
α-*d*-Mannoheptose	.2	.70	.60	.78	+10	−30	−22	.97	− 3
α-*d*-Mannoheptose	.4	.735	.595	.77	+14	−26.5	−23		
d-Ribose	.1		.70			−30		.90	−10
d-Ribose	.2	.52	.69	.58	−17	−31	−42		
d-Ribose	.4	.54		.61			−39		
l-Ascorbic acid	.1	.56	.56	.56	0	−44	−44	.45	−55
l-Ascorbic acid	.4	.945	.92	.965	+ 2.5	− 5.5	− 4.5		
Gentiobiose	.2	1.03	1.03	1.08	0	+ 3	+ 8	1.25	+25
Gentiobiose	.4	1.02	1.02	1.08	0	+ 2	+ 8		
Cellobiose	.2	1.02	1.01	1.24	+ 1	+ 2	+24	1.57	+57
Cellobiose	.4	0.99	0.97	1.23	+ 2	− 1	+23		
Maltose	.2	.83	.92	1.02	− 9	− 8	+ 2	1.52	+52
Maltose	.4	.85	.88	1.02	− 3	−12	+ 2		
Melibiose	.2	1.04	1.09	1.05	− 5	+ 9	+ 5	1.32	+32
Melibiose	.4	1.03	1.05	1.05	− 2	+ 5	+ 5		
Lactose	.2	0.95	0.90	1.07	+ 5	− 5	+ 7	1.54	+54
Lactose	.4	.95	.89	1.06	+ 6	− 5	+ 6		

[a] Concentrations as in Table I.

of the reduction of *d*-tartrate reagent by *d*-glucose. The deviations are defined as follows: X, representing planar influences for *trans* reagents, is the molar equivalent for the *d*-reagent minus that for the *l*-reagent. Y, representing extraplanar influences for *trans* reagents, is the equivalent for that *trans* reagent most reduced by any particular sugar minus the equivalent of the *trans* sugar, *d*-glucose, for the *d*-reagent. Z, representing the total influence upon the *meso* reagent, is the equivalent for this reagent minus that of *d*-glucose for the *d*-reagent.

The deviations of monosaccharides with *trans* tartrate reagents reveal that epimerized *d*-glucose, *d*-glucosamine, *d*-xylose, *d*-lyxose and *l*-sorbose are most symmetrical in a planar sense, since their X deviations approach zero. However, these *trans* sugars have average Y deviations of 0, −4.5, −16, −20 and −17.5, respectively. The presence of the CH_2OH group at position 5 in *d*-glucose therefore increases the *trans* characteristics of the pyranoid molecule. In the three-dimensional strainless model of *d*-glucopyranose, viewed from the plane of the ring, the additional hydroxyl group of carbon 6 balances the other oxygens in both a planar (right and left) and an extraplanar (polar) sense. In *l*-sorbose and *d*-xylose models the oxygens are well balanced in a planar sense but not in an extraplanar sense, since there is no CH_2OH group at pyranoid position 5.

Lengthening the carbon chain therefore results in appreciable alteration of extraplanar influences, which are interrelated with planar influences. The interrelation is demonstrated by the fact that *d*- and *l*-isomerism can be represented alternately as a polar phenomenon relative to the pyranoid cyclic oxygen. Inversion of strainless pyranoid models of *l*-sugars, whose ring systems are thus viewed as identical with those of *d*-sugars, reveals polar interchanges between carbons 1 and 5 and between carbons 2 and 4. Relating sugar antipodes in this fashion facilitates comparisons which are difficult with the usual right and left disymmetric formulas. Since planar and extraplanar influences have a common space coördinate, the substitution of CH_2OH or COOH groups at pyranoid positions 1 or 5 affects both *cis–trans* (Y) and planar (X) influences, the latter causing a "shift to the right" in reagent selection by ketoses and alduronic acids. (Compare these with related aldohexoses in Table III.)

Of the monosaccharides studied, *d*-glucose gives rise to the most symmetrical three-dimensional epimeric system. In a planar sense, epimerized *d*-glucosamine, *d*-xylose, *l*-sorbose and *d*-lyxose are just as symmetrical, while *d*-galacturonic acid, *d*-ribose, *d*-arabinose and *d*-galactose (3,4-*cis* types) are most unsymmetrical. In an extraplanar sense, *d*-glucose, *d*-glucosamine and *d*-fructose are most symmetrical, the latter evidently going to a balanced epimeric system by a Lobry de Bruyn rearrangement; methylpentoses are most unsymmetrical and reduce less copper than other sugars.

The *trans* arrangement of epimerized *d*-glucose and its relatives, *d*-fructose and *d*-glycuronic acid, is also the most favorable influence for reduction of *meso*-tartrate reagent (Table III). With aldopentoses, extraplanar deviations (Y) for *trans* reagents are uniformly less than the total deviations (Z) for the *meso* reagent, and the latter is not always reduced equally by planar antipodes. (See xylose and sorbose in Table III.) Analogous smaller deviations occur even with the non-asymmetric Sumner reagent.

The fact that *d*-glucose reduces *meso* reagent 23% more than does *d*-xylose, indicates again that mutarotation and epimerization of the *trans* pentose are insufficient to balance its molecule in all dimensions and that terminal CH_2OH groups are active. Certain sugars which are not optical antipodes reduce the *meso* reagent equally (*d*-xylose and *d*-sorbose, also *d*-mannose and *d*-galacturonic acid); others (*d*-glucose, *l*-ascorbic acid, the methylpentoses and ketohexoses) have approximately equal Y and Z deviations.

More detailed correlation is problematical because the concentration of certain sugars affects their oxidation. Notable instances are *d*-mannose and *d*-glycuronic acid with *trans* tartrate reagents (Table III), but the most remarkable example is α-glucosan with *d*-tartrate.[7]

The β-glucose-glucosides, cellobiose and gentiobiose, resemble the parent monosaccharide with *trans* reagents, but differ in their effects upon *meso* reagent. Cellobiose presents a space arrangement for *meso* oxidation markedly superior to that of any sugar studied (Table III). The marked reduction of Sumner's reagent by disaccharides is significant.

We have called attention previously to the usefulness of Sumner/Folin–Wu ratios of glucose equivalents for differentiating sugars in solution.[7,9]

(9) Everett, Edwards and Sheppard, *J. Biol. Chem.*, **104**, 11 (1934).

The present study provides a more scientific basis for these ratios and correlates them with sugar structure.

Summary

1. Quantitative studies have been made of the oxidation of twenty-five sugars by *d*-, *l*- and *meso*-tartrate modifications of the Folin–Wu alkaline copper reagent and by Sumner's dinitrosalicylate reagent.

2. The behavior of reducing sugars is determined by the entire sugar molecule, but intramolecular influences can be conveniently classified as planar and extraplanar, *cis–trans* relations being important extraplanar influences.

3. Epimeric sugars have related behaviors, the glucose epimeric system being most symmetrical in all dimensions. *cis*-Sugars are most unsymmetrical in a planar sense and methylpentoses in an extraplanar sense.

4. *meso*-Tartrate reagent is susceptible to both planar and extraplanar influences.

OKLAHOMA CITY, OKLA. RECEIVED JANUARY 7, 1938

[CONTRIBUTION NO. 134 FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Hydantoins Derived from the Analogs of 1,3-Dichloroisopropoxyethyl Methyl Ketone[1]

BY BRUCE B. ALLEN WITH HENRY R. HENZE

As a continuation of attempts to prepare substances possessing soporific properties, attention has now been directed to the synthesis of 5,5-disubstituted hydantoins in which one of the substituents is of the halogenoalkoxyalkyl type. In this Laboratory, the application of Bucherer's[2] hydantoin synthesis has been extended to the preparation of disubstituted heterocyclic compounds from such bifunctional carbonyl substances as alkoxymethyl alkyl (or aryl) ketones[3] and phenoxymethyl alkyl (or aryl) ketones,[4] and has been shown to be advantageous over other accepted methods as regards yield, ease of execution, and degree of purity of product. In the present investigation, then, successful use of the Bucherer method in hydantoin formation from dichloroisopropoxyethyl alkyl or aryl ketones resulted in further extension of the application of the method. The ketones used were, with one exception, of the type $(CH_2Cl)_2CH\text{-}O\text{-}CH(CH_3)\text{-}COR$ where R represents alkyl and includes those groups which have been shown most active physiologically; the preparation and characterization of these ketones have been described by us previously.[5] Since the hydantoin derived from the phenyl analog of this series of ketones represents a halogenoalkoxyl derivative of Nirvanol (5-ethyl-5-phenylhydantoin), a substance shown to possess useful medicinal value,[6] it was deemed pertinent to effect its preparation and subsequent conversion into the corresponding hydantoin.

Experimental

Preparation of α-1,3-Dichloroisopropoxyethyl Alkyl Ketones.—The eight ketones of this series which were employed were prepared from α-1,3-dichloroisopropoxypropionitrile by means of the Grignard reaction, these preparations having been described previously.[5]

Preparation of α-1,3-Dichloroisopropoxyethyl Phenyl Ketone.—The general method as described for the preparation of the alkyl analogs was employed in the synthesis of this ketone. The Grignard reagent from 48.1 g. (0.31 mole) of phenyl bromide, 7.3 g. (0.3 atom) of magnesium in the form of turnings, and 250 cc. of anhydrous ether was treated with the solution of 45.5 g. (0.25 mole) of α-1,3-dichloroisopropoxypropionitrile in an equal volume of ether. Although vigorous reaction occurred throughout the nitrile addition, completion was ensured by refluxing for two hours over a steam-cone. The addition product, which separated as a gray-colored solid, was decomposed in the usual manner with chilled, dilute hydrochloric acid and crushed ice; the resulting ether layer was separated, washed with dilute sodium carbonate solution and then water, and finally dried over anhydrous calcium chloride. The crude material was freed of ether by evaporation and then purified by two fractionations under 4 mm. pressure; the pure ketone is a colorless, almost odorless, quite viscous liquid which develops a deep red coloration upon standing; yield, 45.4 g. (69.6%); b. p. 169° (4 mm.); d^{20}_4 1.2356; n^{20}_D 1.5398; *MR* calcd., 66.18;[7] *MR* found, 65.31; γ^{20} 35.53 dynes/cm.; *P* calcd. (Sugden's atomic constants), 538.4; *P* found, 516.0.

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[1] From a portion of a dissertation presented by Bruce B. Allen to the Faculty of the Graduate School of the University of Texas in partial fulfilment of the requirements for the degree of Doctor of Philosophy, June, 1938.

[2] Bucherer and Lieb, *J. prakt. Chem.*, [2] **141**, 5 (1934).

[3] Rigler with Henze, THIS JOURNAL, **58**, 474 (1936).

[4] Whitney with Henze, *ibid.*, **60**, 1148 (1938).

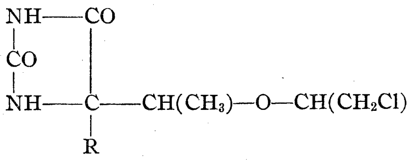
[5] Allen with Henze, *ibid.*, **59**, 540 (1937).

[6] De Rudder, *Chem. Zentr.*, **99**, I, 2628 (1926); Poynton and Schlesinger, *Lancet*, II, 267 (1929); Pilcher and Gerstenberger, *Am. J. Diseases Children*, **40**, 1239 (1930); Jones and Jacobs, *J. Am. Med. Assoc.*, **99**, 18 (1932).

[7] This summation includes the exaltation value due to the C_6H_5-CO- grouping which has been determined for acetophenone by Auwers and Eisenlohr, *J. prakt. Chem.*, [2] **84**, 20 (1911).

TABLE I

5-[1-(2-CHLORO-1-CHLOROMETHYLETHYL)-OXY]-ETHYL-5-ALKYL OR PHENYLHYDANTOINS



-R	M. p., °C. (corr.)	Yield, %	Chlorine, % Calcd.	Chlorine, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
$-CH_3$	229.0–230.0	85.6	26.35	26.38	10.41	10.66
$-CH_2CH_3$	198.5–199.5	84.2	25.05	25.22	9.89	9.92
$-CH_2CH_2CH_3$	211.5–212.5	69.5	23.86	23.97	9.43	9.56
$-CH(CH_3)_2$	146.5–147.5	66.2	23.86	24.09	9.43	9.43
$-CH_2CH_2CH_2CH_3$	206.5–207.5	75.4	22.79	22.70	9.00	9.11
$-CH(CH_3)CH_2CH_3$	149.5–151.0	43.2	22.79	22.79	9.00	8.81
$-CH_2CH_2CH_2CH_2CH_3$	181.0–182.0	87.7	21.80	21.56	8.61	8.77
$-CH_2CH_2CH(CH_3)_2$	187.0–187.5	60.0	21.80	21.64	8.61	8.74
$-C_6H_5$	187.0–188.0	79.7	21.41	21.53	8.46	8.47

Anal. Calcd. for $C_{12}H_{14}Cl_2O_2$: Cl, 27.16. Found: Cl, 26.91.

Synthesis of 5-[1-(2-Chloro-1-chloromethylethyl)-oxy]-ethyl-5-alkyl or -5-phenylhydantoins.—Bucherer's method[2] was applied to the formation of this series of compounds: one mole of the appropriate dichloroisopropoxyethyl alkyl or aryl ketone was added to the suspension of 1.25 moles of potassium cyanide and 3 moles of freshly powdered ammonium carbonate in as much 50% alcohol as would approximate seven times the volume of the ketone, and then the resulting mixture heated from six to eight hours in a flask equipped with an air-condenser and maintained at 55–62°. In most cases, the solid hydantoin began to separate from the warm reaction mixture after heating had continued for three to five hours. After completion of reaction, the mixture was allowed to cool and the solid which had formed was removed by filtration; when the solution was concentrated and again cooled, a second portion of more finely crystalline solid material was obtained. Occasionally, however, the material separating after concentration was in the form of an oil but generally solidified and could then be recrystallized. Finally, acidification of the mother liquor caused separation of still another small amount of solid or oil. Two of the hydantoins, namely, the isopropyl and secondary butyl, failed to conform with this behavior in that there was no separation of material during the reaction period; after concentration of the reaction mixtures to relatively small volumes and acidification, the crude hydantoins separated as dark-colored oils. It was only after prolonged boiling with 20% hydrochloric acid, treatment with Norit, and dissolving in warm alcohol followed by pouring the resulting solutions on crushed ice that the substances were obtained in solid form. The hydantoins could then be recrystallized readily from the usual solvents.

The hydantoins, all white solids, were recrystallized easily from 50–60% alcohol; the butyl and amyl analogs lacked the definite crystalline structure of the lower alkyl and phenyl analogs, separating from the solvent as amorphous solids which were powders when dried, but which possessed sharp melting points. The hydantoins were readily soluble in the organic solvents such as acetone and 95% alcohol and in aqueous alkali, but were quite insoluble in water. The data for melting points, percentage yields, and the analytical results for the nine hydantoins prepared have been summarized in Table I.

It is of interest to note that although the conditions favoring nitrile formation were present during these hydantoin preparations, namely, an alkyl halide in the presence of aqueous-alcoholic potassium cyanide, no replacement of chlorine by cyanide was observed.

Summary

1. The preparation of eight new hydantoins from a series of dichloroisopropoxyethyl alkyl ketones extended the application of Bucherer's method for preparing 5,5-disubstituted hydantoins to include the alkyl halogenoalkoxyalkyl type.

2. From the Grignard reaction, involving interaction of phenylmagnesium bromide and α-1,3-dichloroisopropoxypropionitrile, was obtained the phenyl analog to the dichloroisopropoxyethyl alkyl series of ketones, this synthesis representing the initial preparation of an aryl chloroalkoxyalkyl ketone.

3. The successful conversion of the latter into the corresponding hydantoin further extended the use of Bucherer's method to preparation of a hydantoin of the 5-aryl-5-chloroalkoxyalkyl type and resulted in the formation of a new derivative of the medicinal Nirvanol.

AUSTIN, TEXAS

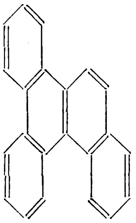
RECEIVED JUNE 3, 1938

[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE]

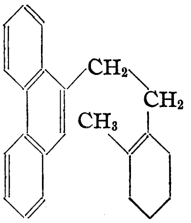
1,2,3,4-Dibenzophenanthrene. I

BY ERNST BERGMANN

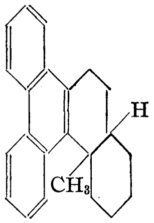
Of the possible aromatic systems consisting of five benzene rings, three are unknown so far: 1,2,3,4-dibenzophenanthrene (I), 1,2,5,6-dibenzophenanthrene and 1′,2′-naphtha-1,2-anthracene.[1] We have undertaken their synthesis and report here experiments for the preparation of (I), which followed the lines worked out for the isolation of the similar 1,2-cyclopentenotriphenylene[2] (I is 1,2-benzotriphenylene). The magnesium derivative of β-(9-phenanthryl)-ethyl chloride reacted upon 2-methylcyclohexanone to give α-(9-phenanthrylethyl)-β-methyl-Δ^{α}-cyclohexene (II), which was cyclized by means of anhydrous stannic chloride. As the product formed by subsequent selenium dehydrogenation gave only very small amounts of an aromatic hydrocarbon of the desired analytical composition, the cyclization product of (II) seems not to be 5,6,7,8,9,10,11,12-octahydro-11-methyl-1,2,3,4-dibenzophenanthrene (III), but a spirane, and the aromatic hydrocarbon, which forms a yellow picrate, a rearrangement product.[3]



I



II



III

In the experimental part some more unsuccessful experiments to synthesize (I) are recorded. The investigation is being continued.[3a]

Experimental

α - (9 - Phenanthryl - ethyl) - β - methyl - Δ^{α}-cyclohexene (II).—When *o*-methylcyclohexanone (10 g.) was added to the solution of β-(9-phenanthryl)-ethylmagnesium chloride (from 2.5 g. of magnesium turnings and 24 g. of the chloride),[2] a vivid reaction took place, which was completed by boiling for three hours. On decomposition with dilute acid, some 1,4-di-(9′-phenanthryl)-butane (1.4 g.) separated. The ether residue decomposed partly when heated on the water-bath, giving off water, and therefore it was heated with potassium hydrogen sulfate (20 g.) to 160° for one hour. Distillation in a good vacuum (0.01 mm.) gave after a small head fraction, which probably was 9-ethylphenanthrene, the desired product (10 g.) as a colorless, viscous oil, b. p. 220°, which could not be induced to crystallize (Calcd. for $C_{23}H_{24}$: C, 92.0; H, 8.0. Found: C, 92.1; H, 8.3). The **picrate**, prepared in concentrated benzene solution, precipitated on chilling as an orange-red powder. From propyl alcohol it formed silky needles, which melted at 124–125° to a dark-red liquid (Calcd. for $C_{29}H_{27}O_7N_3$: C, 65.8; H, 5.1. Found: C, 66.0, 66.0; H, 5.3, 5.5).

Bromine Titration.—0.6594 and 1.3185 g. of the hydrocarbon absorbed 0.3260 and 0.7056 g. of bromine, the theoretical amounts required for 1 double bond being 0.3517 and 0.7032 g., respectively.

Cyclization.—A solution of the foregoing hydrocarbon (II) (15 g.) in benzene (150 cc.) was saturated with dry hydrogen chloride, treated with stannic chloride (6 g.), and kept at room temperature for forty-eight hours. Decomposition with ice and concentrated hydrochloric acid gave the spiranic cyclization product; colorless oil, b. p. 220° (0.01 mm.); yield, 12 g. (Calcd. for $C_{23}H_{24}$: C, 92.0; H, 8.0. Found: C, 91.6; H, 7.9). On mixing its benzene solution with the equivalent amount of picric acid in benzene, a red solution was obtained, which deposited the **picrate** on evaporation. From propyl alcohol this formed orange-red, prismatic needles, m. p. 172° (Calcd. for $C_{29}H_{27}O_7N_3$: C, 65.8; H, 5.1. Found: C, 65.9; H, 5.2).

Cyclization of (II) by means of aluminum chloride did not always give satisfactory results.

Dehydrogenation of the Presumable Spirane.—The above hydrocarbon (3 g.) was heated with selenium (5 g.) at 300–320° for twenty hours in a sealed tube. The reaction product was extracted with chloroform and the residue purified by distillation in a high vacuum (0.01 mm.). After a small head fraction at 160–190° bath temperature, the desired product distilled at a bath temperature of 260–280°. It solidified spontaneously and was triturated with petroleum ether (b. p. 80–100°) and recrystallized from the same solvent, giving faintly yellow, star-like aggregates of prismatic needles, m. p. 184°; yield 1–3%. (Calcd. for $C_{22}H_{14}$: C, 95.0; H, 5.0. Found: C, 95.0; H, 5.1%). The picrate separated from its dark yellow benzene solution in silky, yellow needles, m. p. 220°.

The head fraction mentioned above crystallized from methyl alcohol in the form of leaflets of m. p. 99° and was identified as **phenanthrene.** Its formation is due to thermolytic fission. An analogous observation has been made recently in our laboratory[4] in the dehydrogenative preparation of 2′,1′-naphtha-1,2-fluorene.[5] Its 10-methyl-3,4,9,10-tetrahydro derivative, when heated with selenium, gives partly 3,4-dihydrophenanthrene.

Several other synthetic methods for the preparation of

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(1) Barry, Cook, *et al., Proc. Roy. Soc.* (London), **117B**, 318 (1935).

(2) E. Bergmann and O. Blum-Bergmann, THIS JOURNAL, **58**, 1678 (1936); E. Bergmann and F. Bergmann, *ibid.*, **60**, 1805 (1938).

(3) Compare Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1936, p. 162.

(3a) (I) has recently been synthesized by Hewett, *J. Chem. Soc.*, 193 (1938).

(4) Unpublished results.

(5) Bachmann, Cook, Hewett and Iball, *J. Chem. Soc.*, **54** (1936).

(I) have been tried without success. Dicyclohexenyl (4.5 cc.)[6] and 1,2-naphthoquinone (10.4 g.) condensed at 180° to form an unworkable black resin, and 3-bromo-1,2-naphthoquinone (1.6 g.) did not react at all with this hydrocarbon (1.1 g.) when heated at 100° for four hours in the presence of *sym*-tetrachloroethane[7] (10 cc.). The potassium derivative of ethyl cyclohexanone-*o*-carboxylate could not be coupled with β-(9-phenanthryl)-ethyl chloride, even on prolonged heating,[8] and finally the fact may be recalled,[9] that 9-cyclohexenylphenanthrene does not react with maleic anhydride to form a derivative of 1,2,3,4-dibenzophenanthrene.

Summary

By interaction between 2-methylcyclohexanone and the Grignard derivative of β-(9-phenanthrylethyl) chloride and subsequent cyclization, a spirane is formed instead of the expected octahydro-methyl-1,2,3,4-dibenzophenanthrene. Its dehydrogenation gave small amounts of an aromatic hydrocarbon. Several other methods of synthesis also failed.

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[6] Compare Weizmann, Bergmann and Berlin, THIS JOURNAL, **60**, 1331 (1938).

[7] Compare, for this method, Fieser and Dunn, *ibid*,, **59**, 1016, 1021, 1024 (1937).

[8] With this reaction, we intended to utilize the method of Ruzicka, Ehmann, Goldberg and Hoesli [*Helv. Chim. Acta*, **16**, 833 (1933)] for the synthesis of chrysene and 1,2-cyclopentenophenanthrene.

[9] E. Bergmann and F. Bergmann, THIS JOURNAL, **59**, 1443 (1937).

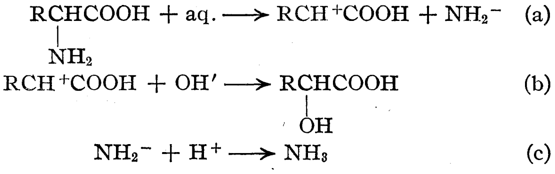
REHOVOTH, PALESTINE RECEIVED MARCH 4, 1938

[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE]

The Photochemical Deamination of Amino Acids in Water Solution. II

BY CH. WEIZMANN, Y. HIRSHBERG AND ERNST BERGMANN

In the first paper on the subject,[1] we were able to demonstrate that under the influence of ultraviolet light water solutions of amino acids undergo hydrolysis according to the scheme



$$\underset{\displaystyle NH_2}{RCHCOOH} + aq. \longrightarrow RCH^+COOH + NH_2^- \qquad (a)$$

$$RCH^+COOH + OH' \longrightarrow \underset{\displaystyle OH}{RCHCOOH} \qquad (b)$$

$$NH_2^- + H^+ \longrightarrow NH_3 \qquad (c)$$

In order to see how the nature of the group R influences the speed of the reaction, we compared alanine and phenylalanine under identical conditions. Phenylalanine decomposes about 2.7 times as quickly as alanine, in 0.1 *N* solution, and 2.2 times as quickly in 0.05 *N* solution. This influence of the phenyl group may be due to two effects, to its loosening the C–N bond and to the increase in light absorption,[2] both effects perhaps being connected in some way. The necessary measurements could be made only in the first stage of the reaction, as phenylalanine undergoes a side reaction, leading to an insoluble coating on the quartz walls and to the formation of an unpleasantly smelling volatile product. In the first minutes of irradiation, however, only ammonia is formed, according to the above scheme. The same complication as with phenylalanine occurs in the case of phenylglycine, $C_6H_5CH(NH_2)COOH$, the decomposition of which therefore could not be studied. Apparently, these side reactions are due to the presence of the aromatic nucleus, as similar observations have been made before with tyrosine solutions.[3]

The constitutional change brought about by coupling alanine with glycine to form alanylglycine also increases the speed of the photochemical deamination. Alanylglycine is hydrolyzed 4.2 times as quickly as alanine in 0.1 *N* solution, and 2.6 times as quickly in 0.05 solution. It is difficult to explain this difference, but it may be assigned to the greater distance between the amino and the free carboxyl group enhancing the ionization of the C–N bond, or to the increased light absorption[4] or to both effects. It may be added that we think it safe to ascribe the ammonia formed exclusively to the decomposition of the $-C-NH_2$ and not of the amide group, since the amide group, as far as we know, is much stabler toward photochemical hydrolysis.[5] It appears that peptides are attacked in the same way as amino

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[1] Weizmann, Bergmann and Hirshberg, THIS JOURNAL, **58**, 1675 (1936).

[2] Compare Allen, Steiger, Magill and Franklin, *Biochem. J.*, **31**, 195 (1937).

[3] Compare Part I. The ultraviolet absorption spectra of tyrosine and phenylalanine are practically identical: Feraud, Dunn and Kaplan, *J. Biol. Chem.*, **112**, 323 (1935).

[4] Magill, Steiger and Allen, *Biochem. J.*, **31**, 188 (1937).

[5] Compare, *e. g.*, the experiments of Paternò, *Gazz. chim. ital.*, **44**, I, 237 (1914). Allen, Steiger, Magill and Franklin[2] have stated recently that in acylated amino acids and peptides hydrolysis of the –CO–NH-group occurs on irradiation. While that may be true in the case of acylated amino acids, which do not contain the amino group necessary for photolysis, there apparently is no need for that assumption with regard to peptides.

acids, although Guillaume and Tanret[6] have failed previously to detect photolysis of peptides.

The quantum yield of the reactions has been studied with greater accuracy. The measurements were carried out with a vertical mercury arc lamp, which had four jackets.[7] The first and the fourth served for cooling with running water, in the second and third we had (a) water and monochloroacetic acid, or (b) the amino acid and monochloroacetic acid of equal normalities. The difference in the decomposition of monochloroacetic acid gave us the light absorbed in the amino acid layer, and its comparison with the degree of decomposition as determined by the amount of liberated ammonia gave the desired quantum yield. (In view of our preparative experiments,[1] it seemed safe to assume that the liberation of ammonia (or trimethylamine) is the only reaction occurring). Naturally, the jacket walls have to be kept extremely clean, as otherwise the translucence would not be identical in all experiments. Our experiments showed that in the case of alanine and glycine the quantum yield is equal to 0.09 and 0.1, respectively, while for betaine 0.06 has been observed. The ratio between the amino acids and betaine is about the same as found in Part I, and may be explained as suggested there,[8] although the absolute values according to our new more accurate measurements are definitely lower. The low absolute values are due, at least partly, to the increase in absorption, which sets in during irradiation according to Allen, Steiger, Magill and Franklin.[9]

The hydrolysis reaction we observe in the cases studied may be interesting from a biochemical point of view, as its occurrence in green plants may account for the relatively wide distribution in them of α-hydroxy acids. Other ways for the hydrolytic fission of amino acids, in any case, seem not to be available to the cell, as has been pointed out already in Part I. It has been suggested occasionally that bacteria are able to produce hydrolysis of the above type,[10] but observations like that of Otani and Ichihari,[11] that *Oospora lactis* produces (+)-lactic acid from both the forms of alanine, suggest that the amino acid is first oxidatively de-aminated and the keto acid formed subsequently hydrogenated. The same holds true for higher animals. Kotake, Kotake and Taniguchi,[12] *e. g.*, obtained after tyrosine feeding *p*-hydroxyphenyllactic acid along with *p*-hydroxyphenylpyruvic acid. For the classical photolytic conversion of amino acids into aldehydes in the presence of oxygen, on the other hand, it seems justified to assume hydroxy acids as intermediary products, although no definitive proof can be advanced.[13] The reducing properties of irradiated amino acid solutions,[14] *e. g.*, could be attributed to hydroxy acid formation.

Experimental

COMPARATIVE PHOTOLYSIS OF PHENYLALANINE AND ALANINE

(a) 0.1 *N* solution (50 cc.)

Time, min.	Cc. of 0.1 *N* NH_3 formed from alanine	Cc. of 0.1 *N* NH_3 formed from phenylalanine
5	0.16	0.55
10	.31	.90
15	.45	1.25
20	.59	1.50
25	.72	1.70
30	.88	1.91
	(b) 0.05 *N* solution (50 cc.)	
5	0.18	0.41
10	.25	.72
15	.38	.90
20	.50	1.08
25	.62	1.29
30	.74	1.47

COMPARATIVE PHOTOLYSIS OF ALANYLGLYCINE AND ALANINE

(a) 0.1 *N* solution (25 cc.)

Time, hours	Cc. of 0.1 *N* NH_3, formed from alanine	Cc. of 0.1 *N* NH_3 formed from alanylglycine
1	1.91	8.65
2	3.54	16.80
3	4.99	21.13
4	6.25	25.46
5	8.23	29.24
	(b) 0.05 *N* solution (25 cc.)	
1	1.55	3.95
2	2.91	6.50
3	4.28	9.55
4	5.52	14.26
5	6.55	17.58

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[6] Guillaume and Tanret, *Compt. rend. acad. sci.*, **201**, 1057 (1935); compare *Bull. soc. biol.*, **18**, 571 (1936).

[7] For a similar device see Farkas and Wansbrough-Jones, *Z. physik. Chem.*, **18B**, 124 (1932).

[8] Compare the analogous views expressed for the case of acrolein by Thompson and Linnett, *J. Chem. Soc.*, 1452 (1935).

[9] Thanks are due to the Referee for drawing our attention to that point.

[10] See, *e. g.*, Ehrlich and Jacobsen, *Ber.*, **44**, 888 (1911).

[11] Otani and Ichihari, *Folia Jap. Pharmacol.*, **1**, 397 (1925); quoted by Heigener, *Centralbl. Bakt.*, *II*, **93**, 83 (1935).

[12] Kotake, Kotake and Taniguchi, *J. Biochem.*, **18**, 395 (1933). Compare Sasaki and Otsuka, *J. Biol. Chem.*, **32**, 533 (1917); Kotake, Chikano and Ichihara, *Z. physiol. Chem.*, **143**, 218 (1925).

[13] Compare Ganassini, *Giorn. Farm. Chem.*, **61**, 439, 481 (1912); *Chem. Centralbl.*, **84**, I, 153 (1913).

[14] Wels, *Naunyn-Schmiedeberg's Archiv*, **181**, 147 (1936).

Quantum Yield of the Glycine Photolysis.—The inner chamber of the quartz lamp contained 115 cc. of water or of the 1 N amino acid solution, respectively, the outer one 200 cc. of 1 N monochloroacetic acid solution. Owing to the fact that glycolic acid as formed from monochloroacetic acid is unstable by itself, the amino acid solution was irradiated for one hour, while during only half of this time the outer jacket was filled with the chloro acid solution. 200 cc. of the 1 N monochloroacetic acid, *e. g.*, gave within thirty minutes 150 cc. of 0.1 N Cl^-, when irradiated through water, and 110 cc. of 0.1 N Cl^-, when irradiated through glycine solution. During one hour of irradiation, this glycine solution liberated 8.8 cc. of 0.1 N ammonia; quantum yield $8.8/2(150-110) = 0.11$. The following figures have been obtained in a number of analogous experiments: 0.11, 0.10, 0.09, 0.10, 0.09, 0.10, 0.12, 0.12, 0.11; average, 0.10.

Quantum Yield of the Alanine Photolysis.—The following figures have been determined: 0.088, 0.086, 0.094, 0.085, 0.087, 0.084; hence average, 0.087.

Quantum Yield of the Betaine Photolysis.—The following data have been secured: 0.065, 0.066, 0.064, 0.064, 0.062; hence average, 0.064.

Summary

The photolysis of alanine in water solution has been compared with that of phenylalanine and alanylglycine; in both cases the speed of the reaction is increased with regard to the velocity of the alanine decomposition. In the case of phenylalanine (and of phenylglycine), secondary reactions also take place, obviously due to the presence of the phenyl group.

The biological importance and the unique position of this photolysis is stressed, no other biological ways of amino acid hydrolysis being known.

The quantum yield of the photolytic fission has been more accurately redetermined in the cases of glycine, alanine and betaine; again, a markedly lower value has been obtained for betaine.

REHOVOTH, PALESTINE RECEIVED MARCH 12, 1938

[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE]

Dipole Moments and Molecular Structure. XIX.[1] Dipole Moments of Anthracene Derivatives and the Stereochemical Mechanism of Addition and Splitting Reactions in the Anthracene Series

BY ERNST BERGMANN AND ANNA WEIZMANN

Recently,[2] one of the present authors, has given a classification of halogen additions to double bonds. Since all mechanisms concerned involve a two-step reaction, it is understood that usually the entering halogen atoms (or ions) arrange themselves as remotely as possible from each other ("*trans*-addition").[2a] Therefore, we think it worth while communicating that the addition of chlorine[3] to 1,5-dichloroanthracene (to form I) and 9,10-diphenylanthracene (to form II) is a pure *cis* reaction,[4] the dichlorides formed having dipole moments of 3.7 and 3.0, respectively. We are inclined to assume that this unexpected course is due to steric factors. The anthracene model shows that a chain of two atoms easily may form a bridge between the 9,10-positions of the anthracene nucleus, so that the *chlorine molecule* will be able to enter the anthracene molecule as such. From this point of view, the chlorination parallels the "Einlagerung" of oxygen molecules (III)[5] or of substances of the maleic anhydride type (IV).[6]

A similar explanation for the course of an ad-

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[1] Part XVIII: Bergmann and Weizmann, *Trans. Faraday Soc.*, **32**, 1327 (1936).

[2] E. Bergmann, *Helv. Chim. Acta*, **20**, 590 (1937); *cf.* Roberts and Kimball, THIS JOURNAL, **59**, 947 (1937).

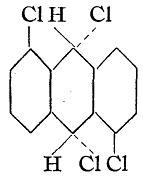
[2a] For a review see G. Wittig, "Stereochemie," Akad. Verlagsgesellschaft, Leipzig, 1930, pp. 120 ff.

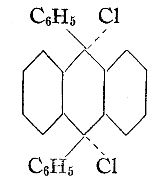
[3] The slight solubility of the corresponding dibromide prevented us from assigning a configurational formula; 0.2431 g. in 20 cc. of α-methylnaphthalene at 52.10° showed no visible difference in the dielectric constant from the pure solvent.

[4] The same structure has been assigned to (I) by de Barry Barnett.[12]

[5] Compare also for references, Dufraisse and Le Bras, *Bull. soc. chim.* [5] **4**, 349 (1937); Willemart, *ibid.*, 357, 510 (1937).

[6] Diels and Alder, *Ann.*, **486**, 191 (1931); *Ber.*, **64**, 2116 (1931); Clar, *ibid.*, **64**, 1676, 2194 (1931); Cook, *J. Chem. Soc.*, 3273 (1931). Compare Bergmann and Fujise, *Ann.*, **480**, 188 (1930).


I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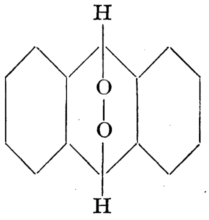
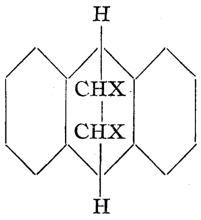
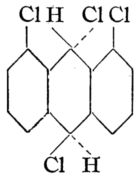

III


IV


V

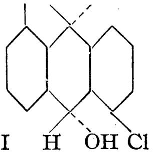
dition reaction has been given recently by K. Ziegler and co-workers[7] in the case of the lithium addition to butadiene, *cis* reaction taking place because of the oriented adsorption of the hydrocarbon on the metal surface.

1,8-Dichloroanthracene apparently adds chlorine "normally" in *trans* reaction, the 1,8-dichloroanthracene-9,10-dichloride (V) having an even smaller dipole moment ($2.4D$) than the parent substance ($\mu = 3.2D$), while the *cis* isomeride of (V) should have a markedly higher moment (4.5–$5D$).[8] Perhaps the close proximity of the two halogen atoms in the positions 1 and 8 prevents the above mechanism from being valid in this case.[9]

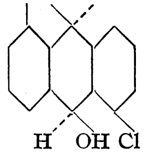
With regard to the numerical values observed, two remarks may be made. It is not clear why I and II do not have identical moments, the moments of di- and triphenylchloromethane being nearly equal:[10] one would suggest an inductive influence of the nuclear halogen atoms in (I)[11] (see below). The unexpectedly high difference in moments between 1,8-dichloroanthracene and its 9,10-dichloride may be due to the presence in the former substance of an ortho-chlorinated styrene system, the effect of which has been studied before by the authors.[1]

In studying the splitting reactions of dihalides of types (I) and (V), de Barry Barnett and his co-workers[12] have assumed that only *cis* reactions are likely to occur, divergent observations being explained by previous steric rearrangement of the dihalide or by its stereochemical inhomogeneity. These suggestions seem unsatisfactory. First of all, the substances used in our work were well-crystallized and certainly homogeneous. Second, it is difficult to understand that heating of 1,8-dichloroanthracene dichloride, *e. g.*, by itself or in presence of boiling xylene or cymene gives different results (removal of hydrogen chloride or chlorine, respectively), if these differences are due to previous rearrangement in one case. Third in terms of Barnett's hypothesis, it is unexplainable why under the above conditions 1,5,9-trichloroanthracene-9,10-dichloride loses hydrogen chloride while 1,8,10-trichloroanthracene-9,10-dichloride loses chlorine under the influence of potassium hydroxide. We prefer the view that there is *no visible rule governing the steric course of the splitting reaction.*

Obviously, in substitution reactions, configurational inversion may occur. One example is that 9,10-diphenyl-9,10-dihydroxy-9,10-dihydroanthracene, a homogeneous substance, reacts with dimethylaniline to yield two isomeric forms of 9,10-diphenyl-9,10-di-(*p*-dimethylamidophenyl)-9,10-dihydroanthracene.[13] 1,5-Dichloroanthracene 9,10-dibromide, on interaction with water in presence of acetone and calcium carbonate, affords according to E. de Barry Barnett[12] two isomeric 1,5-dichloro-9,10-dihydroxy-9,10-dihydroanthracenes (m. p. 210 and 244°, respectively)

VI


and


VII

We have measured the moment of the lower-melting form and found $2.95D$; for the isomeric form, due to its low solubility, we can only say that its moment is smaller. Therefore, the sub-

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[7] Ziegler, Haeffner and Grimm, *Ann.*, **528**, 101 (1937).

[8] Moment of 1,8-dichloroanthracene, plus moment of (I) or (II) perpendicular to it. Compare the dipole moment of *trans*-1,4-dihalogenocyclohexanes: Halmoey and Hassel, *Z. physik. Chem.*, **B15**, 472 (1932).

[9] The instability of the 9,10-dihalides of anthracene itself made the determination of their dipole moments impossible.

[10] Weissberger and Saengewald, *Z. physik. Chem.*, **B20**, 145 (1935); Bergmann, Engel and Wolf, *ibid.*, **B17**, 81 (1932).

[11] Weissberger and Hampson, *Trans. Faraday Soc.*, **30**, 884 (1934); *J. Chem. Soc.*, 393 (1936); THIS JOURNAL, **58**, 2111 (1936).

[12] E. de Barry Barnett, *Rec. trav. chim.*, **43**, 530 (1924); **44**, 217, 728, 818, 894 (1925); **45**, 68, 558 (1926).

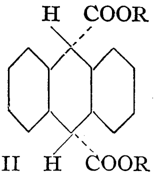
[13] Haller and Guyot, *Compt. rend.*, **140**, 343 (1905).

TABLE I

f	ρ	ϵ	n^2	$P_{1/2}$	$P_{E_{1/2}}$	P	P_E	P_{A+0}
1,5-Dichloroanthracene-9,10-dichloride (I), t 24.8°, α-methylnaphthalene								
0	1.0155	2.6818	2.6044	50.2322	48.7233	....	...	→
0.00883	1.0208	2.8082	2.6053	52.8851	49.0189	350.84	82.21	268.63
0.01166	1.0224	2.8774	2.6063	54.2325	49.1322	393.44	83.80	309.64
P^{∞}_{A+0} = 289.1 (average) $\mu = 3.7D$								
1,8-Dichloroanthracene-9,10-dichloride (V), t 45.0°, dioxane								
0	1.0239	2.2250	1.9901	24.9189	21.3265	....	...	→
0.00731	1.0325	2.2914	1.9997	26.1382	21.7105	191.69	73.86	117.84
0.00841	1.0338	2.2963	2.0009	26.2488	21.7630	183.12	73.22	109.90
P^{∞}_{A+0} = 119.0 $\mu = 2.4D$								
1,8-Dichloroanthracene, t 23.4°, dioxane								
0	1.0316	2.2347	2.0138	24.8724	21.5456	....	...	→
0.00557	1.0362	2.3270	2.0249	26.3069	21.8430	286.05	74.96	211.09
$\mu = 3.2D$								
9,10-Diphenylanthracene-9,10-dichloride (II), t 38.2°, benzene								
0	0.8569	2.2374	2.2337	26.5794	26.5265	....	...	→
0.00228	.8636	2.2685	2.2391	27.0950	26.6506	252.41	80.84	171.53
0.00437	.8698	2.2583	2.2240	27.6081	26.4575	214.455	74.09	140.36
P^{∞}_{A+0} = 175 $\mu = 3.0D$								
1,5-Dichloro-9,10-dihydroxy-9,10-dihydroanthracene, m. p. 210° (VI), t 25.4°, dioxane								
0	1.0296	2.2364	2.0141	24.9441	21.5925	....	...	→
0.00245	1.0322	2.2692	2.0171	25.4824	21.7010	244.24	65.70	178.45
0.00272	1.0335	2.2697	2.0178	25.4718	21.6985	218.67	60.50	158.17
0.00547	1.0354	2.2994	2.0226	25.9944	21.8650	217.09	71.44	145.65
P^{∞}_{A+0} = 180.0 $\mu = 2.95D$								
Dimethyl *cis*-9,10-dihydroanthracene-9,10-dicarboxylate (VIII), t 23.6°, benzene								
0	0.8744	2.2767	2.2396	26.6296	26.0812	....	...	→
0.00811	.8829	2.3597	2.2497	28.1767	26.5681	217.40	86.12	131.28
0.01669	.8919	2.4737	2.2557	30.1513	27.0081	237.62	81.61	156.01
P^{∞}_{A+0} = 143.65 (average) $\mu = 2.6D$								
Dimethyl *trans*-9,10-dihydroanthracene-9,10-dicarboxylate (IX), t 24.2°, benzene								
0	0.8737	2.2755	2.2396	26.6331	26.0965	....	...	→
0.00802	.8818	2.3078	2.2427	27.4575	26.4918	127.03	75.36	51.67
0.01143	.8852	2.3385	2.2485	28.0544	26.7218	150.93	80.79	70.14
P^{∞}_{A+0} = 60.90 (average) $\mu = 1.7D$								
1-Chloroanthraquinone, t 29.60°, dioxane								
0	1.0272	2.2312	2.0042	24.9284	21.4852	....	...	→
0.01397	1.0382	2.3180	....	26.5094	.....	138.03	...	68.75
0.01707	1.0413	2.3567	2.0338	27.1495	21.3440	148.48	69.28	79.20
P^{∞}_{A+0} = 74.0 (average) $\mu = 1.9D$								

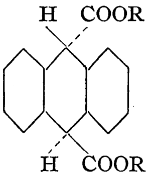
stance of m. p. 210° would be the *cis* diol, the other one the *trans* form, in accordance with Barnett's assumptions. The formation of the *cis* diol from the *trans* dibromide involves a single inversion, the formation of the *trans* form none, or a double one.

In connection with these experiments, the two isomeric dimethyl 9,10-dihydroanthracene-9,10-dicarboxylates described by Schlenk and Bergmann[14] have been investigated. Their dipole moments



VIII

and



IX

have been found to be 2.6D for the β-ester and 1.7D for the α-ester, respectively. As in the case of diethyl maleate and fumarate,[15] the lower moment should correspond to the *trans* isomeride.

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[14] Schlenk and Bergmann, *Ann.*, **463**, 134 ff. (1928).

[15] Smyth and Walls, THIS JOURNAL, **53**, 527 (1931). Compare Briner and co-workers, *Helv. Chim. Acta*, **19**, 1354 (1936).

This is in accordance with the fact that alkali converts the β- into α-acid, probably *via* an enol form.

Finally, the dipole moment of 1-chloroanthraquinone (1.9*D*) may be recorded, the rather high value probably being due to induction or resonance effects.

Experimental

1. Materials

1,5-Dichloroanthracene.[16]—Commercial 1,5-dichloroanthraquinone (50 g.) is heated with 20% ammonia solution (1 liter) on a steam-bath, and zinc dust (250 g.) gradually added. The mass, first blood-red, becomes slightly reddish, it is filtered after standing for ten hours and extracted several times, while still wet, with acetone. The acetone residue on crystallization from butanol gives yellow 1,5-dichloroanthracene, m. p. 187°, while a colorless product remains in the mother liquors; from petroleum ether this gives needles, m. p. 102–103°. It is 1,5-dichloro-9-hydroxy-9,10-dihydroanthracene (Calcd. for $C_{14}H_{10}OCl_2$: C, 63.4; H, 3.8. Found: C, 63.0, 63.3; H, 4.0, 4.0). On dissolving this in hot propyl alcohol and adding a few drops of concd. hydrochloric acid, 1,5-dichloroanthracene precipitates in a pure state. The most convenient method, therefore, is to dissolve the crude acetone residue in the minimum amount of propyl or butyl alcohol and to add a few drops of hydrochloric acid; yield 30 g.

1,5-Dichloroanthracene-9,10-dichloride (I) was prepared according to Liebermann and Beudet[17] at 0° from 1,5-dichloroanthracene and an excess of chlorine solution in carbon tetrachloride. After three hours the product was collected, washed with ligroin and dried; m. p. 214–215° (Calcd. for $C_{14}H_8Cl_4$: C, 52.8; H, 2.5. Found: C, 52.3; H, 2.7). The bromide was prepared in the same way; m. p. 220° (after short sintering).

1,8-Dichloroanthracene from toluene, m. p. 185°, and its **dichloride** (V), m. p. 184° (dec.), were obtained in the same way as the 1,5-compounds, **9,10-diphenylanthracene-9,10-dichloride** (II) from 9,10-diphenylanthracene and chlorine or more conveniently according to Bergmann and Blum-Bergmann.[18] 1-Chloroanthraquinone (commercial sample) was recrystallized.

1,5-Dichloro-9,10-dihydroxy-9,10-dihydroanthracenes.[12] (a) *cis* **Isomeride.**—1,5-Dichloroanthracene-9,10-dibromide (16 g.) was heated with acetone (190 cc.) and water (120 cc.) for four hours. The filtered solution (residue mainly 1,5-dichloroanthracene) deposits a yellowish precipitate which is carefully recrystallized from toluene to a constant m. p. of 210–212°; colorless prisms; yield 1.65 g. (b) *trans* **Isomeride.**—1,5-Dichloroanthracene-9,10-dibromide (31 g.), acetone (300 cc.) and calcium carbonate (8.5 g.) were boiled for eight hours. The insoluble product (the solution contains mainly the *cis* diol) was collected and recrystallized several times from xylene; fractionation removed a small quantity of a yellow substance (apparently 1,5-dichloroanthracene); m. p. 241°; yield 0.5 g.

The *trans* compound was too slightly soluble for a series of measurements. At a molar fraction of 0.0272, the dioxane solutions of the two isomerides had the same refractive index, but with the *trans* compound the dielectric properties of the solution were not markedly different from those of the pure solvent.

2. Measurements

The significance of the figures is as in previous communications. The data for α-methylnaphthalene have been reported by Bergmann and Schuetz.[19]

Summary

Dipole moment measurements reveal that the addition of chlorine to 1,5-dichloroanthracene and 9,10-diphenylanthracene is a *cis* reaction; it is suggested that, in contradistinction to the usual behavior, the chlorine *molecule* is added. 1,8-Dichloroanthracene adds chlorine in *trans* reaction. The splitting reactions of anthracene-9,10-dihalides show no recognizable regularity.

Hydrolysis of 1,5-dichloroanthracene-9,10-dibromide is accompanied, at least partially, by Walden inversion; the dipole moment of the corresponding *cis* diol has been measured. On the basis of the dipole moments, the spatial arrangement of the isomeric dimethyl 9,10-dihydroanthracene-9,10-dicarboxylates has been determined.

REHOVOTH, PALESTINE RECEIVED APRIL 30, 1938

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[16] *Cf.* v. Braun and Bayer, *Ber.*, **59**, 914 (1928).

[17] Liebermann and Beudet, *ibid.*, **47**, 1011 (1914).

[18] Bergmann and Blum-Bergmann, THIS JOURNAL, **59**, 1439 (1937).

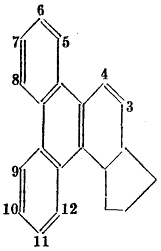
[19] Bergmann and Schuetz, *Z. physik. Chem.*, **B19**, 398 (1932).

[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE]

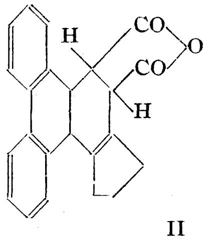
1,2-Cyclopentenotriphenylene. II

BY ERNST BERGMANN AND FELIX BERGMANN

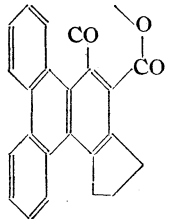
In a previous paper,[1] synthetic experiments had been reported expected to yield 1,2-cyclopentenotriphenylene (I). In the course of this synthesis, three hydrocarbons were isolated, to which, on the basis of mere analogies, the following formulas were assigned: "cyclopentenotriphenylene" m. p. 171–172.5°; picrate, m. p. 172–173°; "9-methyl-3,4-benzpyrene,"[2] m. p. 157.5–159.5°; picrate, m. p. 153–155°; "1,2,3,4-dibenzfluorene," m. p. 115–116°; picrate, m. p. 165–167°. In order to determine definitely the structure of the three products, we have tried both chemical and physical methods. A possible synthesis of 1,2-cyclopentenotriphenylene by an unambiguous method was suggested by our observation[3] that this hydrocarbon system can be obtained easily by the diene reaction of 9-cyclopentenylphenanthrene and maleic anhydride. When the condensation product (II) was treated with lead tetraacetate[4] four hydrogen atoms were removed, leaving 1,2-cyclopentenotriphenylene-3,4-dicarboxylic acid anhydride (III). Direct decarboxylation proved difficult, but eventually two different stepwise methods have been worked out. (a) With quinoline and basic cupric carbonate,[5] a monocarboxylic acid "A" was formed, m. p. 299–300° (methyl ester, m. p. 197–198°), the potassium salt of which was decarboxylated thermally with relative ease, giving the desired cyclopentenotriphenylene (I).[6] (b) The anhydride (III), on heating with soda-lime, gave an isomeric cyclopentenotriphenylene carboxylic acid (3 or 4) "B," m. p. 249° (methyl ester, m. p. 117°). This, when treated with basic cupric carbonate in quinoline, gave again the desired hydrocarbon (I). The substance was identified in each case by the characteristic orange-yellow picrate, m. p. 165–167°. Therefore, the hydrocarbon formerly supposed to be 1,2,3,4-dibenzfluorene, actually is 1,2-cyclopentenotriphenylene.



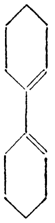
I



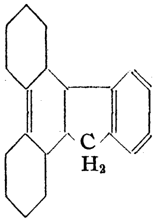
II



III



IV



V

The spectrum of the substance formerly supposed to be cyclopentenophenanthrene ($C_{21}H_{16}$) shows even on qualitative examination[7] so close a resemblance to 3,4-benzpyrene[8] that we definitely may assign to it the structure of 9(?)-methyl-3,4-benzpyrene,[9] ($C_{21}H_{14}$). The intense green-yellow fluorescence of our substance points in the same direction; even the melting point of our hydrocarbon is almost identical with that of 3,4-benzpyrene[10] and is not depressed by its admixture.[11,12]

The third of the above hydrocarbons (m. p. 157.5–159.5°) finally has been identified as 1,2,-3,4-dibenzfluorene. After some unsuccessful attempts, reported in the experimental part, it was synthesized by a method based on a recent observation by Alder and Rickert.[13] Dicyclohexenyl (IV)

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[1] Bergmann and O. Blum-Bergmann, THIS JOURNAL, **58**, 1678 (1936).

[2] This hydrocarbon was previously called 7-methyl-1,2-benzpyrene; this name has been changed according to the suggestions of Cook and co-workers, *Amer. J. Cancer*, **29**, 279 (1937).

[3] E. Bergmann and F. Bergmann, THIS JOURNAL, **59**, 1443 (1937).

[4] (a) Haworth and co-workers, *J. Chem. Soc.*, 635, 643 (1935); (b) 352, 1000 (1936); (c) Weizmann, Bergmann and Berlin, THIS JOURNAL, **60**, 1331 (1938).

[5] Fieser, Fieser and Hershberg, *ibid.*, **58**, 2324 (1936).

[6] The same result was obtained when the monocarboxylic acid A was distilled over zinc dust *in vacuo*.

[7] The detailed report on the spectrographic analysis will be published later.

[8] Mayneord and Roe, *Proc. Roy. Soc.* (London), **152B**, 299 (1935).

[9] The analytical figures for $C_{21}H_{14}$ and $C_{21}H_{16}$ and for the respective picrates are relatively similar, so that a definite decision on the basis of the combustion analyses was not to be expected.

[10] Compare Cook and Hewett, *J. Chem. Soc.*, 403 (1933). The two respective picrates, although almost identical in appearance, have different m. p's. (172–173° as against 197–198°).

[11] The possibility that the methyl group is situated at C_8 of the pyrene skeleton has to be borne in mind, in view of the observation by Vollmann [*Ann.*, **531**, 36 (1937)], that in the synthesis of 1,2-cyclopentenophenanthrene 3-methyl-pyrene is formed along with the 4-isomer.

[12] The same conclusion on the structure of our hydrocarbon has been expressed recently by Hewett, *J. Chem. Soc.*, 193 (1938).

[13] Alder and Rickert, *Ber.*, **71**, 379 (1938).

was condensed with indene by heating at 180°[14] to give the dodecahydro derivative (V) of 1,2,3,4-dibenzfluorene, which could be dehydrogenated easily. The hydrocarbon so obtained melted at 158–159°; picrate, m. p. 153–155°. The melting points were not depressed by admixture of the appropriate preparations described in our previous paper on the subject.

Experimental

1,2 - Cyclopentenotriphenylene - 3,4 - dicarboxylic Acid Anhydride (III).—(a) A solution of the tetrahydro compound (II)[3] (1 g.) in glacial acetic acid (25 cc.) and acetic anhydride (25 cc.) was cooled to 75° and added to a suspension of lead tetraacetate[15] (25 g.) in glacial acetic acid (10 cc.). The reaction mixture, immediately turning yellow, is kept on the water-bath for twenty minutes and then in the refrigerator for two hours. The melting point (296°) of the crystals is not raised by recrystallization from xylene, decalin or ethyl benzoate; yellow needles, yield 100 mg. (*Anal.* Calcd. for $C_{23}H_{14}O_3$: C, 81.7; H, 4.2. Found: C, 81.9, 81.8; H, 4.6, 4.4.) (b) A somewhat less pure product was obtained when the anhydride (15 g.) suspended in glacial acetic acid (100 cc.) was mixed with lead tetraacetate (30 g.) in glacial acetic acid (100 cc.) and the mass heated for two hours on the water-bath. The yield in this case was 8.5 g., but the product had to be recrystallized several times.

1,2 - Cyclopentenotriphenylene - 3(4?) - carboxylic Acid ("A").—The above anhydride (III, 4 g.) was boiled for two hours with quinoline (25 cc.) and basic cupric carbonate (0.8 g.). The reaction product was poured into dilute sulfuric acid, extracted with ether and isolated by vacuum distillation. The brown oil, b. p. 245–255° (0.7 mm.), solidified on trituration with acetone and was recrystallized from butyl acetate or ethyl benzoate: clusters of needles, m. p. 299–300°. (*Anal.* Calcd. for $C_{22}H_{16}O_2$: C, 84.6; H, 5.1. Found: C, 84.4; H, 5.5.) The **methyl ester** prepared by means of diazomethane can be recrystallized most conveniently from acetic anhydride, giving needles, m. p. 197–198°. (*Anal.* Calcd. for $C_{23}H_{18}O_2$: C, 84.7; H, 5.5. Found: C, 84.7; H, 5.6.)

1,2 - Cyclopentenotriphenylene - 4(3?) - carboxylic Acid ("B").—The anhydride (III, 6 g.) was heated with soda-lime (18 g.) to 180° for one hour and to 300° for two hours in a sealed tube. The product was poured into hydrochloric acid and extracted with chloroform. The residue of this solution crystallized spontaneously; it was triturated with methyl alcohol and recrystallized from a mixture of butyl acetate and ligroin: shiny needles, m. p. 249°. (*Anal.* Calcd. for $C_{22}H_{16}O_2$: C, 84.6; H, 5.1. Found: C, 83.7; H, 5.9.) The **methyl ester,** prepared as above, does not crystallize well. It was obtained as a sirupy mass, which was distilled in high vacuum and then treated with a mixture of isopropyl alcohol and acetone; m. p. 117°.

1,2-Cyclopentenotriphenylene (I).—(a) The methyl ester (0.6 g.) of the monocarboxylic acid ("A") was boiled for one hour with alcoholic potassium hydroxide (2 mols). The alcohol was distilled off and the residue heated to 320–250° for four hours in a sealed tube. Water and ether were added and the product isolated by high vacuum distillation; b. p. 250–330° (0.3 mm.). The distillate was dissolved in benzene and directly converted into a picrate by means of alcoholic picric acid solution: orange needles, m. p. and mixed m. p. with the product of E. Bergmann and O. Blum-Bergmann, 165–167°. (b) The monocarboxylic acid ("B") (0.6 g.) was boiled with quinoline (15 cc.) and basic cupric carbonate (1.2 g.) for twenty-four hours and the mass worked up as usual. The product boiled at 260–280° (2.5 mm.) and again was converted into the characteristic picrate; m. p. and mixed m. p. 165–167°, after recrystallization from a mixture of benzene and alcohol. (c) The monocarboxylic acid ("A") (0.2 g.) was mixed with zinc dust (20 g.) and distilled slowly at 30 mm. The distillate was taken up with acetone and the acetone residue distilled at 25 mm. and converted into the picrate; m. p. 165–167°.

Dodecahydro-1,2,3,4-dibenzfluorene (V).—Dicyclohexenyl (IV, 50 g.) and indene (25 g.), both freshly distilled, were mixed and heated at 180° for twenty hours in a sealed tube, and the product fractionated in vacuum (0.3 mm.). The condensation product was secured in two portions, the first one boiling at 180–185° (14 g.) and the second at 185–190° (12 g.). It may be that they represent different steric forms of the condensation product (V), although diene condensations generally take place in a sterically homogeneous manner (Fraction I: Calcd. for $C_{21}H_{26}$: C, 90.7; H, 9.3. Found: C, 90.5; H, 9.2. Fraction II: Found: C, 90.5; H, 9.0). Both gave the same results on dehydrogenation.

1,2,3,4-Dibenzfluorene.—The dodecahydro derivative (V) (6 g.) was heated with selenium (20 g.) at 300° for twenty hours. The reaction product was removed mechanically from the excess selenium and recrystallized several times from isopropyl alcohol and butyl alcohol; needles, m. p. 158–159°; the picrate, prepared according to E. Bergmann and O. Blum-Bergmann,[1] melted at 153–155°; yield 3.8 g.

Unsuccessful Experiments to Synthesize 1,2,3,4-Dibenzfluorene.—We applied to our problem the chrysene synthesis devised by Ruzicka, Ehmann, Goldberg and Hoesli,[16] which has been utilized in the analogous case of 1′,2′-naphtha-2,3-fluorene by Cook, Dansi, *et al.*[17] 9-Chloromethylphenanthrene, which was prepared easily from 9-phenanthrylcarbinol, reacted with the sodium derivative of ethyl cyclohexanone-2-carboxylate to yield ethyl 2-(9′-phenanthryl-methyl)-cyclohexanone-2-carboxylate (VI), but unfortunately cyclization according to the scheme

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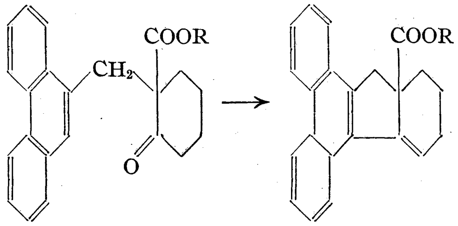
[14] For other diene reactions with dicyclohexenyl, see ref. 4c.

[15] For the preparation of lead tetraacetate, the following method has proved very convenient. To glacial acetic acid (250 cc.), minium (75 g.) is added in small portions at room temperature, while the mass is stirred thoroughly. The operation takes about thirty minutes; the product starts crystallizing during this time. The mass is kept in the icebox for two hours and filtered. The crystals, containing only traces of unchanged minium, are transferred, while still wet, to a desiccator. Working at room temperature permits a much quicker addition of minium, as no decomposition is to be feared.

[16] Ruzicka, Ehmann, Goldberg and Hoesli, *Helv. Chim. Acta*, **16**, 833 (1933).

[17] Cook, Dansi, *et al.*, *J. Chem. Soc.*, 1319 (1935).



(VI) (VII)

occurred to a negligible extent only.

9-Phenanthrylcarbinol[18] (14 g.) (from benzene as needles, m. p. 150°) is mixed with dimethylaniline (12 g.) and benzene (40 cc.) and treated at 0° with thionyl chloride (7 cc.). The crystalline cake formed is kept for ten hours at room temperature and then heated to 100°, until the evolution of sulfur dioxide ceases. On addition of water and ether, part of the 9-chloromethylphenanthrene separates spontaneously; the remainder was obtained by evaporation of the ethereal layer. From light petroleum the m. p. is 98°; it is useful to induce crystallization by scratching; yield 12 g.[19]

Ethyl 2-(9′-Phenanthrylmethyl)-cyclohexanone-2-carboxylate (VI).—9-Chloromethylphenanthrene (3.7 g.) was added to ethyl sodio-cyclohexanone-2-carboxylate (from 0.4 g. of sodium and 3.1 g. of the ester, b. p. 119° (26 mm.)) in toluene (25 cc.) and the whole boiled for six hours. After treatment with dilute sulfuric acid, the toluene was evaporated and the oily residue triturated with methanol and acetone. It gave 2.5 g. of the desired product, which was recrystallized from light petroleum as dimorphous white needles and yellow stout prisms; m. p. 118–119°. (*Anal.* Calcd. for $C_{24}H_{24}O_3$: C, 80.0; H, 6.7. Found: C, 79.3; H, 6.)

Cyclization VI ⟶ VII.—The foregoing ester (10 g.) was heated at 140° for twelve hours with water (100 cc.) and concentrated sulfuric acid (55 cc.). The organic material was extracted with ether and benzene and distilled *in vacuo*. At 230° (0.03 mm.) a viscous, nearly colorless oil distilled and on treatment with glacial acetic acid gave a crystalline mass (2.9 g.). It consisted almost completely of the starting material, which was recovered by recrystallization from propyl alcohol. A small amount of material proved insoluble in this solvent and was subsequently recrystallized from ethyl malonate. The analysis of the prisms, m. p. 250°, so obtained, was consistent with (VII). (*Anal.* Calcd. for $C_{24}H_{22}O_2$: C, 84.2; H, 6.4. Found: C, 83.8; H, 6.2.) From the glacial acetic acid mother liquor no homogeneous material could be isolated, even after dehydrogenation with platinum black at 320–340°.

Summary

The three hydrocarbons, previously obtained from 9-phenanthrylmagnesium bromide and cyclopentanone, are now identified as 1,2-cyclopentenotriphenylene, 9(?)-methyl-3,4-benzpyrene and 1,2,3,4-dibenzfluorene, respectively.

1,2-Cyclopentenotriphenylene was synthesized from the addition product of 9-cyclopentenylphenanthrene and maleic anhydride by dehydrogenation and subsequent stepwise decarboxylation.

For the synthesis of 1,2,3,4-dibenzfluorene, dicyclohexenyl was condensed with indene and the addition product dehydrogenated by means of selenium. The attempt to apply Ruzicka's chrysene synthesis to the case of 1,2,3,4-dibenzfluorene was unsuccessful.

REHOVOTH, PALESTINE RECEIVED MAY 3, 1938

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[18] Bachmann, THIS JOURNAL, **56**, 1363 (1934).

[19] Compare v. Braun, *Ber.*, **70**, 984 (1937).

[CONTRIBUTION FROM THE CELLULOSE DEPARTMENT, CHEMICAL FOUNDATION, BOYCE THOMPSON INSTITUTE FOR PLANT RESEARCH, INC.]

Optical Properties of Cellulose Dispersed in Cuprammonium Hydroxide Solution[1]

BY JACK COMPTON

The current concept regarding the nature of the colloidal solutions resulting from the dispersion of cellulose by cuprammonium hydroxide solution, Schweizer's reagent, depends on the theories of cellulose fiber structure, namely, the continuous, or macromolecular, theory, and the discontinuous, or micellar, theory.

The continuous, or macromolecular, theory, developed by Staudinger on the basis of viscosity measurements, may be summed up in the following statement:[2] "Accordingly cellulose and its derivatives are molecular colloids and on the length and form of their macromolecules depends the colloidal behavior of their solutions." The macromolecules in cellulose fibers are considered regularly lined up under the influence of covalent forces in a direction parallel to the fiber axis.

The discontinuous, or micellar, theory, postulated by von Nägeli[3] and extended to cellulose by Karrer[4] in 1921, assumes that the micelle of cellu-

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[1] Presented before the Division of Cellulose Chemistry at the 94th meeting of the American Chemical Society, Rochester, N. Y., Sept. 9, 1937.

[2] H. Staudinger, *Ber.* **70**, 2514 (1937).

[3] C. von Nägeli, "Die Stärkekörner," Friedrich Schulthess, Zurich, 1858.

[4] P. Karrer and F. Widmer, *Helv. Chim. Acta*, **4**, 174 (1921).

lose is formed by the union, or bundling, of many molecules of the elementary substance. Hess and co-workers,[5] in applying the law of mass action to the optical behavior of cellulose dispersed in cuprammonium solution, obtained results that were best explained when the cellulose molecule was assumed to be $C_6H_{10}O_5$. To explain the high viscosity of cellulose in cuprammonium solution on the basis of so small a unit, he assumed that the $C_6H_{10}O_5$ groups are associated to form a larger molecular aggregate. Later Hess[6] concluded that the cellulose fiber should be regarded as a physical aggregation of small units and Meyer and Mark[7] postulated that the cellulose micellae were formed from primary valence chains held together by "micellar forces." Recently, Lieser,[8] in summing up his results, writes: "It may be stated as most important that cellulose in viscose and ammoniacal copper oxide forms micellar solutions, in organic bases and inorganic acids solutions with a not yet clearly definable character. It was further shown that all celluloses regenerated from solution are of micellar structure." The dimensions of the micelle in cellulose fibers have been estimated[9] to be approximately 50 Å. diameter and over 500 Å. long.

The observations of Farr and Eckerson[10] that cotton fibers are composed of microscopic, ellipsoidal, cellulose particles of uniform size (1.1 × 1.5 μ), arranged with their long axis parallel to the fiber axis and held together by an intercrystalline "cementing" material, are of fundamental importance. Cellulose particles obtained from cotton fibers possess all the properties recognized as characteristic of native cellulose other than high viscosity in cuprammonium solution. The low viscosity of the separated particles is attributed by Farr[11] to the removal, or destruction, of the viscosity producing "cementing" material. Qualitative examination of cuprammonium dispersions of cotton fibers with the slit ultramicroscope, or working carefully with the stage microscope, revealed the presence of the apparently unchanged cellulose particles. Upon regeneration, these dispersions yielded a product containing randomly distributed particles similar to the original aggregates. From a study of the X-ray diffraction patterns of cellulose particles, Sisson[12] has concluded that a microscopic unit of cellulose particle dimensions (1.1 × 1.5 μ) adequately satisfies the fundamental requirements of the micelle, with the exception of size.

Since it is commonly accepted that the micelles are composed of macromolecules of cellulose, the theories of cellulose fiber structure do not necessarily conflict. There are, however, many divergent views as regards the nature of the cellulose dispersions in reagents such as cuprammonium solution. The purpose of the present investigation is: first, to investigate the entire cuprammonium viscosity range of cotton fiber to determine if, at any time, a relation exists between the viscosity and optical rotation of the cuprammonium dispersions; second, to determine in general the contribution of each component of native cotton fiber, *i. e.*, crystalline cellulose particles and the intercrystalline phase, to the phenomena of viscosity and optical activity of cuprammonium dispersions; third, to study quantitatively the effect of varying the concentration of differently treated celluloses dispersed in cuprammonium solution on the microscopic particle count, using the slit ultramicroscope; fourth, to study the mechanism of the dispersion phenomenon of crystalline cellulose particles by cuprammonium solution.

Experimental

Apparatus.—The equipment of the Leitz slit ultramicroscope included a micro cell and an eyepiece micrometer ruled in 1.0-mm. squares. In all counts reported in Table II, a 6L objective and a 10X eyepiece were used.

The optical rotations were determined in a Schmidt and Haensch Polariscope with an 85-watt capillary mercury arc lamp as the light source. A combination of monochromatic glass filters (No. 7) recommended by the Corning Glass Works was used to transmit only the 0.4358 μ blue mercury line.

Viscometers of the type recommended by Clibbens and Geake,[13] slightly modified by the addition of ground glass stoppers in place of the rubber stoppers previously specified were used in determining the viscosities of the celluloses dispersed in cuprammonium solution.

Preparation of the Cuprammonium Solution.—The cuprammonium solution prepared by the method of Clibbens and Geake,[13] containing 15 g. of copper, 240 g. of ammonia and 1 g. of sucrose per liter was satisfactory for determining the viscosity, optical activity, and particle

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[5] (a) K. Hess and E. Messmer, *Ann.*, **435**, 7 (1923); *Kolloid Z.*, **36**, 260 (1925); (b) K. Hess, E. Messmer and N. Ljubitsch, *Ann.* **444**, 315 (1925).

[6] K. Hess, "Die Chemie der Cellulose," Leipzig, 1928, p. 301.

[7] K. H. Meyer and H. Mark, *Ber.*, **61**, 607 (1928).

[8] T. Lieser, *Ann.*, **528**, 291 (1937).

[9] J. Hengstenberg and H. Mark, *Z. Krist.*, **69**, 271 (1928).

[10] W. K. Farr and S. H. Eckerson, *Contrib. Boyce Thompson Inst.*, **6**, 309 (1934).

[11] W. K. Farr, "Disintegration of Cellulose Membranes." Paper presented before the Division of Cellulose Chemistry of the American Chemical Society, Pittsburgh, Penna., Sept. 7, 1936.

[12] W. A. Sisson, *Textile Research*, **5**, (3), 119 (1935).

[13] D. A. Clibbens and A. Geake, *J. Textile Inst.*, **19**, 79T (1928).

counts of the various cellulose dispersions. It was possible to carry out all three determinations on one dispersion when necessary.

Preparation of Cellulose Samples Used in Studying the Effect of Various Treatments on the Viscosity, Optical Rotation, and Particle Count after Dispersion in Cuprammonium Solution.—Raw cotton (*Gossypium hirsutum* L.) was extracted with alcohol–benzene (1:1) in a Soxhlet extractor for twenty-four hours, thoroughly washed with water, and air-dried at room temperature. This material was used in the experiments listed below.

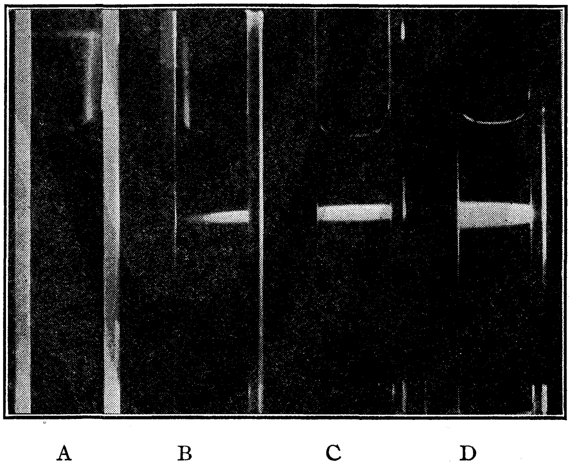

Fig. 1.—Effect of increase in concentration of cellulose dispersed in cuprammonium solution on the Tyndall phenomenon: (A) cuprammonium solution, control; (B) 0.5%, (C) 1.0%, and (D) 2.00% dispersions of cellulose particles in cuprammonium solution.

(1) **Treatment of Cotton Cellulose with 0.01 *N* Hydrochloric Acid Solution at 75°.**[14]—Ten grams of cotton cellulose was placed in 1 liter of 0.01 *N* hydrochloric acid solution previously heated to 75° and after vigorous stirring and shaking samples were removed at stated intervals of time, Table I. The sample was rendered neutral immediately after removal by plunging it into a large volume of ice-cold sodium bicarbonate solution. After agitating for ten minutes the sample was washed thoroughly with distilled water and air-dried at room temperature.

(2) **Treatment of Cotton Cellulose with Concentrated Hydrochloric[10] Acid (d. 1.18) at 25°.**—Cotton cellulose (10 g.) was placed in concentrated hydrochloric acid (250 cc.) at 25°. The removal and treatment of samples was effected in the manner described above (1). After twenty-two hours, slight pressure on the cover glass of a microscopic slide of this material destroyed the fiber structure completely. Many free cellulose particles could thus be disengaged from the fragments of fibers.

(3) **Treatment of Cotton Cellulose with 0.04 *N* Sodium Hypochlorite[15] Solution of *p*H 9 at 25°.**—Ten grams of cotton cellulose was treated with two liters of 0.04 *N* sodium hypochlorite solution containing 1.42 g. of available chlorine per liter, the solution being buffered at *p*H 9. Samples were removed at definite intervals of time, Table I, immediately washed with water, and given the standard acid wash. After again thoroughly washing in water the samples were air-dried at room temperature.

(4) **Treatment of Cotton Cellulose with Excess Hydrogen Peroxide in the Presence of 4% Sodium Hydroxide Solution.**[14]—Five grams of cotton cellulose was placed in 200 cc. of 4% sodium hydroxide solution and heated to boiling during the portion-wise addition of 3% hydrogen peroxide solution over a period of ten hours. The fiber structure could be disrupted completely by pressure at the end of this time, yielding microscopic cellulose particles. The fine white powder was washed with water, dilute acetic acid, and with water until neutral. After final washings with alcohol and ether, the material was allowed to air-dry at room temperature. The fluffy white material was then pulverized by light grinding in a mortar.

(5) **Preparation of Cellodextrin (Biosan).**—Cellodextrin was prepared according to the procedure of Hess and Friese.[16] Analysis of this material confirmed the observation[17] that it has a chain length of from eight to twelve glucose anhydride units.

Method Employed in the Dispersion of Cellulose in Cuprammonium Solution.—The method employed in the dispersion of the various cellulose samples listed in Tables I and II, and Fig. 2, was essentially the same as that described by Clibbens and Geake.[13]

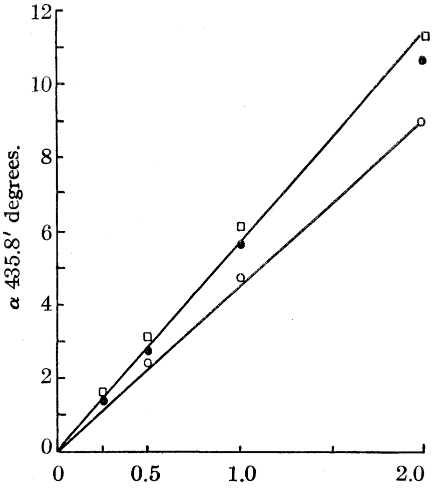

Fig. 2.—Effect of increase in concentration on the optical rotation of: ○, cellodextrin (biosan); ●, cellulose particles, expts. (2) and (4); □, kiered and bleached cotton, dispersed in cuprammonium solution.

Samples of celluloses were taken to yield dispersions of the per cent. actual cellulose concentration specified when dissolved in a volume equal to that of the calibrated viscometers. The material was finely divided, and, in the case of cotton fibers, the material was cut across with scissors into lengths not greatly exceeding a sixteenth of an inch (1.6 mm.). The samples were conveniently weighed

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(14) R. A. Joyner, *J. Chem. Soc.*, **121**, 2395 (1922).

(15) D. A. Clibbens and B. P. Ridge, *J. Text. Inst.*, **18**, 135T (1927).

(16) K. Hess and H. Friese, *Ann.*, **450**, 40 (1926).

(17) K. Freudenberg, *Ber.*, **62**, 383 (1929).

TABLE I

THE VISCOSITIES AND OPTICAL ROTATIONS[a] OF THE CUPRAMMONIUM DISPERSIONS OF COTTON CELLULOSE AFTER TREATMENT WITH VARIOUS REAGENTS

Length of treatment, min.	(1) Action of 0.01 *N* HCl at 75°		(2) Action of concd. HCl (d. 1.18) at 25°		(3) Action of 0.04 *N* sodium hypochlorite at *p*H 9, 25°	
	η, cp.	α	η, cp.	α	η, cp.	α
0	46.0	−3.00°	46.0	−3.00°	46.0	−3.00°
5	–	–	3.4	3.12	–	–
10	35.3	3.01	2.7	3.09	–	–
15	–	–	–	–	22.5	3.06
30	28.6	3.06	2.2	3.06	18.4	–
60	25.3	3.01	2.0	3.02	16.3	3.02
180	17.1	3.02	1.9	3.04	12.1	3.03
240	14.4	3.01	–	–	–	–
270	–	–	–	–	10.4	3.03
480	10.3	3.01	–	–	–	–
510	–	–	–	–	7.9	3.06
22 hrs.	–	–	1.9	3.02	5.0	3.01
32 hrs.	4.5	3.04	–	–	–	–
Action of excess H_2O_2 in presence of 4% NaOH at 100°; 10 hrs.					1.9	3.06

[a] All viscosities and optical rotations were determined with cellulose concentration of 0.5% (0.5 g. subs. in 100 cc. soln., moisture-free basis); the former at 25°, the latter in mercury light (435.8) at 32° in a 0.5-dm. tube, η, cp., cuprammonium solution 1.2.

TABLE II

VARIATION OF PARTICLE COUNT WITH CONCENTRATION OF DIFFERENT CELLULOSES DISPERSED IN CUPRAMMONIUM SOLUTION

		Number of particles observed in volume of soln. 2.02×10^{-9} cc.				
		Cotton cellulose particles				
Concn., %	Theoretical no.[a] of particles in volume 2.02×10^{-9} cc.	Cellodextrin (biosan) (5)	Prepd. by action of HCl (2)	H_2O_2 in presence of 4% NaOH 100° (4)	Wood pulp (Kipawa)	Kiered and bleached cotton
0.00	0.0	0.0	0.0	0.0	0.0	0.0
.25	3.5	.0	2.8	2.8	3.6	3.4
.50	7.0	1.8	6.3	5.5	5.7	7.5
1.00	14.0	3.2	13.8	9.4	8.8	13.2
2.00	28.0	3.7	–	–	–	22.2

[a] Calculation made on basis of uniform cellulose particle, 1.1 × 1.5 μ, with density 1.5.

on a small watch-glass and quantitatively transferred to the viscometers. A moisture content of 4% was assumed, previous experiments having shown that this figure was a representative average value.

A small amount of the cuprammonium solution was drawn up into the capillary end of the viscometer and closed off by folding over the attached rubber tube. The tube was fixed in an upright position, 0.7 cc. of clean mercury run in from a 1-cc. pipet, and the cellulose transferred to the viscometer by means of small tweezers and tapping the conical-shaped paper which holds it. The tube was then half filled with cuprammonium solution and the cellulose stirred in the solvent for a few seconds to remove entangled air. The viscometer was filled with the solvent to within an inch (2.5 cm.) of the top, the rod being washed at the same time. Finally, the viscometer was filled completely with cuprammonium solution and the stopper inserted, so that the excess liquid, displacing all air, overflowed through the top capillary and rubber tube, which was then folded over and made tight with a rubber band; the ground-glass stopper was fastened in place by use of steel springs. The viscometer was fastened securely in a box and placed in an apparatus constructed so as to make four revolutions per minute. The end over end motion of the instrument and the resulting motion of the mercury produced an agitation in the liquid which was continued until a homogeneous dispersion was obtained. A uniform period of eighteen hours was sufficient for complete dispersion of the high viscosity celluloses prepared above. The mixture was maintained at a temperature of 4° during dispersion by placing the whole apparatus in a cold room thermostatically controlled.

To measure the viscosities of the resulting dispersions, the viscometers were removed from the box and immersed[13] in a thermostat at 25°. After standing for thirty minutes, the stopper was removed from the viscometer and the solution allowed to flow freely through the capillary. The time in seconds necessary for the liquid meniscus to fall from the top to the bottom ring was noted with a stop watch.

In determining the optical rotations and particle counts, Tables I and II and Fig. 2, after viscosity measurements, the dispersions were stoppered and centrifuged (1800 r. p. m.) to remove any entangled mercury droplets. The apparently clear homogeneous dispersions thus obtained were transferred to the polarimeter tube and the micro cell of the ultramicroscope and the optical rotations and particle counts determined.

Effect of Increasing the Concentration of Cellulose in Cuprammonium Solution on the Tyndall Phenomenon.—A typical example of this effect is shown in Fig. 1. Cellulose particles (Expt. 2 above) were dispersed in cuprammonium solution in the manner previously described, and a strong beam of light focused into the solutions.

Method Used in Making Particle Counts on Cuprammonium Dispersions of Cellulose Using the Slit Ultramicroscope.—Refinement of the Tyndall phenomenon by use of the slit ultramicroscope enables one to arrive at a quantitative estimate of the number of cellulose particles present in a definite volume of the dispersions. The cuprammonium dispersions of the various cellulose samples were introduced into the micro cell and sealed immediately with a cover glass to prevent evaporation and formation of hydrated copper oxide. The light was then properly focused into the cell and the number of particles in a unit area counted. The average of ten counts at various positions of the field were taken, and this value checked similarly by an independent observer. Controls were run on the cuprammonium solution alone and corrections applied to the particle counts. Cuprammonium solutions containing more than one-tenth of a particle in the unit volume were rejected. Knowing the focal depth, and the calibration of the eyepiece micrometer for the microscopic lens system used, the unit volume in which the particle counts are made can be calculated. The dimensions of the unit volume were: focal depth (2.4 μ) × unit area on eyepiece micrometer (29 × 29 μ) = 2018.4 $\bar{\mu}^3$, or 2.018×10^{-9} cc. The results obtained are recorded in Table II.

To calculate the theoretical number of particles that should be present in the unit volume at a definite concentration, it is necessary to know, first, the average volume of the cellulose particle and, second, the total volume of cellulose dispersed in the solution. The volume of the cellulose particle, V_1, may be calculated from the dimension $1.1 \times 1.5\ \mu$ by substituting in the equation for the volume of a prolate spheroid, $V_1 = 4/3\pi ab^2$, where a and b are the major and minor semi-axes, respectively. Thus, $V_1 = 4.189 \times 0.75\ \mu \times (0.55\ \mu)^2 = 0.95\ \bar{\mu}^3$, or 9.5×10^{-13} cc. For a 0.5% (0.5 g. cellulose in 100 cc.) dispersion of cellulose the actual cellulose volume, $V = 0.5$ g./1.5, density of cellulose = 0.33 cc. In the unit volume, 2.018×10^{-9} cc. there would be, accordingly, a cellulose volume, V_2, of 6.66×10^{-12} cc. The theoretical number of cellulose particles, N, in the unit volume is obtained from the formula $N = V_2/V_1$. Thus, $N^{18} = 6.66 \times 10^{-12}$ cc./9.5×10^{-13} cc. = 7.0, for a 0.5% soln. The corresponding values for other concentrations may be calculated in a similar manner.

Effect of Increasing the Concentration of Various Celluloses in Cuprammonium Solution on the Optical Rotation.—The experiments were carried out essentially in the manner described by Hess,[7] with the exception that a cuprammonium solution containing 15 g. of copper, 240 g. of ammonia and 1 g. of sucrose per liter was employed. Dispersion of the various celluloses was carried out as described above. The results obtained are plotted in Fig. 2.

Determination of the "Saturation Point" of Cellulose Particles in Cuprammonium Solution.—The possibility of the existence of a mass action equilibrium between the cellulose–copper complex and cellulose in cuprammonium dispersions has been considered previously.[5,19] In the present experiment cellulose particles (Expts. 2 and 4 above) have been used to determine the point at which the cuprammonium solution could no longer cause permanent dispersion. When the concentration was increased beyond 4.5%, the excess undispersed cellulose could be centrifuged unchanged (1800 r. p. m.) from the permanently dispersed phase. That this saturation point is not connected with the copper content of the cuprammonium solution was shown by the fact that the same "saturation point" occurred when A. C. S. cuprammonium solution (containing 30 g. copper, 165 g. ammonia, and 10 g. sucrose per liter) was used.

Discussion

The two general methods employed for the gradual disintegration of cellulose fibers are: first, the action of dilute acids, and, second, the action of mild oxidizing agents. The disintegrating action of these reagents, which is accompanied by a lowering of the cuprammonium viscosity, Table I, has been interpreted previously as indicating a decrease in the chain length of the cellulose molecules. Based on the dual structure of the cellulose fiber, however, a new interpretation is now placed on this behavior. Since the crystalline phase, or cellulose particles, remains largely intact by these treatments, it follows that the intercrystalline "cementing" material is the phase easily modified or destroyed. The conclusion may also be drawn that this unstable, reactive phase of native cellulose fibers is largely responsible for their high viscosity when dispersed in cuprammonium solution. This interpretation is somewhat similar to that of Joyner,[14] who postulated the existence of a cellulose A with high and a cellulose B with low viscosity in native cellulose fibers.

The high optical activity of cellulose colloidally dispersed in cuprammonium solution was considered by Hess[5] to be due to the uniform formation of an asymmetric complex cellulose–copper compound $[(C_6H_{10}O_5)_2Cu][Cu(NH_3)_4]$. It was further shown that with low viscosity celluloses there was no relation between optical activity and change in cuprammonium viscosity. The present work extends this conclusion to the entire viscosity range possible with cotton cellulose, Table I. Thus, the cellulose particle, or crystallite, seems to be responsible for the high optical activity, for as the viscosities of the cuprammonium dispersions are lowered, indicating removal of the intercrystalline "cementing" material, the rotations remain constant. The high optical activity of celluloses of high viscosity shows that either the rotation of the intercrystalline–copper complex is very similar to that of the cellulose particle–copper complex, or that the intercrystalline phase is present in quantities so minute as to escape detection.

It has long been recognized that cuprammonium is not a true solvent for cellulose[20] but in many researches this fact has been neglected. The Tyndall phenomenon characteristic of colloidal dispersions is exhibited clearly by cellulose dispersed in cuprammonium solution, Fig. 1. The slit ultramicroscope enables one to examine such dispersions in strong light under high magnification. Thus examination of cuprammonium dispersions of disintegrated cotton fibers whose viscosity had reached a constant low value, Table I, showed practically the theoretical possible number of cellulose particles to be present, Table II. The

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(18) Due to the variable values reported for the true density of cellulose [*cf.* A. J. Stamm and L. A. Hansen, *J. Phys. Chem.*, **41**, 1007 (1937)] and allowing for possible slight error in the dimensions of the cellulose particle, the values of N cannot be considered absolute, but do not exceed a possible correction of more than ± 20%.

(19) D. MacGillavry, *Rec. trav. chim.*, **48**, 18 (1929); E. Valkó, *Kolloid. Z.*, **51**, 130 (1930).

(20) E. Heuser, "Textbook of Cellulose Chemistry," 2d ed. German translation by C. J. West and G. J. Esselen, Jr., McGraw-Hill Book Co., Inc., New York, N. Y., 1924, p. 138.

variable deviations of the observed number of particles from the theoretical with increasing concentration is due to the difficulty of obtaining an absolute estimate from relatively few counts. When the number of counts on the samples was increased, the average value more closely approached the theoretical. The significant fact, however, is the trend toward an increase in particle count with increase in cellulose concentration. Due to the Brownian movement of the dispersed particles and the convection currents set up in the micro cell by heat from the light beam, an accurate count is difficult to obtain on more than one per cent. concentrations of low viscosity cellulose. With high viscosity cellulose, however, such as kiered and bleached cotton, motion in the dispersion is greatly reduced. Wood pulp dispersed in cuprammonium solution showed the same particle count tendency as cotton celluloses, thus indicating that both are composed of the same elementary units.

Inasmuch as cuprammonium dispersions of cellulose contain microscopically visible particles and possess high optical activity, it would appear that the organized units must be able both to transmit and reflect light. In ordinary light without high magnification, these dispersions seem to be true solutions due to even lighting from all directions of the transparent cellulose particle–copper complex.

Cuprammonium dispersions of a cellodextrin such as "biosan" are slightly less optically active than cellulose (Fig. 2). Dilute dispersions are optically void when examined in the slit ultramicroscope, but upon increasing the concentration a few particles are observed, Table II. It thus appears that this cellulose-like substance is dispersed beyond the limits of microscopic visibility. The conclusion thus may be drawn that regardless of the state of aggregation of the cellulose–copper complex, the optical rotation is of the same order of magnitude.

The existence of a definite equilibrium between the permanently dispersed cellulose particle–copper complex phase and the excess undispersed solid cellulose at concentrations exceeding 4.5% is shown by the fact that saturation is reached at this point. The saturation point is independent of the copper concentration and has only been observed with cellulose particles (Expt. 2) as the viscosity of native cellulose is much too high to make the point distinguishable. The excess undispersed cellulose phase may be almost entirely recovered unchanged upon centrifuging cuprammonium dispersions containing more than 4.5% cellulose particles. X-Ray diffraction analysis[21] shows the excess undispersed phase, thus recovered from a more than saturated cuprammonium dispersion, to be native cellulose, whereas the permanently dispersed phase upon regeneration gives a mercerized or hydrated cellulose pattern. Since the undispersed cellulose phase is not combined with the copper or ammonia in any way, it appears that the intermediary formation of the cellulose–copper complex is necessary for the transformation of native cellulose into the mercerized form, or that copper complex compound formation and dispersion of cellulose occur simultaneously.

Summary

1. The successive lowering of the cuprammonium viscosity of native cotton fibers by the action of dilute acids or mild oxidizing agents is not accompanied by a change in the optical activity of the resulting dispersions, a conclusion in agreement with the work of Hess on celluloses of low viscosity.

2. From (1) it follows that the optical activity of cellulose dispersions in cuprammonium solutions is dependent upon the formation of a cellulose particle–copper complex.

3. Quantitative examination of various celluloses dispersed in cuprammonium solutions, using the slit ultramicroscope, reveals the presence of approximately the theoretical number of cellulose particles (1.1 × 1.5 μ).

4. Further evidence that cellulose–copper compound formation precedes dispersion of cellulose in cuprammonium solution is presented.

5. Visible cellulose particles (1.1 × 1.5 μ) observed in the living cytoplasm, cellulose fibers and dispersions of cellulose in cuprammonium solution possess the essential features, with the exception of size and shape, of the hypothetical micelles.

YONKERS, N. Y. RECEIVED FEBRUARY 3, 1938

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[21] Prior to the author's independent observation, W. A. Sisson of this Laboratory noted this apparent equilibrium from a qualitative examination of cuprammonium dispersions of cellulose particles.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF AGRICULTURE, UNIVERSITY OF WISCONSIN]

The Preparation of *d*-Galacturonic Acid from *d*-Galactose[1]

BY HAROLD M. SELL AND KARL PAUL LINK

The synthesis of *d*-galacturonic acid from the parent sugar *α-d*-galactose involves the following transformations: I, the acetonation of *d*-galactose to 1,2,3,4-diacetone-*d*-galactose; II, the oxidation of diacetone-*d*-galactose to diacetone-*d*-galacturonic acid with alkaline potassium permanganate; III, the conversion of the potassium salt of diacetone-*d*-galacturonic acid to diacetone-*d*-galacturonic acid; IV, the hydrolysis of diacetone-*d*-galacturonic acid to *d*-galacturonic acid and subsequent crystallization of the free acid.

Ohle and Berend,[2] the originators of this method of synthesizing *d*-galacturonic acid, did not obtain the acid in a crystalline condition and resorted to the use of derivatives (brucine and osazone phenylhydrazine salts). In 1934 Niemann and Link[3] were able to put the method on a more practical basis in that they were able to realize the acid in a crystalline condition, with a yield of 30% of the theoretical. Reichstein and coworkers[4] introduced an improvement in step IV by eliminating the use of a mineral acid in the hydrolysis of the acetone residues.

For most laboratories the logical starting product for the synthesis of *d*-galacturonic acid is the parent sugar *α-d*-galactose. Consequently, we have made a careful study of each stage of the synthesis and have worked out the conditions necessary for success under average conditions.

The major change made in step I is the elimination of the necessity for the purification of the diacetone-*d*-galactose by a high vacuum distillation. The yield of diacetone-*d*-galactose has been increased from 60 to 92%.[2,5] In step II the oxidation has been placed on a firmer basis by increasing the ratio of potassium permanganate from 3 to 5 moles per mole of diacetone-*d*-galactose to be oxidized. By employing anhydrous acetone as the means of inducing the crystallization of the potassium diacetone-*d*-galacturonate this intermediate can be obtained in an analytically pure condition free from the troublesome hygroscopic properties that are usually encountered when the procedure of Ohle and Berend is used.[2] Reichstein and co-workers[4] had placed step IV on such a basis that further improvement was not necessary.

If the procedure outlined below is followed carefully the preparation of pure *d*-galacturonic acid can be realized with ease.

Experimental

Acetonation of *α-d*-Galactose.[2,3]—In a 6-liter wide-necked bottle with ground-glass stopper are placed 90 g. (0.5 mole) of finely pulverized *α-d*-galactose (m. p. 170°; $[\alpha]^{20}{}_{\rm D}$ +80.3°; dried for ten hours at 90° over phosphorus pentoxide in a vacuum oven), 200 g. (1.25 moles) of powdered anhydrous copper sulfate,[6] 10 cc. of sulfuric acid (sp. gr. 1.84), and 2 liters (27.4 moles) of dry alcohol-free acetone (dried over anhydrous calcium chloride). After the mixture has been shaken on a mechanical shaker for twenty-four hours it is filtered and the filter cake washed with dry acetone. To the filtrate is added 25 g. of powdered calcium hydroxide and the mixture is shaken for about two hours. The addition of 25-g. portions and the shaking are continued until the solution gives a neutral reaction to Congo red paper. A total of approximately 100 g. (1.35 moles) of calcium hydroxide is required to neutralize the sulfuric acid. The acid must be removed completely to avoid the hydrolysis of the acetone residues during the concentration of the solution.

After the unreacted calcium hydroxide and the calcium sulfate have been removed by filtration, the filter cake is washed with dry acetone. The filtrate is concentrated, first to a thin sirup at atmospheric pressure, then at 50° and 15 mm. (water pump), and, finally, to remove the last traces of acetone, at 100° and 6 mm. (oil pump). The yield of crude diacetone-*d*-galactose, as a thick sirup, is 100–120 g. (76–92%). Pure diacetone-*d*-galactose distils at 130–140° under 0.01–0.001 mm. pressure; $[\alpha]^{20}{}_{\rm D}$ −54.7 (*c*, 3.565; $CHCl_3$); negative Fehling's test.

Oxidation of Diacetone-*d*-galactose.[2]—To a solution of 100 g. (0.38 mole) of crude diacetone-*d*-galactose in water (4.5 liters) and potassium hydroxide (104 cc., 7.5 *N*) contained in a six-liter jar is added 300 g. (1.9 moles) of powdered potassium permanganate in 60-g. portions over a period of five hours. The solution is stirred mechanically throughout the oxidation, which is usually complete in twenty-four hours. If an excess of potassium permanganate is present, it is destroyed by the addition of hydrogen peroxide. The manganese dioxide is removed by filtration on an asbestos mat on a Büchner funnel and washed thoroughly with water. The filtrate is treated with car-

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[1] Published with the permission of the Director of the Wisconsin Agricultural Experiment Station.

[2] H. Ohle and G. Berend, *Ber.*, **58**, 2585 (1925).

[3] C. Niemann and K. P. Link, *J. Biol. Chem.*, **104**, 195 (1934).

[4] T. Reichstein, and co-workers, *Helv. Chim. Acta*, **16**, 1033 (1933).

[5] P. Levene and G. M. Meyer, *J. Biol. Chem.*, **92**, 257 (1931).

[6] The anhydrous copper sulfate is best prepared by drying the pentahydrate in an oven at 110° for several days and then heating in a casserole over a free flame until the powder is white. It should be used immediately after dehydration.

bon dioxide gas until the solution gives no color with phenolphthalein.[7] Concentration of the aqueous solution at 6 mm. and not over 65° leaves a dry residue which is extracted twice with 300-cc. portions of boiling ethanol, the insoluble portions remaining on the filter. Removal of the alcohol (15 mm. and 50°) and addition of 300 cc. of dry acetone (in which monoacetone-*d*-galactose and the unreacted diacetone-*d*-galactose are soluble) yields the crystalline potassium salt of diacetone-*d*-galacturonic acid. Addition of dry acetone to the concentrated mother liquors gives a second crop of the potassium salt, which is recrystallized by dissolving in a small volume of ethanol and then adding acetone. The yield of the potassium diacetone-*d*-galacturonate is 60–80 g. (49–65%); m. p. 200–205° (dec.); $[\alpha]^{20}D$ −61.1 (*c*, 2.046; H_2O).

Conversion of Diacetone-*d*-galacturonic Acid Potassium Salt to Diacetone-*d*-galacturonic Acid.[2]—A solution of 60 g. (0.19 mole) of the *carbonate-free* potassium salt ($C_{12}H_{17}O_7K \cdot 0.5H_2O$) in sulfuric acid (376 cc. of 0.5 *N*) is extracted four times with 250-cc. portions of ether. The combined ethereal extractions, dried over anhydrous sodium sulfate, are concentrated to dryness at 15 mm. and 50°. The residue is dissolved in 50 cc. of warm benzene. Crystallization is induced by adding 200 cc. of petroleum ether. The yield of diacetone-*d*-galacturonic acid is 40–45 g. (78–88%); m. p. 157°; $[\alpha]^{20}D$ −84.0°.

Hydrolysis of Diacetone-*d*-galacturonic Acid to *d*-Galacturonic Acid.[4]—A solution of 40 g. (0.15 mole) of diacetone-*d*-galacturonic acid (m. p. 157°) in water (120 cc.) is heated on a water-bath at 95 to 100° for two hours. After decolorizing with 5 g. of activated carbon the clarified solution should be concentrated *immediately* as *rapidly* as possible to a mobile sirup (50°, 6 mm.). The sirup is transferred to an evaporating dish and upon vigorous scratching it will set to a solid crystalline cake.[8] The product is collected on a Büchner funnel, washed with ethanol, dry ether, and dried over phosphorus pentoxide at 25° and 12 mm. pressure. The yield of *d*-galacturonic acid is 20–25 g. (65–81%). The product, being a mixture of the α- and β-forms, will show an initial rotation of $+60° \longrightarrow +80°$ depending on the time involved in concentrating the final solution. Pure α-*d*-galacturonic acid sinters at 110–111° and decomposes at 159–160°. The $[\alpha]^{20}D$ is +98° initial, final value +50.9° (*c*, 2.1; H_2O).

Summary

An improved method for the synthesis of *d*(+)-galacturonic acid has been described. The yield is 50 g. of *d*(+)-galacturonic acid from 100 g. α-*d*-galactose.

MADISON, WISCONSIN

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[7] It is convenient to invert a glass funnel in a jar whose diameter is slightly greater than that of the funnel. The carbon dioxide gas is then introduced into the solution through the stem of the funnel.

[8] If the crystallization is not spontaneous it can be induced by the addition of absolute alcohol.

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 644]

The Molecular Structure of Arsenious Oxide, As_4O_6, Phosphorus Trioxide, P_4O_6, Phosphorus Pentoxide, P_4O_{10}, and Hexamethylenetetramine, $(CH_2)_6N_4$, by Electron Diffraction

BY G. C. HAMPSON AND A. J. STOSICK

In a recent paper,[1] which was published while this work was in progress, there were reported the results of an electron diffraction investigation of the structures of phosphorus trioxide, phosphorus pentoxide and arsenious oxide. The values which we have obtained for P_4O_6 and As_4O_6 are in good agreement with those of Maxwell, Hendricks and Deming. On the other hand, the latter authors were unable to deduce a structure for P_4O_{10} and came to the conclusion that the molecule probably has lower symmetry than that of the point group T_d. The reason for their failure probably lies in the fact that the molecule has an abnormally short P–O distance and we were led to our final structure, which gives an excellent fit with the photographs, only after very many models had been shown to be wrong.

The visual method of measurement was used, the results being compared in the usual way with the approximate scattering formula

$$I = \Sigma_{ij} Z_i Z_j \frac{\sin sr_{ij}}{sr_{ij}}$$

in which r_{ij} is the distance between the *i*th and *j*th atoms, Z_iZ_j their atomic numbers and $s = (4\pi \sin \theta/2)/\lambda$, where θ is the scattering angle and λ the wave length of the electrons. Radial distribution curves[2] were also calculated and interatomic distances deduced from them. When a molecule contains several approximately equal distances, the radial distribution method fails to resolve the closely spaced maxima and very little information can be obtained from the curve. A modification of the method, suggested by Dr. V. Schomaker of these Laboratories, in which the estimated intensities are multiplied by a factor

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[1] Maxwell, Hendricks and Deming, *J. Chem. Phys.*, **5**, 626 (1937).

[2] Pauling and Brockway, THIS JOURNAL, **57**, 2684 (1935).

TABLE I

Max.	Min.	I	c	s_0	s(VII)	s(VIII)	s_{VII}/s_0	s_{VIII}/s_0
	1			1.602	1.41	1.45	(0.881))	(0.905)
1		20	3	2.365	2.33	2.34	.986	.989
	2			3.273	3.19	3.20	.975	.978
2		30	20	4.239	4.25	4.26	1.002	1.005
	3			5.434	5.39	5.37	0.992	0.988
3		6	12	6.240	6.24	6.23	1.000	.998
	4			7.055	6.95	6.94	0.986	.984
4		10	50	8.121	7.95	7.99	.979	.984
	5			9.213	9.20	9.18	.999	.996
5		4	25	10.278	10.42	10.35	1.014	1.007
	6			11.261	11.00	10.90	0.977	0.968
6		4	35	12.353	11.84	11.89	.959	.963
	7			13.292	13.12	13.11	.987	.986
7		4	45	14.218	14.33	14.36	1.007	1.010
	8			15.347	15.37	15.41	1.002	1.004
8		1	12	16.309	16.15	16.18	0.991	0.992
	9			17.298	17.05	17.09	.986	.988
9		2	25	18.212	18.13	18.17	.996	.998
	10			19.246	19.17	19.22	.996	.999
10		2	25	20.224	20.08	20.03	.993	.990
	11							
11		1	10	22.087	21.84	21.89	.990	.991
							Mean .9909	Mean .9909

$s^3e^{-as^2}$, with a chosen such that the exponential factor is equal to one-tenth for the last measured ring, gave a satisfactory resolution of most of the distances, and was invaluable in fixing the model for P_4O_{10}.

As_4O_6, P_4O_6, P_4O_{10}, and $(CH_2)_6N_4$ were measured in Oxford using the apparatus described by de Laszlo;[3] for his assistance in operating the electron diffraction camera we are greatly indebted to Dr. A. H. Gregg. The measurements on As_4O_6, P_4O_6, and P_4O_{10} were then repeated in Pasadena using the apparatus described by Brockway,[4] and the two sets of results were found to agree to within 1%. With the latter apparatus two or three extra outer rings were obtained, but the longer jet-to-camera distance employed in the de Laszlo apparatus enabled some inner fine structure to be resolved which was of great help in the P_4O_{10} investigation.

Experimental

The As_4O_6 used was the C. P. arsenious oxide of commerce which was not further treated.

The P_4O_6 was prepared by the method of Wolf and Schmager,[5] a modification of the older method of Thorpe and Tutton.[6] The trioxide so prepared contains 1 to 2% of free yellow phosphorus even after repeated vacuum distillation. The greater share of this free phosphorus was removed by irradiating the impure oxide for two days with a mercury vapor lamp. This treatment largely converts the yellow form into the much less volatile red form permitting separation by a subsequent distillation *in vacuo*.

The P_4O_{10} used was commercial C. P. phosphorus pentoxide which was sublimed in a stream of oxygen to remove lower oxides. This treatment is necessary since the lower oxides are all more volatile.

The hexamethylenetetramine was a commercial sample purified by vacuum sublimation.

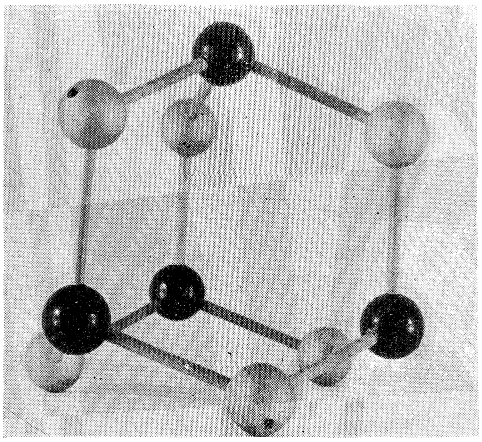

Fig. 1.—Photograph of model of As_4O_6, P_4O_6, or $(CH_2)_6N_4$. The black balls represent As, P, or N; the silver balls represent O or CH_2.

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[3] De Laszlo, *Proc. Roy. Soc.* (London), **A146**, 672 (1934).

[4] Brockway, *Rev. Modern Phys.*, **8**, 231 (1936).

[5] Wolf and Schmager, *Ber.*, **62**, 771 (1929).

[6] Thorpe and Tutton, *J. Chem. Soc.*, **57**, 545 (1890).

Arsenious Oxide.—The models tried for As_4O_6 consist of four As atoms at the positions (v,v,v), ($\bar{v}$,$\bar{v}$,v), ($\bar{v}$,v,$\bar{v}$) and (v,$\bar{v}$,$\bar{v}$) and six O atoms at the positions ($\pm$u,0,0), (0,$\pm$u,0) and (0,0,$\pm$u) (Fig. 1).

The photographs of As_4O_6 show thirteen maxima, eleven of which were measurable. The first, second and fourth maxima are strong. Preceding the fifth maximum and following the sixth maximum there are deep minima of about equal depth. The fifth and sixth maxima are of equal intensity. The values of s_0 for the maxima and minima and the estimated intensities of the maxima are given in Table I together with the weighted intensity values, c, used in the modified radial distribution method. The corresponding values of s for models VII and VIII are also given.

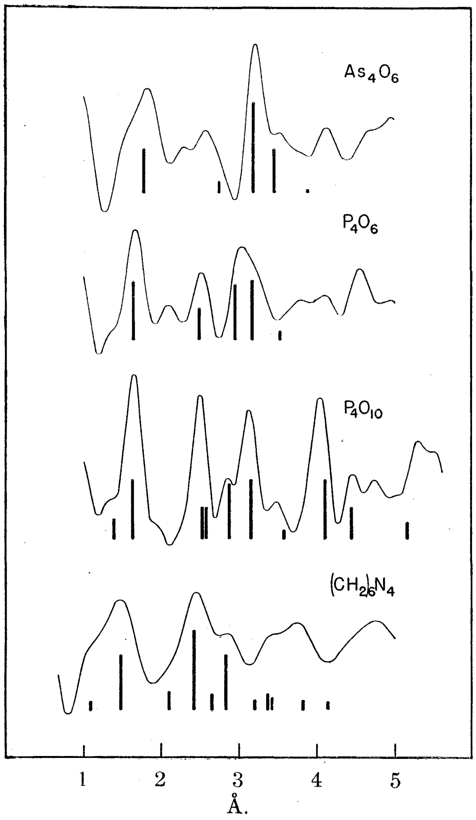

Fig. 2.—Radial distribution curves.

In Table II the parameters of all the models for which intensity curves were calculated are given.

Models VII and VIII are both satisfactory since both are in qualitative agreement with the photographs. Model V is not satisfactory because for it the eighth maximum becomes a shelf, and model VI is not satisfactory because the sixth maximum has become weaker than the fifth.

Table II

Model	u	v	As–As	As–O	O–As–O	As–O–As
I	2.310	1.155	3.26 Å.	2.00 Å.	109°28′	109°28′
II	2.057	1.308	3.70	2.00		
III	1.890	1.160	3.27	1.79		
V	1.890	1.142	3.23	1.78	97°20′	130°14′
VI	2.038	1.142	3.23	1.84	102°34′	121°58′
VII	1.981	1.142	3.23	1.82	100°39′	125°6′
VIII	1.959	1.142	3.23	1.81	99°54′	126°20′

Models VII and VIII lead to the following values of the interatomic distances and valence angles

Model VII	Model VIII
As–As = 3.20 Å.	As–As = 3.20 Å.
As–O = 1.80 Å.	As–O = 1.79 Å.
O–As–O = 100°39′	O–As–O = 99°54′
As–O–As = 125°6′	As–O–As = 126°20′

The radial distribution method applied to the As_4O_6 photographs gives a curve with maxima at 1.82 and 3.21 Å. corresponding to the values given above for the distances in the molecule. The curve for this calculation is given in Fig. 2. In Fig. 3 the theoretical intensity curves for As_4O_6 are

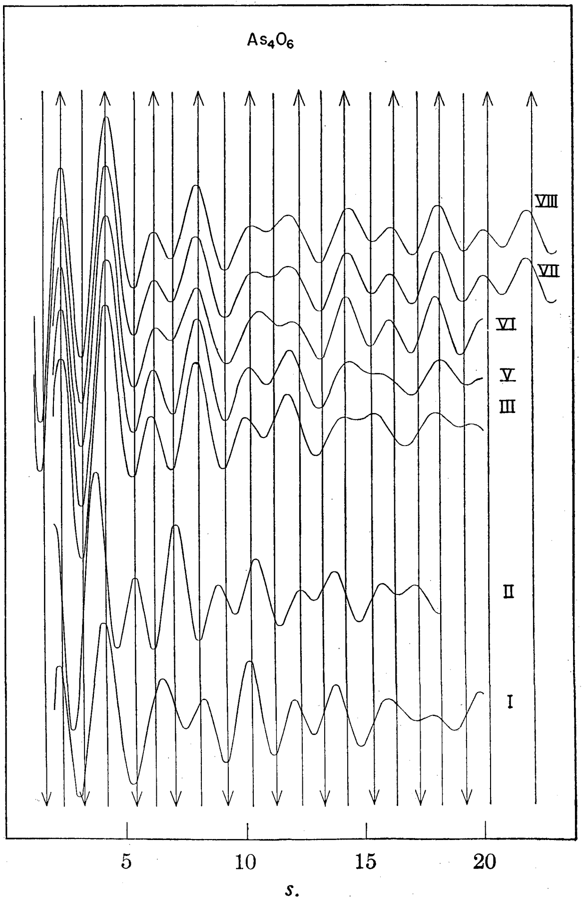

Fig. 3.—Calculated intensity curves for As_4O_6.

TABLE III

Max.	Min.	I	c	s_0	s(VI)	s(VIII)	s_{VI}/s_0	s_{VIII}/s_0
	1			1.803	1.60	1.62	(0.887)	(0.899)
1		12	2	2.659	2.49	2.47	(.936)	(.929)
	2			3.581	3.40	3.39	.949	.947
2		10	8	4.591	4.57	4.56	.995	.993
	3			5.623	5.86	5.91	(1.042)	(1.051)
3		1	2	6.641	6.30	6.30	0.949	0.949
	4			7.542	7.08	7.02	.939	.931
4		5	20	8.514	8.39	8.37	.985	.983
	5			9.634	9.70	9.68	1.007	1.005
5		1	6	10.687	10.72	10.71	1.003	1.002
	6			11.820	11.23	11.19	0.950	0.947
6		2	16	12.863	12.49	12.42	.971	.966
	7			14.319	14.09	14.05	.984	.981
7		2	18	15.548	15.69	15.62	1.009	1.005
	8				16.95	16.84		
8		1			17.70	17.58		
	9				18.52	18.44		
9		2	16	19.90	19.71	19.63	0.990	0.9866
							Mean .9802	Mean .9769

given. As final values of the distances the following are given:

As–As = 3.20 ± 0.03 Å. As–O–As = 126 ± 3°
As–O = 1.80 ± 0.02 Å. O–As–O = 100 ± 1.5°

Maxwell, Hendricks and Deming[1] give As–As = 3.20 ± 0.05 Å. They were unable to fix the oxygen parameter because of the much greater scattering power of the As atoms. Fair agreement was found with the oxygen valence angle As–O–As equal to 120°, 127.5° or 140°.

Phosphorus Trioxide.—The models used for P_4O_6 are of the same type as for As_4O_6. The four P atoms are at positions (v,v,v), $(\bar{v},\bar{v},v)$, $(\bar{v},v,\bar{v})$, and $(v,\bar{v},\bar{v})$, and the six O atoms at $(\pm u,0,0)$, $(0,\pm u,0)$, and $(0,0,\pm u)$.

The photographs of P_4O_6 show nine maxima, eight of which are measurable. The first, second and fourth maxima are strong; the second maximum is followed by a weak, almost shelf-like maximum; the sixth and seventh maxima are strong, of nearly equal intensity, separated by a broad and deep minimum; and the minimum following the weak eighth maximum is slightly deeper than that which precedes.

The values of s_0 for the maxima and minima and the estimated intensities of the maxima are given in Table III. Values of the parameters of models for which theoretical intensity curves were calculated are listed in Table IV.

Models VI and VIII were found to be in satisfactory qualitative agreement with the photographs. Model VII is unsatisfactory because the minimum following the eighth maximum has become weaker than that which precedes. Also any model with the value of the parameter u greater than that of model VIII would make this same minimum too deep in comparison with the preceding one.

TABLE IV

Model	u	v	P–P	P–O	O–P–O	P–O–P
IV	1.600	1.064	3.010	1.597	90°11′	140°48′
I	1.664	1.064	3.010	1.620	93°10′	136°31′
V	1.750	1.064	3.010	1.654	96°53′	130°59′
VII	1.780	1.064	3.010	1.666	98°6′	129°6′
VI	1.800	1.064	3.010	1.675	98°50′	127°52′
VIII	1.820	1.064	3.010	1.684	99°41′	126°39′
III	1.900	1.064	3.010	1.721	102°36′	121°53′
II	2.128	1.064	3.010	1.843	109°28′	109°28′

Models VI and VIII lead to the following values of the interatomic distances:

Model VI	Model VIII
P–P = 2.95 Å.	P–P = 2.94 Å.
P–O = 1.64 Å.	P–O = 1.65 Å.
O–P–O = 98°50′	O–P–O = 99°41′
P–O–P = 127°52′	P–O–P = 126°39′

A final choice of model must lie between models VI and VIII, possibly favoring model VI. This leads to the final values of the distances:

P–P = 2.95 ± 0.03 Å.
P–O = 1.65 ± 0.02 Å.
O–P–O = 99° ± 1°
P–O–P = 127.5 ± 1°

The results given by Maxwell, Hendricks and Deming[1] are:

P–P = 3.00 ± 0.05 Å.
P–O = 1.67 ± 0.03 Å.
P–O–P = 128.5 ± 1.5°

Radial distribution calculations result in a curve (Fig. 2) with maxima corresponding to interatomic distances of 1.66 and 3.03 Å. The theoretical intensity curves for P_4O_6 are given in Fig. 4.

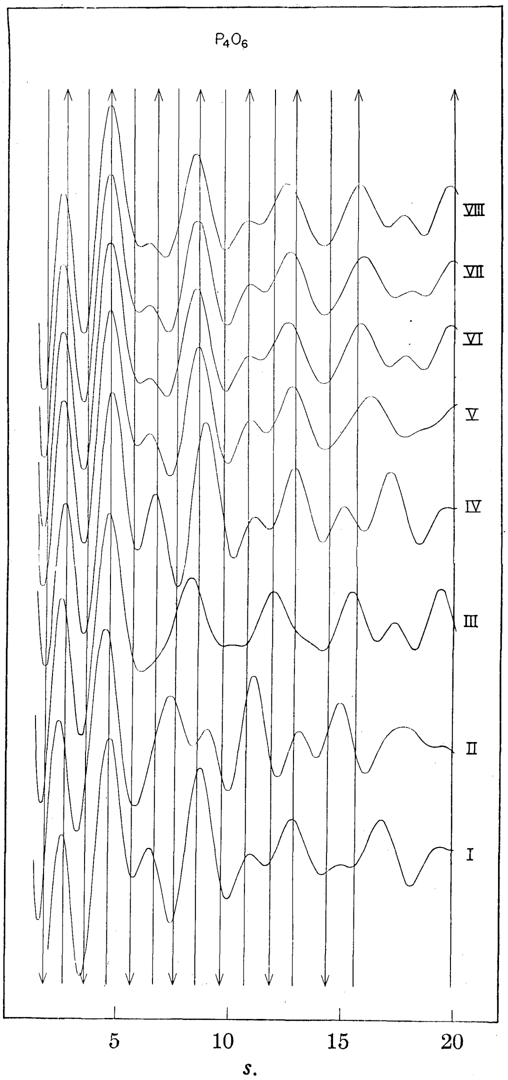

Fig. 4.—Calculated intensity curves for P_4O_6.

Phosphorus Pentoxide.—The photographs taken show eleven measurable maxima. The second maximum is the strongest and is followed by a shelf with no observable minimum interposed; and the third maximum is moderately strong and is followed by a broad shelf-like region. On photographs which were taken using a longer jet-to-camera distance (28.0 cm.) this shelf appears as two very weak maxima with poorly marked minima interposed. With the shorter camera distance (10.85 cm.) the doublet is not resolved. Following the eighth measured maximum there is another doublet of which only the outer ring is measurable. The second ring of this doublet is followed by a fairly pronounced minimum and a much stronger maximum. The last measured maximum is broad, and is preceded by a well marked minimum. The minima immediately preceding and following the weak seventh maximum are both weak, the outermost being possibly a little deeper. The measured values of s_0 of the maxima and minima and the estimated intensities of the maxima are listed in Table V. In Table VI the models for which theoretical intensity curves were calculated are listed.

TABLE V

Max.	Min.	I	c	s_0	s (XIV)	s_{XIV}/s_0
1		10	2	2.823	2.82	(0.999)
	1			3.965	3.75	(.946)
2		15	17	5.015	4.91	.979
	2	Absent				
3		5	10	6.300	6.20	.984
	3			7.215	7.05	.977
4		8	35	8.345	8.50	1.019
	4			9.86		
5		2	16	11.102	11.00	0.991
	5			12.097	11.72	.969
6		3	31	12.922	12.76	.988
	6			13.730	13.72	.999
7		1	12	14.491	14.25	.983
	7			15.351	14.84	.967
8		2	27	16.043	15.86	.989
	8	Not measurable				
9		1	14	18.645	18.46	.990
	9			19.662	19.24	.979
10		2	27	20.470	20.23	.988
	10			21.525	21.38	.993
11		1	12	22.943	23.00	1.003
					Mean	0.9873

TABLE VI

Model	a	b	c	P–P	P–O	P–O′	OPO	POP
I	1.064	1.820	2.011	3.01	1.68	1.64	99°41′	126°39′
III	0.910	1.820	1.926	2.57	1.58	1.76	109°28′	109°28′
IV	.903	1.867	1.919	2.56	1.60	1.76	111°12′	106°4′
V	.923	1.785	1.943	2.61	1.57	1.77	107°24′	112°50′
VI	1.030	1.785	1.830	2.91	1.64	1.39	100°38′	125°24′
VII	1.018	1.805	1.844	2.88	1.64	1.43	102°18′	122°40′
VIII	0.992	1.720	2.008	2.81	1.58	1.76	100°36′	125°15
IX	.993	1.840	1.795	2.81	1.64	1.39	104° 0′	117°46′
X	1.045	1.750	1.830	2.96	1.64	1.36	98° 0′	129°14′
XI	1.022	1.795	1.829	2.89	1.64	1.40	101°30′	123°42′
XII	1.040	1.795	1.829	2.94	1.65	1.40	100°18′	125°39′
XIII	1.020	1.800	1.836	2.88	1.64	1.41	101°49′	123°12′
XIV	1.018	1.792	1.827	2.88	1.63	1.40	101°39′	123°28′

All of the models are for the four P atoms at positions (a,a,a), $(\bar{a},\bar{a},a)$, $(\bar{a},a,\bar{a})$, and $(a,\bar{a},\bar{a})$, six O atoms at positions (±b,0,0), (0,±b,0), and (0,0,±b), and the remaining four O atoms at the positions (c,c,c), $(\bar{c},\bar{c},c)$, $(\bar{c},c,\bar{c})$, and $(c,\bar{c},\bar{c})$. Models XI, XIII and XIV are all satisfactory in their qualitative agreement with the photographs. Model XIV is roughly the mean of models XI and XIII, and it has been used for the final calculations of the interatomic distances of the molecule. The following distances result from these calculations:

P–P = 2.84 ± 0.03 Å. OPO = 101.5 ± 1°
P–O = 1.62 ± 0.02 Å. POP = 123.5 ± 1°
P–O′ = 1.39 ± 0.02 Å. OPO′ = 116.5 ± 1°

The angle designated by OPO′ is the angle formed by the P atom at (a,a,a) and the O atoms at (b,0,0) and (c,c,c) (Fig. 5). It may be seen from an inspection of the models listed that the valence angles are very closely limited. Model XII differs from model XI only in the phosphorus coördinates, causing a change in the P valence angle of only about one degree, but it is not in qualitative agreement with the photographs in that for it the shelf-like region following the fourth maximum has become a real maximum with a preceding minimum. The short P–O′ distance is also fixed closely by the disagreement of model VII. This model differs from the satisfactory models only in that the coördinates of the outer four O atoms are changed by a very small amount.

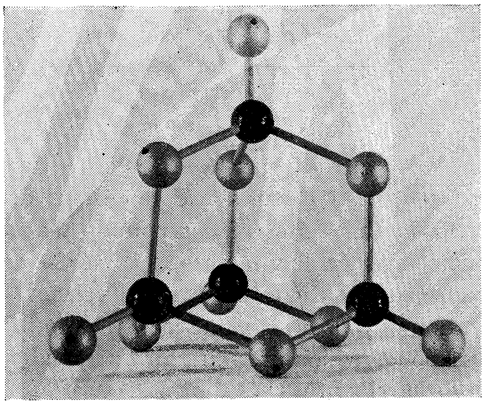

Fig. 5.—Photograph of model of P_4O_{10}. The black balls represent P; the silver balls represent O.

The modified radial distribution method suggested by Dr. Schomaker gave a remarkably good resolution of the various peaks, nearly all the interatomic distances in the molecule appearing as separate maxima. The curve is shown in Fig. 2. From the data which it provided, the three parameters could be determined within narrow limits, these parameters agreeing well with those chosen for the final model.

The theoretical intensity curves for the models of Table VI are shown in Fig. 6.

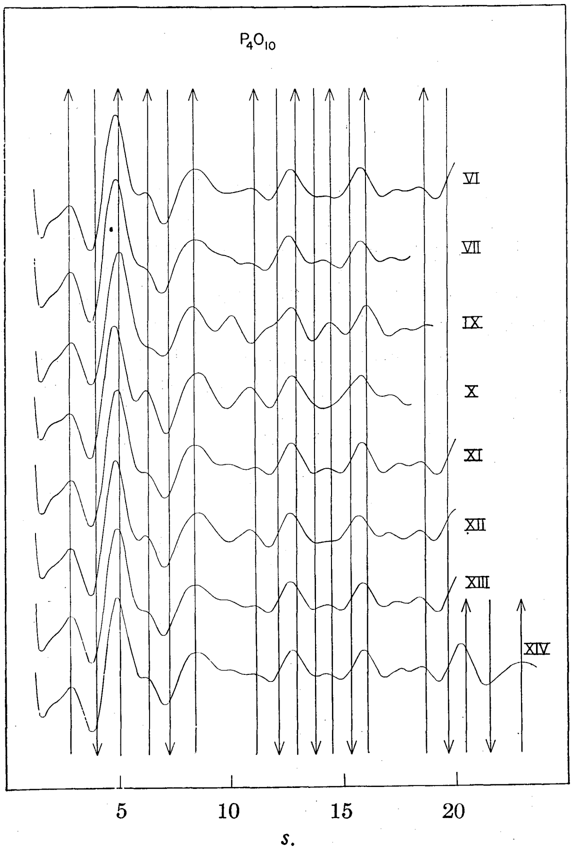

Fig. 6.—Calculated intensity curves for P_4O_{10}.

Hexamethylenetetramine.—The photographs of this substance were taken using a long jet-to-camera distance and show six maxima. The first two are strong, the third broad and diffuse, the fourth very weak, the fifth fairly strong and the sixth very weak.

The hexamethylenetetramine model is essentially the same as that for P_4O_6 and As_4O_6. Four N atoms are in positions (v,v,v), ($\bar{v}$,$\bar{v}$,v), ($\bar{v}$,v,$\bar{v}$) and (v,$\bar{v}$,$\bar{v}$), six C atoms in positions (±u,0,0), (0,±u,0) and (0,0,±u) and the twelve H atoms in positions (x,$\bar{x}$,z), ($\bar{x}$,x,z), etc. The hydrogen parameter could not be deduced from the photographs and an assumed value of 1.09 Å. for the C–H distance was used in computing the theoretical intensity curves. A model in which all the angles had the regular tetrahedral value of 109.5° and with a C–H distance of 1.48 Å. (N–N or C–C = 2.42 Å.) was found to agree well with the photographs. The curve for this model is shown in Fig. 7. Table VII gives the measured values of

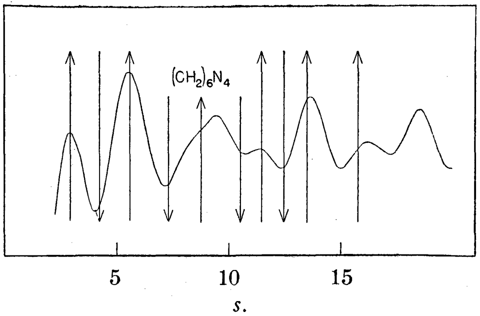

Fig. 7.—Calculated intensity curve for $(CH_2)_6N_4$.

s_0 for the maxima and minima together with the estimated intensities of the maxima; the s values for the above model are also listed, and the average value of s/s_0 is seen to be practically unity.

Table VII

Max.	Min.	I	c	s_0	s	s/s_0
1		10	2	2.966	2.93	0.988
	1			4.261	4.06	.953
2		8	15	5.606	5.56	.992
	2			7.303	7.15	.979
3		4	5	8.774	9.41	1.073
	3			10.54	10.75	1.020
4		2	2	11.47	11.40	0.995
	4			12.49	12.35	0.989
5		4	10	13.52	13.68	1.012
6		1	4	15.79	16.25	1.029
					Mean	1.003

The radial distribution curve shown in Fig. 2 gives C–N = 1.47 Å. and C–C or N–N = 2.43 Å. agreeing well with the above model.

Discussion of Results

Of the substances reported in this paper, two, hexamethylenetetramine and arsenious oxide, have been studied in the solid form. Hexamethylenetetramine crystallizes in a body-centered cubic lattice, Dickinson and Raymond[7] reporting a regular tetrahedral arrangement of valences with C–N = 1.44 Å. Gonell and Mark[8] gave C–N = 1.48 Å. and C–C = 2.58 Å., and this same type of structure has also been confirmed by Wyckoff and Corey,[9] who give C–N = 1.42 ± 0.08 Å. The sum of the covalent single-bond radii[10] of carbon and nitrogen is 1.47 Å. in good agreement with the value which we find here.

Arsenolite, cubic As_4O_6, was reported by Bozorth[11] to be a lattice of As_4O_6 molecules in a diamond-type arrangement. Both the As and the O valence angles are tetrahedral in this solid, the As–As distance 3.28 Å. and the As–O distance 2.01 Å. There are two strong bonds for each O atom to two As atoms in the same molecule, and two weak bonds to two As atoms of a neighboring molecule. This attraction between neighboring molecules apparently draws the O atom out, increasing the As–O distance and decreasing the oxygen valence angle from the values observed for the vapor molecule to those observed in the solid. To a smaller extent this applies to the As atoms too, since each forms three strong bonds to oxygens in the same molecule and three weak bonds to oxygens of adjacent molecules. A redetermination of the crystal parameters was made by Harker and Eskijian[12] in these Laboratories confirming the older values but fixing them more closely (to within about 0.03 Å.).

Arsenic apparently has a tendency to form bonds at angles smaller than the tetrahedral angle, as As_4O_6 is not unique in this respect. In this compound where the atoms form closed rings it might be thought that the As valences are strained into taking up this angle because of the tendency of the oxygen angle to expand beyond the tetrahedral value[13] but even in compounds where the groups attached to the As atom form no other bonds, the As bond angle is considerably less than 109°28′. Examples are $AsCl_3$ 103°,[14,15] 101 ± 4°,[16] $AsBr_3$ 100 ± 2°,[16] $As(CH_3)_3$ 96 ± 5°.[17]

The remarkable constancy of this angle of around 100° already has been remarked upon.[16] Steric effect and electrostatic repulsions are so different in this series of compounds that they cannot be the deciding factors in fixing the angle. According to the theory of directed valency[18] the utilization of p orbitals alone leads to the formation of bonds which are mutually perpendicular. Hybridization with the s orbital gives rise to stronger bonds which, if hybridization is complete, as with carbon compounds, are at an angle of 109°28′. If, however, there are unshared electrons, as in the case we are considering, hybridization may not be complete, for there are two opposing tendencies. On the one hand, hybridization tends to stabilize the bonds but at the same

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[7] Dickinson and Raymond, This Journal, **45**, 22 (1923).

[8] Gonell and Mark, *Z. physik. Chem.*, **107**, 181 (1923).

[9] Wyckoff and Corey, *Z. Krist.*, **89**, 462 (1934).

[10] Pauling and Huggins, *ibid.*, **87**, 205 (1934).

[11] Bozorth, This Journal, **45**, 1621 (1923).

[12] Unpublished work.

[13] Sutton and Hampson, *Trans. Faraday Soc.*, **31**, 945 (1935).

[14] Brockway and Wall, This Journal, **56**, 2373 (1934).

[15] Pauling and Brockway, *J. Chem. Phys.*, **2**, 867 (1934).

[16] Gregg, Hampson, Jenkins, Jones and Sutton, *Trans. Faraday Soc.*, **33**, 852 (1937).

[17] Springall and Brockway, This Journal, **60**, 996 (1938).

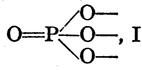
[18] Pauling, *ibid.*, **53**, 1367 (1931).

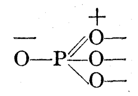
time this means that the unshared electrons also tend to become hybridized between the *s* and *p* orbitals, whereas the unshared pairs of electrons are always most stable when they occupy the *s* orbitals. As usual the actual configuration taken up is that which gives the lowest energy.

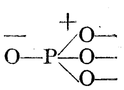
The sum of the covalent single-bond radii[10] of arsenic and oxygen is 1.87 Å. The decrease from the sum of the radii to the observed value of 1.80 Å. may be explained as the result of double bond character caused by unshared pairs from the oxygen atoms forming double bonds with the As atoms.[14–16] The value 126 ± 3° which is observed for the oxygen angle is close to 125°16′, the angle between a double and a single bond on the regular tetrahedral model.

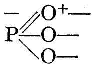
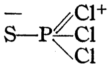
Phosphorus, like arsenic, shows a tendency to form bond angles less than the tetrahedral angle. In P_4O_6 it is found to be 99°. In other substances where the groups attached form no other bonds the same behavior is noted. Examples are PF_3 99 ± 4°,[14] PCl_3 100 ± 2°,[14] PBr_3 100 ± 2°,[16] PI_3 98 ± 4°,[16] $POCl_3$ 104°,[19] $P(CH_3)_3$ 100 ± 4°.[17]

The sum of the covalent radii[10] for phosphorus and oxygen is 1.76 Å. Again the observed value is lower presumably because of double-bond character, as with As_4O_6.

In P_4O_{10} the phosphorus angles are 101.5 and 116.5°. The latter angle is that between an outer oxygen atom and one within the P_4O_6 "kernel." Addition of this outer oxygen atom has had very little effect on the other bond angles and this might have been anticipated from the values given for PCl_3 and $POCl_3$. The most startling feature of the P_4O_{10} molecule is the unusually short distance of 1.39 Å. between each P atom and the "extra" O atom. The value found is about 79% of the sum of the single bond radii (1.76 Å.) and is approximately that expected for a triple bond between the two atoms. A similar anomaly has been observed in thiophosphoryl chloride, $PSCl_3$,[20] where the P–S distance is found to be 1.94 Å. instead of the normal single bond distance of 2.14 Å. It is clear that double bond character in a structure such as , I, is not sufficient to explain such a large shortening as is observed. The addition of four extra oxygen atoms to P_4O_6 has very little effect on the dimensions of this P_4O_6 "kernel," and since we have postulated single-double bond resonance in P_4O_6, it seems reasonable to conclude that it also occurs in P_4O_{10}. The important systems are probably II and III in resonance with I.


II


III

There is another piece of evidence which favors this conclusion. In P_4O_6 the contribution of a double-bonded structure IV  was postulated to explain the shortening of the P–O bond below the single bond value. In this structure the phosphorus and oxygen atoms carry opposite charges and so there is no "formal charge effect"[21] influencing the bond length. On the other hand, in structures II and III of P_4O_{10} the positive charge on the oxygen or phosphorus atom is not compensated by a negative charge within the P_4O_6 "kernel" and hence because of the increased effective nuclear charge we should expect the bond length to be diminished. The P–O distance in P_4O_6 is 1.65 Å. and the corresponding distance in P_4O_{10} is indeed shorter, being 1.62 Å. The difference may be due to experimental error, although in view of the above argument it may be of some significance. As regards the other P–O distance having the extremely low value of 1.39 Å., the "formal charge effect" in structure II (negative charge on the oxygen, no charge on the phosphorus) would lead one to expect an increase rather than a decrease. One is forced to conclude that the predominant factor here must be the polar character of the bond. In discussing $PSCl_3$, Beach and Stevenson[20] ruled out any effect of ionic character and formal charges on the length of the bond, but concluded that the shortening of the P–S distance must be due to a considerable (about one half) contribution of  without, however, giving any reasons. The short P–O distance in P_4O_{10} is in accord with the chemical properties of this molecule. Such short bonds are presumably extremely stable, and the thermal stability and resistance to reduction of P_4O_{10} are well known.

We wish to express our thanks to Professor Brockway, Professor Pauling and Professor Sidgwick for their help and interest in this work,

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(19) Brockway and Beach, THIS JOURNAL, **60**, 1836 (1938).

(20) Beach and Stevenson, *J. Chem. Phys.*, **6**, 75 (1938).

(21) Elliott, THIS JOURNAL, **59**, 1380 (1937).

and the Commonwealth Fund for a Fellowship to one of us (G. C. H.).

Summary

Electron diffraction measurements on arsenious oxide, phosphorus trioxide and hexamethylenetetramine show that the molecules consist of four phosphorus or nitrogen atoms in positions (vvv) $(\bar{v}\bar{v}v)$ $(\bar{v}v\bar{v})$ and $(v\bar{v}\bar{v})$ and six oxygen atoms or methylene groups in the positions $(\pm u00)$ $(0 \pm u0)$ and $(00 \pm u)$. In phosphorus pentoxide there are four additional oxygen atoms in the positions (www) $(\bar{w}\bar{w}w)$ $(\bar{w}w\bar{w})$ and $(w\bar{w}\bar{w})$.

The interatomic distances and angles are: for As_4O_6, As–O = 1.80 ± 0.02 Å., O–As–O = 100 ± 1.5°, As–O–As = 126 ± 3°, for P_4O_6, P–O = 1.65 ± 0.02 Å., O–P–O = 99 ± 1°, P–O–P = 127.5 ± 1°, for $N_4(CH_2)_6$, C–N = 1.47 ± 0.02 Å., C–N–C = N–C–N = 109.5°, for P_4O_{10}, P–O = 1.62 ± 0.02 Å., P–O′ = 1.39 ± 0.02 Å., O–P–O = 101.5 ± 1°, P–O–P = 123.5 ± 1° and O–P–O′ = 116.5 ± 1°.

The shortening of the bond distances in As_4O_6, P_4O_6 and P_4O_{10} below the theoretical single-bond values is attributed to single-bond double-bond resonance. It is concluded that the abnormally low value of 1.39 Å. for the P–O′ bond in P_4O_{10} is due to the polar character of the bond.

Pasadena, Calif. Received May 31, 1938

[Contribution from the Gates and Crellin Laboratories of Chemistry, California Institute of Technology, No. 647]

The Properties of Osmium Tetroxide in Carbon Tetrachloride Solutions. The Thermodynamic Constants of Osmium Tetroxide[1]

By LeRoy H. Anderson and Don M. Yost

Introduction

Osmium tetroxide is known to be moderately soluble in water and very soluble in carbon tetrachloride. Von Wartenberg[2] determined the solubility to be 6.47 g. per 100 g. of water, and about 250 g. per 100 g. of carbon tetrachloride, at 20°. The distribution ratio of osmium tetroxide between carbon tetrachloride and water was determined by Yost and White[3] for dilute solutions to be 13 when the concentrations are expressed in moles per liter of both solvents. Distribution ratios were determined independently, and at about the same time, by Tschugajeff and Lukashuk[4] with essentially the same results. These authors also made solubility determinations in water but the result, 6.23 g. per 100 g. of water at 25°, does not seem to be consistent with that of Von Wartenberg.

The distribution ratio calculated from solubilities is much higher than that found in the experiments on dilute solutions. This fact indicated that either the concentrated solutions in carbon tetrachloride were exhibiting some abnormal behavior, or that in the distribution experiments water possibly was associated with the tetroxide in carbon tetrachloride layer, thus forming a different solute. In order to settle this point, distribution experiments were made with solutions whose concentrations varied from very dilute to saturation, the solubilities of osmium tetroxide in both water and carbon tetrachloride were redetermined, and the vapor pressures of carbon tetrachloride above solutions of osmium tetroxide in it were measured for the range of concentrations up to saturation.

Preparation of Materials and Experimental Methods

Osmium Tetroxide.—Osmium metal freed from ruthenium was heated to 300–400° in a glass tube in a stream of dried oxygen. The vapors of osmium tetroxide (b. p. 130°) were condensed in the distribution vessel or capsules by means of a solid carbon dioxide–alcohol bath.

All other chemicals used were of the best grade obtainable. The carbon tetrachloride was further purified by fractional distillation.

Analytical Methods.—Osmium tetroxide is frequently determined iodimetrically,[4,5] but the colored tetravalent osmium solutions hide the end-point in all but rather dilute solutions, and atmospheric oxygen affects the results. After some experimentation the following procedure was

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[1] Presented at the Second Annual Symposium of the Division of Physical and Inorganic Chemistry on the Less Familiar Elements, Cleveland, Ohio, December 27, 28 and 29, 1937.

[2] Von Wartenberg, *Ann. Chem.*, **440**, 97 (1924); **441**, 318 (1925); Bichowsky and Rossini, "Thermochemistry of Chemical Substances," Reinhold Publishing Corp., New York, N. Y., 1936, p. 82.

[3] Yost and White, This Journal, **50**, 81 (1928).

[4] Tschugajeff and Lukashuk, *Z. anorg. Chem.*, **172**, 223 (1928).

[5] For other methods see Crowell, This Journal, **54**, 1324 (1932).

adopted: the weighed sample of osmium tetroxide solution was placed in a glass-stoppered flask containing 25 cc. of an acidified (0.35 *N* in hydrochloric acid) potassium iodide solution that had been saturated previously with carbon dioxide. After about thirty minutes of gentle shaking in the dark, the resulting solution was diluted to 200 cc. with distilled water saturated with carbon dioxide, and was then titrated with standard thiosulfate with starch as an indicator. Although this method can be made to give reproducible results, it cannot be said to be highly satisfactory, and, except for the dilute solutions, was replaced by a gravimetric method in which metallic osmium was weighed.

In the gravimetric method 0.1 to 0.3 g. of hydrazine hydrochloride was dissolved in 10 cc. of 3 *N* hydrochloric acid contained in a glass-stoppered flask. After warming this solution to 55–65°, the weighed sample of osmium tetroxide solution was introduced, and the resulting mixture was digested over a water-bath for an hour. This mixture was transferred to a weighed, glazed Rose crucible, and evaporated to dryness on a hot-plate. A stream of hydrogen was started through the crucible and the latter heated over a Bunsen burner for twenty to thirty minutes. The stream of hydrogen was continued until the crucible had cooled to room temperature, and then the hydrogen remaining was displaced with carbon dioxide. This last precaution is necessary to avoid the rapid combustion of hydrogen in the presence of the finely divided metallic osmium when the crucible cover is removed.

The Distribution and Solubility Experiments.—The distribution experiments were carried out in a 20-cc. cylindrical all-glass vessel equipped with two 1-mm. diameter tubes which extended into the carbon tetrachloride and aqueous layers, respectively. A little air pressure served to force samples of either layer out through the 1-mm. tubes and into a weighing bottle or capsule. The distribution vessel itself was fastened to a mechanical shaker operating in a thermostat so that equilibrium was certainly attained in all experiments. At no time did the tetroxide solutions come in contact with oxidizable substances.

In some of the distribution experiments, and in all of the solubility determinations, small, weighed, evacuated capsules equipped with long narrow outlet tubes were used for sampling. The outlet tubes were bent at right angles near their tips, and the short tips could be broken easily under the solution. The fragment of glass broken off was recovered and weighed.

The solubility experiments were carried out in a 10-cc. glass-stoppered tube that was shaken in the thermostat at 25° for twenty-four hour periods. Solubility equilibrium was approached from both directions.

The Vapor Pressure Experiments.—The apparatus used for the vapor pressure measurements consisted of a 20-cc. cylindrical glass container equipped with an all glass "click" gage and with side-arms which held easily breakable Capsules of osmium tetroxide and carbon tetrachloride. The capsules were broken when desired by means of glass enclosed, magnetically operated iron plungers. To attain more conveniently the higher dilutions, a separate calibrated carbon tetrachloride container was connected through a stopcock and a long (20 cm.) 0.5-mm. glass capillary tube to the solution container. The carbon tetrachloride was distilled into the solution container by cooling the latter with liquid air. In order to make sure that the solution was homogeneous at all times a stirrer consisting of a glass enclosed piece of soft iron was placed in the solution container and caused to move up and down by means of an external solenoid. The osmium tetroxide could at no time come in contact with any substance other than glass. Its low partial vapor pressure and the slow diffusion through the long capillary tube prevented appreciable loss of osmium tetroxide by reaction with the stopcock grease. The whole apparatus was highly evacuated and then closed off from the pumps. From time to time the contents of the system were condensed with liquid air and pressure measurements made to assure that no air had leaked into the apparatus.

Results of the Experiments

In Table I are presented the results of the distribution experiments made at 25°. All concentrations are expressed in mole fractions.

TABLE I

RESULTS OF THE DISTRIBUTION EXPERIMENTS AT 25°

Formula mole fraction OsO_4 in water layer, N_w	Formula mole fraction OsO_4 in CCl_4 layer, N_c	Distribution ratio $R = N_c/N_w$
0.0001464	0.01204	82.2
.000405	.0320	79.0[a]
.000582	.0424	72.9
.000614	.0498	81.2[a]
.000653	.0530	81.2[a]
.000715	.0582	81.4[a]
.00135	.109	80.7
.00137	.117	85.4[a]
.00189	.1563	82.7[a]
.00196	.175	89.3[a]
.00234	.22	94[a]
.002715	.2564	94.5
.00381	.426	112.0
.00423	.520	123
.00459	.6065	132.2
.00470	.598	127.3
.00507[s]	.693[s]	136.5[s]

Solubility OsO_4 in 100 g. water at 25° = 7.24 ± 0.01 g.
Solubility OsO_4 in 100 g. CCl_4 at 25° = 375 ± 17 g.

[a] Iodimetric determinations. All others were gravimetric. [s] From solubility measurements.

The experimental error of 17 g. or 4.5% in the solubility in carbon tetrachloride arises from the fact that the solutions are very concentrated, that they have a tendency to supersaturate, and that the solubility appears to have a large temperature coefficient. The result given here is the mean of four determinations which seemed free of criticism.

In the first and second columns of the table are given the formula mole fractions of tetroxide in the aqueous and carbon tetrachloride layers, respectively, that is, the mole fractions calculated from the results of analyses on the assumption that OsO_4 is present as such. Most of the ratios are the average of two or more values obtained for the same distribution experiment. At low concentrations the error in the gravimetric method of analysis is high due to the small amount of osmium weighed. At high concentrations the volumetric method of analysis is worthless due to the errors in taking small samples of the carbon tetrachloride phase or to the errors described above.

The distribution ratio, $R = N_c/N_w$, increases slowly at first and then more rapidly with concentration. It is also evident that the ratio at the high concentrations is approaching the last value in the table which was calculated from the solubility measurements. It would appear, therefore, that the carbon tetrachloride layer contains no water associated with the osmium tetroxide.

In order to establish still more definitely that the non-ideality of the carbon tetrachloride solution is independent of the presence of water, vapor pressure measurements were made on solutions of osmium tetroxide in dry carbon tetrachloride. The results are presented in Table II. The total vapor pressures observed were corrected for the small partial pressures of osmium tetroxide on the assumption that the laws of perfect solutions were valid. For such small corrections this assumption is justified. The last column of the table contains vapor pressures calculated on the basis of an assumption to be discussed below.

Table II

The Partial Vapor Pressure of Carbon Tetrachloride above its Solutions of Osmium Tetroxide at 25°

Formula mole fraction OsO_4, N_c	Partial vapor of CCl_4 in cm. P	Vapor pressure calcd. from Raoult's law concn. = N_c	Vapor pressure calcd. from Raoult's law but assuming $4OsO_4 = (OsO_4)_4$
0.000	11.46	11.46	11.46
.0402	11.02	11.00	11.00
.081	10.56	10.55	10.55
.1105	10.05	10.20	10.20
.395	7.86	6.92	7.72
.5982	6.19	4.61	5.97
.693	5.39	3.52	5.17

It is clear from column three of the table that the vapor pressures calculated from Raoult's equation and the formula mole fractions in column one are not equal to the observed pressures, that is, the solutions are not ideal. Now it is known from electron diffraction experiments[6] and the Raman spectrum[7] that the osmium tetroxide molecule is highly symmetrical, the four oxygen atoms being at the corners of a tetrahedron with the osmium atom at the center. Carbon tetrachloride has the same symmetrical structure. In spite of this high symmetry, mixtures of the two substances do not form ideal solutions.

The results of equilibrium experiments on non-ideal binary solutions may be treated quantitatively in either of two ways. (1) By the application of the thermodynamically exact Gibbs-Duhem equation and the definition of fugacity, the fugacities of the components may be calculated for any concentration. The results of such calculations are useful and necessary for the calculation of thermodynamic quantities. (2) The assumption may be made that Raoult's equation is the expression of a law and that deviations from it are to be interpreted as indicating the formation of ions, compounds or polymers. This orthodox way of treating experimental results, especially results obtained with concentrated solutions of the kind presented here, has been criticized[8] for several reasons, one of which is that it sometimes requires the assumption of polymers in the case of inert substances such as the noble gases.

If the results of the present distribution experiments are assumed to indicate the formation of an $(OsO_4)_n$ polymer in the carbon tetrachloride solutions, it is not difficult to show that they are in accord with the assumption that the following rapid reversible reaction takes place.

$$4OsO_4 = (OsO_4)_4$$
$$K = (OsO_4)_4/(OsO_4)_4 = 6.3$$

To evaluate the equilibrium constant the limiting value of $R = 78$ for infinitely dilute solutions was determined graphically.

The vapor pressure measurements are in quantitative agreement with the assumption of this polymerization as can be seen by comparing the second and last columns of Table II.

This analysis of the results is not, however, unique, it being possible to obtain equally satisfactory agreement with the distribution and vapor pressure experiments by assuming equilibria involving a series of polymers. This would still be true if a very high degree of accuracy were feasible. Such behavior is characteristic of this method of treatment.

If the osmium tetroxide is present in carbon

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[6] L. O. Brockway, *Rev. Modern Phys.*, **8**, 260 (1936).

[7] Langseth and Quiller, *Z. physik. Chem.*, **B27**, 79 (1934).

[8] Hildebrand, "Solubility," Reinhold Publishing Corp., New York, N. Y., Second Edition, 1936. See also this author and others for a general discussion on liquids and solutions, *Trans. Faraday Soc.*, **33**, 1–279 (1937).

tetrachloride solutions as an equilibrium mixture of polymers, the nature of the bonds or interaction becomes of interest. One type of bond could be assumed to consist of an oxygen atom shared by two osmium atoms. This would imply that the normal oxygen–osmium–oxygen bond angle is distorted to make way for the shared oxygen. A less conventional but perhaps more rational picture of the assumed association of tetroxide molecules is provided by London's dispersion effect.[9] This effect gives rise to an additive interaction energy of attraction between molecules, even though the molecules themselves possess no average dipole (or multipole) moment. The additive property makes the interaction energy between any two molecules of a cluster practically independent of the number of molecules in the cluster. Accordingly, when only this type of interaction obtains there is no effect of saturation, and clusters of two, three and more molecules are conceivable. If the clusters can be regarded as polymers in equilibrium with each other then it is proper to treat the deviations from Raoult's equation of the type shown by osmium tetroxide in carbon tetrachloride as indicating polymer formation, providing, of course, that the clusters are, on the average, sufficiently far apart so that their interaction with each other is small.

It is possible that the interactions between the assumed clusters are of the same order of magnitude as those between the molecules in the clusters. In that event the calculation of equilibrium constants for assumed polymer formation in concentrated solutions of the type reported here provides no more than a convenient empirical method for expressing the properties of the solutions.

The shape and size of the osmium tetroxide molecule were determined by Brockway[6] from electron diffraction experiments. Langseth and Quiller[7] photographed the Raman spectrum. From these results the standard entropy of osmium tetroxide gas may be calculated. The heat of formation and the vapor pressures of the tetroxide were measured by von Wartenberg.[2] The entropy of metallic osmium was calculated by Lewis and Gibson,[10] and that of oxygen has been determined by Giauque and Johnston.[11] This information taken together permits the calculation of the free energies of formation of both gaseous and solid osmium tetroxide. The necessary data and the results of the calculations are presented in Table III.

TABLE III

THE THERMODYNAMIC CONSTANTS OF OSMIUM TETROXIDE

Interatomic distance Os— O $= 1.66 \pm 0.05$
Symmetry number $\sigma = 12$

Raman frequencies in cm.$^{-1}$ and their degeneracies (in parentheses)

$\omega_1(1)$	$\omega_2(2)$	$\omega_3(3)$	$\omega_4(3)$
971	568	1187	688

Standard entropies at 25° and one atmosphere in cal./deg.

OsO_4(g), 65.65 Os(s), 7.8 ± 0.5 O_2(g), 49.03

Solubility in water = 0.0284 mole/kg. water at 25°

Free energies and heat contents.

$Os(s) + 2O_2(g) = OsO_4(s)$
$\Delta F^\circ_{298} = -70{,}900$ cal. $\Delta H = -93{,}600$ cal.
$OsO_4(s) = OsO_4(g)$
$\Delta F^\circ_{298} = 2{,}800$ cal. $\Delta H = 13{,}500$ cal.
$Os(s) + 2O_2(g) = OsO_4(g)$
$\Delta F^\circ_{298} = -28{,}000$ cal. $\Delta H = -80{,}100$ cal.
$Os(s) + 2O_2(g) = OsO_4(aq)$
$\Delta F^\circ_{298} = -68{,}788$ cal.

The stability of osmium tetroxide is shown by the large negative value of ΔF°_{298}. The observation made by von Wartenberg that the tetroxide does not decompose at 1500° may be shown by an easy calculation to be consistent with the above free energy and heat content values.

The free energy values might also be combined with the results of Kirschman and Crowell[12] to obtain the free energies of some of the reduced forms of osmium in aqueous solutions.

Summary

The distribution ratios of osmium tetroxide between carbon tetrachloride and water have been measured at 25° for the whole range of concentrations up to saturation and found to vary from $R = N(\text{in } CCl_4)/N(\text{in } H_2O) = 78$ to $R = 136$. The results of solubility measurements are in agreement with the ratio at high concentrations.

The vapor pressures of dry carbon tetrachloride above its solutions of osmium tetroxide were measured at 25° and over the range of concentrations up to saturation. The results do not accord with Raoult's equation.

Electron diffraction, spectroscopic and thermal data are used to evaluate the free energies of gaseous, solid and aqueous osmium tetroxide.

PASADENA, CALIF. RECEIVED MAY 2, 1938

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[9] London, *Trans. Faraday Soc.* **33**, 8 (1937).

[10] Lewis and Gibson, THIS JOURNAL, **39**, 2554 (1917).

[11] Giauque and Johnston, *ibid.*, **51**, 2300 (1929).

[12] Kirschman and Crowell, *ibid.*, **55**, 488 (1933).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

The Heat Capacity and Entropy of Barium Fluoride, Cesium Perchlorate and Lead Phosphate

BY KENNETH S. PITZER,[1] WENDELL V. SMITH AND WENDELL M. LATIMER

While the calculation of ionic entropies was the immediate purpose for which these heat capacity measurements were made, the data so obtained should, nevertheless, have considerable value from other points of view. The present paper contains the heat capacity results together with calculations of the entropies of the three salts. The ionic entropy calculations will be presented in another publication.

Materials.—The precipitation of barium fluoride from aqueous solution gives a very fine powder which would seem questionable as a thermodynamic reference state. The sample employed in the following measurements was prepared by melting "C. P." barium nitrate and potassium fluoride together in a platinum crucible, and then extracting the potassium nitrate and excess barium nitrate from the cooled melt with hot water. The extraction was continued until the wash water gave no test for either potassium ion or nitrate ion. The product appeared to be definitely crystalline on examination with a microscope. Analysis by precipitation of barium sulfate from dilute nitric acid solution gave 99.7 ± 0.5% of the theoretical barium content. The authors wish to extend their thanks to Dr. Oliver L. I. Brown for the greater part of the work in preparing this sample.

The tertiary lead phosphate was prepared from lead acetate and Na_2HPO_4, both of "C. P." grade. Hot, dilute solutions of the two salts were slowly mixed with vigorous stirring, and the resulting precipitate was washed thoroughly and then dried by heating for several days at 300°. Electrolytic analysis showed the theoretical amount of lead within 0.2%.

The cesium perchlorate was prepared from samples of "C. P." cesium nitrate and iodochloride by the addition of perchloric acid in dilute solution. Chemical tests indicated the absence of appreciable amounts of nitrate or iodochloride, while the absence of other alkali metals was established by spectroscopic examination. The product was dried by prolonged heating at 140°. The lack of any rise near the ice point in the heat capacity curves shows that none of the salts contained an appreciable amount of water.

Heat Capacity Measurements.—The general method of Latimer and Greensfelder[2] was followed, including, however, certain improvements which also have been reported.[3] The calibrated thermocouple in the calorimeter was rechecked against the vapor pressure and triple point of hydrogen between the measurements on barium fluoride and those on lead phosphate and cesium perchlorate, while the heat capacity of the empty calorimeter was remeasured after their conclusion. The results are expressed in terms of a defined calorie (=4.1833 int. joules). The barium

TABLE I

HEAT CAPACITY OF BARIUM FLUORIDE

BaF_2, 175.37 g. = 1 mole

T, °K.	Molal C_p	T, °K.	Molal C_p
13.79	0.25	130.01	12.91
15.25	.29	134.94	13.22
17.72	.42	139.63	13.49
23.23	.90	144.10	13.65
26.20	1.20	149.75	14.01
27.70	1.37	155.28	14.21
29.35	1.56	160.66	14.41
30.00	1.65	166.14	14.62
32.43	1.96	173.17	14.92
34.73	2.27	177.59	15.02
38.08	2.72	178.32	15.13
41.45	3.18	183.31	15.27
44.96	3.62	188.17	15.39
49.20	4.20	193.05	15.54
54.24	4.90	198.09	15.65
59.34	5.61	203.93	15.85
64.36	6.34	210.14	15.96
64.64	6.38	216.91	16.14
68.65	6.94	223.27	16.22
74.76	7.79	229.73	16.32
79.83	8.36	237.32	16.49
84.72	8.94	244.95	16.62
89.48	9.49	252.69	16.68
94.41	9.99	259.32	16.76
99.52	10.44	266.35	16.81
104.78	10.98	272.87	16.89
110.11	11.47	273.94	16.91
115.03	11.84	279.44	16.90
119.76	12.19	293.08	16.90
124.79	12.56	300.69	16.98

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[1] Shell Research Fellow, Academic Year 1936–1937.

[2] Latimer and Greensfelder, THIS JOURNAL, **50**, 2202 (1928).

[3] (a) Brown, Smith and Latimer, *ibid.*, **58**, 1758 (1936); (b) Ahlberg and Latimer, *ibid.*, **56**, 856 (1934).

TABLE II

HEAT CAPACITY OF LEAD PHOSPHATE

$Pb_3(PO_4)_2$, 811.7 g. = 1 mole

T, °K.	Molal C_p	T, °K.	Molal C_p
15.70	3.47	154.25	44.92
17.90	4.25	159.47	45.75
21.71	6.19	164.95	46.57
25.29	8.05	170.23	47.40
28.32	9.70	175.35	48.14
31.57	11.48	180.32	48.89
35.61	13.67	185.07	49.67
40.72	16.23	190.23	50.37
56.60	22.46	195.62	51.07
61.30	24.11	200.84	51.90
66.59	25.89	206.48	52.52
72.20	27.58	207.68	52.44
77.57	29.11	212.22	53.10
83.23	30.64	215.17	53.76
89.16	32.21	221.67	54.30
94.56	33.53	228.11	54.91
100.36	34.81	234.74	55.70
106.42	36.17	241.56	56.44
112.09	37.37	248.21	57.14
117.43	38.40	254.87	57.85
122.50	39.39	262.16	58.38
127.92	40.34	269.06	59.00
133.72	41.45	276.26	59.70
139.08	42.49	283.79	60.12
144.32	43.35	291.96	61.31
149.43	44.14		

TABLE III

HEAT CAPACITY OF CESIUM PERCHLORATE

$CsClO_4$, 232.27 g. = 1 mole

T, °K.	Molal C_p	T, °K.	Molal C_p
15.09	2.15	144.69	19.10
18.38	3.36	146.76	19.20
21.90	4.62	152.45	19.49
25.49	5.86	157.89	19.75
29.51	7.16	163.14	19.99
33.67	8.98	168.25	20.25
38.16	9.72	173.66	20.60
42.62	10.79	180.21	21.05
46.83	11.67	187.17	21.15
50.87	12.37	193.48	21.57
55.92	13.15	200.04	21.91
61.53	13.86	206.36	22.13
70.58	14.81	213.10	22.41
76.05	15.21	220.00	22.83
81.82	15.64	226.91	23.03
87.43	16.01	235.16	23.49
93.53	16.41	242.30	23.86
99.93	16.80	249.30	24.10
105.95	17.13	256.97	24.40
111.52	17.42	264.85	24.69
117.65	17.76	274.66	25.17
124.03	18.07	283.47	25.41
130.96	18.38	292.01	25.54
138.00	18.70		

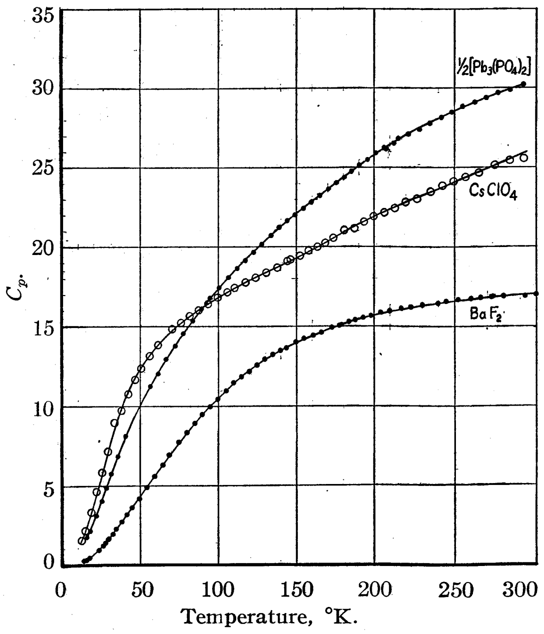

Fig. 1.—Heat capacity in cal. per degree for one mole of barium fluoride and cesium perchlorate and for one-half mole of lead phosphate.

TABLE IV

SMOOTHED VALUES OF THE HEAT CAPACITY AT EVEN TEMPERATURES

T, °K.	Molal C_p		
	BaF_2	$CsClO_4$	$Pb_3(PO_4)_2$
15	0.28	2.12	3.25
20	.60	3.89	5.28
25	1.07	5.71	7.91
30	1.65	7.31	10.61
35	2.31	8.83	13.33
40	2.98	10.19	15.88
45	3.63	11.30	18.14
50	4.32	12.24	20.15
60	5.71	13.69	23.66
70	7.13	14.74	26.94
80	8.41	15.53	29.81
90	9.53	16.19	32.40
100	10.53	16.80	34.75
110	11.43	17.36	36.90
120	12.21	17.88	38.90
130	12.90	18.37	40.77
140	13.48	18.87	42.55
150	13.98	19.37	44.27
160	14.41	19.87	45.87
170	14.79	20.38	47.37
180	15.13	20.90	48.90
190	15.45	21.41	50.35
200	15.74	21.91	51.71
220	16.20	22.83	54.16
240	16.54	23.71	56.35
260	16.77	24.53	58.25
280	16.90	25.29	59.93
300	16.98	26.00	61.45

fluoride sample weighed 242.88 g. (1.3849 moles); the lead phosphate sample, 196.59 g. (0.24220 mole); while the cesium perchlorate weighed 139.12 g. (0.59896 mole). All weights are reduced to a vacuum basis. The results are presented in Tables I, II and III and shown as a function of the temperature in Fig. 1. Smooth values of the heat capacity for even temperatures are listed in Table IV.

TABLE V

MOLAL ENTROPIES OF BARIUM FLUORIDE, LEAD PHOSPHATE, AND CESIUM PERCHLORATE IN CAL. PER DEGREE

Substance	BaF_2	$Pb_3(PO_4)_2$	$CsClO_4$
Debye extrapolation, 0–15°K.	0.09	1.07	0.82
Graphical from data, 15–298.1°K.	22.94	83.38	41.07
Entropy at 298.1°K.	23.03 ± 0.1	84.45 ± 0.4	41.89 ± 0.2

Entropies.—The entropies were calculated by graphical integration, using large scale plots of C_p against log T, combined with extrapolations to the absolute zero, using the Debye specific heat equation. The calculations are summarized in Table V.

Summary

The heat capacities of barium fluoride, tertiary lead phosphate, and cesium perchlorate have been measured from 15 to 300°K. Their entropies have been calculated to be 23.03 ± 0.1, 84.45 ± 0.4, and 41.89 ± 0.2 cal. per degree, respectively, at 298.1°K.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

The Heats of Solution of Cesium Perchlorate, Rubidium Perchlorate, Rubidium Chlorate, and Lead Phosphate

BY KENNETH S. PITZER

Using the calorimeter described in an earlier publication,[1] the integral heat of solution has been measured for the four salts listed in the title. These data were of particular interest in connection with the calculation of the entropies of the ions involved. The calculations will be presented in a later publication.

Material.—The cesium perchlorate and rubidium chlorate were taken from samples used in low temperature heat capacity investigations.[2] The rubidium perchlorate was prepared by precipitation from a dilute solution of the pure rubidium chlorate sample with perchloric acid. The lead nitrate and sodium phosphate solutions which were used in the precipitation of lead phosphate were prepared from "C. P." salts.

Heat of Solution Measurements.—The results of the heat of solution measurements are presented in Table I. The heat capacity of the calorimeter was determined frequently by electrical heating experiments. The volume of water was 885 ml. in each experiment.

TABLE I

THE HEATS OF SOLUTION OF CESIUM PERCHLORATE, RUBIDIUM PERCHLORATE, AND RUBIDIUM CHLORATE IN WATER AT 25°

Wt., g.	Molal concn. of final soln.	Heat absorbed, cal. per mole	Estimated ΔH of diln.	ΔH^0, cal. per mole
		$CsClO_4$		
1.7438	0.00848	13,160	−10	13,150
1.4462	.00704	13,400	−10	13,390
1.6530	.00804	13,190	−10	13,180
0.4932	.00240	13,320	−10	13,310
				13,260 ± 100
		$RbClO_4$		
1.2159	.00743	13,610	−10	13,600
2.2001	.01344	13,540	0	13,540
				13,570 ± 60
		$RbClO_3$		
1.5743	.01053	11,470	−20	11,450
1.7452	.01167	11,400	−20	11,380
				11,410 ± 60

Heat of Precipitation of Lead Phosphate.—It was found to be impractical to measure the heat of solution of tertiary lead phosphate, due to the slow rate of solution even in solvents which would eventually dissolve a very considerable amount. Consequently a heat of precipitation was measured. The reaction chosen was the following

$$3Pb^{++} + 4HPO_4^{--} = Pb_3(PO_4)_2 + 2H_2PO_4^-$$

Four measurements were made on the heat absorbed when 10 ml. of 0.5 molal lead nitrate solution was mixed with 875 ml. of 0.01 molal Na_2HPO_4 solution. The results obtained were

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(1) Pitzer, THIS JOURNAL, **59**, 2365 (1937).

(2) (a) Pitzer, Smith and Latimer, *ibid.*, **60**, 1826 (1938); (b) J. E. Ahlberg, Ph.D. Dissertation, University of California, 1930.

4.45, 5.25, 4.00 and 3.90 cal. with an average of 4.4 ± 0.4 cal. The heat absorbed in the dilution of 10 ml. of 0.5 molal lead nitrate solution with 875 ml. of water was also measured, with the results: 8.40, 8.30, 9.45, and 9.00 cal., average 8.8 ± 0.4 cal. Combining this value with the data of Plake,[3] the heat absorbed in the dilution to zero concentration of the lead nitrate solution was found to be 9.3 cal. With the aid of the Debye–Hückel theory, the increase in heat content with dilution was estimated to be 0.8 cal. greater for the final solution than for the initial phosphate solution. Combining these quantities, one finds $\Delta H^0 = -2460 \pm 360$ cal. for the above equation.

Making use of the heats of ionization of phosphoric acid recently published by the writer,[1] one obtains also the following results

$Pb_3(PO_4)_2 + 2H^+ = 3Pb^{++} + 2HPO_4^{--}$; $\Delta H^0 = 860 \pm 400$ cal.

$Pb_3(PO_4)_2 = 3Pb^{++} + 2PO_4^{---}$; $\Delta H^0 = 7860 \pm 1000$ cal.

All values given are for 25°.

Summary

Values have been obtained for the heats of solution at infinite dilution and 25° of the following substances: $CsClO_4$, $\Delta H^0 = 13{,}260 \pm 100$ cal.; $RbClO_4$, $\Delta H^0 = 13{,}570 \pm 60$ cal.; $RbClO_3$, $\Delta H^0 = 11{,}410 \pm 60$ cal.; $Pb_3(PO_4)_2$, $\Delta H^0 = 7860 \pm 1000$ cal.

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[3] Plake, *Z. physik. Chem.*, **A162**, 257 (1932).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

The Entropies of Aqueous Ions

BY WENDELL M. LATIMER, KENNETH S. PITZER AND WENDELL V. SMITH

In the course of the research program for the evaluation of the entropies of aqueous ions, in progress for some time in this Laboratory, a considerable body of data has accumulated which makes possible the calculation of the entropies of eleven additional ions. Because in most cases the entropy values depend on those for other ions, an extensive revision would be necessary in order to make these new values the best possible. Consequently it seemed best to make a complete revision of all ionic entropies and to include the new ions at the same time.

In order to avoid unnecessary length, specific references have been given only where the data are not included in some summary publication. Most of the new calculations are based upon data taken from recent publications in this research series[1] and from the references cited in the earlier summary paper.[2] In general entropies have been taken from the excellent summaries of Kelley,[3] heats of reaction from Bichowsky and Rossini,[4] and activity coefficients and other free energy data from the Landolt–Börnstein Tabellen.[5]

The calculations are summarized in Table I and the best values of the ionic entropies collected in Table II. Different methods of obtaining a given entropy are included only if they are independent in the least accurate step. An attempt has been made to include all sources of error in estimating the uncertainty in the final values. For this reason the uncertainty given for a final value is often much larger than the difference between the various values for that quantity would indicate.

The standard state for ionic entropies has been defined in several earlier papers, wherein the theoretical significance and practical importance of ionic entropies also have been discussed. As the body of data becomes larger, however, its consistency becomes more notable, and offers more and more evidence of the validity of the third law of thermodynamics when applied to crystalline inorganic salts. The possibility of difficulties in the case of hydrated crystals has arisen recently and has been discussed elsewhere.[1b] It is felt that errors from this source cannot have any serious effect on the values obtained in this paper.

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[1] (a) Pitzer, Smith and Latimer, THIS JOURNAL, **60**, 1826 (1938); (b) Pitzer and Coulter, *ibid.*, **60**, 1310 (1938), (c) Pitzer, *ibid.*, **60**, 1828 (1938); **59**, 2365 (1937); (d) Smith, Pitzer and Latimer, *ibid.*, **59**, 2640, 2642 (1937); (e) Pitzer and Smith, *ibid.*, **59**, 2633 (1937); (f) Smith, Brown and Pitzer, *ibid.*, **59**, 1213 (1937); (g) Brown, Smith and Latimer, *ibid.*, **58**, 1728, 2144, 2228 (1936); **59**, 921 (1937).

[2] Latimer, Schutz and Hicks, *J. Chem. Phys.*, **2**, 82 (1934).

[3] Kelley, *Bur. Mines Bull.*, 350, 1932 and 394, 1936.

[4] Bichowsky and Rossini, "Thermochemistry of Chemical Substances," Reinhold Publishing Corporation, New York, N. Y., 1936.

[5] Landolt–Börnstein "Physikalisch-chemische Tabellen," including Supplements 1, 2 and 3, Verlag von Julius Springer, Berlin, 1923–1936.

TABLE I

SUMMARY OF ENTROPY CALCULATIONS

Units: cal. per degree per mole

Reaction	$\Delta S^\circ_{298.1}$	Ion	
$H_2O(l) = H^+ + OH^-$	−19.24[1c]	$S^\circ_{OH^-}$	− 2.49 ± 0.06
$HCl(g) = H^+ + Cl^-$	−31.14	$S^\circ_{Cl^-}$	13.52 ± .15
$AgCl(s) + {}^1/_2H_2 = H^+ + Cl^- + Ag$	−14.89		13.49 ± .15
$Ag_2O(s) + 2H^+ = 2Ag^+ + H_2O(l)$	22.58[1e]	$S^\circ_{Ag^+}$	17.46 ± .2
$AgCl(s) = Ag^+ + Cl^-$	8.15[1e]		17.62 ± .2
$AgBr(s) + Cl^- = AgCl(s) + Br^-$	3.69	$S^\circ_{Br^-}$	19.8 ± .2
$AgBr(s) + {}^1/_2H_2 = H^+ + Br^- + Ag$	−11.4[6]		19.6 ± .3
$0.5Br_2(l) + Cl^- = 0.5Cl_2(g) + Br^-$	14.3		19.5 ± .4
$AgI(s) + 0.5H_2 = H^+ + I^- + Ag$	− 7.6[13]	$S^\circ_{I^-}$	25.4 ± .5
$0.5I_2(s) + 0.5H_2(g) = H^+ + I^-$	− 4.3		25.2 ± .7
$KCl(s) = K^+ + Cl^-$	17.96	$S^\circ_{K^+}$	24.2 ± .2
$KBr(s) = K^+ + Br^-$	21.4		24.3 ± .8
$BaCl_2 \cdot 2H_2O(s) = Ba^{++} + 2Cl^- + 2H_2O(e)$	14.2[1g]	$S^\circ_{Ba^{++}}$	2.3 ± .3
$KNO_3(s) = K^+ + NO_3^-$	27.4	$S^\circ_{NO_3^-}$	35.0 ± .3
$Ba(NO_3)_2(s) = Ba^{++} + 2NO_3^-$	21.1[1g]		35.0 ± .3
$NaCl(s) = Na^+ + Cl^-$	10.4	$S^\circ_{Na^+}$	14.1 ± .5
$NaNO_3(s) = Na^+ + NO_3^-$	21.5		14.3 ± .5
$Na + H^+ = Na^+ + 0.5H_2(g)$	17.1		13.7 ± .5
$CaCO_3(s) + 2H^+ = Ca^{++} + H_2O(l) + CO_2(g)$	34.2	$S^\circ_{Ca^{++}}$	−11.4 ± .3
$SrCO_3(s) + 2H^+ = Sr^{++} + H_2O(l) + CO_2(g)$	37.4[7]	$S^\circ_{Sr^{++}}$	− 7.3 ± 1.5
$Na_2SO_4 \cdot 10H_2O(s) = 2Na^+ + SO_4^= + 10H_2O(l)$	57.7[1b]	$S^\circ_{SO_4^=}$	4.4 ± 1.0
$Ag_2SO_4(s) = 2Ag^+ + SO_4^=$	− 8.3		4.5 ± 2
$CaSO_4 \cdot 2H_2O(s) = Ca^{++} + SO_4^= + 2H_2O(l)$	−21.8		2.5 ± 2
$PbSO_4(s) + 2H_2O = H_2(g) + PbO_2(s) + SO_4^= + 2H^+$	−16.0[8]		3.2 ± 2
$Hg_2SO_4(s) + H_2(g) = 2Hg + 2H^+ + SO_4^=$	−37.0[9]		5.2 ± 2
$SO_4^= + H^+ = HSO_4^-$	26.3[1c]	$S^\circ_{HSO_4^-}$	30.6 ± 2
$CO_2(g) + H_2O(l) = H_2CO_3(aq)$	−22.7	$S^\circ_{H_2CO_3}$	45.1 ± 0.7
$H_2CO_3 = H^+ + HCO_3^-$	−22.9[1c]	$S^\circ_{HCO_3^-}$	22.2 ± .8
$HCO_3^- = H^+ + CO_3^=$	−35.2[1c]	$S^\circ_{CO_3^=}$	−13.0 ± 1.0
$H_2S(g) = H_2S(aq)$	−19.7	$S^\circ_{H_2S(aq)}$	29.4 ± 0.3
$H_2S(aq) = H^+ + HS^-$	−14.5	$S^\circ_{HS^-}$	14.9 ± 1.0
$HCN(g) = H^+ + CN^-$	−23	$S^\circ_{CN^-}$	25 ± 5
$NH_3(g) + H_2O(l) = NH_4OH(aq)$	−19.8	$S^\circ_{NH_4OH}$	42.8 ± 0.4
$NH_4OH = NH_4^+ + OH^-$	−18.9[1c]	$S^\circ_{NH_4^+}$	26.4 ± .5
$SO_2(g) + H_2O(l) = H_2SO_3(aq)$	−21.4	$S^\circ_{H_2SO_3}$	54.7 ± 1.0
$H_2SO_3 = H^+ + HSO_3^-$	−22.1	$S^\circ_{HSO_3^-}$	32.6 ± 1.5
$HSO_3^- = H^+ + SO_3^=$	−30	$S^\circ_{SO_3^=}$	3 ± 3
$Cl_2(g) + 2OH^- = H_2O + Cl^- + ClO^-$	− 8.1	$S^\circ_{ClO^-}$	10.0 ± 2.0
$Li_2CO_3 = 2Li^+ + CO_3^=$	−25.1[1g]	$S^\circ_{Li^+}$	4.7 ± 1.0
$KClO_3 = K^+ + ClO_3^-$	29.4	$S^\circ_{ClO_3^-}$	39.4 ± 0.5
$KClO_4 = K^+ + ClO_4^-$	31.7	$S^\circ_{ClO_4^-}$	43.6 ± .5
$RbClO_3 = Rb^+ + ClO_3^-$	32.0[10]	$S^\circ_{Rb^+}$	28.9 ± .8
$RbClO_4 = Rb^+ + ClO_4^-$	33.6[11]		28.5 ± 1.0
$CsClO_4 = Cs^+ + ClO_4^-$	33.5[1a]	$S^\circ_{Cs^+}$	31.8 ± 0.6
$TlNO_3 = Tl^+ + NO_3^-$	27.6[1g]	$S^\circ_{Tl^+}$	31.0 ± .5
$Tl + AgCl = Ag + Tl^+ + Cl^-$	15.3		30.1 ± .5
$AgNO_2 = Ag^+ + NO_2^-$	16.8	$S^\circ_{NO_2^-}$	29.9 ± 1.0
$Ag_2CrO_4 = 2Ag^+ + CrO_4^=$	− 6.2	$S^\circ_{CrO_4}$	10.5 ± 1.0
$AgClO_2 = Ag^+ + ClO_2^-$	9.5	$S^\circ_{ClO_1^-}$	24.1 ± 0.5
$KMnO_4 = K^+ + MnO_4^-$	29.9	$S^\circ_{MnO_4^-}$	46.7 ± .4
$KBrO_3 = K^+ + BrO_3^-$	27.2	$S^\circ_{BrO_3^-}$	38.7 ± 1
$Ba(BrO_3)_2 \cdot H_2O = Ba^{++} + 2BrO_3^- + H_2O(l)$	26.5		38.1 ± 2
$KIO_3 = K^+ + IO_3^-$	15.9	$S^\circ_{IO_3^-}$	27.9 ± 1
$AgIO_3 = Ag^+ + IO_3^-$	10.1[12]		28.3 ± 3

TABLE I (*Concluded*)

Reaction	$\Delta S^{\circ}_{298.1}$	Ion	
$HF(g) = H^+ + F^-$	−43.9	$S^{\circ}_{F^-}$	− 2.4 ± 2
$BaF_2 = Ba^{++} + 2F^-$	−21.5[1a]		− 0.4 ± 2
$CaF_2 = Ca^{++} + 2F^-$	−36.2		− 4.2 ± 2
$Cu + 2H^+ = Cu^{++} + H_2$	− 2.7	$S^{\circ}_{Cu^{++}}$	−25.9 ± 3
$Cu + 2Ag^+ = Cu^{++} + 2Ag$	−49.2		−26.6 ± 1
$Zn + 2H^+ = Zn^{++} + H_2$	− 4.5	$S^{\circ}_{Zn^{++}}$	−25.7 ± 1
$Cd + 2H^+ = Cd^{++} + H_2$	2.5	$S^{\circ}_{Cd^{++}}$	−16.4 ± 1.5
$Fe + 2H^+ = Fe^{++} + H_2$	− 1.2	$S^{\circ}_{Fe^{++}}$	−25.9 ± 1
$Fe^{++} + H^+ = Fe^{+++} + 0.5H_2$	−19.8	$S^{\circ}_{Fe^{+++}}$	− 61 ± 5
$Sn + 2H^+ = Sn^{++} + H_2$	14.0	$S^{\circ}_{Sn^{++}}$	− 4.9 ± 1
$2Hg + 2H^+ = Hg_2^{++} + H_2$	11.9	$S^{\circ}_{Hg_2^{++}}$	17.7 ± 3
$PbCl_2 = Pb^{++} + 2Cl^-$	− 1.7	$S^{\circ}_{Pb^{++}}$	3.9 ± 0.9
$Mg(OH)_2 + 2H^+ + Mg^{++} + 2H_2O$	−13.3	$S^{\circ}_{Mg^{++}}$	31.6 ± 3
$CsAl(SO_4)\cdot_2 12H_2O(s) = Cs^+ + Al^{+++} + 2SO_4^= + 12H_2O(l)$	2	$S^{\circ}_{Al^{+++}}$	−76 ± 10
$CaC_2O_4\cdot H_2O = Ca^{++} + C_2O_4^= + H_2O(l)$	−22.5	$S^{\circ}_{C_2O_4^=}$	9.6 ± 1
$Ag^+ + 2NH_3(aq) = Ag(NH_3)_2^+$	−11.9[1f]	$S^{\circ}_{Ag(NH_3)_2^+}$	57.8 ± 1
$Pb_3(PO_4)_2 + 2H^+ = 3Pb^{++} + 2HPO_4^=$	−77.3[1a]	$S^{\circ}_{HPO_4^=}$	− 2.3 ± 1.5
$HPO_4^= + H^+ = H_2PO_4^-$	30.3	$S^{\circ}_{H_2PO_4^-}$	28.0 ± 1.5
$H_2PO_4^- + H^+ = H_3PO_4(aq)$	16.0	$S^{\circ}_{H_3PO_4}$	44.0 ± 1.5
$HPO_4^= = H^+ + PO_4^{\equiv}$	−43	$S^{\circ}_{PO_4^{\equiv}}$	−45 ± 2

TABLE II

ENTROPIES OF AQUEOUS IONS AT 298.1°K.

Units: cal. per degree per mole.

H^+	0.00	Cl^-	13.50 ± 0.10
Li^+	4.7 ± 1.0	Br^-	19.7 ± .2
Na^+	14.0 ± 0.4	I^-	25.3 ± .5
K^+	24.2 ± .2	ClO^-	10.0 ± 2
Rb^+	28.7 ± .7	ClO_2^-	24.1 ± 0.5
Cs^+	31.8 ± .6	ClO_3^-	39.4 ± .5
Ag^+	17.54 ± .15	ClO_4^-	43.6 ± .5
NH_4^+	26.4 ± .5	BrO_3^-	38.5 ± 1.0
Tl^+	30.5 ± .4	IO_3^-	28.0 ± 1.0
$Ag(NH_3)_2^+$	57.8 ± 1.0	HS^-	14.9 ± 1.0
Mg^{++}	−31.6 ± 3	HSO_3^-	32.6 ± 1.5
Ca^{++}	−11.4 ± 0.3	SO_3^{--}	3 ± 3
Sr^{++}	− 7.3 ± 1.5	HSO_4^-	30.6 ± 2
Ba^{++}	2.3 ± 0.3	SO_4^{--}	4.4 ± 1.0
Fe^{++}	−25.9 ± 1.0	NO_2^-	29.9 ± 1.0
Cu^{++}	−26.5 ± 1.0	NO_3^-	35.0 ± 0.2
Zn^{++}	−25.7 ± 1.0	$H_2PO_4^-$	28.0 ± 1.5
Cd^{++}	−16.4 ± 1.5	HPO_4^{--}	− 2.3 ± 1.5
Hg_2^{++}	17.7 ± 3	PO_4^{---}	−45 ± 2
Sn^{++}	− 4.9 ± 1.0	HCO_3^-	22.2 ± 0.8
Pb^{++}	3.9 ± 0.9	CO_3^{--}	−13.0 ± 1
Al^{+++}	−76 ± 10	$C_2O_4^{--}$	9.6 ± 1
Fe^{+++}	−61 ± 5	CN^-	25 ± 5
OH^-	− 2.49 ± 0.06	MnO_4^-	46.7 ± 0.4
F^-	− 2.3 ± 2	CrO_4^{--}	10.5 ± 1.0

Summary

The calculation of the entropies of aqueous ions have been completely revised and extended to include eleven additional ions.

BERKELEY, CALIF. RECEIVED MARCH 30, 1938

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(6) Harned, Keston and Donelson, THIS JOURNAL, **58**, 989 (1936); **59**, 1280 (1937).

(7) Heat of solution: Zimmerman, private communication.

(8) Hamer, THIS JOURNAL, **57**, 9 (1935).

(9) (a) Harned and Hamer, *ibid.*, **57**, 27 (1935); (b) ($S^{\circ}_{Hg_2SO_4}$ = 48.0 cal. per degree per mole); Schutz, Ph.D. Dissertation, Univ. of California, 1933.

(10) ($S^{\circ}_{RbClO_3}$ = 36.3 cal. per degree per mole), Ahlberg, Ph.D. Dissertation, Univ. of California, 1930.

(11) ($S^{\circ}_{RbClO_4}$ = 38.5) estimated from values for $CsClO_4$,[1a] $KClO_4$, $RbClO_3$ and $KClO_3$, using the formula of Latimer, THIS JOURNAL, **43**, 818 (1921).

(12) (ΔF of soln. of $AgIO_3$), Kolthoff and Lingane, *J. Phys. Chem.*, **42**, 133 (1938).

(13) Owen, THIS JOURNAL, **57**, 1526 (1935).

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE PORTLAND CEMENT ASSOCIATION]

The Reactions between Silica and Calcium Oxide in Aqueous Solutions and their Relation to Pozzolanic Action

BY ALFRED E. BEITLICH[1]

Our modern conception of pozzolanas defines them as materials which, though not cementitious in themselves, contain constituents which will combine with calcium oxide at ordinary temperatures in the presence of water to form stable insoluble compounds possessing cementitious properties. Most natural or artificial pozzolanic materials are generally composed of silica, alumina, iron oxide, and calcium oxide. There may also be present magnesia, potassium, and sodium oxides, and possibly other elements in very small quantities. In contrast to portland cement, no definite chemical composition can be ascribed to pozzolanas; the type of oxides present and their percentages vary within wide limits. They are materials of very complex mineralogic aspects, and complete petrographic researches are still lacking. Only one thing is common to all pozzolanas, and that is their ability to harden under water or in air in the presence of moisture when mixed with calcium oxide or a material which liberates calcium oxide.

Many investigations have failed to produce fundamental data because of the complexities of the systems studied. From previous work it has been established that the presence of water, silica, and calcium oxide is important for the development of pozzolanic action. It was decided, therefore, to confine the present study to the reactions between silica and calcium oxide in aqueous solutions, thus eliminating many complicating factors.

Experimental Part

Apparatus and Procedure.—An electrical conductivity method was selected, since this gave promise of providing a ready means of following continuously the reactions taking place. All experiments were carried out at a constant temperature of 30 ± 0.01° in a thermostatically controlled water-bath. For measuring the electrical conductivity, a precision slide wire Wheatstone bridge hookup was employed with a conductivity cell of the dip type. The constant of the cell was determined at 30° with 0.01 N potassium chloride solution and was found to be 0.1191. Conductivity water, prepared in a specially designed Pyrex still which produced a satisfactory water with a specific conductivity of less than 1.2×10^{-6} mho, was used in all experiments.

It was necessary to determine the conductivities of calcium oxide solutions at various concentrations, which was done over the range of from very dilute solutions to the saturation point. The stock solution with an excess of the oxide to ensure constant saturation was stored in a paraffin-lined glass bottle. The concentration of the solution was determined gravimetrically and by titration with standardized hydrochloric acid.

For the conductivity measurements mentioned above, measured quantities of the stock solution were diluted with conductivity water so as to provide the desired range of concentration. The results were plotted on large-scale coördinate paper in terms of grams of calcium oxide per liter and the corresponding electrical conductivities of the solutions. With this graph it was possible to determine accurately and rapidly the concentration of any calcium oxide solution by determining its electrical conductivity.

The silica used in this study was C. P. silicic acid, containing 80.00% SiO_2, ground to pass a 300-mesh sieve. In the first series of experiments, which were necessary to obtain information on the general nature and rate of reaction and the best manner of proportioning the three reacting agents (silica, calcium oxide, and water), the reaction chamber consisted of a 3-necked Pyrex flask. One liter of calcium oxide solution of the desired concentration was transferred to the flask immersed in the water-bath. The center tubulature was provided with a mercury seal stirrer rotating at a speed of 1000 r. p. m. Extreme care was taken to protect all calcium oxide solutions from exposure to air. The conductivity of the solution was determined after the solution had reached the bath temperature. Then a weighed amount of silica was introduced and conductivity readings again taken immediately. While the solution was being agitated continuously, measurements were made at short intervals until equilibrium was reached.

The conductivity method for determining the rate of combination of calcium oxide with silica proved very convenient and successful. The procedure permitted following accurately the reactions from the very earliest stages to final equilibrium without disturbing the system by the withdrawal of portions of the solution. The time required for one measurement was only thirty seconds. The method is distinguished by perfect reproducibility, and the entire course of the reactions can be plotted in small intervals over the entire range.

The amount of silica per liter of calcium oxide solution was kept constant at 0.8954 g. in this series of tests, and the concentration of the solutions ranged from 0.025 to 1.191 g. of calcium oxide per liter. In all cases the measurements showed a decided drop in electrical conductivity during the first few minutes of contact of the reacting agents, indicating a lowering of the calcium oxide content of the solution. As the time of agitation progressed, the rate of drop in conductivity became less, and finally a state was approached asymptotically in which there was no more

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change in conductivity. The more concentrated the initial calcium oxide solution was, the more slowly the final state of equilibrium was reached, requiring agitation periods of several months. Because of this slowness of reaction and to enable several tests to be run at the same time, a shaker was installed in which eight Erlenmeyer flasks of 500-cc. capacity were agitated simultaneously. To facilitate the interpretation of the results, silica and calcium oxide in the suspensions were proportioned on a molecular basis rather than on the gram basis used in earlier experiments.

The second series included thirty-four samples in which the molecular ratios of CaO to SiO_2 at the beginning of the experiment (initial ratios) were varied from 0.05 to 3.75. The amount of calcium oxide ranged from 1.0 to 75.0 milliequivalents (m. e.). The amount of silicon dioxide was 20.0 m. e. in most cases, although some samples contained 10.0 and 30.0 m. e. of silicon dioxide in order to broaden the field of investigation. In the range of high calcium oxide, above the point of saturation, solid calcium oxide was added, together with the silicon dioxide, to the saturated calcium oxide solution.

Equilibria in the System Calcium Oxide–Silica–Water.—The data on equilibria secured in this system are best explained by means of Table I and Fig. 1. In the first two columns of Table I are recorded the amounts of calcium oxide and silica which were allowed to react in water until equilibrium had been reached. The term equilibrium in this report refers to an apparently steady state in which there is practically no further change in conductivity with time. It is understood that such a state does not represent a true equilibrium, but the latter is attained exceedingly slowly at the temperature of the experiment, and the differences between apparent and true equilibria can be neglected without affecting the findings of this investigation. The initial ratios of CaO to SiO_2 are recorded in the third column. The conductivities of the solutions when equilibrium has been reached are given in the fourth column, and the amounts of uncombined calcium oxide remaining in solution at equilibrium (which were calculated from the conductivity data) are listed in the fifth column. The last column shows the ratio of combined CaO to SiO_2 at equilibrium.

Interpretation of Results.—An attempt was made to establish the nature of the combination of calcium oxide with silica, the question being whether it is a chemical reaction or an adsorption, or both. It was sought to determine whether the removal of calcium oxide from solution by the silica follows the Freundlich adsorption isotherm, which is generally taken as characteristic of a surface adsorption, or whether the observed data would suggest a different interpretation. Since the Freundlich adsorption isotherm is usually expressed by the equation

$$X = aC^{1/n} \text{ or } \log X = \log a + 1/n \log C \quad (1)$$

a straight line should result if the logarithms of the adsorbed quantities are plotted against the logarithms of the corresponding concentrations.

Table I

Equilibrium Data of the CaO–SiO_2 Reactions

M. e. per liter		Ratio of CaO to SiO_2 at start	Conductivity of soln. at equil., mho	Uncombined CaO in soln. at equil. m. e. per liter	Ratio of comb. CaO to SiO_2 at equil.
CaO	SiO_2				
1.0	20.0	0.05	0.000053	0.21	0.040
1.0	10.0	.10	.000086	.35	.065
2.0	20.0	.10	.000110	.44	.078
3.0	30.0	.10	.000115	.46	.085
3.0	20.0	.15	.000160	.64	.118
4.0	20.0	.20	.000215	.86	.157
6.0	30.0	.20	.000237	.95	.168
5.0	20.0	.25	.000278	1.12	.194
6.0	20.0	.30	.000327	1.32	.234
9.0	30.0	.30	.000348	1.39	.254
7.0	20.0	.35	.000362	1.46	.277
8.0	20.0	.40	.000374	1.50	.325
12.0	30.0	.40	.000374	1.50	.350
9.0	20.0	.45	.000375	1.50	.375
10.0	20.0	.50	.000370	1.49	.426
15.0	30.0	.50	.000370	1.49	.450
12.0	20.0	.60	.000368	1.48	.526
14.0	20.0	.70	.000445	1.79	.611
16.0	20.0	.80	.000548	2.20	.690
18.0	20.0	.90	.000647	2.60	.770
20.0	20.0	1.00	.001056	4.27	.782
22.0	20.0	1.10	.001525	6.24	.788
24.0	20.0	1.20	.002001	8.42	.779
26.0	20.0	1.30	.002350	10.06	.797
28.0	20.0	1.40	.002576	11.10	.845
30.0	20.0	1.50	.002763	11.95	.903
32.0	20.0	1.60	.003068	13.37	.932
34.0	20.0	1.70	.003206	14.05	.998
37.0	20.0	1.85	.003453	15.23	1.089
40.0	20.0	2.00	.003792	16.83	1.159
48.0	20.0	2.40	.004834	21.93	1.304
56.0	20.0	2.80	.005497	25.32	1.534
70.0	20.0	3.50	.006908	32.52	1.874
75.0	20.0	3.75	.007610	36.09	1.946

Figure 1 shows the results of the experiments entered on log–log paper. The concentrations of the calcium oxide solution at equilibrium in milliequivalents ($C \times 10^3$) are plotted as abscissas and the ratios of combined CaO/SiO_2 (X) as ordinates (Columns 5 and 6, Table I). A graph consisting of several straight lines is obtained by connecting the points. The numerals accompanying these points give the molecular ratios of CaO/SiO_2 at the start of the experiments (Column 3, Table I).

The portion A–B represents equilibria attained with suspensions having initial ratios of CaO/SiO_2 from 0.05 to 0.30. The fact that all points fall upon or very close to a straight line indicates that the Freundlich equation is applicable in that range and that the calcium oxide is adsorbed by the silica in suspension. Evaluating the constants $1/n$ and a yielded the equation

$$X = 159.6\ C^{0.98} \qquad (2)$$

which enables the calculation of the adsorption of calcium oxide in the range A–B, that is, from 0.05 to 0.30 initial CaO/SiO_2 ratios.

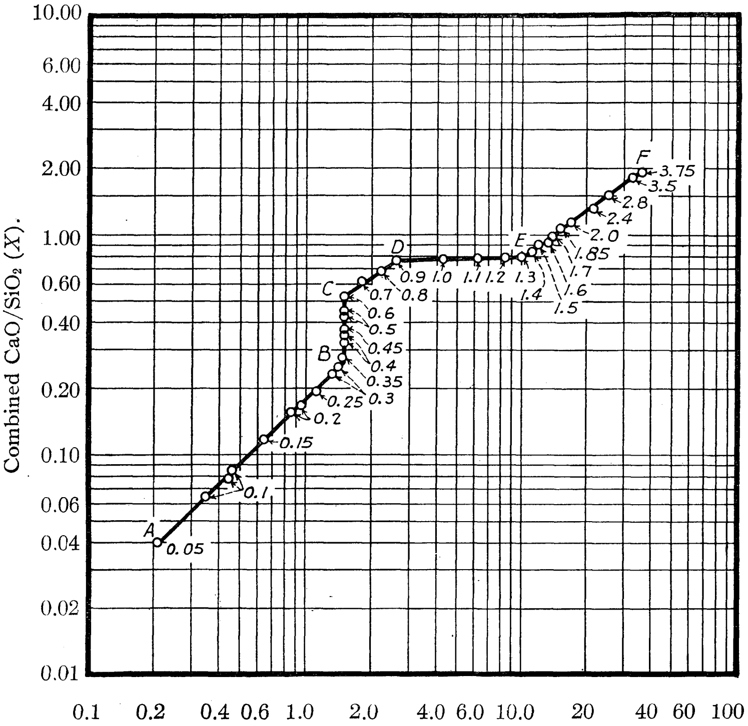

Fig. 1.—Relationship between molecular ratio of combined CaO/SiO_2 and concentration of CaO in the liquid phase.

As the concentration is increased above the ratio of 0.30, the line connecting the points in the graph makes a sharp turn upward and continues in a vertical straight line to point C. This indicates that comparatively more of the available calcium oxide is combined with silica than in the range A–B, and equilibria are being attained when the concentrations of the calcium oxide solutions have been reduced to one containing approximately 1.5 m. e. of calcium oxide per liter. C, which is at the end of this range, is located near a point where the ratio of combined CaO/SiO_2 is 1 to 2. Therefore, it seems justified to assume that, after the first phase of adsorption reactions has been completed and an equilibrium concentration of 1.5 m. e. of calcium oxide per liter has been reached, a further increase in calcium oxide concentration leads to chemical combination of calcium oxide and silica to form a hydrated $CaO \cdot 2SiO_2$. This combination is completed when the initial ratio of CaO/SiO_2 has been raised to 0.60.

From point C to point D the straight connecting line proceeds upward at an angle, and Freundlich's adsorption isotherm is again applicable for that range. It appears that further increases of the calcium oxide concentration lead to an adsorption of calcium oxide onto the newly formed $CaO \cdot 2SiO_2$ hydrate. The adsorption equation for this range is

$$X = 44.95\ C^{0.68} \qquad (3)$$

Point D on the graph is reached with a sample having an initial CaO/SiO_2 ratio of 0.9, and the ratio of combined CaO/SiO_2 becomes 4 to 5. On increasing the initial CaO/SiO_2 ratio from 0.9 to 1.3, no more adsorption is taking place. The line leads horizontally to point E. In this range, D–E, the combination of calcium oxide and silica proceeds to a state in which the ratio of 4CaO to $5SiO_2$ is maintained, and only after increasing the initial CaO/SiO_2 ratio above 1.3 is more calcium oxide being combined.

Beyond point E, the line proceeds upward again, indicating a third range of adsorption reactions. The calculation of the constants gives the adsorption equation

$$X = 23.38\ C^{0.74} \qquad (4)$$

for the range of initial CaO/SiO_2 ratios from 1.3 to 3.75. The ratio of combined CaO/SiO_2 in the adsorption product at point F is 1.946 to 1, and the solution in which it is stable at equilibrium is very close to the saturation point of calcium oxide at that temperature. This suggests that a hydrated $2CaO \cdot SiO_2$ exists in a saturated solution of calcium oxide. The exploration of the field with still higher concentrations of calcium oxide is not possible with the conductivity method used in this investigation, since its usefulness ends when the solution at equilibrium is saturated.

Discussion

The study of the reactions of calcium oxide and silica in the presence of water revealed that, under the conditions of the experiment, definitely identified adsorption reactions take place. It also showed that chemical compounds are formed in which the ratios of calcium oxide to silicon dioxide are very close to 1:2, 4:5, and 2:1, corresponding to $CaO \cdot 2SiO_2 \cdot xH_2O$, $4CaO \cdot 5SiO_2 \cdot xH_2O$, and $2CaO \cdot SiO_2 \cdot xH_2O$.

The adsorptive capacity of hydrated silica for calcium oxide has been studied by Shaw and MacIntire[2] in connection with a research on the components of soils. These investigators found that "the adsorption of $Ca(OH)_2$ by hydrated silica occurs in accordance with the Freundlich adsorption isotherm, when the final concentrations of $Ca(OH)_2$ are above 0.005 N. When the final concentrations are less than 0.005 N, several inflections appear in the adsorption curve and these point to a series of chemical combinations between the $Ca(OH)_2$ and the SiO_2." No information is given in their paper about the causes of these inflections and the nature of the chemical combinations. The adsorption isotherm calculated by Shaw and MacIntire does not agree with the equation established in this paper for the same range of concentrations. This discrepancy can be explained easily by the fact that the former equation expresses the adsorption phenomena for a contact period of only five days, while the latter was established after equilibrium had been attained. The chemical combinations in concentrations below 0.005 N strength, or less than 5 m. e. calcium oxide per liter, the existence of which was held possible by Shaw and MacIntire, have been established in the present paper, together with the two additional ranges of adsorption reactions in the lower field of concentrations.

The possibility that adsorption reactions can take place in the system $CaO–SiO_2–H_2O$ has been advanced also by Baylis,[3] who stated that there may be a definite chemical reaction between calcium hydroxide and hydrous oxides of silica forming a compound closely approaching $CaO \cdot SiO_2$. In addition to this, considerable calcium hydroxide appears to be adsorbed by this compound when the concentration of calcium hydroxide in the surrounding solution is increased over that necessary to form the definite compound. Although the present investigation proves the existence of adsorption phenomena, a definite hydrated calcium silicate in which the ratio of calcium oxide to silicon dioxide is unity, was not found.

Flint and Wells[4] carried out an extensive study of the reactions of calcium oxide and silica in the presence of water and state that the solid phase in equilibrium with solutions which contain only a few hundredths of a mole of calcium oxide per mole of silicon dioxide may consist of hydrated silica with a small amount of adsorbed calcium oxide. Determinations of the OH ion concentration showed that calcium oxide and silica in solution are combined in a ratio of less than 1CaO to $1SiO_2$ at low calcium oxide concentrations and at a ratio greater than 1 to 1 at high calcium oxide concentrations. It appeared that the molar ratio $2CaO:1SiO_2$ is approached when the solid phase is in equilibrium with a saturated calcium oxide solution.

The findings of the present study support the assumption of Flint and Wells that calcium oxide is adsorbed by silica at low concentrations and that a hydrated $2CaO \cdot SiO_2$ is stable in saturated calcium oxide solution. There are, however, some differences in the findings about the formation of chemical compounds in the intermediate range. While Flint and Wells obtained data which they assume to represent compositions of the ratio $1CaO:2SiO_2$ and $1CaO:1SiO_2$, the conductivity determinations revealed the formation of two hydrated silicates in which the ratios of calcium oxide to silicon dioxide are 1:2 and 4:5. No hydrated monocalcium silicate was found.

By agitating an excess of diatomaceous earth in calcium oxide solutions, Cummins and Miller[5] obtained in the solid phase a compound having a molecular ratio of CaO to SiO_2 of 5:6, corresponding to the formula $5CaO \cdot 6SiO_2$.

The question concerning the types of hydrated calcium silicates which may exist in aqueous solutions was attacked in the opposite direction by Kühl and Mann[6] by preparing anhydrous melts of calcium oxide and silica of various predetermined compositions and agitating them in calcium oxide solutions of varying concentrations. These investigators found that a hydrated calcium silicate which is less basic than $CaO \cdot SiO_2 \cdot xH_2O$ does not exist. A gel of the composition $CaO \cdot SiO_2 \cdot aq.$ is stable in a solution containing 0.131 g. calcium oxide per liter, and a series of hydrated calcium silicates exists having ratios of calcium

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[2] W. M. Shaw and W. H. MacIntire, *Soil Sci.*, **29**, 429–56 (1930).

[3] J. R. Baylis, *J. Phys. Chem.*, **32**, 1236–1262 (1928).

[4] E. P. Flint and L. S. Wells, *Bur. Standards J. Research*, **12**, 751–783 (1934).

[5] A. B. Cummins and L. B. Miller, *Ind. Eng. Chem.*, **26**, 688–693 (1934).

[6] H. Kühl and A. Mann, *Tonind. Ztg.*, **58**, 862–5, 896–7, 918–19, 930–2, 944–5, 955–7, 990–1, 1003, 1014–16 (1934).

oxide to silicon dioxide ranging from 1:1 to 2:1. Since the materials used by Kühl and Mann were synthetic melts and the products at equilibrium not formed by the combination of the basic constituents calcium oxide and silica but by hydrolysis or hydration of the silicates, the results do not lend themselves to a direct comparison with the observations reported here.

Summary

On the basis of the results secured by means of the conductivity method and under the conditions of the experiment, the reactions between calcium oxide and silica proceed in the following manner:

With dilute solutions the silica adsorbs calcium oxide in accordance with the Freundlich adsorption isotherm. Above an initial ratio of CaO/SiO_2 of 0.30 and up to 0.60, chemical combination takes place, and a reaction product is formed in which the ratio of CaO/SiO_2 is 1 to 2. This product is stable in a solution containing 1.5 m. e. of calcium oxide per liter.

On increasing the calcium oxide concentration further above an initial ratio of 0.60, adsorption takes place again, which proceeds until the initial ratio of CaO/SiO_2 is 0.90 and the ratio of combined CaO/SiO_2 is 4 to 5.

The reaction product with the ratio of 4CaO to $5SiO_2$ is stable up to an equilibrium concentration of 10 m. e. of calcium oxide per liter. With higher concentrations of calcium oxide and initial ratios from 1.3 to 3.75, a third range of adsorption reactions takes place. As the point of saturation of the calcium oxide solution at equilibrium is reached, the ratio of CaO/SiO_2 in the reaction product approaches 2:1, indicating the probable existence of a hydrated $2CaO \cdot SiO_2$ in saturated calcium oxide solution.

CHICAGO, ILL. RECEIVED APRIL 23, 1938

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY No. 648]

The Electron Diffraction Investigation of the Molecular Structures of (1) Phosphorus Oxytrichloride, Oxydichlorofluoride, Oxychlorodifluoride, Oxytrifluoride, Fluorodichloride, Pentafluoride, and Trifluorodichloride, and of (2) Disilane, Trichlorosilane, and Hexachlorodisilane

BY L. O. BROCKWAY[1] AND J. Y. BEACH[2]

The molecular structures of the halogen derivatives of the non-metals are of special interest because of the systematic deviations from additivity of bond radii which are observed in many of these substances.[3,4] With the exception of those of the first row elements, the observed distances in the halogen derivatives are all smaller than the sum of the corresponding radii for single covalent bonds. This decrease is apparently greatest in the silicon compounds and is less marked in the elements toward the right and in the lower rows of the periodic table. The effect, moreover, is greatest in the fluorides and decreases in order with the other halogens. While the regular way in which the effect varies from one element to another suggests that the same causes are operating in all of them, the nature of the causes is not entirely certain. It seemed desirable to extend the investigation of phosphorus and silicon compounds, where the effect is greatest, and we have determined the structures of a number of mixed fluorine and chlorine derivatives of phosphorus, including some oxygen compounds, as well as those of three silicon compounds.

The diffraction patterns were obtained in the usual way,[5] whereby a beam of electrons traverses a sample of the vapor and the diffracted electrons are recorded on a photographic emulsion. The apparent maxima as well as some of the minima were measured visually on a comparator, and the observed diameters were converted to the s_0 values [equal to $4\pi (\sin \theta/2)/\lambda$] listed in the tables below. The s_0 values for the maxima were used with the visually estimated intensities, I_k, in the calculation of the functions shown in Figs. 1 and 8 representing the observed radial

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[1] At present Fellow of the John Simon Guggenheim Memorial Foundation.

[2] At present National Research Fellow at Princeton University.

[3] L. O. Brockway and F. T. Wall, THIS JOURNAL, **56**, 2373 (1934); L. O. Brockway and H. O. Jenkins, *ibid.*, **58**, 2036 (1936).

[4] A. H. Gregg, G. C. Hampson, G. I. Jenkins, P. L. F. Jones and L. E. Sutton, *Trans. Faraday Soc.*, **33**, 852 (1937).

[5] L. O. Brockway, *Rev. Modern Phys.*, **8**, 231 (1936).

distributions[6] of scattering matter for the various substances. In cases where the total range of estimated intensities was greater than ten to one, a "corrected intensity" was used, namely, $s^2e^{-as^2}I_k$, with a given the value which made the range of "corrected intensities" equal to ten to one.[7] The principal peaks in the distribution functions correspond to internuclear distances in the molecules. While the positions of the peaks are most reliable in the curves based on eight or nine measured maxima, curves are shown for all of the substances having more than three measurable maxima in the photographs. For the sake of comparison the vertical lines in Figs. 1 and 8 mark the internuclear distances as determined with the aid of theoretical intensity curves; the heights of the lines show the relative scattering powers associated with the atom pairs.

The other figures show various theoretical intensity curves calculated from the approximate scattering function, $I = \Sigma_{ij} Z_iZ_j(\sin sr_{ij})/sr_{ij}$, in which the summation extends over all of the atoms in the molecule, Z_i is the atomic number of the ith atom and r_{ij} is the separation of the ith and jth atoms. A choice was made among the molecular models on the basis of the selection of the curve which best reproduces the qualitative features of the observed diffraction pattern. In the tables the s values, corresponding to the maxima and minima in the curve, are compared quantitatively with the s_0 values, and the r_{ij} values assumed in the model are multiplied by the average of the s/s_0 ratios to obtain the observed interatomic distances. Wherever the measured diameter is unreliable because of excessive back-intensity or a marked asymmetry in the maximum, the corresponding s/s_0 ratio has been excluded in taking the average.

The samples of POF_3, POF_2Cl, $POFCl_2$, and $PFCl_2$ were provided by Professor H. S. Booth, A. R. Bozarth, and Fred Dutton of Western Reserve University. For $POCl_3$ the commercial product was used after fractional distillation. Preparations of PF_5 and PF_3Cl_2 were made by V. Schomaker and J. B. Hatcher under the direction of Professor D. M. Yost in this Laboratory. The sample of Si_2Cl_6 was prepared by Dr. Fred Stitt, and those of Si_2H_6 and $SiHCl_3$ were furnished by Professor Warren C. Johnson of the University of Chicago.

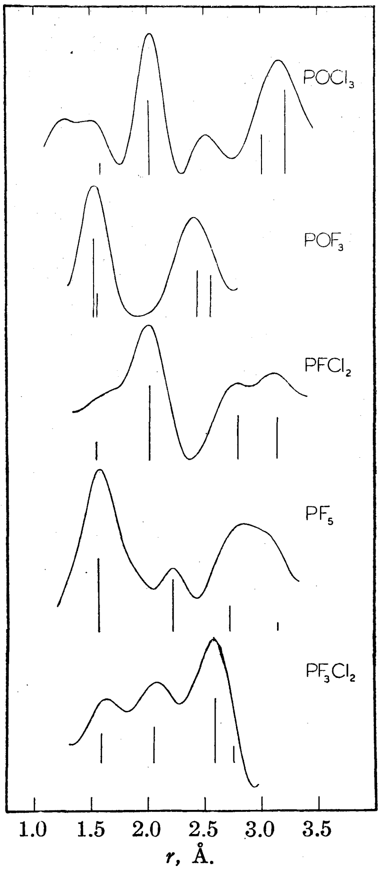

Fig. 1.—Observed radial distributions of scattering matter in the phosphorus compounds. The vertical lines represent the internuclear distances as determined by the comparison of the photographs with theoretical intensity curves.

TABLE I

PHOSPHORUS OXYTRICHLORIDE

Max.	Min.	I_k	s_0	s^a	s^b	s^a/s_0	s^b/s_0
1		8	(2.54)	2.58	2.55		
2		20	4.34	4.33	4.26	0.998	0.982
3			5.55	5.45	5.42	.982	.977
3		16	6.60	6.61	6.59	1.002	.998
4		4	(8.20)	8.44	8.09		
5		12	10.18	10.25	10.11	1.007	.993
	6		11.71	11.48	11.35	0.980	.969
6		10	13.04	12.80	13.50	.981	1.035
	7		14.85	14.98	14.78	1.009	0.995
7		6	16.21	16.30	15.97	1.006	.985
8		2	19.25	19.77	19.64	1.027	1.020
9		1	22.21	22.09	21.86	0.994	0.984
					Average	0.999	0.994
					Cl–Cl, Å.	3.207	3.240
					P–Cl	2.018	2.008

[a] Calculated for P–Cl = 2.02 Å., P–O = 1.58 Å., and ∠ClPCl = 105°. [b] Calculated for P–Cl = 2.02 Å., P–O = 1.58 Å., and ∠ClPCl = 107.5°.

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[6] L. Pauling and L. O. Brockway, THIS JOURNAL, **57**, 2684 (1935).

[7] The significance of the correction factors will be discussed by V. Schomaker and C. Degard in a later paper.

Phosphorus Oxytrichloride.—The photographs of $POCl_3$ show nine rings with the relative intensities and s_0 values given in Table I. With the exception of the first and fourth maxima the decline in intensity is fairly regular. The fourth maximum is very faint in comparison with the third and fifth, while the sixth is relatively broad with a slight shelf on the outer edge. The radial distribution curve (Fig. 1) shows two principal peaks. The first at 2.02 Å. represents the P–Cl distance and the second near 3.2 Å. represents the O–Cl and Cl–Cl distances unresolved.

Six theoretical curves were calculated having the assumed distances P–Cl = 2.02 Å., P–O = 1.58 Å., and ∠ClPCl = 90, 100, 105, 107.5, 110, and 120°, respectively. The first and last failed to reproduce any of the distinguishing features of the observed diffraction pattern. The other four are shown in Fig. 2. The 100° model is incorrect because its curve shows a too strong fourth maximum and an extra maximum between the sixth and seventh. In the 110° curve the fourth maximum has turned into a shelf and an extra maximum appears between the fifth and sixth, and this, too, is incorrect. The best general agreement is given by a model lying between those for 105 and 107.5°; and on the basis of the observed appearance of the fourth and sixth maxima the ClPCl angles are fixed at 106 ± 1°. The data of Table I and the radial distribution curve lead to the distances P–Cl = 2.02 ± 0.03 Å., and Cl–Cl = 3.22 ± 0.03 Å. A preliminary value of 104 ± 4° for the angle was reported previously.[5]

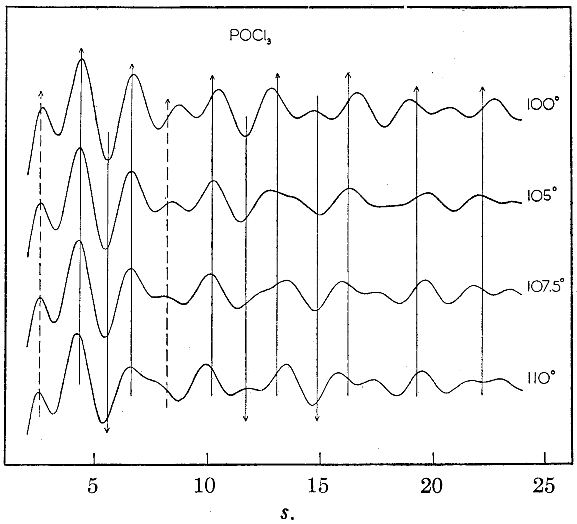

Fig. 2.—Theoretical intensity curves for phosphorus oxytrichloride. The arrows show the positions of the maxima and minima as measured on the photographs.

The low scattering power of the oxygen atom relative to that of the phosphorus and chlorine atoms means that its position cannot be as accurately fixed. The value, 3.01 Å., for the Cl–O distance occurring in the model accepted above is supported by the position of the second strong peak in the radial distribution curve. The displacement of this peak toward the Cl–Cl position is in agreement with the greater scattering power associated with the Cl–Cl terms. The corresponding P–O distance, 1.58 Å., is supported within 0.02 Å. by the more direct determination in POF_3.

Phosphorus Oxytrifluoride.—Photographs of POF_3 were obtained over the same range of scattering angle as observed for $POCl_3$, but on account of the smaller size of the POF_3 molecule only five maxima appeared. These are quite regular except for the shelf on the second. The five term radial distribution function shows peaks at 1.53 and 2.42 Å., the first representing P–F and P–O and the second F–F and O–F.

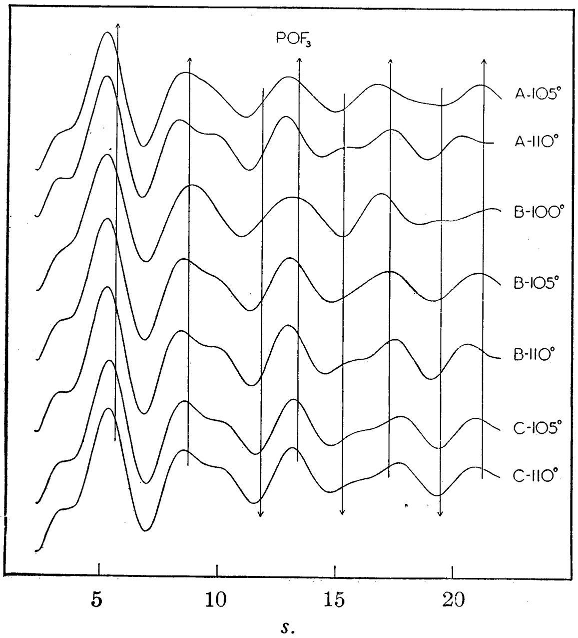

Fig. 3.—Theoretical intensity curves for phosphorus oxytrifluoride.

Thirteen intensity curves were calculated covering a range of the ratio P–O/P–F from 0.90 to 1.07° and a range of the FPF angle from 95 to 115°. The seven shown in Fig. 3 were calculated with the following parameter values: P–F = 1.56 Å., in all curves; A, P–O = 1.67 Å., ∠FPF = 105, 110°; B, P–O = 1.58 Å., ∠FPF = 100, 105, 110°; C, P–O = 1.49 Å., ∠FPF = 105, 110°. Among those not shown three curves were calculated having P–O = 1.40 Å. and P–F bond angles from 100 to 110°. These have two maxima instead of one between s = 14 and 19. The C curves with P–O = 1.49 Å. are somewhat better but the fourth maximum still lacks the symmetrical shape observed in the photographs. It may be noted that C-105° and C-110° are scarcely distinguishable because the change in angle has only the effect of interchanging the F–F and O–F distances. In the B curves (P–O = 1.58 Å.) the 100° model has no shelf on the second maximum, the 110° model has a faulty fourth maximum, while the 105° curve is reasonably satisfactory. In the A curves (P–O = 1.67 Å.) the small maximum preceding the fourth in the 110° model is incorrect, while the 105° curve is much better.

TABLE II

PHOSPHORUS OXYTRIFLUORIDE

Max.	Min.	I_k	s_0	s^a	s/s_0
1		8	(5.63)	5.23	(0.929)
2		10	8.71	8.45	.970
	3		11.82	11.29	.955
3		8	13.35	12.92	.968
	4		15.27	14.67	.961
4		3	17.25	17.20	.997
	5		19.43	19.11	.984
5		1	21.24	20.84	.981
				Average	0.974
				P–F, Å.	1.519
				P–O	1.568
				F–F	2.442

[a] Calculated for P–F = 1.56 Å., P–O = 1.61 Å., and ∠FPF = 107°.

A survey of all the models shows that among those definitely eliminated are all those with FPF bond angles as large as 110° and those in which the O–F distances are not larger than the F–F distances. On the other hand, the angle is not less than 105°, so that the P–O distance cannot be appreciably less than the P–F distance. The most probable values for the P–O/P–F ratio and the FPF bond angle chosen for the best qualitative agreement between curve and photographs are 1.03 and 107°. In the table the s values for the model having these parameter values are compared with the s_0 values. The final results for the distances are P–F = 1.52 ± 0.02 Å., P–O = 1.56 ± 0.03 Å., and F–F = 2.44 ± 0.02 Å., with ∠FPF = 107 ± 2°.

Phosphorus Oxydifluorochloride and Oxyfluorodichloride.—Six rings were observed in the photographs of POF_2Cl and $POFCl_2$, but in each case a heavy background obscured the first three and only the outer ones were really distinctly resolved. Because of the lack of reliable measurements on the inner rings radial distributions were not calculated. For the same reason it was scarcely possible to make a complete treatment of the several parameters required to fix the molecular model. On the other hand, the occurrence of the same bond angles in $POCl_3$ and POF_3 suggested that there would be no appreciable variations in the structures of the two intermediate compounds. Accordingly, a theoretical curve was calculated for each with the distances and angles observed in the two previous cases, *i. e.*, P–Cl = 2.02 Å., P–F = 1.52 Å., P–O = 1.57 Å., and ∠FPF = ∠FPCl = ∠ClPCl = 106°.

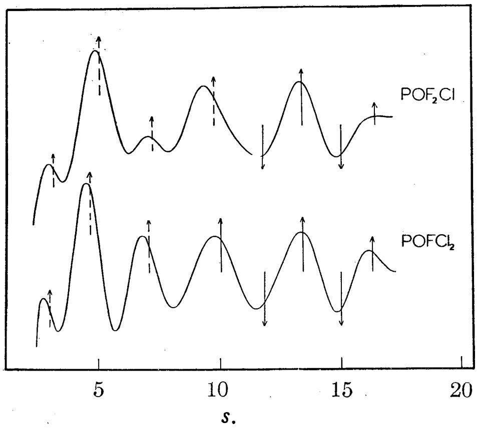

Fig. 4.—Theoretical intensity curves for phosphorus oxydifluorochloride and -fluorodichloride.

The two curves in Fig. 4 represent very well the qualitative feature in the photographs. In particular, the third ring in POF_2Cl is observed to be much weaker than the fourth, whereas in $POFCl_2$ the third and fourth rings are nearly equal. In the quantitative comparisons in Tables III and IV only the outer rings are used as indicated. Although the results for the two compounds differ by 1%, this is not significant in view of the probable experimental error which is estimated to be ±2% in this case. The values for POF_2Cl are P–Cl = 2.01 ± 0.04 Å., P–F = 1.51 ± 0.03 Å., P–O = 1.55 ± 0.03 Å., and ∠FPF = ∠FPCl = 106 ± 3°; for $POFCl_2$, P–Cl = 1.99 ± 0.04 Å., P–F = 1.50 ± 0.03 Å., P–O = 1.54 ± 0.03 Å., ∠FPCl = ∠ClPCl = 106 ± 3°.

Table III

Phosphorus Oxydifluorochloride

Max.	Min.	s_0	s^a	s/s_0
1		(3.10)	3.00	(0.968)
2		(5.07)	4.94	(.974)
3		(7.26)	7.11	(.979)
4		(9.82)	9.42	(.959)
	5	11.82	11.67	.987
5		13.45	13.35	.993
	6	15.07	14.88	.987
6		16.47	16.53	1.004
			Average	0.993
			P–Cl, Å.	2.006
			P–F	1.509
			P–O	1.549

[a] Calculated for P–Cl = 2.02 Å., P–F = 1.52 Å., P–O = 1.56 Å., ∠FPF = ∠FPCl = 106°.

Table IV

Phosphorus Oxyfluorodichloride

Max.	Min.	s_0	s^a	s/s_0
1		(2.99)	2.75	(0.920)
2		(4.67)	4.53	(.970)
3		(7.11)	6.86	(.965)
4		10.08	9.80	.972
	5	11.84	11.49	.970
5		13.45	13.39	.996
	6	15.02	14.86	.989
6		16.36	16.18	.989
			Average	0.983
			P–Cl, Å.	1.986
			P–F	1.495
			P–O	1.535

[a] Calculated for P–Cl = 2.02 Å., P–F = 1.52 Å., P–O = 1.56 Å., ∠FPCl = ∠ClPCl = 106°.

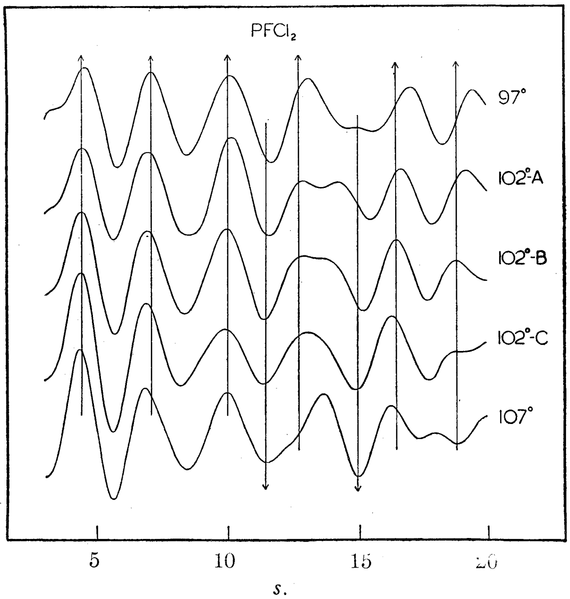

Fig. 5.—Theoretical intensity curves for phosphorus fluorodichloride.

Phosphorus Fluorodichloride.—The six term radial distribution function for $PFCl_2$ (Fig. 1) has a sharp peak at 2.01 Å., corresponding to the P–Cl distance in the molecule. The F–Cl and Cl–Cl distances are also represented but are not well enough resolved for distance determinations. In the calculation of theoretical curves the three bond angles were assumed to be equal and were varied from 90 to 120° with P–Cl = 2.02 Å. and P–F = 1.52 Å. Angle values outside of the range 97 to 107° (Fig. 5) were rejected because the curves showed extra maxima not observed in the photographs. The 97 and 107° curves are not satisfactory because they do not reproduce the rather broad fourth maximum followed by a sharp minimum. For the 102° curves the P–F distance has the assumed values A, 1.42 Å., B, 1.52 Å., C, 1.62 Å. A shows a doubled fourth maximum, which is not observed. Comparison of B and C suggests that the correct model lies between the two but nearer to B.

The data of Table V show how little the positions of the maxima are affected by the change in P–F distance in going from 102°-B to 102°-C (Fig. 5). This distance may be fixed within rather broad limits by the qualitative comparison. The final values are P–Cl = 2.02 ± 0.03 Å., P–F = 1.55 ± 0.05 Å., ∠FPCl = ∠ClPCl = 102 ± 3°. These are consistent with the observed radial distribution curve. The preliminary value for P–Cl reported earlier[5] has been increased by 0.02 Å. in the complete analysis.

Table V

Phosphorus Fluorodichloride

Max.	Min.	I_k	s_0	s^a	s^b	s^a/s_0	s^b/s_0
1		5	4.40	4.42	4.38	1.005	0.995
2		7	7.08	6.93	6.92	0.979	.977
3		6	10.01	10.00	9.92	.999	.991
	4		11.46	11.43	11.45	.997	.999
4		4	12.70	12.93	13.10	1.016	1.031
	5		14.93	15.19	14.94	1.017	1.001
5		2	16.42	16.46	16.31	1.002	0.993
6		1	18.81	18.84	18.85	1.002	1.002
					Average	1.002	0.999
					P–Cl, Å.	2.024	2.018
					P–F	1.523	1.618
					Cl–Cl	3.146	3.137
					F–Cl	2.774	2.832

[a] Calculated for P–Cl = 2.02 Å., P–F = 1.52 Å., bond angles = 102°. [b] Calculated for P–Cl = 2.02 Å., P–F = 1.62 Å., bond angles = 102°.

Phosphorus Pentafluoride.—In the six ring pattern observed in the PF_5 photographs the first ring is very heavy and broad and difficult to measure, while the fourth ring is the weakest of all those observed. The principal peak in the radial distribution function occurs at 1.58 Å., and is to be identified with the P–F distance.

Of the two types of molecular models considered the first is the trigonal bipyramid with the phosphorus atom at the center of an equilateral triangle of three fluorine atoms and the other two fluorine atoms on opposite sides of the phosphorus atom on a line perpendicular to the triangle. Curve A (Fig. 6) represents this model with P–F = 1.60 Å. The other models (designated B) are square pyramids with one fluorine atom at the apex and the other four at the corners of the square base. The angles between the P–F bond directed toward the apex and the bonds directed to the corners of the base were varied from 90 to 120°.

The B models with bond angles greater than 95° are unsatisfactory in that the fourth maximum is missing. Model B-90° and model A both show good agreement with the photographs; and since they differ only in the first maximum, which is poorly defined in the photographs, a choice between these two models cannot be made by means of the electron diffraction curves. It may be argued, however, that if the PF_5 molecule were based on a square pyramidal model the angles between the apex bond and the other bonds would be greater than 90° because of the unbalanced repulsions between the fluorine atoms. A simplified calculation based on Coulomb forces between the fluorine atom pairs leads to an angle value of 105° for the configuration of minimum potential energy. Such a model is definitely eliminated by the observed diffraction pattern.

TABLE VI

PHOSPHORUS PENTAFLUORIDE

Max.	Min.	I_k	s_0	s^a	s/s_0
1		10	(4.86)	4.96	(1.021)
2		8	9.17	8.98	0.979
	3		11.02	10.72	.973
3		6	12.34	12.17	.986
4		2	14.29	14.00	.980
	5		15.73	15.25	.969
5		4	17.18	16.86	.981
	6		19.04	18.73	.984
6		3	20.43	20.45	1.001
				Average	0.982
				P-F, Å.	1.571

[a] Calculated for trigonal bipyramid with P–F = 1.60 Å.

The dipole moment of the gas has been measured and found to be zero.[8] This could be true of a square pyramidal model having equal bond moments only if the angle between the apex bond and the others were 104.5°, a value in disagreement with the diffraction evidence. The trigonal bipyramidal model, on the other hand, agrees both with the observed dipole moment and the electron diffraction pattern; and it may be concluded with certainty that this is the correct model for PF_5. The quantitative comparison of Table VI leads to a value of P–F = 1.57 ± 0.02 Å. in excellent agreement with the radial distribution curve.

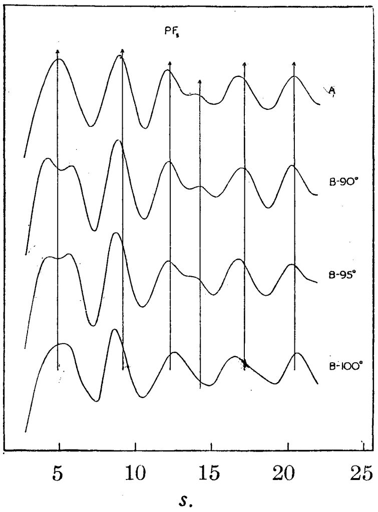

Fig. 6.—Theoretical intensity curves for phosphorus fluoride.

A preliminary report of this value was given in 1936.[5] In the meantime Braune and Pinnow[9] have investigated PF_5 by electron diffraction and have also chosen the configuration of the trigonal bipyramid. Their value for P–F is 1.54 Å., 2% smaller than reported in the present investigation.

Phosphorus Trifluorodichloride.—The eight rings observed in the PF_3Cl_2 photographs lead to a radial distribution curve with a sharp peak at 2.57 Å. and less reliable ones at 2.07 Å. and 1.63 Å. These correspond to F–Cl, P–Cl, and P–F distances. In the diffraction pattern the first five rings are much stronger than the last three. The third and fourth are weaker than the fifth, and the sixth is weaker than the seventh.

Because of the constancy of the bond angles in the PX_3 and in the POX_3 groups of compounds, it was assumed that the PX_5 group would also show no variation. Accordingly, only models of the trigonal bipyramidal configuration were calcu-

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(8) R. Linke and W. Rohrmann, *Z. physik. Chem.*, **B35**, 256 (1937).

(9) H. Braune and P. Pinnow, *ibid.*, **B35**, 239 (1937).

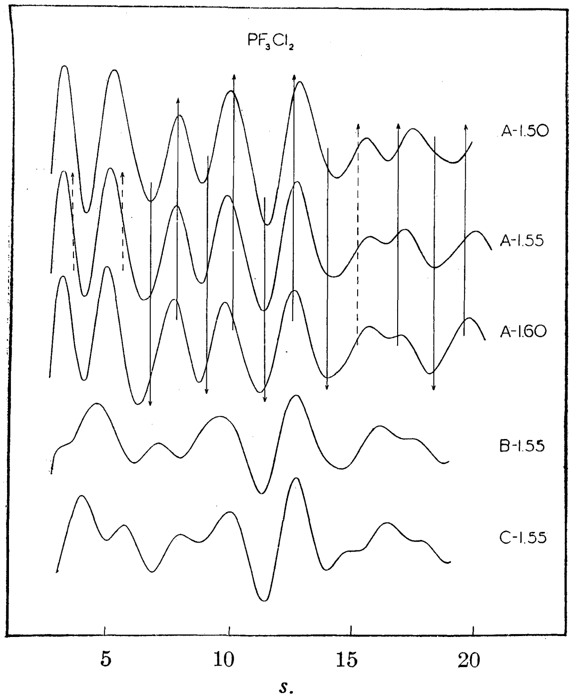

Fig. 7.—Theoretical intensity curves for phosphorus trifluorodichloride. The scale of the molecular models has been changed in plotting the curves by a factor of 1.023.

lated. In the A models (Fig. 7) the three fluorine atoms are in the equatorial plane and the two chlorine atoms at the poles, with P–Cl = 2.00 Å. and P–F = 1.50, 1.55, and 1.60 Å., as indicated. The B model has one chlorine atom in the equator with P–Cl = 2.00 Å., and P–F = 1.55, Å., and the C model has both chlorine atoms in the equator with P–Cl = 2.00 Å. and P–F = 1.55 Å.

The B and C models show pronounced qualitative disagreements with the photographs throughout the range observed; and it is evident that the agreement would not be much improved with any reasonable value for the P–F/P–Cl ratio. Model A-1.55 agrees quite well with the photographs; it is superior to A-1.50 and A-1.60 in the region of the sixth and seventh maxima. The final results based on the data of Table VII and the radial distribution curve are P–F = 1.59 ± 0.03 Å., P–Cl = 2.05 ± 0.03 Å., and F–Cl = 2.59 ± 0.03 Å.

TABLE VII

PHOSPHORUS TRIFLUORODICHLORIDE

Max.	Min.	I_k	s_0	s^a	s/s_0
1		12	(3.70)	3.38	(0.914)
2		9	(5.70)	5.28	(.926)
	3		(6.80)	6.71	(.987)
3		7	7.89	8.04	1.019
	4		9.09	9.05	0.996
4		6	10.18	10.14	.996
	5		11.47	11.69	1.019
5		9	12.61	13.06	1.036
	6		14.05	14.59	1.038
6		1	(15.00)	16.12	
7		2	16.88	17.58	1.041
	8		18.27	18.85	1.032
8		2	19.63	20.53	1.046
				Average	1.026
				P–F, Å.	1.589
				P–Cl	2.050
				F–Cl	2.593

[a] Calculated for trigonal bipyramid with fluorine atoms in equator and P–F = 1.55 Å., P–Cl = 2.00 Å.

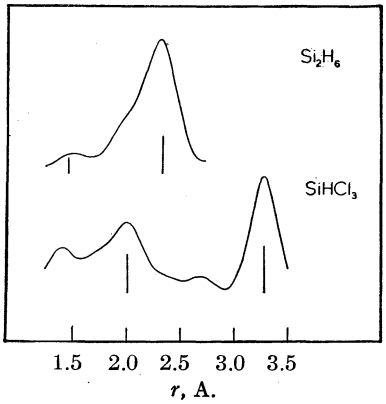

Fig. 8.—Observed radial distributions of scattering matter in disilane and trichlorosilane.

Disilane.—The seven maxima observed in photographs of Si_2H_6 with the s_0 and intensity values shown in Table VIII give a radial distribution with a strong peak at 2.31 Å. This represents the Si–Si bond distance.

TABLE VIII

DISILANE

Max.	Min.	I_k	s_0	s^a	s/s_0
1		15	(3.56)	3.27	(0.918)
2		20	6.10	6.02	.987
	3		7.52	7.41	.985
3		15	8.69	8.74	1.006
4		8	11.49	11.08	0.964
	5		12.66	12.70	1.003
5		12	13.96	14.12	1.011
	6		15.47	15.50	1.002
6		5	16.69	16.78	1.006
7		3	19.26	19.10	0.992
				Average	0.995
				Si–Si, Å.	2.329
				Si–H	1.473

[a] Calculated for Si–Si = 2.34 Å., Si–H = 1.48 Å., ∠HSiSi = 109.5°.

For comparison with theoretical intensity curves five models were assumed with Si–Si distances of 2.34 Å., Si–H bond angles of 109.5°, and Si–H bond distances ranging from 1.35 to 1.55 Å. The H–H terms were neglected. The curves differ mainly in the fourth maximum, which is too strong in those corresponding to Si–H distances of 1.45 Å. or less, and too weak in those corresponding to Si–H distances of 1.50 Å. or more. The intermediate curve in Fig. 9 shows good agreement with the photographs. The final values for the interatomic distances are Si–Si = 2.32 ± 0.03 Å., Si–H = 1.47 ± 0.03 Å.

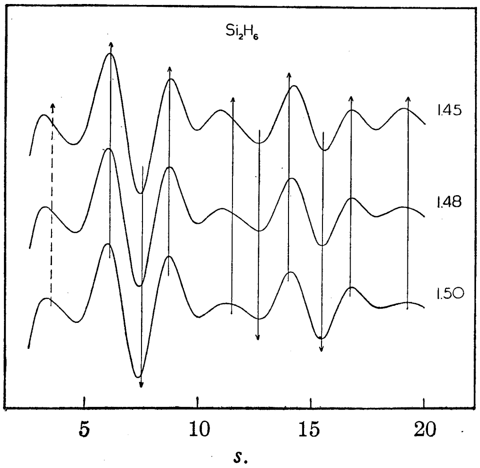

Fig. 9.—Theoretical intensity curves for disilane.

Trichlorosilane and Hexachlorodisilane.—The photographs of $SiHCl_3$ are exceptionally clear, showing a characteristic pattern of nine rings. Two well-resolved peaks in the radial distribution curve occur at 3.28 and 2.00 Å., corresponding to Si–Cl bond angles of 110°. Intensity curves (Fig. 10) were calculated for the molecular models having Si–Cl distances of 2.00 Å. and Si–Cl bond angles of 109.5 and 112°. The observed pattern is very well represented by the first of these, while in the second curve the third maximum is too strong relative to the second and the eighth is too strong relative to the seventh. While the bond angle may be 110° as suggested by the radial distribution curve, it can scarcely be as large as 112°.

In the comparison of s_0 and s values in Table IX it will be noted that the observations on the second and third maxima are displaced in opposite directions with respect to the corresponding s values. This is in accordance with the St. John effect previously observed when two maxima lie close together and are separated by only a shallow minimum. The s/s_0 values from these maxima are not included in the average value of the ratio. The values reported on the basis of the radial distribution curve and the quantitative and qualitative comparison of the intensity curves with the photographs are Si–Cl = 2.01 ± 0.03 Å., Cl–Cl = 3.29 ± 0.03 Å., ∠ClSiCl = 110 ± 1°.

TABLE IX

TRICHLOROSILANE

Max.	Min.	I_k	s_0	s^a	s/s_0
1		30	(4.36)	4.16	(0.954)
2		25	6.27	6.46	(1.031)
3		20	7.92	7.78	(0.982)
	4		9.04	8.92	.987
4		25	10.06	10.08	1.002
	5		11.11	11.27	1.015
5		10	12.04	12.15	1.010
6		15	13.82	13.71	0.992
	7		14.85	14.85	1.000
7		10	15.82	16.09	1.017
8		4	17.60	17.48	0.993
9		8	19.29	19.66	1.020
				Average	1.004
				Si–Cl, Å.	2.008
				Cl–Cl	3.283

[a] Calculated for Si–Cl = 2.00 Å., ∠ClSiCl = 109.5°.

Since the preliminary report of this value was given,[5] another electron diffraction investigation[10] has been made, with the reported values Si–Cl = 2.05 Å., Cl–Cl = 3.39 Å., ∠ClSiCl = 111 ± 4°. The determination of the Cl–Cl distance is not affected by small uncertainties in the value of the bond angle, and the 3% difference between this

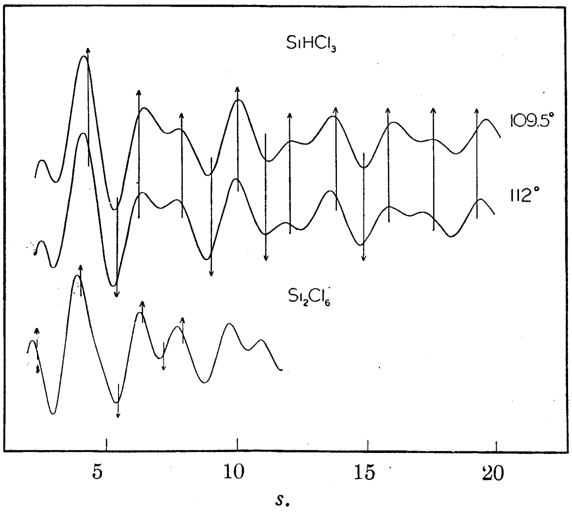

Fig. 10.—Theoretical intensity curves for trichlorosilane and hexachlorodisilane.

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(10) M. de Hemptinne and J. Wouters, *Nature*, **138**, 884 (1936); *ibid.*, **139**, 928 (1937).

value for Cl–Cl and that found in the present investigation is larger than the experimental error of the present result.

A sample of Si_2Cl_6 was photographed some time ago with a diffraction camera allowing a range of pattern only to $s = 11$. Five rings were observed in this range although the last was too faint to be measured. Since the inner rings show the usual displacement characteristic of measurements made at s values below about five, only two maxima could be measured well, and the radial distribution function was not calculated.

Tests were made, however, on two models. In each the assumed Si–Cl distance, 2.00 Å., was based on the observed values in $SiHCl_3$ and $SiCl_4$, the Si–Si distance was assumed to be 2.32 Å. from the value observed in Si_2H_6, and tetrahedral angles were used throughout. In the "*cis*" model the $SiCl_3$ groups were oriented so that the plane of each Si–Cl bond with the Si–Si bond also contained an adjacent Si–Cl bond in the other half of the molecule. In the "*trans*" model one $SiCl_3$ group was rotated by 60° around the Si–Si bond direction. In the "*cis*" curve the third maximum is partially resolved into two. The "*trans*" curve (shown in Fig. 10) is superior in this respect and it reproduces the qualitative features of the photographs. The quantitative measurements (Table X) suggest a decrease in the lengths of the more important interatomic distances. The curves calculated for the mixture of "*cis*" and "*trans*" molecules, most of the molecules being "*trans*," give somewhat better quantitative agreement with the photographs. This suggests that there is some freedom of rotation around the Si–Si bond. From the meager quantitative data it is impossible to determine the degree of freedom of internal rotation if the bond angles are different from the tetrahedral angle. A calculation of the steric repulsion of the six chlorine atoms indicates that the potential energy of the "*cis*" configuration is 650 cal./mole higher than that of the "*trans*" model. It may be concluded that the "*trans*" model is approximately correct with Si–Cl = 2.00 ± 0.05 Å. and Si–Si = 2.32 ± 0.06 Å.

TABLE X

HEXACHLORODISILANE

Max.	Min.	s_0	s^a	s/s_0
1		(2.32)	2.14	(0.923)
2		(4.05)	3.88	(.959)
	3	5.48	5.38	.982
3		6.40	6.32	.988
	4	7.23	7.05	.975
4		7.96	7.74	.973
			Average	0.980

[a] Calculated for "*trans*" model with tetrahedral bond angles, Si–Cl = 2.00 Å., Si–Si = 2.33 Å.

Discussion

The observed bond distances and angles in the phosphorus compounds including PF_3 and PCl_3[3,6] are collected in Table XI.

The P–F bonds ranging in length from 1.50 to 1.59 Å. represent three types of molecules, but the variations in bond length accompanying the change from one to another of these types are much smaller than those occurring among the molecules ordinarily classed together in the PX_3 type. The PX_3 molecules represent the normal valence compounds of phosphorus; there are apparently two distinct types of bonding within this group according to whether the attached radical X has unshared electron pairs, which by "back coördination" to the phosphorus may under certain conditions produce a degree of double bond character in the P–X bonds. When X is a methyl radical or another phosphorus atom, the bond is a normal single covalent bond. The observed distances in P_4 molecule, 2.21 Å.,[11] and in phosphorus trimethyl, 1.84 Å.,[12] give a phosphorus radius of 1.10 Å. in agreement with the value in the table of covalent radii. The sum of this radius and that for fluorine, 0.64 Å.,[13] is 1.74 Å. and is the length of a normal single covalent P–F bond. The observed bond distances in PF_3 and $PFCl_2$ fall below this by 0.2 Å. and indicate a considerable departure from the bond type occurring in P_4 and $P(CH_3)_3$. While the present results throw no new light on the nature of this change in bond type, it is evident that the change in going from PX_3 to POX_3 and PX_5 with constant X is less pronounced than the change occurring among the different PX_3 molecules. These effects are shown to a lesser degree by the observed P–Cl bond lengths, whose deviations from their average value, 2.01 Å., are smaller than the fall below the P–Cl radius sum, 2.09 Å.

The apparent difference in the P–F bond lengths in PF_3 and $PFCl_2$ may have some significance in spite of the large experimental errors. It has

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[11] L. R. Maxwell, S. B. Hendricks and V. M. Mosley, *J. Chem. Phys.*, **3**, 699 (1935).

[12] H. D. Springall and L. O. Brockway, THIS JOURNAL, **60**, 996 (1938).

[13] This value for the fluorine radius is obtained both by extrapolation of the carbon, nitrogen, and oxygen radii and from the observed distance in methyl fluoride.

TABLE XI

BOND DISTANCES AND ANGLES IN PHOSPHORUS COMPOUNDS

	P–F, Å.	P–Cl, Å.	P–O, Å.	∠FPF	∠ClPCl
PF_3	1.52 ± 0.04			104 ± 4°	
PCl_3		2.00 ± 0.02			101 ± 2°
$PFCl_2$	1.55 ± .05	2.02 ± .03			102 ± 3°
POF_3	1.52 ± .02		1.56 ± 0.03	107 ± 2°	
$POCl_3$		2.02 ± .03	(1.58)		106 ± 1°
POF_2Cl	1.51 ± .03	2.01 ± .04	1.55 ± 0.03	106 ± 3°	
$POFCl_2$	1.50 ± .03	1.99 ± .04	1.54 ± .03		106 ± 3°
PF_5	1.57 ± .02			90°; 120°; 180°	
PF_3Cl_2	1.59 ± .03	2.05 ± .03		120°	±180°

been observed that in the fluoromethanes and fluorochloromethanes[14] the C–F bond length decreases by about 0.05 Å. in going from the molecules with one fluorine atom to those with two or more. This effect may also occur in phosphorus compounds, but in the two substances investigated here having only one fluorine atom per molecule ($PFCl_2$ and $POFCl_2$) the more powerfully scattering chlorine atoms interfere with a precise location of the fluorine atom. Investigations are to be made on more suitable substances.

In the POX_3 compounds the P–X bond distances are not different from those in the PX_3 compounds for either fluorine or chlorine. From a comparison of the observed P–O distance, 1.56 Å., with the P–O double bond radius sum, 1.57 Å., and the P–O distances observed in phosphates, 1.56–1.61 Å., we conclude that the oxygen is held to the phosphorus atom by a double bond. The formation of the bond involves the previously unshared pair of electrons on the phosphorus atom and a pair from the oxygen atom, but in spite of the use of an additional bond orbital on the phosphorus atom the P–X bonds are not disturbed seriously.

While the increase in coördination number from three to four has no effect, the increase to five lengthens the bonds by 0.05 or 0.06 Å. In PF_5 the shortest F–F distances are just equal to that in CH_2F_2, 2.22 Å. This fact suggests that the mutual fluorine atom repulsions have lengthened the bonds in PF_5, but the conclusion is not certain because the tetrahedral bond angle in CH_2F_2 shows that at 2.22 Å. the fluorine atoms may not be as close as the critical distance of approach. In PF_3Cl_2 the P–F and P–Cl bonds have both been lengthened, and the F–Cl distance, 2.59 Å., is just that in CH_2FCl; but here again the lack of an increase in the bond angle in the substituted methane leaves the conclusion in doubt. An alternative explanation for the increase in the P–X bond lengths is that the degree of double bond character in each bond is decreased with the formation of additional bonds, *i. e.*, some of the 3*d* orbitals on phosphorus are utilized more easily than others.

The change of bond angles in going from PX_3 to POX_3 is of interest especially in view of the constant bond lengths. In the former compounds the XPX angles are close to 102° and in the latter they have risen to 106°. The angles between the P–O bond and the P–X bonds are 112°. This is additional evidence that the four atoms are not held by ordinary tetrahedral bonds. The small importance of repulsions between the attached atoms here is illustrated by the 106° ClPCl angle compared with the 112° OPCl angle.

There are many questions about the nature of phosphorus–halogen bonds which cannot be answered at the present state of information, and the problem remains of collecting data on many related substances before a complete discussion can be given.

The silicon compound measurements reported here illustrate the variation in bond type among the normal valence compounds of silicon. The Si–Si distance, 2.32 Å., observed in Si_2H_6 agrees with that in the crystalline form of the element, and the bond is of the normal single covalent type. In $SiHCl_3$ the SiCl bond is 2.01 Å. or 0.15 Å. less than the Si–Cl radius sum. The same situation exists in $SiCl_4$[3,6] with bonds of 2.00 Å. In Si_2Cl_6 the silicon atoms show both bond types in the same molecule. The Si–H distance, 1.47 Å., in Si_2H_6 leads to a hydrogen radius of 0.30 Å. in agreement with the values from other non-metallic hydrides. The bond angle of 110 ± 1° in $SiHCl_3$ does not show the increase above the tetrahedral value which is observed in $CHCl_3$. The increase in size of the central atom has increased the chlorine atom separations from 2.93 to 3.29 Å., and their mutual repulsions are not great enough to

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[14] L. O. Brockway, *J. Phys. Chem.*, **41**, 185, 747 (1937).

distort the bond angles in the silicon compound.

We are indebted for the furnishing of materials to Professor H. S. Booth of Western Reserve University, Professor Warren C. Johnson of the University of Chicago, Professor D. M. Yost of this Laboratory, Dr. Fred Stitt, and their associates. We also wish to thank Messrs. V. Schomaker and K. J. Palmer for assistance in preparing some of the photographs. To Professor Linus Pauling we express our appreciation of unfailing encouragement and help.

Summary

The molecular structures of seven phosphorus compounds have been investigated with the results shown in Table XI. The P–F bond distances in the PX_3 and POX_3 molecules are all close to 1.52 Å., and in PF_5 and PF_3Cl_2 are 1.57 and 1.59 Å. An increase in bond length with coördination number occurs at coördination number five but not four. The observed lengths are all smaller than the covalent radius sum, 1.74 Å. The P–Cl bond lengths show similar variations but the decreases below the radius sum, 2.09 Å., are only from 0.04 to 0.08 Å.

The XPX bond angles increase by 4° in going from PX_3 (102°) to POX_3 (106°). The P–O bond, 1.56 Å. in length, is a double bond and stands at angles of 112° to the three P–X bonds.

In Si_2H_6 the Si–Si bond length is 2.32 ± 0.03 Å., within 0.02 Å. of the length in elementary silicon. In $SiHCl_3$ and Si_2Cl_6 the Si–Cl bonds are 2.01 ± 0.03 Å., and 2.00 ± 0.05 Å.; the same value has been observed in $SiCl_4$. This value is 0.15 Å. below the Si–Cl radius sum. The ClSiCl angle in $SiHCl_3$ is distorted from the tetrahedral value by less than 1°.

PRINCETON, N. J. RECEIVED MAY 31, 1938

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, NO. 650]

The Crystal Structure of Cesium Aurous Auric Chloride, $Cs_2AuAuCl_6$, and Cesium Argentous Auric Chloride, $Cs_2AgAuCl_6$

BY NORMAN ELLIOTT AND LINUS PAULING

The substances cesium aurous auric chloride, $Cs_2AuAuCl_6$, and cesium argentous auric chloride, $Cs_2AgAuCl_6$, discovered by Wells,[1] are of interest because of their jet black color, which has been ascribed[2] to the presence of the same element or two closely similar elements in two valence states.[3] In a preliminary investigation carried out some time ago[4] the substances were found to be diamagnetic, showing that they contain gold and silver in the univalent and trivalent oxidation states rather than the bivalent state. Powder photographs were also prepared with molybdenum X-radiation. These photographs, each with about fifteen lines, were interpreted as showing the crystals to have a structure closely related to the cubic perovskite type, the unit cube, with $a_0 \cong 5.33$ Å. for each substance, containing 1 Cs at 000, 1 (Au,Ag) at $\frac{1}{2}\frac{1}{2}\frac{1}{2}$, and 3 Cl at $\frac{1}{2}\frac{1}{2}0$, $\frac{1}{2}0\frac{1}{2}$, $0\frac{1}{2}\frac{1}{2}$. Although the agreement between the intensities of X-ray reflection calculated for this structure and the observed values was good in general, there were one or two points of pronounced discrepancy for each substance, and the conclusion was reached that the structures are actually distorted somewhat from the ideal perovskite arrangement.

In the course of the investigation described below X-ray powder photographs were prepared with copper and iron radiation, giving greater dispersion, and it was found that cesium aurous auric chloride is tetragonal, and contains the complex ions $[AuCl_2]^-$, which is linear, and $[AuCl_4]^-$, which is square. A similar structure occurs for heat-treated samples of cesium argentous auric chloride, which also exists in a cubic modification involving some randomness in atomic arrangement.

The Determination of the Structure of Cesium Aurous Auric Chloride.—Powder photographs of cesium aurous auric chloride were prepared with copper Kα radiation filtered through nickel and with iron K radiation, the camera radius being 5.005 cm. The photographs show about fifty well-defined lines, occurring as multiplets near

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(1) H. L. Wells, *Am. J. Sci.*, **3**, 315 (1922).

(2) H. L. Wells, *ibid.*, **3**, 417 (1922).

(3) Norman Elliott, *J. Chem. Phys.*, **2**, 298 (1934); magnetic data for (NH$_4$)$_4$Sb^{III}Sb^{V}Br$_{12}$.

(4) Norman Elliott, *ibid.*, **2**, 419 (1934).

the angles expected for reflections from a cubic crystal. This suggests that the unit of structure of the crystal is closely related to a cube. The observation that the cubic line {200} occurs as a doublet, with the outer component twice as strong as the inner one, suggests that the crystal is tetragonal. This is supported by the multiplet structure of the other lines, the octahedral reflections being single, reflections with two indices equal double, and those with all three indices different triple.

The tetragonal unit of structure with $a_0 = 7.49 \pm 0.02$ Å. and $c_0 = 10.87 \pm 0.02$ Å. accounts for the presence of all observed lines.[5] The lattice can be taken as body-centered, no reflections with $h + k + l$ odd being observed. No classes of planes other than those indicated by the lattice are absent on the photographs. The space group is accordingly $D_{4h}^{17} - I4/mmm$ or one of its subgroups with the same unit. It was found possible with the assumption of holohedry to determine an atomic arrangement which accounts completely for the X-ray data; it is accordingly probable that the space group of the crystal is D_{4h}^{17}.

The density of the substance was determined by displacement of benzene to have the value 4.57 g./cc. This corresponds to 1.94 $Cs_2AuAuCl_6$ per unit, the calculated value of the density for two molecules per unit being 4.72 g./cc. There are 4 Cs, 2 Au^{I}, 2 Au^{III}, and 12 Cl atoms to be located. The sets of equivalent positions for D_{4h}^{17} are[6]

2a: $000,\ \frac{1}{2}\frac{1}{2}\frac{1}{2}$
2b: $00\frac{1}{2},\ \frac{1}{2}\frac{1}{2}0$
4c: $0\frac{1}{2}0,\ \frac{1}{2}00,\ \frac{1}{2}0\frac{1}{2},\ 0\frac{1}{2}\frac{1}{2}$
4d: $0\frac{1}{2}\frac{1}{4},\ \frac{1}{2}0\frac{1}{4},\ \frac{1}{2}0\frac{3}{4},\ 0\frac{1}{2}\frac{3}{4}$
4e: $00z,\ 00\bar{z},\ \frac{1}{2}\frac{1}{2}\frac{1}{2}+z,\ \frac{1}{2}\frac{1}{2}\frac{1}{2}-z$
8h: $xx0,\ \bar{x}\bar{x}0,\ x\bar{x}0,\ \bar{x}x0,\ \frac{1}{2}+x\ \frac{1}{2}+x\frac{1}{2},\ \frac{1}{2}-x\frac{1}{2}-x\frac{1}{2},$
$\frac{1}{2}+x\frac{1}{2}-x\frac{1}{2},\ \frac{1}{2}-x\frac{1}{2}+x\frac{1}{2}$

together with 8f, 8g, 8i, 8j, and positions for sets of 16 and 32 equivalent atoms. The photographs show that the atoms are in positions close to those of the perovskite arrangement. This can be achieved only in the following way

2 Au^{III} in 2a
2 Au^{I} in 2b
4 Cs in 4d
4 Cl in 4e, with $z \cong 1/4$
8 Cl in 8h, with $x \cong 1/4$

(The assignment of Au^{III} to 2b and Au^{I} to 2a leads to the same structures.)

The parameters x and z were evaluated from the intensity data given in Table I. The ob-

TABLE I

POWDER PHOTOGRAPHIC DATA FOR CESIUM AUROUS AURIC CHLORIDE, COPPER RADIATION, $\lambda = 1.539$ Å.

hkl	*d* obsd., Å.	*d* calcd., Å.		*I* obsd.	*I* calcd.
002	5.46	5.43		100	128
110	5.28	5.22		200	250
112 200	3.76	3.75		2400	2230
103	3.28	3.26		13	16
121	3.21	3.20		9	7
202	3.11	3.08		16	14
004	2.71	2.72		300	340
220	2.645	2.647		600	660
114 301	2.414	2.420	2.425	50	52
310 222	2.369	2.370	2.390	100	106
204	2.200	2.200		300	315
312	2.169	2.177		600	660
105	2.097	2.112		4	2
224	1.892	1.910		450	420
400	1.868	1.872		200	209
006	1.804	1.809		10	10
411 314	1.790	1.793	1.787	26	27
402 330	1.774	1.772	1.767	26	30
116	1.712	1.735		200	191
332 420	1.678	1.698	1.674	300	333
404	1.537	1.546		200	214
226 235	1.498	1.508	1.510	18	18
334 501	1.483	1.485	1.483	13	13
510	1.466	1.467		13	13
136	1.439	1.450		200	213
244	1.423	1.430		175	172
152	1.415	1.417		175	185
008	1.360	1.358		30	32
118 440	1.320	1.335	1.323	110	131
208 530	1.276	1.292	1.283	50	50
336	1.262	1.272		75	76
600 352	1.248	1.230	1.250	200	214
228	1.207	1.220		100	87
444 620	1.190	1.192	1.184	200	188
156	1.140	1.147		100	114
604	1.133	1.136		40	45
408	1.100	1.100		75	67
264 0·0·10	1.085	1.086	1.086	100	112
338		1.085			
446	1.069	1.074		40	36
1·1·10 550	1.059	1.063	1.060	50	46
710		1.060			
248	1.050	1.053		55	57
356	1.043	1.045		140	147
370 554 266	0.986	0.983	0.988	150	140
3·1·10 714		.955	.998		
		.988			
372 644 528	.966	.968	.971	150	136
		.976			
448 4·0·10	.951	.948	.950	50	55
800 538	.937	.937	.939	35	32
3·3·10 802	.927	.924	.925	50	50
556 608	.917	.917	.917	75	87

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[5] This unit is obtained from the small pseudo-cubic unit by rotating about c through 45° and doubling c_0. It corresponds to the dimensions $a_0 = 5.28$ Å., $c_0 = 5.44$ Å. for the small pseudo-unit, with axial ratio 1.03.

[6] "International Crystal Structure Tables."

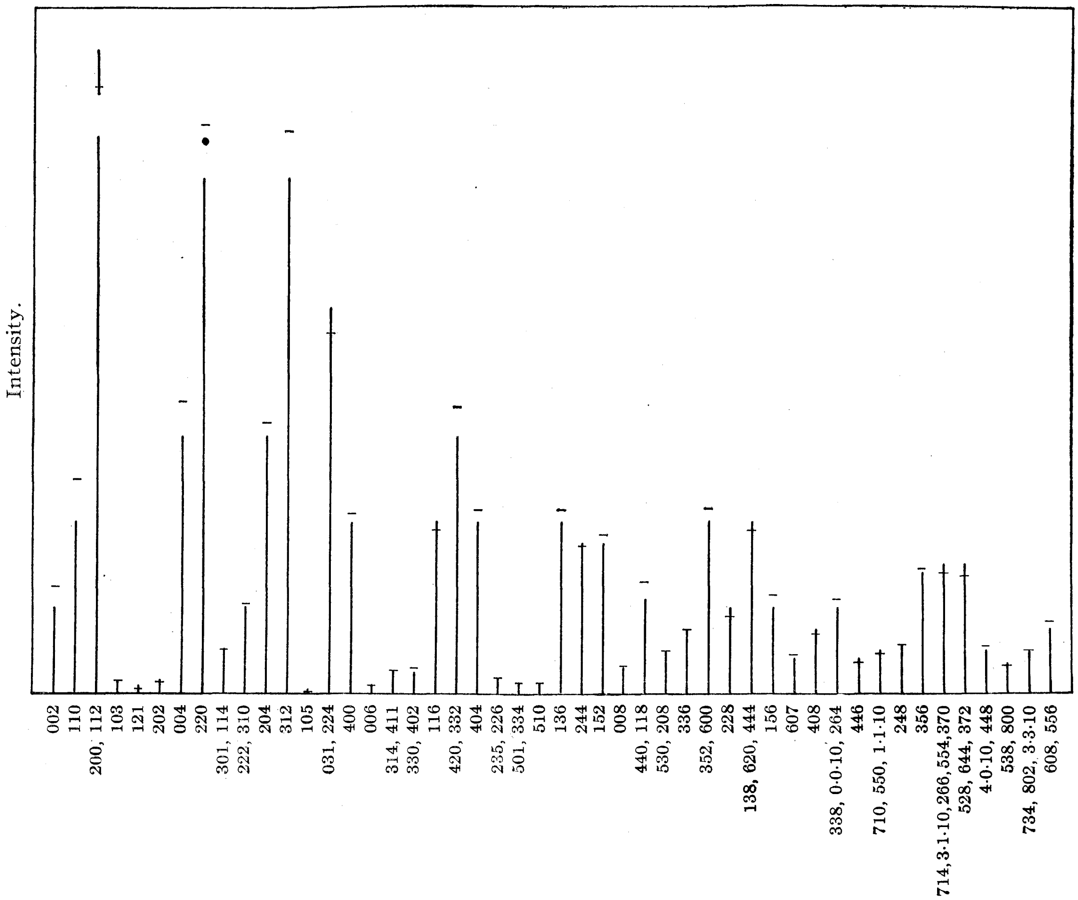

Fig. 1.—Calculated and observed intensities of reflections on powder photographs of cesium aurous auric chloride. The vertical lines show the observed values of the relative intensities, and the horizontal crossbars the calculated values.

served intensity values $I_{\text{obsd.}}$ were obtained from microphotometer records of the photographs and from visual estimates made on a series of photographs taken under identical conditions except for varied time of exposure. Intensity values were calculated with the equation

$$I_{\text{calcd.}} \sim \frac{1 + \cos^2 \Theta}{\cos \Theta \sin^2 \Theta} hF^2$$

in which h is the frequency factor and F the structure factor. F is given by the equation

$$F = f_{\text{Au}} + f_{\text{Au or Ag}} \cos 2\pi \frac{h+k}{2} + (-1)^{l/2} f_{\text{Cs}} \left\{ \cos 2\pi \frac{h}{2} + \cos 2\pi \frac{k}{2} \right\} + 2f_{\text{Cl}} \left\{ \cos 2\pi u(h+k) + \cos 2\pi u(h-k) + \cos 2\pi lv \right\}$$

Screening-constant f values were used,[7] without temperature correction. The parameter values obtained in this way, with especial emphasis on comparisons between adjacent lines on the photographs, are $x = 0.228 \pm 0.003$ and $z = 0.288 \pm 0.003$. The excellence of the agreement between observed and calculated intensities with these parameter values is shown in Table I and Fig. 1.

The Determination of the Structure of Cesium Argentous Auric Chloride.—Copper radiation photographs of samples of cesium argentous auric chloride which had been standing at room temperature since their preparation two to three years before were found to show only reflections (about thirty in number) which could be explained by a cubic unit of structure with $a_0 = 5.28 \pm 0.01$ Å., containing $\frac{1}{2}$ $Cs_2AgAuCl_6$. The lines on the photographs are sharp, and the absence of fine structure comparable in magnitude with the clearly resolved $CuK\alpha_1$-α_2 doublet for the wide-angle reflections shows that the approximation to a cubic structure is within 0.1%.

After the sample had been heated in a sealed evacuated tube at 350° for seventy-two hours and

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[7] L. Pauling and J. Sherman, *Z. Krist.*, **81**, 1 (1932).

cooled slowly to room temperature over a period of about five hours, it gave quite different X-ray photographs, the cubic lines being split into components similar to those for the aurous-auric compound, but with still greater separation. The photographs could be indexed completely on the basis of a tetragonal unit with a_0 = 7.38 ± 0.02 Å. and c_0 = 11.01 ± 0.02 Å. The unit is body-centered, and the observed reflections correspond to the space-group $D_{4h}^{17} - I4/mmm$ or one of its subgroups. The atomic arrangement described above for $Cs_2AuAuCl_6$, with Ag^I replacing Au^I and with the parameter values $x = 0.220 \pm 0.03$ and $z = 0.285 \pm 0.003$, accounts completely for the observed intensities, as shown in Table II and Fig. 2.

TABLE II

POWDER PHOTOGRAPHIC DATA FOR CESIUM ARGENTOUS AURIC CHLORIDE, COPPER RADIATION, λ = 1.539 Å.

hkl	*d* obsd., Å.	*d* calcd., Å.	*I* obsd.	*I* calcd.
101	6.12	6.10	40	50
002	5.50	5.50	25	26
110	5.24	5.22	50	46
112	3.77	3.77	600	637
200	3.685	3.690	250	270
103	3.275	3.280	50	49
202	3.055	3.054	50	44
004	2.750	2.750	170	163
220	2.601	2.598	260	290
114 301 123	2.436	2.430 2.393	30	29
		2.440		
222 310	2.329	2.350 2.325	18	15
204	2.206	2.203	150	136
105 132	2.145	2.107 2.140	265	270
321 303	2.050	2.05 2.06	30	36
224	1.896	1.890	250	220
006 400	1.842	1.830 1.835	125	105
215		1.825		
314 411	1.783	1.775 1.760	35	36
323		1.780		
330 402	1.735	1.732 1.740	135	145
116	1.678	1.690	25	21
332 420	1.655	1.652 1.644	160	170
206		1.640		
107 226	1.530	1.536 1.500	120	126
325 404		1.494 1.525		
316 510	1.444	1.440 1.442	120	117
217 424	1.415	1.418 1.412	100	105
512	1.400	1.395	100	107
415 433	1.382	1.384 1.380	25	20
503		1.381		
008	1.373	1.375	16	20
440	1.305	1.300	40	36
406 208	1.293	1.295 1.288	25	29
514 442	1.267	1.277 1.265	50	52
530 336		1.261 1.259		
532	1.232	1.229	60	55
600 426 435	1.220	1.225 1.223	60	62
505 228		1.222 1.222		
		1.215		
318 602	1.181	1.183 1.195	55	57
417 444		1.178 1.175		
620	1.170	1.167	55	56
622 516	1.138	1.140 1.135	75	74
534		1.145		
408	1.107	1.100	60	58
1·1·10	1.083	1.082	50	54
624	1.076	1.078	100	110
428	1.062	1.055	80	80
710 550	1.045	1.044 1.044	85	83
536		1.039		
640 712	1.026	1.024 1.025	120	130
3·1·10 518	1.003	0.994 0.997	90	100
556 716	0.910	.905 .905	100	110
628	.890	.888	90	85
5·1·10	.880	.875	90	85
804	.876	.873	50	45
5·3·10 558	.830	.836 .836	90	93
718		.836		

Discussion of the Structures.—The structure found for the tetragonal form of cesium argentous auric chloride (after heating at 350°) is shown in Fig. 3. The structure is closely related to the perovskite structure, the arrangement of the large cesium and chlorine atoms corresponding approximately to cubic closest packing, with the silver and gold atoms alternating in positions at the centers of chlorine octahedra. The distortion from the ideal perovskite structure is such as to show the presence of $[AgCl_2]^-$ and $[AuCl_4]^-$ complexes. Each silver atom has two closest chlorine atoms at the distance 2.36 Å., which is just the sum of the covalent radii for silver (with coördination number two) and chlorine;[8] the other four chlorine atoms of the distorted octahedron are 2.92 Å. from the silver atom. The $[Cl\text{-}Ag\text{-}Cl]^-$ complexes are linear, and are oriented parallel to the *c* axis of the crystal. Each gold atom has four nearest chlorine neighbors, arranged about it at the corners of a square, at the distance 2.30 Å., which is the sum of the covalent radii of trivalent gold and chlorine. The distance from the gold atom to the two other chlorine atoms in its neighborhood is 3.13 Å.

The linear configuration of the $[AgCl_2]^-$ complex ion is expected, in view of the analogy of the complex to the linear $[Ag(CN)_2]^-$ complex in the crystal $KAg(CN)_2$, studied by Hoard.[9] The square configuration of the chloroaurate ion $[AuCl_4]^-$ is similar to that observed[10] for the isoelectronic chloroplatinite ion $[PtCl_4]^=$, and is ex-

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[8] L. Pauling and M. L. Huggins, *Z. Krist.*, **87**, 205 (1934).

[9] J. L. Hoard, *ibid.*, **84**, 231 (1933).

[10] R. G. Dickinson, THIS JOURNAL, **44**, 2404 (1922).

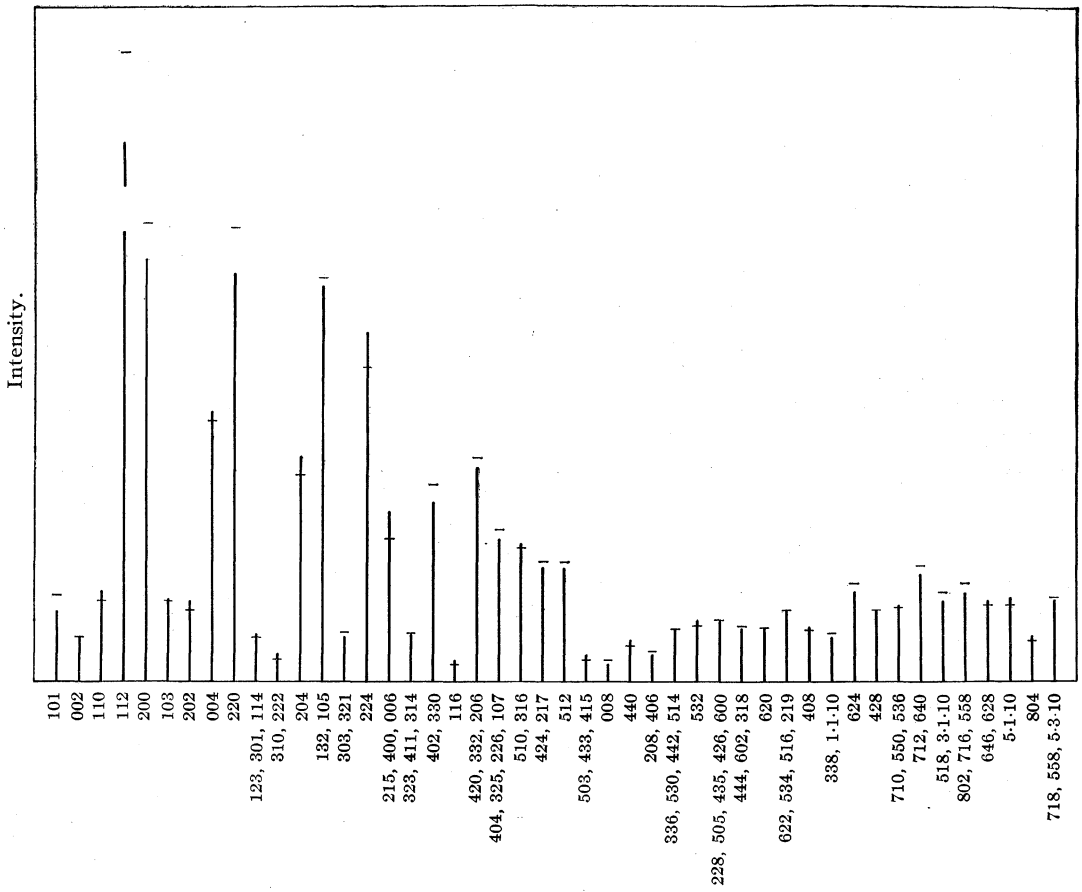

Fig. 2.—Calculated and observed intensities of reflections on powder photographs of the tetragonal modification of cesium argentous auric chloride. The vertical lines show the observed values of the relative intensities, and the horizontal crossbars the calculated values.

pected from quantum mechanical considerations.[11]

From these results it is seen that cesium argentous auric chloride is a compound of cesium dichloroargentite, $CsAgCl_2$, and cesium tetrachloroaurate, $CsAuCl_4$, with the stability of the compound to be attributed to the close packing of the pseudo-perovskite arrangement. The formula of the compound might well be written as $CsAgCl_2 \cdot CsAuCl_4$ or $Cs_2AgCl_2AuCl_4$.

The cubic modification of the substance must involve some randomness of atomic arrangement, since the X-ray data show that silver and gold atoms are randomly distributed in such a way as to give no reflections requiring a larger unit. It is probable that the crystal contains linear $[AgCl_2]^-$ complexes and square $[AuCl_4]^-$ complexes with random distribution and random orientation relative to its three orthogonal axes.

The structure found for cesium aurous auric chloride is similar to that of the tetragonal modification of the argentous auric compound. The structure involves linear $[AuCl_2]^-$ groups, with Au^{I}–Cl = 2.31 Å., and square $[AuCl_4]^-$ groups, with Au^{III}–Cl = 2.42 Å. The longer Au–Cl distances are Au^{I}–Cl = 2.98 Å. and Au^{III}–Cl = 3.13 Å.

There is some evidence that the structure found for this substance represents some deviation from the ideal structure. The axial ratio c/a for tetragonal $Cs_2AgAuCl_6$ is 1.491, whereas that found for $Cs_2AuAuCl_6$ is 1.452, which is considerably closer to the value for no distortion from the cubic perovskite structure, 1.414. It is to be expected, however, because of the very small difference in radii of silver and gold atoms, that the structures of the substances would be identical. The low value of the axial ratio of the aurous auric compound suggests that in the sample of this substance used for preparing the photographs the ideal structure with completely oriented complex ions had not been achieved,

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(11) L. Pauling, THIS JOURNAL, **53**, 1367 (1931).

and that some of the complexes were oriented in a random manner. Some further support for this idea is given by the value of the parameter x, which makes the Au^{III}–Cl distance 0.12 Å. larger than in the argentous auric compound; it seems likely that the change in intensities of the lines caused by the partial randomness of the structure has caused a small error in the parameter determination. An effort to test this hypothesis was made by heating the sample of $Cs_2AuAuCl_6$ to 350° for twenty-four hours; the photograph obtained of the sample after this treatment was identical with the earlier ones, however, showing that the partial randomness of structure, if it exists, represents the stable state at ordinary temperatures and not a metastable state.

An investigation of cesium aurous auric chloride and cesium argentous auric chloride has been reported recently by Ferrari,[12] leading to results different from ours. Ferrari reported the substances to give powder photographs (taken with iron radiation) corresponding to cubic units with a_0 = 5.23 Å. in each case, except that a few very faint lines were observed indicating the true units to have values of a_0 twice as large. He suggested a structure involving distortion from the ideal perovskite arrangement such as to give $[AuCl_6]^{=}$ complexes with the configuration of a regular octahedron. It seems to us improbable that this complex exists; and we believe that the samples studied by Ferrari represent random structures, as described above, with admixture of the tetragonal ordered modifications in sufficient amounts to give the faint extra lines which he observed.

Summary

Crystals of tetragonal cesium aurous auric chloride have a body-centered unit of structure, with $a_0 = 7.49 \pm 0.02$ Å., and $c_0 = 10.87 \pm 0.02$ Å. containing 2 $Cs_2AuAuCl_6$. The space group is $D_{2h}^{17} - I4/mmm$, and the atoms are in the following positions of this space group: 2 Au^{III} in 2a; 2 Au^{I} in 2b; 4 Cs in 4d; 4 Cl in 4e, with $z = 0.288 \pm 0.003$; 8 Cl in 8h, with $x = 0.228 \pm 0.003$. Tetragonal cesium argentous auric chloride, $Cs_2AgAuCl_6$, has a similar unit, with

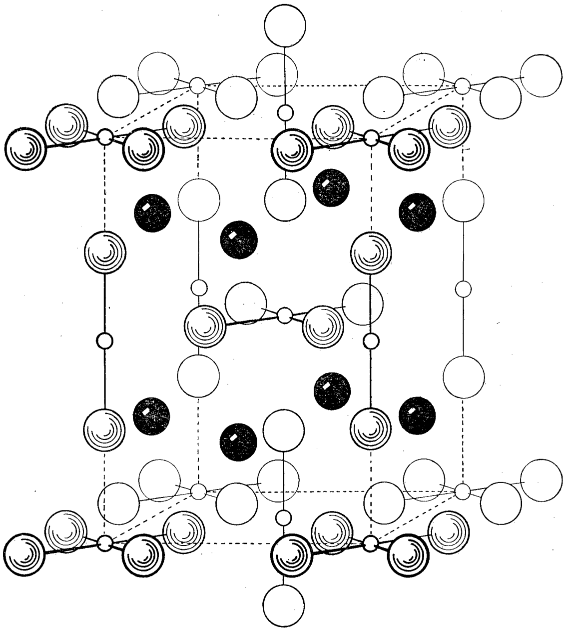

Fig. 3.—The atomic arrangement in tetragonal crystals of $Cs_2AgAuCl_6$ and $Cs_2AuAuCl_6$. Large full circles represent cesium atoms, large open circles chlorine atoms, and small circles gold and silver atoms.

$a_0 = 7.38 \pm 0.02$ Å., and $c_0 = 11.01 \pm 0.02$ Å., and a similar atomic arrangement (with Ag^{I} replacing Au^{I}), the parameter values being $z = 0.285 \pm 0.003$ and $x = 0.220 \pm 0.003$. These crystals contain linear $[AgCl_2]^-$ and $[AuCl_2]^-$ ions, similar to $[Ag(CN)_2]^-$, and square coplanar $[AuCl_4]^-$ ions, similar to the $[PdCl_4]^{=}$ and $[PtCl_4]^{=}$ ions.

In addition a metastable cubic modification of $Cs_2AgAuCl_6$, capable of conversion into the stable tetragonal modification by heating, was studied. The apparent unit of structure of this is cubic, with $a_0 = 5.28 \pm 0.01$ Å. It contains $\frac{1}{2}$ $Cs_2AgAuCl_6$, and appears to have the perovskite structure, with $\frac{1}{2}$(Ag + Au) at $\frac{1}{2}\frac{1}{2}\frac{1}{2}$, Cs at 000, 3 Cl at approximately $\frac{1}{2}\frac{1}{2}0$, $\frac{1}{2}0\frac{1}{2}$, $\frac{1}{2}\frac{1}{2}0$. It is probable that the crystal contains $[AgCl_2]^-$ and $[AuCl_4]^-$ complexes with random distribution among the positions and orientations provided by the perovskite structure. Evidence for the existence of a similar modification of $Cs_2AuAuCl_6$ is given by the work of Ferrari.

PASADENA, CALIF. RECEIVED MAY 31, 1938

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[12] A. Ferrari, *Gazz. chim. ital.*, **67**, 94 (1937).

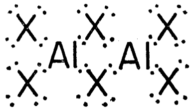
[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY OF THE CALIFORNIA INSTITUTE OF TECHNOLOGY, NO. 651]

The Electron Diffraction Investigation of Aluminum Chloride, Bromide, and Iodide

BY K. J. PALMER AND NORMAN ELLIOTT

The unusual physical and chemical properties of aluminum chloride, bromide, and iodide lend considerable interest to the electron diffraction investigation of these compounds in the gas phase. Vapor density measurements have shown that in the gaseous state below approximately 400° the substances exist as the dimeric molecules Al_2Cl_6, Al_2Br_6, and Al_2I_6.

The same configuration is suggested for these molecules by considerations based on the extreme ionic and the extreme covalent points of view. The radius ratio of the ions Al^{3+} and Cl^- is 0.40 (ratio of univalent radii[1]), which corresponds to tetrahedral coördination. This can be achieved for a molecule Al_2X_6 by the sharing of an edge between two tetrahedra, as shown in Fig. 1. From the covalent point of view this configuration would be expected as the result of the tendency of the aluminum atoms to complete their octet valence shells, the electronic structure of the molecule being



The suggestion of this as a possible structure for the aluminum halides was made by Fajans.[2]

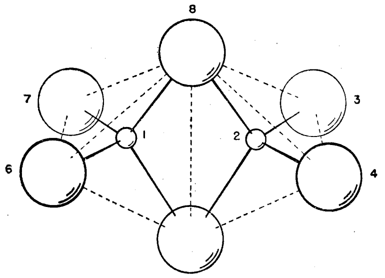


Fig. 1.—The spatial configuration of the dimeric molecule Al_2X_6. Positions 1 and 2 correspond to the aluminum atoms; the remaining positions are occupied by halogen atoms.

We have carried out the study of these substances by the electron diffraction method, and have verified the double-tetrahedral configuration of Fig. 1, with some deformation of the tetrahedra, as described below.

Experimental

The electron diffraction photographs were obtained and interpreted in the usual way.[3] The wave length of the electrons was 0.0613 Å. and the camera distance 10.85 cm. for the chloride and bromide and 20.16 cm. for the iodide.

The strong tendency of the aluminum halides to hydrolyze made it necessary to transfer the samples to the high temperature nozzle inside a moisture proof box. The nozzle[4] could then be sealed and inserted into the electron diffraction apparatus, the sample not being allowed to come into contact with moist air. This procedure proved to be satisfactory, as was verified by inspection of the nozzle after the exposures were made. In no case was there any sign of decomposition.

Merck C. P. aluminum chloride was used without further purification. The aluminum bromide was made by the method of Richards and Krepelka.[5] The aluminum iodide was prepared by heating iodine with excess aluminum in an evacuated glass tube held in a vertical position. The temperature was maintained at 300° for six hours, in which time the color due to the iodine vapor had disappeared completely. The aluminum iodide which collected in the lower part of the tube along with the excess aluminum was separated from the latter by distilling it to the upper part of the tube and then sealing the tube off at the center. The product appeared in the form of colorless highly refractive crystals. There was no evidence of any iodine vapor being present either during or after the distillation. These crystals were used without further purification.

Aluminum Chloride.—The photographs of aluminum chloride show nine maxima. The averaged values of s_0, I (the visually estimated intensities), and C (equal to $Is_0^2e^{-as_0^2}$) are given in Table I. The qualitative appearance of the photographs is well represented by curve F of Fig. 3

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[1] Linus Pauling, THIS JOURNAL, **49**, 765 (1927).

[2] K. Fajans, *Z. Elektrochemie*, **34**, 502 (1928).

[3] L. O. Brockway, *Rev. Modern Phys.*, **8**, 231 (1936).

[4] L. O. Brockway and K. J. Palmer, THIS JOURNAL, **59**, 2181 (1937).

[5] T. W. Richards and H. Krepelka, *ibid.*, **42**, 2221 (1920).

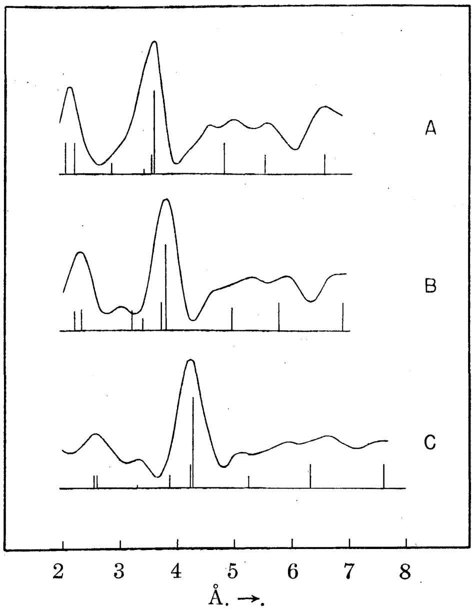

Fig. 2.—Radial distribution curves for (A) aluminum chloride, (B) aluminum bromide and (C) aluminum iodide.

which was calculated for the finally accepted model. The radial distribution curve,[6] curve A of Fig. 2, calculated using the values of C (Table I) in place of I, shows principal peaks at 3.56 and 2.11 Å. These values are interpreted as the Cl–Cl and the short Al–Cl distances, respectively. The ratio of these, 1.69, is close to that (1.633) for a regular tetrahedral arrangement of chlorine atoms about the aluminum atoms. Strong support for this structure is provided by the simplified theoretical intensity curve calculated for the regular tetrahedral model (curve A of Fig. 3), which shows good, although not complete, agreement with the characteristics of the photographs.

In order to find a model in which the ratio of Cl–Cl to Al–Cl is 1.69, all of the edges of the two tetrahedra except the shared edge were assumed to have the value 3.56 Å., and the eight smallest Al–Cl distances the value 2.11 Å. The shared edge would then have the value 2.58 Å. Although this distance is much less than the distance of closest approach (2.86 Å.) observed for two non-bonded chlorine atoms, a theoretical intensity curve was calculated for this model (curve B, Fig. 3), which again is in good but not complete agreement with the photographs. Curves C and D, Fig. 3, were calculated for models in which the shared edge has the value 2.75 and 2.85 Å., respectively. The other ten edges have the values 3.56 Å. in model C and 3.54 Å. in model D and the smallest Al–Cl distances the values 2.12 and 2.11 Å., respectively. These curves do not agree with the photographs quite so well as does curve B.

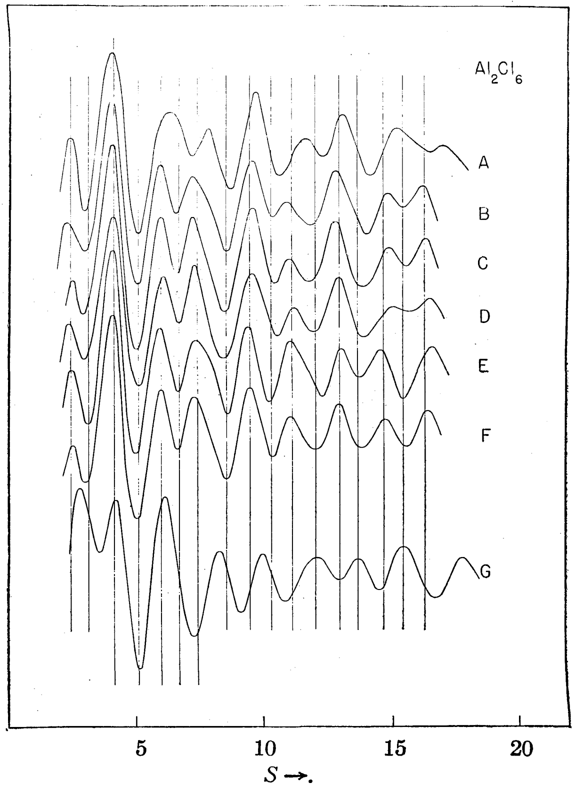

Fig. 3.—Theoretical intensity curves for aluminum chloride.

A very large decrease in the value of the shared edge is necessary in order to obtain the ratio 1.69 when at the same time one keeps the other edges of the tetrahedron about equal to 3.56 Å. and the short Al–Cl distances all equal to 2.11 Å. Thus it is evident that the models so far assumed have been oversimplified, and that the stable configuration, although approximating two regular tetrahedra sharing an edge, is in reality considerably distorted. In order to obtain an insight into the type of distortion to be expected the following calculation was made.

The molecule is assumed to be completely ionic, and to be represented by the potential function

$$V = -\sum_{ij} \frac{e_i e_j}{r_{ij}} + \sum_{ij} \frac{B_{ij} e_i e_j}{r_{ij}^n}$$

in which r_{ij} is the distance between the ith and jth atoms, B_{ij} is the Born coefficient, n is a con-

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[6] L. Pauling and L. O. Brockway, THIS JOURNAL, **57**, 2684 (1935). The use of the values of C in place of I has been suggested by V. Schomaker and C. Degard. They will publish an account of their investigation soon in THIS JOURNAL.

stant, taken to have the value 9 for this calculation, and e_i, e_j are the charges on the ith and jth atoms, taken equal to -1 and $+3$ for chlorine and aluminum, respectively. It was further assumed that the ratio of the B's is given by the expression

$$\frac{B_{\text{Al-Cl}}}{B_{\text{Cl-Cl}}} = \frac{(R_{\text{Al}} + R_{\text{Cl}})^8}{(2R)_{\text{Cl}}{}^8}$$

where R_{Al} and R_{Cl} are the ionic radii of aluminum and chlorine, respectively. The absolute magnitudes of the B's were obtained by setting $\partial V/\partial r = 0$ and using r_{ij}'s corresponding to two regular tetrahedra with all short Al–Cl distances equal to 2.11 Å. The values so obtained are $B_{\text{Al-Cl}} = 48.15$ and $B_{\text{Cl-Cl}} = 1755$. These values were retained throughout the calculation.

A method of successive approximations was used to carry out the calculation. Each of the four independent parameters necessary to specify the structure was successively varied, the process being repeated once. The final values of the parameters so obtained indicate the type of distortion to be expected in such a structure. With a charge of $+3$ assumed to reside on each of the two aluminum atoms the repulsion between them is very strong, and the most notable changes in going from two regular tetrahedra to the final equilibrium configuration are the decrease in the length of the shared edge and the increase in the Al–Al distance. This latter effect changes the values of the short Al–Cl distances by a large amount. The final values of the interatomic distances calculated in this way are Al_1–Al_2 = 3.60, Al_2–Cl_3 = 1.99, Al_2–Cl_8 = 2.31, Al_2–Cl_6 = 4.89, Cl_3–Cl_4 = 3.49, Cl_3–Cl_8 = 3.57, Cl_5–Cl_8 = 2.90, Cl_3–Cl_7 = 5.52, Cl_3–Cl_6 = 6.52 Å. The subscripts on the atomic symbols refer to the position of the atoms as given in Fig. 1. The average of the four Al_2–Cl_3 distances, equal to 1.99 Å., and the four Al_2–Cl_8 distances, equal to 2.31 Å., (refer to Fig. 1) is 2.15 Å., in fair agreement with the radial distribution peak at 2.11 Å. However, if this were the correct model, the two shortest Al_2–Cl distances probably would appear as separate peaks in the radial distribution curve. Moreover, the intensity curve calculated for this model (curve E, Fig. 3) does not agree qualitatively with the photographs; the sixth maximum is too high and the eighth and ninth minima are not of equal depth.

Seven additional intensity curves were calculated for models in which the four parameters were varied. The model finally selected gives an intensity curve (curve F, Fig. 3) which reproduces the qualitative features of the photographs in every respect. The values of the interatomic distances for this model are listed in Table II. Table I gives the values of s and s_0 and their ratio, s/s_0, for model F.

TABLE I

ELECTRON DIFFRACTION DATA FOR ALUMINUM CHLORIDE

Max.	Min.	I	C	s_0	s^a	s/s_0
1		5	2	2.24	2.35	(1.049)
	2			3.08	2.91	(0.946)
2		10	14	4.08	3.93	(.963)
	3			4.96	4.91	(.989)
3		5	12	5.86	5.86	1.000
	4			6.61	6.51	0.985
4		3	10	7.43	7.18	.967
	5			8.33	8.40	1.008
5		4	16	9.23	9.32	1.009
	6			10.11	10.20	1.009
6		1	4	10.98	10.90	0.993
	7			11.90	11.91	1.000
7		3	12	12.71	12.77	1.005
	8			13.42	13.71	1.022
8		1	3	14.47	14.60	1.009
	9			15.22	15.41	1.013
9		2	5	16.07	16.30	1.014
				Average		1.003
				Average deviation		0.010

[a] Calculated for model F.

TABLE II

INTERATOMIC DISTANCES IN ALUMINUM CHLORIDE

	Distance, Å.	Number of times distance occurs in molecule
Al_2–Cl_3	2.06 ± 0.04	4
Al_2–Cl_8	2.21 ± .04	4
Cl_5–Cl_8	2.83 ± .10	1
Cl_3–Cl_4	3.53 ± .04	2
Cl_3–Cl_8	3.56 ± .02	8
Al_1–Al_2	3.41 ± .20	1
Cl_3–Cl_7	5.49 ± .05	2
Cl_3–Cl_6	6.52 ± .05	2
Al_2–Cl_6	4.77 ± .15	4

Aluminum Bromide.—The photographs of aluminum bromide show seven well-defined rings and have the same qualitative features as those for aluminum chloride. The radial distribution curve has two well-defined peaks at 2.28 and 3.77 Å. The ratio of 3.77 to 2.28 is 1.65, indicating that the tetrahedra in this molecule probably are not distorted to so great an extent as for the chloride. Curve A of Fig. 4 was calculated for two regular tetrahedra sharing an edge. The curve is in good but not complete qualitative agreement with the photographs. Curves B and C of

Fig. 4 were calculated for models having the same type of distortion as that found for the chloride, but smaller in magnitude. The two models are essentially the same except for the length of the shared edge. In model B this edge was assumed to be 3.36 Å. and in model C 3.20 Å. The Al_2–Br_3 and Al_2–Br_8 distances were taken equal to 2.21 and 2.33 Å., respectively, in model C, and 2.21 and 2.35 Å. in model B.

The qualitative agreement of curve C with the photographs is better than that of curve B in that the fifth maximum in the former is slightly more intense than the fourth, in agreement with the appearance of the photographs. The differences in these two curves are, however, very slight in spite of the fact that the Br_5–Br_8 distance has been changed by 0.16 Å. The insensitiveness of the intensity curves to variations in this parameter makes it necessary to assign to it a large probable error. In Table III there are listed the values of I, C, s_0, s (for model C), and the ratio of s/s_0, and in Table IV there are given the values of the interatomic distances for the molecule and their estimated probable errors.

TABLE III

ELECTRON DIFFRACTION DATA FOR ALUMINUM BROMIDE

Max.	Min.	I	C	s_0	s^a	s/s_0
1		5	2	2.11	2.11	1.000
	2			2.85	2.87	1.007
2		10	11	3.78	3.72	0.998
	3			4.68	4.61	.999
3		6	11	5.48	5.60	1.022
	4			6.28	6.22	0.990
4		4	9	7.02	6.88	.980
	5			7.85	7.88	1.004
5		5	13	8.73	8.78	1.006
	6			9.59	9.68	1.009
6		1	2	10.38	10.35	0.997
	7			11.19	11.17	.998
7		2	3	11.84	12.08	1.023
				Average		1.003
				Average deviation		0.009

[a] Calculated for model C.

TABLE IV

INTERATOMIC DISTANCES IN ALUMINUM BROMIDE

	Distance, Å.	Number
Al_2–Br_3	2.21 ± 0.04	4
Al_2–Br_8	2.33 ± .04	4
Br_5–Br_8	3.20 ± .10	1
Br_3–Br_4	3.72 ± .03	2
Br_3–Br_8	3.78 ± .03	8
Al_1–Al_2	3.39 ± .10	1
Br_3–Br_7	5.76 ± .10	2
Br_3–Br_6	6.86 ± .10	2
Al–Br	4.93 ± .10	4

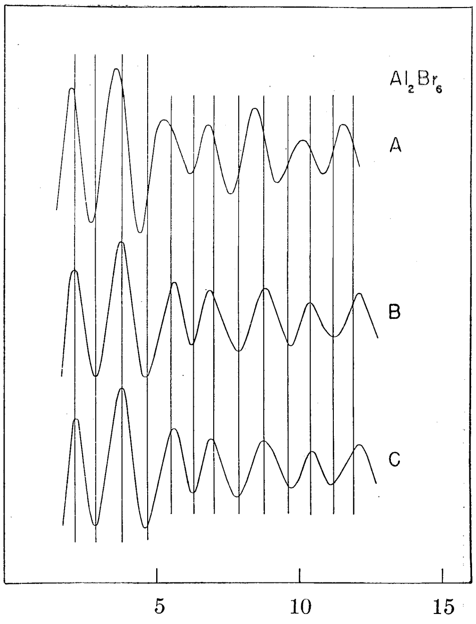

Fig. 4.—Theoretical intensity curves for aluminum bromide.

Aluminum Iodide.—The photographs of aluminum iodide, taken with a camera distance of 20.16 cm., show seven well-defined maxima, the general appearance of the photographs being closely similar to that for the chloride and bromide. This similarity is strong evidence for the assumption that the structures of the three molecules are similar in configuration.

The radical distribution curve (curve C, Fig. 2), shows principal peaks at 2.58 and 4.23 Å. The ratio of the latter to the former distance is 1.64, indicating that the structure is very nearly that of two regular iodine tetrahedra sharing an edge.

The ratio of the scattering due to the iodine atoms to that due to the aluminum atoms is very large in aluminum iodide; this makes the determination of the positions of the aluminum atoms with any degree of accuracy impossible. The intensity curves shown in Fig. 5 were calculated for models approximating those described for aluminum bromide. Curve A is for undistorted tetrahedra, and curves B and C for tetrahedra whose shared edge has the value 4.00 and 3.85 Å., respectively, and for which the Al_2–I_3 and Al_2–I_8 distances have the values 2.58 and 2.54 Å., respectively. Curve A does not agree with the photographs in that the relative intensities of the maxima are unsatisfactory. Curve C gives a somewhat better representation of the appearance of the photographs than curve B, but the differences in these two curves, namely, the variation of the intensities of the third, fourth, and fifth maxima, are so small that, as in the case of the bromide, it is impossible to determine the length of the shared edge with much accuracy.

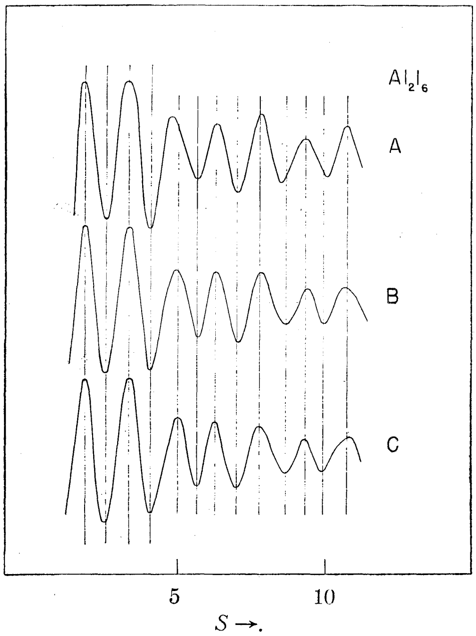

Fig. 5.—Theoretical intensity curves for aluminum iodide.

The values of the interatomic distances with their estimated probable errors are given in Table VI. The quantitative comparison of the s values obtained from curve C with the observed s_0 values is given in Table V.

Table V

Electron Diffraction Data for Aluminum Iodide

Max.	Min.	I	C	s_0	s^a	s/s_0
1		9	3	1.88	1.87	0.995
	2			2.51	2.52	1.004
2		10	9	3.32	3.33	1.003
	3			4.14	4.08	0.986
3		7	10	4.85	4.99	1.029
	4			5.56	5.65	1.016
4		6	9	6.29	6.26	0.995
	5			7.03	7.00	.996
5		5	10	7.80	7.75	.994
	6			8.62	8.67	1.006
6		2	3	9.27	9.29	1.002
	7			9.95	9.89	0.994
7		1	1	10.67	10.70	1.003
				Average		1.002
				Average deviation		0.008

[a] Calculated for model C.

Table VI

Interatomic Distances in Aluminum Iodide

	Distance, Å.	Number
Al_2–I_3	2.53 ± 0.04	4
Al_2–I_8	2.58 ± .04	4
I_5–I_8	2.90 ± .15	1
I_3–I_4	4.20 ± .03	2
I_3–I_8	4.24 ± .02	8
Al_1–Al_2	3.24 ± .15	1
I_3–I_7	6.24 ± .15	2
I_3–I_6	7.54 ± .10	2
Al_2–I_6	5.22 ± .15	4

Discussion

The only report on the structures of aluminum chloride, bromide, or iodide previous to the present one is that of Ketelaar[7] on the structure of aluminum chloride crystals. He found that the chlorine atoms are in hexagonal closest packing, this arrangement being compatible with that found for the gas molecule in this investigation. However, he chose to place two aluminum atoms inside an octahedron of chlorine atoms, and only 0.56 Å. apart, rather than one each inside of two tetrahedra sharing an edge, both of these possibilities being provided by the hexagonal closest packed arrangement. The extent to which the X-ray data can be accounted for by this latter configuration is being investigated by one of us. Curve G, Fig. 2, is the simplified theoretical intensity curve calculated for the "octahedral" model of Ketelaar; it is apparent from a comparison with curve F that this model cannot represent the structure of the gas molecule.

The large difference in electronegativity between aluminum and the halogen atoms leads one to expect that the Al–X bond will be largely ionic, and this is confirmed by the observed contraction of the shared edge. The percentage decrease in length of the shared edge is found to be largest in the chloride and least in the iodide, which is in accordance with expectation.

The sums of the tetrahedral radius of aluminum and the normal radii for the halogen atoms are 2.25, 2.40, and 2.59 Å. for the chloride, bromide, and iodide, respectively. These values are to be compared with the observed values, 2.06, 2.21, and 2.53 Å., which are the Al_2–X_3 distances, and 2.21, 2.33, and 2.58 Å., which are the Al_2–X_8 distances, for the chloride, bromide, and iodide, respectively. The observed shortening in the case of the Al_2–X_3 distances is probably due to the excited structures in which an X_3 halogen atom

(7) J. A. A. Ketelaar, *Z. Krist.*, **90**, 237 (1935).

swings in a pair of electrons and forms a double bond with the aluminum atom. This type of resonance is not expected to occur to the same degree for halogen atoms forming two bonds, which accounts for the fact that the observed Al_2–X_8 distances are nearly equal to the sum of the appropriate radii.

It is interesting to note that the observed values of the Al_2–X_3 distances show a greater tendency for the chlorine and bromine atoms to form double bonds than of iodine atoms; this is compatible with the results of other investigations.

We wish to express our thanks to Professor Linus Pauling for his aid and helpful criticism during the course of this investigation.

Summary

It is shown that in the gaseous state the dimeric molecules of aluminum chloride, bromide, and iodide consist of two tetrahedra sharing an edge with six halogen atoms at the corners, each tetrahedron containing one aluminum atom. The final values of the interatomic distances are as follows

The subscripts on the atomic symbols refer to their positions in the molecule as given in Fig. 1.

	Al_2Cl_6	Al_2Br_6	Al_2I_6
Al_1–Al_2	3.41 ± 0.20 Å.	3.39 ± 0.10 Å.	3.24 ± 0.15 Å.
Al_2–X_3	2.06 ± .04	2.21 ± .04	2.53 ± .04
Al_2–X_8	2.21 ± .04	2.33 ± .04	2.58 ± .04
Al_2–X_6	4.77 ± .15	4.93 ± .10	5.22 ± .15
X_3–X_4	3.53 ± .04	3.72 ± .03	4.20 ± .03
X_3–X_8	3.56 ± .02	3.78 ± .03	4.24 ± .02
X_5–X_8	2.83 ± .10	3.20 ± .10	2.90 ± .15
X_3–X_7	5.49 ± .05	5.76 ± .10	6.24 ± .15
X_3–X_6	6.52 ± .05	6.86 ± .10	7.54 ± .10

PASADENA, CALIF. RECEIVED MAY 31, 1938

[CONTRIBUTION FROM THE METCALF CHEMICAL LABORATORY OF BROWN UNIVERSITY]

Photochemical Studies. XXVI. A Further Study of the Fluorescence of Acetone Vapor and its Relationship to the Photochemical Decomposition

BY MAX S. MATHESON AND W. ALBERT NOYES, JR.

The fluorescence of acetone vapor was reported by Damon and Daniels,[1] who stated that it is greenish and is changed to blue by the presence of small amounts of oxygen. The oxygen disappears during illumination and this fact has been used as a means of determining small amounts of this substance.[2]

Two regions, one extending from 4100 to 4820 Å. (maximum 4580 Å.) and the other from 4990 to the limit of plate sensitivity (5210 Å.), were found by Damon and Daniels.[1] Norrish, Crone and Saltmarsh[3] report three bands of fluorescent emission (all diffuse) with maxima at 5117, 5572 and 6095 Å. More recently Padmanabhan[4] has found that the bands are not devoid of structure but consist of diffuse bands superimposed upon a continuous spectrum. Ten bands, two considered to be doubtful, were reported.

Herzberg[5] first found a discrete structure in the near ultraviolet absorption of acetone vapor and this has been confirmed by other workers.[3,6] The detailed analysis of these bands and their interpretation is still lacking, but the existence of such a structure is in conformity with the fact that fluorescence is observed. However, structure is difficult to observe in many polyatomic molecules even though fluorescence is found. Such seems to be the case with ethyl methyl ketone[7] and diethyl ketone.[8]

All authors who have studied the quantum yield of acetone decomposition in the near ultraviolet at room temperature agree that it is low.[9] The explanation of this fact is not complete. Damon and Daniels[1] state that the fluorescence is too weak to be the primary cause of this effect. However Fisk and Noyes[10] studied the fluorescence excited by the 3130 Å. line of mercury and found (with the very low intensities used) a Stern–Volmer mechanism to be obeyed. At moderate pressures it was found that the number of quanta absorbed was roughly equal to the sum

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(1) Damon and Daniels, THIS JOURNAL, **55**, 2363 (1933).

(2) Damon, *Ind. Eng. Chem., Anal. Ed.*, **7**, 133 (1935); Fugassi, THIS JOURNAL, **59**, 2092 (1937); Fugassi and Daniels, *ibid.*, **60**, 771 (1938).

(3) Norrish, Crone and Saltmarsh, *J. Chem. Soc.*, 1456 (1934).

(4) Padmanabhan, *Proc. Ind. Acad. Sci.*, **5A**, 594 (1937).

(5) For mention see Scheibe, Povenz and Linström, *Z. physik. Chem.*, **20B**, 292 (1933).

(6) Noyes, Duncan and Manning, *J. Chem. Phys.*, **2**, 717 (1934); Noyes, *Trans. Faraday Soc.*, **33**, 1495 (1937).

(7) Duncan, Ells and Noyes, THIS JOURNAL, **58**, 1454 (1936).

(8) J. W. Zabor, M.S. Thesis, Brown University, 1938.

(9) See refs. 1 and 3, Leermakers, THIS JOURNAL, **56**, 1900 (1934).

(10) Fisk and Noyes, *J. Chem. Phys.*, **2**, 654 (1934).

of the three quantities: (a) number of molecules which fluoresce; (b) number of molecules which dissociate; (c) number of activated molecules deactivated by collision. However, the mechanism used to accomplish this balance disagreed quite definitely with some of the photochemical facts, particularly with the supposed decrease in quantum yield with acetone pressure.

That the mechanism of acetone photodecomposition may be quite complex is suggested by the work of Spence and Wild.[11] These authors find approximately one molecule of carbon monoxide for each molecule of ethane at 3130 Å., but a considerable deficiency of carbon monoxide at shorter wave lengths. This agrees with the fact, first reported by Barak and Style,[12] that appreciable amounts of biacetyl are formed at room temperature during photodecomposition of acetone. At 60° the amount of biacetyl was found to be negligible, due perhaps to the instability of the CH_3CO radical at that temperature.

To attempt to elucidate the phenomenon of a low quantum yield coupled with a relatively small amount of fluorescence it was thought desirable to study the fluorescence over as wide a range of conditions as practicable. Unfortunately the absorption coefficient of acetone is so low at 3130 Å. that it did not prove feasible to use pressures low enough to permit a decision to be made as to the effect of collisions on this reaction.

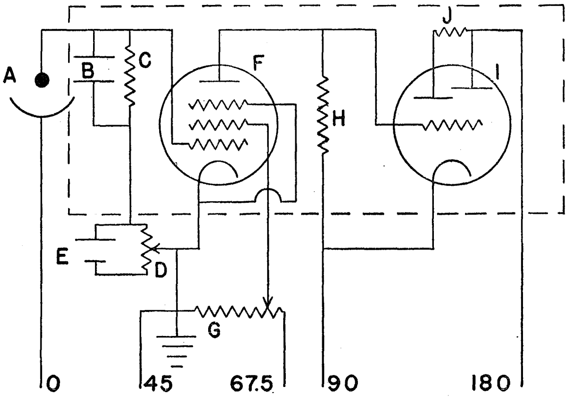

Fig. 1.

Experimental

Purification of Acetone.—Reagent quality acetone was purified by the method of Shipsey and Werner[13] by crystallizing from an acetone solution of anhydrous sodium iodide. The acetone was distilled from the salt over a steam-bath and then carefully fractionated, the middle portion boiling at 55.8° (uncorr.) being retained. After placing in the vacuum line, it was refluxed for forty-eight hours over boron trioxide at low temperatures and then fractionated. No stopcocks or joints involving grease were present in the line.

Purification of Biacetyl.—Biacetyl (Eastman) was fractionally distilled three times, the final middle fraction boiling at 87–88° being retained. After placing in the vacuum line, it was subjected to five low pressure fractionations at room temperature, the first three condensations taking place at liquid air temperatures and the last two with dry ice.

The Fluorescence Cells.—Two all-quartz cells having a T shape were used at different times. These were sealed to the rest of the line with graded seals. The length of the main limb was 4 cm. and the windows were 2 cm. in diameter.

The Light Source.—A General Electric H3 quartz high pressure mercury arc operated at 85 watts was used. A hole was blown in the glass envelope surrounding the arc to permit the exit of wave lengths below 3500 Å.

The light was passed through a water-cooled Red Purple Corex A filter and then through either one or two quartz plates lightly silvered (by sputtering) according to the directions given by R. W. Wood.[14] A quartz lens was used to bring the radiation to a focus at the center of the cell, although the beam was nearly parallel.

The radiation transmitted by the optical system was photographed with an E3 Hilger spectrograph on Eastman 33 plates. Microphotometer tracings[15] showed the following distribution of radiation: (a) 3130 Å., 79%; (b) 3340 Å., 8%; (c) 3650 Å., 12%; (d) all others less than 1%. (No trace of lines below 3130 Å. could be found on the plates which were microphotometered.)

The Measurement of the Incident Radiation.—For some runs the incident radiation was measured by a cesium oxide photoelectric cell with quartz envelope. For others a similar cell with Pyrex envelope was used. One or the other of these cells was placed on the exit side of the long limb of the T so that transmitted radiation was measured.

The current from this photoelectric cell was amplified and measured by the circuit shown in Fig. 1.[16] The photoelectric cell is shown at A. F is a Sylvania type 77 vacuum tube. I is a 6E5 magic eye radio tube. D is a student potentiometer. C is a 10-megohm composition resistor and B is a 0.1 microfarad condenser. H is a 1 megohm composition resistor and J is a 0.5 megohm composition resistor. G is a 10^5-ohm screen potentiometer. E is a battery of three dry cells. The figures at the bottom refer to voltages obtained by the use of four B batteries.

This amplifier was used as a null point indicator, the null point used being the just closed condition of the fan-shaped shadow on the fluorescent screen of the 6E5 tube (I). The change in the reading of the student potentiometer D necessary to just close the shadow gave a measure

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[11] Spence and Wild, *J. Chem. Soc.*, 352 (1937).

[12] Barak and Style, *Nature*, **135**, 307 (1935); see Spence and Wild, *ibid.*, **138**, 206 (1936).

[13] Shipsey and Werner, *J. Chem. Soc.*, **103**, 1255 (1913).

[14] Wood, "Physical Optics," The Macmillan Co., New York, N. Y., 1929, p. 15.

[15] The authors wish to express their appreciation to Professor W. W. Watson of Yale University for his kindness in having the microphotometer tracings made.

[16] J. W. Tukey, M.S. Thesis, Brown University, 1937.

of the intensity of light falling on the photoelectric cell. The linearity of amplification was tested by use of the inverse square law of intensities obtained from a filament lamp placed at distances of two meters or greater.

Since the fraction of radiation transmitted by the exit window of the fluorescence cell was constant, it was possible to calculate quantities proportional to the incident intensity with the use of the known absorption coefficients of acetone vapor.[17] Absorption of the mercury line at 3130 Å. was alone considered.

The Measurement of the Fluorescent Radiation.—The fluorescent radiation was measured by a photoelectric cell with quartz envelope and having a plane window in front of the cathode. Current from this photoelectric cell was measured with a DuBridge circuit using an FP54 tube.[18]

Sample Experiment.—The method of introducing acetone from a cooled reservoir until it reached the desired pressure was used previously.[10] Biacetyl, when used, was introduced from calibrated volumes where the pressure was known. At low pressures the ratio of pressures could be determined exactly even if the absolute pressure was uncertain.

Both amplifiers and the arc were turned on and a half hour allowed to elapse in order to obtain steady conditions. The DuBridge and Brown[18] amplifier was balanced as described by these authors in order to minimize the drift of the galvanometer.

A shutter in front of the light source prevented any decomposition of acetone vapor while the pressure of the latter was being adjusted. Since the DuBridge and Brown amplifier had a lag of about three minutes, the transmitted and the fluorescent radiation were both measured over an interval of four or five minutes at least. Table I shows a sample set of readings.

TABLE I

DATA OF A TYPICAL EXPERIMENT

Time	G_f		G_t	Operation
3:33 P. M.	−11.40		1078.0	Light shut off from cell
3:34	−11.40	(−11.40)	1078.5	(Pressure acetone = 152.8 mm.)
3:35	+14.00	(13.99)	972.0	Light on, P = 152.8 mm.
3:36	14.72	(14.69)	971.0	
3:37	15.12	(15.08)	971.5	
3:38	14.99	(14.93)	972.0	
3:39	4.20	(4.13)	956.0	Light on, P = 0 (liquid air on trap)
3:40	3.25	(3.17)	954.5	
3:41	3.00	(2.90)	954.5	
3:42	3.05	(2.94)	954.5	
3:43	−10.70	(−10.83)	1077.5	Light off
3:44	−11.20	(−11.34)	1077.5	
3:45	−11.25	(−11.40)	1077.5	

G_f is measure of fluorescence intensity. G_t is obtained from measurements of transmitted intensity.

Under G_f it is seen that a drift of the readings toward more positive values has taken place during the experiment. Experimentally this drift was found to be nearly uniform. The drift per minute is, therefore, (11.40–11.25)/11. The figures under G_f are then corrected for drift with the results given in parentheses. The value 14.93 obtained at 3:38 is due to scattered plus fluorescent radiation, while the value 2.94 obtained at 3:42 is due to scattered radiation alone. The difference (11.99) is proportional to the intensity of the fluorescence. At low acetone pressures the scattered radiation may be a large fraction of the total measured, so that the accuracy is small.

The average of G_t at 3:34 and 3:44 is 1078.0 and is the value with the light off. By subtracting the reading at 3:42 one obtains 123.5, which is proportional to the radiation transmitted when no acetone is in the cell.

Since the amount of 3130 Å. radiation absorbed is small it will vary nearly linearly with the path length. From the geometry of the system the length of path from which radiation could be incident on the photoelectric cell measuring the fluorescence is 2.8 cm., but since relative results only are necessary this figure is not very critical.

Let A be the fraction of the radiation transmitted by the back window, D_t the measured intensity at 0 acetone pressure (=123.5 above), D_t' the intensity in front of the back window and D_t'' the intensity in back of the front window both with acetone in the cell.

Then

$$D_t'' = D_t/A \qquad (1)$$

From Beer's law

$$D_t' = D_t'' \exp.(-kcl) = D_t/A \exp.(-kcl) \qquad (2)$$

where l is the cell length (4 cm.), c is the concentration in moles per liter and k = 6.63 for 3130 Å. radiation.[17] Using the perfect gas law one finds (omitting A which is constant)

$$D' = D_t \times 10^{-61.735 \times 10^{-5}P} \qquad (3)$$

where P is in millimeters.

The effective path (2.8 cm.) begins 0.5 cm. back of the front window. Use of Beer's law indicates that the absorbed intensity is given by

$$I_a = D_t \times 10^{-61.735 \times 10^{-5}P} (10^{5.41 \times 10^{-4}P} - 10^{0.996 \times 10^{-4}P}) \qquad (4)$$

where the quantity in parentheses is the fraction of the light absorbed in the effective path (2.8 cm.).

In the above example

$$I_a = 17.28 \qquad (5)$$

and

$$I_a/I_f = 1.44 \text{ (at } P = 152.8 \text{ mm.)} \qquad (6)$$

A series of values of I_a/I_f could be made. As shown previously[10] the intensity units cancel

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[17] Porter and Iddings, THIS JOURNAL, **48**, 40 (1926).

[18] DuBridge and Brown, *Rev. Sci. Instruments*, **4**, 532 (1933).

when a plot is made of this quantity against the pressure and the slope is divided by the intercept.

The estimated accuracy of I_a/I_f is about ±5%, although this tends to increase at low pressures of acetone where the fluorescence is very weak.

When biacetyl was mixed with the acetone or used alone the procedure was exactly similar to that described above, except that with pure biacetyl the fraction of light absorbed was assumed to be proportional to the pressure since accurate absorption coefficients of this substance have not been obtained.

Discussion of Results

It should be kept in mind that the incident intensity in the present work was much larger (100 to 1000 times) than that used in the previous experiments.[10]

Since it was the object of the present work to ascertain what effect collisions have in deactivating acetone molecules, values of I_a/I_f were desired over a large pressure range and particularly at low pressures. However, it became evident quite early that measurements below pressures of 1 to 2 cm. were unreliable due to the small absorption by the acetone and consequent weak fluorescence.

Attempts to verify the previous work[10] at higher pressures by plotting I_a/I_f against pressure and dividing the slope by the intercept gave not only results differing from those published, but the results were erratic and not reproducible. Figure 2 shows plots of I_a/I_f *vs.* P (cm.) for two different runs in which each point involved an exposure of the acetone to the radiation during ten minutes. Both of these runs were made by starting at low acetone pressures and adding acetone for each successive point without, however, evacuating the line between points.

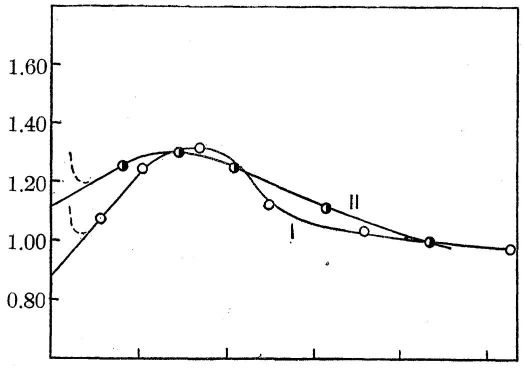

Fig. 2.

As stated above, experiments at low pressures are accompanied by a large error, although it may be significant that I_a/I_f apparently increased at pressures of a centimeter or below as indicated roughly by the dotted lines.

In the previous work it was found that

$$\text{Slope/Intercept} = 0.052\ (\text{Av.})^{10}\ (P \text{ in cm.}) \quad (7)$$

In the present experiments many values of slope/intercept were found which agree approximately with this figure providing one considers only points at low pressures obtained before the acetone had been subjected to a long exposure to the radiation. Thus in Fig. 2, 0.134 and 0.036 (approximately) were obtained for slope/intercept for the lower points. It seems evident that the conclusions of Fisk and Noyes[10] need not be seriously modified, although they were based on data obtained over a limited range of experimental conditions.

However, it should be pointed out that in every case the I_a/I_f *vs.* pressure curve passes through a maximum (see also Fig. 3). Although the data obtained previously indicate that the slope tends to become less at higher pressures, this fact had not been observed.

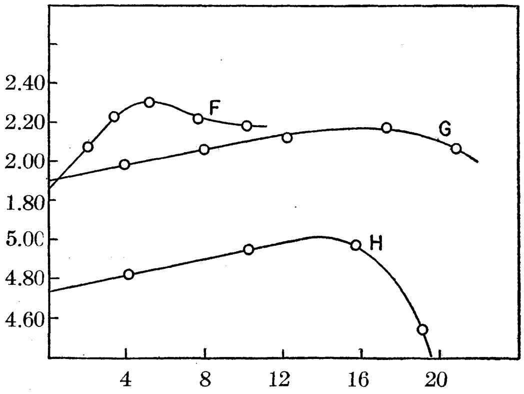

Fig. 3.—F, 2-minute exposure; G, D_t one-fourth that for F, same exposure time; H, D_t same as for F, 4-minute exposure, fresh acetone used for each point.

The following observations are also important:

(1) As the intensity is increased the value of I_a/I_f decreases, this effect being more noticeable with long than with short exposures. Previously it had been found (for very low intensities) that I_a/I_f was approximately independent of intensity, although the data were not very satisfactory on this point.

(2) At a given pressure and a given intensity I_a/I_f decreases with increasing time. However, if

the acetone is condensed with liquid air the value of this ratio returns almost exactly to its initial value. This indicates that some relatively nonvolatile substance is responsible for this phenomenon, since the mere interposition of a shutter did not produce this effect.

(3) When short exposures were used for the measurement of each point (curves F, H and G, Fig. 3) the point of inflection tended to come at higher pressures than was the case with long exposures. A greater displacement was observed with low intensities (curve G). (It should be kept in mind that with the exception of H (Fig. 3) successive points were obtained by adding acetone without intervening evacuation.)

(4) If the line was evacuated between successive points (curve H, Fig. 3) the maximum was displaced toward higher pressures even though high intensities were used.

(5) Results obtained by starting at a high pressure and removing acetone to reduce the pressure between points did not agree with those obtained by the procedure normally used.

All of these facts point to the formation during illumination of some substance which has a marked effect in increasing the fluorescence.

Neglecting secondary reactions of relatively minor importance at room temperature, the photochemical decomposition of acetone proceeds mainly in two ways

$$(CH_3)_2CO = C_2H_6 + CO^{1,3,11} \qquad (8)$$

$$2(CH_3)_2CO = (CH_3CO)_2 + C_2H_6{}^{11,12} \qquad (9)$$

(In the presence of water Damon and Daniels[1] state that diacetone alcohol may be formed.)

Of the products in (8) and (9) biacetyl would be the least volatile and from other considerations might be expected to be the one responsible for the phenomena discussed above. It was decided, therefore, to examine the effect of biacetyl on the fluorescence of acetone.

Table II presents results obtained during one run in which the acetone pressure and the incident intensity were maintained nearly constant.

TABLE II

EFFECT OF DIACETYL ON FLUORESCENCE OF ACETONE

Acetone press., mm.	69.6	69.8	69.0	69.2	69.9	70.7	68.7
Biacetyl press., mm.	0.50	0.34	0.23	0.16	0.11	0.07	0
ft	29.08	23.22	24.05	25.68	25.24	25.41	4.68
(D	148.0	142.0	141.0	137.5	135.3	135.75	133.0
D_t/I_f	5.1	6.1	5.9	5.4	5.4	5.3	28.4

(D_t/I_f is very closely proportional to I_a/I_f)

Biacetyl alone at the pressures shown in Table II would absorb an amount of radiation too small to measure and yet it seems to increase the apparent amount of fluorescence five or sixfold. This large effect at once raises the question as to whether acetone itself fluoresces.

The decisive answer to the question here raised cannot be made at once, but the following facts point to a fluorescence of acetone itself:

(1) After condensation by liquid air the fluorescence diminishes and reproduces the value obtained at the beginning of illumination. Several minutes of illumination are necessary, except at higher acetone pressures where the absorption is high, before the fluorescence begins to increase markedly.

(2) The fluorescence changes from green to blue when oxygen is present.[1] The interpretation of this fact is tentative and will be discussed later.

The conclusions to which the above experimental evidence seemed to lead necessitated an investigation of the fluorescence spectrum. The spectrum was photographed both with a small Hilger glass prism spectrograph and with an E3 spectrograph with glass train. The silvered quartz plates were removed from the optical system (see above) so that the incident radiation was less monochromatic than in the rest of the experiments. Cramer Iso Presto and Wratten and Wainwright panchromatic plates were used.

The following results were obtained:

(1) With pure acetone (102 mm.), frozen down every seven minutes to lessen the effect of biacetyl and a three-hour exposure with the small spectrograph, two bands at approximately 5100 and 5600 Å. were observed. These are almost certainly the bands at 5117 and 5572 Å. reported by Norrish, Crone and Saltmarsh.[3] When photographed with the larger spectrograph the band at 5117 Å. seemed to consist of several maxima as found by Padmanabhan.[4]

(2) With pure biacetyl (45 mm.), two-hour exposure with the small spectrograph, the same bands as in (1) appeared and in addition a faint band about 6100 Å. The latter is probably the band at 6095 Å. reported by Norrish, Crone and Saltmarsh.[3]

(3) Acetone (65 mm.) and biacetyl (0.5 mm.) and a two-hour exposure with the small spectrograph showed the same bands as in (1).

No trace of the region extending from 4100 to 4800 Å. reported by Damon and Daniels[1] could be found, but this means in all probability that it is weak compared to the fluorescence at longer wave lengths. (The plates used by Damon and Daniels were not sensitive at wave lengths longer than 5200 Å.) The blue color of the fluorescence when oxygen is present indicates that wave lengths below 5000 Å. must be present. The observed bands at longer wave lengths, which were alone observed by Norrish, Crone and Saltmarsh,[3] are evidently much more intense than any fluorescent emission in the blue region.

These results seem to indicate beyond any question that the supposed emission of acetone is the same as that of biacetyl with the possible exception of wave lengths below 5000 Å. The effect of oxygen on the fluorescence of biacetyl and of acetone was observed visually. With acetone oxygen weakened the fluorescence considerably and changed its color from greenish to blue in agreement with the results of Damon and Daniels.[1] With biacetyl the fluorescence was weakened and became less yellow although it did not acquire the characteristic blue of acetone. At the same time biacetyl gave a heavy deposit on the windows.

If the emitter is the same for both biacetyl and acetone the following possibilities suggest themselves:

(1) Acetone may dissociate into CH_3 and CH_3CO, the latter being either formed in an excited state or raised to an excited state by collisions of the second kind with excited molecules. Biacetyl would perhaps dissociate to give two CH_3CO radicals.

The energy required to dissociate acetone by the equation

$$(CH_3)_2CO = CH_3CO + CH_3 \qquad (10)$$

is uncertain, but is probably not less than 75 kcal. Quanta of 3130 Å. radiation correspond to about 91 kcal. per mole. Thus neither free radical could possess enough potential energy to be capable of fluorescing in the visible spectrum (approximately 50 kcal. per mole would be required at 6000 Å.). Roughly the same discrepancy would exist for dissociation and subsequent fluorescence of biacetyl.

Thus if emission by the CH_3CO radical takes place this must follow an activation by a collision of the second kind. A detailed mechanism considering the possible secondary reactions leads to a kinetic expression too complex to be capable of any sort of rigorous test. The enhancement of the fluorescence due to the addition of small amounts of biacetyl would have to be due to the dissociation of the latter into CH_3CO radicals by collisions of the second kind with excited acetone. Thus two excited acetone molecules would be necessary in each sequence of events leading to fluorescence. Whether or not the incident intensity would appear as the square in the expression for the fluorescent intensity would depend on other steps used in the mechanism.

(2) The major portion of the fluorescence may be due to excited biacetyl molecules. This substance absorbs[19] at least to 4700 Å. If excited biacetyl molecules are reduced to the zero vibration level by collisions prior to fluorescence,[20] the operation of the Franck–Condon principle *might* cause the maximum intensity of fluorescent emission to lie at longer wave lengths than the long wave absorption limit at room temperature.

If (2) is the correct explanation, the effect of oxygen is to prevent the formation of biacetyl and the weak blue fluorescence observed with oxygen present[1] would be due to acetone itself. The second explanation may be expressed by the following mechanism

$$\begin{array}{llrcll}
k_1 I & & \mathrm{Ac} + h\nu & = & \mathrm{Ac}_1 & (11) \\
k_2 & & \mathrm{Ac}_1 & = & \mathrm{M} & (12) \\
k_3 & & \mathrm{Ac}_1 & = & \mathrm{Ac} + h\nu_1 & (13) \\
k_4 & & \mathrm{Ac}_1 + \mathrm{Ac} & = & 2\mathrm{Ac} & (14) \\
k_5 & & \mathrm{Ac}_1 + \mathrm{B} & = & \mathrm{B}_1 + \mathrm{Ac} & (15) \\
k_6 & & \mathrm{B}_1 + \mathrm{Ac} & = & \mathrm{B} + \mathrm{Ac} & (16) \\
k_7 & & \mathrm{B}_1 & = & \mathrm{B} + h\nu_2 & (17) \\
k_8 & & \mathrm{B}_1 & = & \mathrm{N} & (18)
\end{array}$$

Ac represents a normal and Ac_1 an excited acetone molecule. B is a normal and B_1 an excited biacetyl molecule. M and N are dissociation products. These equations lead to

$$I/I_f = \frac{(k_2 + k_3 + k_4(\mathrm{Ac}) + k_5(\mathrm{B}))(k_6(\mathrm{Ac}) + k_7 + k_8)}{k_1k_3(k_6(\mathrm{Ac}) + k_7 + k_8) + k_1k_5k_7(\mathrm{B})} \qquad (19)$$

Since biacetyl has a very large effect on the fluorescence, this equation probably reduces to

$$k_1I/I_f = (k_6(\mathrm{Ac}) + k_7 + k_8)/k_7 \qquad (20)$$

and I/I_f is independent of biacetyl pressure unless the latter is very low. This is in accord with the facts.

In order to find an expression for the effect of intensity and time on the ratio of I/I_f, it is necessary to introduce a rate of biacetyl formation. If this is assumed to be of such a nature that

$$(\mathrm{B}) = KI_0(\mathrm{Ac})t \qquad (21)$$

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(19) *Cf.* Sponer, "Molekülspektren," Verlag von Julius Springer, Berlin, 1935, Vol. I, p. 117.

(20) *Cf.* Gradstein, *Z. physik. Chem.*, **22B**, 384 (1933).

where I_0 is the incident intensity and t is the time, equation (19) becomes

$$I/I_f = \frac{(k_2 + k_3 + k_4(\mathrm{Ac}) + k_5KI_0(\mathrm{Ac})t)(k_6(\mathrm{Ac}) + k_7 + k_8)}{k_1k_3(k_6(\mathrm{Ac}) + k_7 + k_8) + k_1k_5k_7KI_0(\mathrm{Ac})t} \tag{22}$$

This equation is a quadratic in (Ac) divided by a first order expression in (Ac) and may be made to fit the data presented. When I_0t is very small, (22) reduces to

$$k_1I/I_f = 1 + (k_2 + k_4(\mathrm{Ac}))/k_3 \tag{23}$$

which is the equation used by Fisk and Noyes.[10]

Therefore it is possible to explain the observed facts by means of the mechanism included in equations (11) to (18), but it is unsafe to conclude that fluorescence of the acetyl radical does not take place or may not be mainly responsible for the phenomena described.

The Raman spectrum of biacetyl has not been investigated very completely.[21] Except, possibly, for the line at 1725 cm.$^{-1}$, no close agreements are found with differences in wave numbers among the bands found by Padmanabhan.[4] However, this is not evidence at present against the interpretation given since the electronic spectrum of this molecule has not been analyzed.

Acetone seems to have no effect on the fluorescence of biacetyl, when the latter is at a pressure of about 50 mm. and the former at a pressure of a few millimeters. Thus the seemingly good resonance for deactivation of acetone by biacetyl does not carry over to the deactivation of biacetyl by acetone. This is not incompatible with the mechanism suggested.

The various facts concerning the photochemical decomposition of acetone and the fluorescence phenomena discussed above, indicate that the following reactions take place

$$(\mathrm{CH_3})_2\mathrm{CO} + h\nu = ((\mathrm{CH_3})_2\mathrm{CO})_1 \tag{24}$$
$$((\mathrm{CH_3})_2\mathrm{CO})_1 = (\mathrm{CH_3})_2\mathrm{CO} + h\nu_1 \tag{25}$$
$$= \mathrm{CH_3CO} + \mathrm{CH_3} \tag{26}$$
$$\mathrm{CH_3CO} + \mathrm{CH_3CO} = (\mathrm{CH_3CO})_2 \tag{27}$$
$$\mathrm{CH_3} + \mathrm{CH_3} = \mathrm{C_2H_6} \tag{28}$$
$$\mathrm{CH_3CO} = \mathrm{CH_3} + \mathrm{CO} \tag{29}$$
$$((\mathrm{CH_3})_2\mathrm{CO})_1 + (\mathrm{CH_3CO})_2 = ((\mathrm{CH_3CO})_2)_1 + (\mathrm{CH_3})_2\mathrm{CO} \tag{30}$$
$$((\mathrm{CH_3CO})_2)_1 = 2\mathrm{CH_3CO} \tag{31}$$
$$= (\mathrm{CH_3CO})_2 + h\nu_2 \tag{32}$$
$$(\mathrm{CH_3})_2\mathrm{CO} + ((\mathrm{CH_3CO})_2)_1 = (\mathrm{CH_3CO})_2 + (\mathrm{CH_3})_2\mathrm{CO} \tag{33}$$
$$(\mathrm{CH_3})_2\mathrm{CO} + ((\mathrm{CH_3})_2\mathrm{CO})_1 = 2(\mathrm{CH_3})_2\mathrm{CO} \tag{34}$$

It is possible that methyl radicals may react with acetone

$$\mathrm{CH_3} + (\mathrm{CH_3})_2\mathrm{CO} = \mathrm{C_2H_6} + \mathrm{CH_3CO} \tag{35}$$

Direct dissociation instead of the formation of active molecules doubtless takes place in the continuum.

That the $\mathrm{CH_3CO}$ radical is relatively unstable is indicated by the almost total absence of biacetyl formation at 60°[11] and the fact that the photochemical decomposition of biacetyl at 100° gives almost solely ethane and carbon monoxide.[22]

Spence and Wild[11] find the ratio of ethane to carbon monoxide to increase with intensity when radiation in the continuum is absorbed by acetone, approaching a limiting value of 2.5. This is to be ascribed to the influence of reaction (27). In the full arc this ratio passes through a maximum and then decreases toward a limiting value of about 1.5. This would be due to (30), (31) and (29). In the banded region also the $\mathrm{C_2H_6/CO}$ ratio is nearly one, which would be ascribed to the high efficiency of (30) and the subsequent reactions (31) and (29). Thus biacetyl would have little chance of continued existence in the presence of excited acetone molecules.

While reactions (24) to (35) account for many of the experimental facts, the resulting kinetic expression would be so complex that it cannot be tested with data now available.

The effect of biacetyl formation is to tend to lower the ratio of slope to intercept in the previous work.[10] The calculated mean life for excited acetone would be, if anything, too small and, as concluded previously for other reasons, the value of 4×10^{-10} sec. is a lower limit.

In conclusion the authors wish to express their appreciation to Dr. C. F. Fisk, who built the DuBridge and Brown amplifier and made some preliminary runs on the work herein presented.

Summary

1. An apparatus for studying the fluorescence of gases is described.

2. The ratio of absorbed to fluorescent intensity of acetone is a function both of incident intensity and of time of exposure. Only at very low intensities is a Stern–Volmer equation obeyed.

3. The fluorescence spectra of acetone and of biacetyl are identical at wave lengths longer than 5000 Å. The fluorescence in the blue, which alone appears when oxygen is present, is much weaker than the fluorescence at longer wave lengths and could not be photographed.

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(21) Kohlrausch and Pongratz, *Ber.*, **67B**, 976 (1934).

(22) Porter, Ramsperger and Steel, THIS JOURNAL, **45**, 1827 (1923).

4. Small amounts of biacetyl greatly increase the fluorescence of acetone.

5. It is concluded that the fluorescent emitters are the same for both acetone and biacetyl, at least as regards the bands at 5000 Å. and longer wave lengths.

6. Mechanisms to account for these facts are advanced. An adequate explanation is based on a very probable deactivation of excited acetone molecules by biacetyl, the excited biacetyl being responsible for the fluorescence. However, fluorescence of the CH_3CO radical cannot be excluded.

PROVIDENCE, RHODE ISLAND RECEIVED MAY 6, 1938

[CONTRIBUTION FROM THE METCALF CHEMICAL LABORATORY OF BROWN UNIVERSITY]

The Absorption Spectrum of Biacetyl between 1500 and 2000 Å.

BY VICTOR R. ELLS

In connection with work on the spectroscopy and photochemistry of ketones it was thought advisable to study the absorption spectrum of biacetyl. This substance is formed during the photochemical decomposition of acetone[1] and is a possible product, along with other diketones, during the irradiation of ethyl methyl ketone. Since absorption coefficients of the ketones below 2000 Å. are far higher than in the near ultraviolet, it was hoped that the absorption spectrum might be used to detect even small amounts of biacetyl.

As would be expected the juxtaposition of two chromophoric groups causes a displacement of the absorption spectrum toward longer wave lengths. Thus in the near ultraviolet biacetyl vapor absorbs to 4670 Å.,[2] whereas acetone[3] and ethyl methyl ketone[4] show absorption to only between 3200 and 3300 Å. Below these absorption regions both biacetyl and the other ketones show a broad zone of transmission extending to below 2000 Å., where an intense absorption takes place.

Biacetyl shows bands with fine structure from 4670 to 4400 Å. at which point the bands become diffuse. Continuous absorption is observed below 2800 Å.[2] and extending to about 2500 Å.

Lardy[5] and Luthy[6] have investigated the spectra of biacetyl and of glyoxal, respectively, in hexane solution. In biacetyl four bands occur between 4512 and 4054 Å., a wide band at 2800 and another at 1950 Å. being observed also. Glyoxal between 4613 and 3119 Å. shows seventeen bands and in addition there are bands at 2800 and 1950 Å. The substitution of a CH_3 group for a hydrogen atom widens the narrow bands, reduces their number and increases the absorption coefficient.

Experimental

The biacetyl (Eastman) was fractionated several times before being introduced into the storage bulb, after which it was again fractionated three times at low pressures in the vacuum line. Calcium chloride was used as a drying agent and the boiling point of the fraction taken was 87–88°. The freezing point was approximately −4°, although no value is recorded in the literature. No vapor pressure data could be found, but the observed vapor pressures were about 0.01 mm. at −70°, 1 mm. at −30° and 13 mm. at 0°.

A quartz cell with relatively thin windows was interposed between the hydrogen discharge tube and the slit of the vacuum spectrograph to avoid introducing the biacetyl directly into the spectrograph. Thus an absorbing column about 15 cm. in length and vapor pressures from 0.01 to 15 mm. were used. The spectrograph has been described.[3] Ilford I plates were used.

The dispersion of the spectrograph with the setting used was found to be 8.48 Å. per mm. in the first order. The 1931.027 Å. line of C III and a number of the fourth positive bands of carbon monoxide were used[7] as wave length standards. Since a quartz cell was employed, the lower limit of observation was about 1550 Å.

Results

Twenty-six bands of biacetyl were found in all. These are listed in Table I, together with rough estimates of the intensities based on the pressure at which the bands appeared and their visually estimated intensities on the plates. The red edges of the bands appeared to be most sharp and are reported. Most of the bands were sufficiently

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[1] Barak and Style, *Nature*, **135**, 307 (1935); Spence and Wild, *ibid.*, **138**, 206 (1936).

[2] *Cf.* Sponer, "Molekülspektren," Verlag von Julius Springer, Berlin, Vol. I, 1935, p. 117.

[3] Noyes, Duncan and Manning, *J. Chem. Phys.*, **2**, 717 (1934). This paper contains references to earlier work. See also Noyes, *Trans. Faraday Soc.*, **33**, 1495 (1937).

[4] Duncan, Ells and Noyes, THIS JOURNAL, **58**, 1454 (1936).

[5] Lardy, *Compt. rend.*, **176**, 1548 (1923).

[6] Luthy, *ibid.*, **176**, 1547 (1923).

[7] Read, *Phys. Rev.*, **46**, 571 (1934).

sharp so that the error should not exceed ten wave numbers, although a few of the more diffuse bands may not be accurate to better than 30 cm.$^{-1}$. Bands measured only once may be considered to be somewhat doubtful.

TABLE I

BIACETYL BANDS, 1600–2000 Å.

Wave length, Å.	Wave number cm.$^{-1}$	Relative intensities	No. times measured
1691.45	59121	75	8
1705.09	58648	50	8
1720.13	58135	20	2
1730.88	57774	40	8
1745.35	57295	100	9
1883.77	53085	2	3
1905.45	52481	3	5
1928.08	51865	4	3
1951.07	51254	12	11
1960.78	51000	1	1
1962.44	50957	4	5
1963.56	50928	4	4
1964.64	50900	4	4
1965.95	50866	5	8
1967.30	50831	1	1
1968.16	50809	3	1
1969.05	50786	3	1
1970.06	50760	4	3
1970.99	50736	8	8
1972.08	50708	6	12
1973.09	50682	12	12
1974.45	50647	12	15
1975.82	50612	2	3
1977.14	50578	2	2
1982.87	50432	1	1
1984.40	50393	1	1

One upper electronic state probably leads to all the bands in the table except the first five. These twenty-one bands are found in three regions, as are those from 50,634 to 53,119 cm.$^{-1}$ in ethyl methyl ketone[4] and those from 51,000 to 54,954 cm.$^{-1}$ in acetone (four regions). The bands present many similarities in all three compounds.

In biacetyl, as in the other two ketones, the structure is sharpest in the region of longest wave length and very diffuse in the other two.

From intensity considerations the 50,647 band is probably the origin of the system. Absorption is practically complete above 56,000 cm.$^{-1}$ at the optimum pressure for observing the bands from 50,600 to 54,000.

The prominent bands in the three regions referred to above are separated by about 1200 cm.$^{-1}$ as follows:

50,647 51,865 53,085
1218 1220

It is true that frequency differences very close to this seem to be found in other ketones,[8] but it is less clear with biacetyl whether this difference is significant, since it is possible to put five of the important bands in a progression using a frequency approximately half as great:

50,647 51,254 51,865 52,481 53,085
607 611 616 604

However, similarities to the spectra of the other ketones would indicate the 1200 cm.$^{-1}$ frequency to be characteristic of the upper state of the carbonyl group, especially since the bands 50,647, 51,865 and 53,085 belong in different regions.

The Raman spectrum of biacetyl is probably not known in detail, although Kohlrausch and Pongratz[9] have found the following frequencies (intensities in parentheses): 375 (0), 690 (2), 1275 ($^1/_2$), 1444 (0), 1725 (2), 2940 (3), 3023 ($^1/_2$). Frequency differences of 375 and 690 do not occur prominently, if at all, in the bands in Table 1. Therefore it is impossible to identify, even tentatively, any transitions from upper vibration levels in the ground state.

Some eight differences of approximately 220 cm.$^{-1}$ occur. This is rather low to be a fundamental frequency of either the upper or lower state and may possibly be ascribed to a difference between upper and lower state fundamentals. Further attempts at a vibration analysis seem inappropriate at present.

The first five bands in Table I doubtless involve a second upper electron state as do the bands 60,086 to 62,529 in acetone and 58,110 to 59,360 in ethyl methyl ketone. 1350 occurs twice and 475 occurs twice as frequency differences among these bands, but the significance of these numbers is uncertain.

Since a quartz cell was used, the spectrum below 1550 Å. was not investigated. In acetone Duncan[10] found a Rydberg series among the bands at shorter wave lengths, but such a series, if it exists, could not have been found in the present experiments.

As the pressure is increased continuous absorption appears at the shorter wave lengths studied and gradually spreads until it reaches 2000 Å. In this respect biacetyl somewhat resembles the other ketones.

(8) Henri, *Compt. rend.*, **199**, 849 (1934); **203**, 67 (1936); Eastwood and Snow, *Proc. Roy. Soc.* (London), **A149**, 434 (1935); see Noyes, *J. Phys. Chem.*, **41**, 81 (1937).

(9) Kohlrausch and Pongratz, *Ber.*, **67B**, 976 (1934).

(10) Duncan, *J. Chem. Phys.*, **3**, 131 (1935).

Certain of the bands of biacetyl occur, as would be expected, at longer wave lengths than similar bands for the other ketones hitherto investigated. Since absorption coefficients in the absorption regions below 2000 Å. are, generally speaking, very high, it probably would be possible to use these bands for a semi-quantitative as well as a qualitative estimate of the amount of biacetyl present along with acetone and ethyl methyl ketone.

In conclusion the author wishes to express his appreciation to Dr. W. A. Noyes, Jr., who suggested this problem.

Summary

The absorption spectrum of biacetyl vapor has been investigated with a vacuum grating spectrograph between 2000 and 1550 Å. Absorption regions are found which correspond in general to those in acetone and ethyl methyl ketone, although they are displaced to longer wave lengths as would be expected due to the juxtaposition of two carbonyl groups. A prominent frequency difference of about 1220 cm.$^{-1}$ is found in the upper state, although the presence of another difference almost exactly half as great renders the interpretation ambiguous. Certain bands occur at wave lengths sufficiently displaced from those in acetone and ethyl methyl ketone to permit them to be used for the identification of biacetyl in the presence of these other substances.

Providence, R. I. Received May 6, 1938

[Contribution from the Department of Chemistry, Stanford University]

Phase Rule Studies of Soap Systems.
I. Applicability of the Phase Rule

By J. W. McBain, R. D. Vold and M. J. Vold*

The purpose of this introductory paper is to justify the application of the phase rule to soap systems.

It has been shown[1] that many colloid systems are formed spontaneously from their crystalloidal components, and exhibit properties which are independent of previous history and are solely dependent upon composition and temperature, and that they are thermodynamically stable in the same sense as are crystals or solutions of sugar or salts. It will be shown that therefore the phase rule in its usual form, ($F = C + 2 - P$), must apply to all thermodynamically stable colloid systems, without the introduction of any new variable.

Empirically, it has been found in many contributions since that of McBain and Burnett in 1922 that the behavior of systems of soap, water and electrolytes can be represented quantitatively on the usual Gibbs triangular diagram.[2] A large body of knowledge has been thus assembled and the work of previous authors[3] also has been found to fit into the same systematic description and analysis. The results have led to a greatly clarified understanding of the processes and phenomena of soap-boiling.

The same phases occur for sodium palmitate,[4] potassium laurate,[5] and potassium oleate.[6] The observations of temperatures at which phase changes occur and the analytical data on the composition of separated phases fit into the phase rule diagrams. Similar results have been obtained in experiments on the mixed fatty acids from coconut oil and in the experiments of Elford with commercial oils and fats on a full commercial scale. Ferguson and Richardson[7] likewise found that the phases of commercial soaps are the same as those in soaps from a single fatty acid.

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* Née M. J. Young.

(1) J. W. McBain and A. J. Burnett, *J. Chem. Soc.*, **121**, 1320 (1922); J. W. McBain, Fourth Colloid Symposium Monograph, **4**, 7 (1926); *Kolloid-Z.*, **40**, 1 (1926); This Journal, **58**, 2610 (1936); **60**, 223 (1938).

(2) See also J. W. McBain and E. Walls, Fourth Colloid Report of the British Association for the Advancement of Science, 1922, p. 244.

(3) F. Merklen, "Études sur la Constitution des Savons du Commerce," Marseilles, 1906; German edition by F. Goldschmidt, Halle-a.S., 1907; T. Richert, Diss., "Über das Aussalzen von Seifen," Karlsruhe, 1911; F. Bätz, Diss., Karlsruhe, 1918; M. Thörl, Diss., Karlsruhe, 1918.

(4) J. W. McBain and G. M. Langdon, *J. Chem. Soc.*, **127**, 852 (1925); also J. W. McBain, L. H. Lazarus and A. V. Pitter, *Z. physik. Chem.*, **A147**, 87 (1930); this paper contains an extensive bibliography.

(5) J. W. McBain and M. C. Field, *J. Phys. Chem.*, **30**, 1545 (1926).

(6) J. W. McBain and W. J. Elford, *J. Chem. Soc.*, 421 (1926).

(7) R. H. Ferguson and A. S. Richardson, *Ind. Eng. Chem.*, **24**, 1329 (1932).

It was an important finding,[2] confirmed by all subsequent work, that for practical purposes, apart from processes involving graining or salting out, the complex contents of the soap kettle may be regarded as a three-component system of soap, water and electrolyte.[7,8]

All this work together with the papers which presently are being communicated illustrates the utility of the phase rule in giving a comprehensive quantitative description of the behavior of soap systems. The very different methods used in these studies: namely, analysis of separated phases, visual observation of temperatures and concentrations at which phases appear and disappear, observations with the microscope and the polarizing microscope with heating stage,[9] vapor pressures, and dilatometer, are all in complete agreement.

The Phase Rule and Colloids

Theoretically, the phase rule may be regarded as an extension to chemistry of the algebraic principle that n equations are needed for a unique determination of n independent variables. In heterogeneous equilibria the variables are temperature, pressure and composition of the phases, and the relations between them are derived from the thermodynamic criterion of equilibrium that the chemical potential or partial molal free energy of each component must be the same in all phases throughout the system. The phases must be effectively homogeneous, uninfluenced by "capillarity," and in true equilibrium with each other.

No phase is homogeneous on an atomic or molecular scale, and the difficulty is often felt to be accentuated when colloidal particles are present. Büchner[10] has given a satisfactory answer by pointing out that heterogeneity has only a relative and not an absolute meaning and that heterogeneous systems are not necessarily two-phase systems. Even optically heterogeneous colloid systems become homogeneous in the Gibbsian sense if the volume element selected is large compared with the micelle instead of the molecule.

A colloid is thermodynamically a single phase only if its external properties such as vapor pressure, freezing point, distribution ratio, etc., etc., are solely and completely defined by temperature, pressure and composition. Although the effects of capillarity are explicitly excluded in the deduction of the phase rule,[11] yet since temperature, pressure and concentration in a stable reversible colloidal system coincidentally determine the capillary state of the system, there is no effect upon the application of the phase rule to external equilibria.[12]

Attainment of Equilibrium

It is a prerequisite for the legitimate application of the phase rule that true reversible equilibrium is attained and is thereafter independent of time. The same final state should be attainable from higher and lower concentrations or from higher and lower temperatures. Of course, the phase rule applies to reversible metastable equilibria as well, just as it applies to the solubility curve of anhydrous sodium sulfate or even of the slowly hydrolyzing substance ethyl acetate where hydrolysis is slow in comparison with the measurement. It is essential to show not only that the system has been brought into equilibrium but that this has not been displaced or distorted by the method of examination. Mere cooling of a soap system may introduce a phase which only slowly disappears again and may thus be misleading. This is one source of the experimental discrepancies which have been discussed at length in the German literature.[12]

Phases and Nomenclature in Soap Systems

Apart from false "equilibria," much of the denial of the applicability of thermodynamics to soap systems has arisen from the great confusion in the terminology employed in describing them, especially in translation. For clarity, therefore, the phases of soap systems will be listed.[13] It is helpful to refer to the two component diagram of Fig. 1, and to the schematic three component diagram, Fig. 2, where the corners represent soap, water and salt, respectively, and the composi-

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(8) J. W. McBain and A. V. Pitter, *J. Chem. Soc.*, 893 (1926); R. H. Ferguson, *Oil and Soap*, **14**, 115 (1937).

(9) K. MacLennan, *J. Soc. Chem. Ind.*, **42**, 393T (1923).

(10) E. Büchner, "Colloids as One-Phase Systems," in Alexander's "Colloid Chemistry," Vol. I, 1926, Chapter 4, p. 126.

(11) Scientific Papers of J. Willard Gibbs, Vol. I, Longmans, Green and Co., 1906, pp. 62 and 96.

(12) Compare the voluminous literature summarized by Wo. Ostwald and H. Erbring, *Kolloidchem. Beihefte*, **31**, 291 (1930). Likewise, Kruyt and de Jong hesitate to give the name phase to the liquid layers separating out in colloid systems, rejecting the phase rule and terming the process "coacervation," the colloid richer liquid "coacervat" and the liquid poor in colloid "liquide d'équilibre"; H. G. Bungenburg de Jong, "La Coacervation, les Coacervats, et leur Importance en Biologie," Tomes I and II, Actualités Scientifiques et Industrielles No. 397, Herman et Cie., Paris, 1936.

(13) For full descriptions, see J. W. McBain in Alexander's "Colloid Chemistry," Vol. I, 1926, Chapter 5, p. 138; J. W. McBain and M. C. Field, THIS JOURNAL, **55**, 4776 (1933). For examples of German terms, see E. L. Lederer, "Kolloidchemie der Seifen," Th. Steinkopff, Dresden, 1932, p. 299.

tions are proportional to the distances from these corners.

1. Clear Isotropic Solution. Nigre. Lye.—It is seen from Fig. 1 that there is only one body of isotropic solution which at sufficiently high temperatures embraces all proportions of soap and water, as they are completely miscible above the true melting point of the soap. Nevertheless in Fig. 2, which refers to a single temperature, it is evident that there is a region, which may be called the isotropic bay region,[14] where two portions of the isotropic solution may exist in equilibrium with each other as separate liquid phases. The one containing much salt with but little soap is called lye, or "Unterlauge," or "dünne Lauge." The other containing a moderate concentration of soap is the soap boilers' nigre, or "Leimniederschlag," "schwärzliche Flüssigkeit," "Leimseife," or "Leim." The isotropic solution in general is commonly called soap solution, "isotrope Seifenlösung," "isotrope homogene Lauge," or "Seifensol."

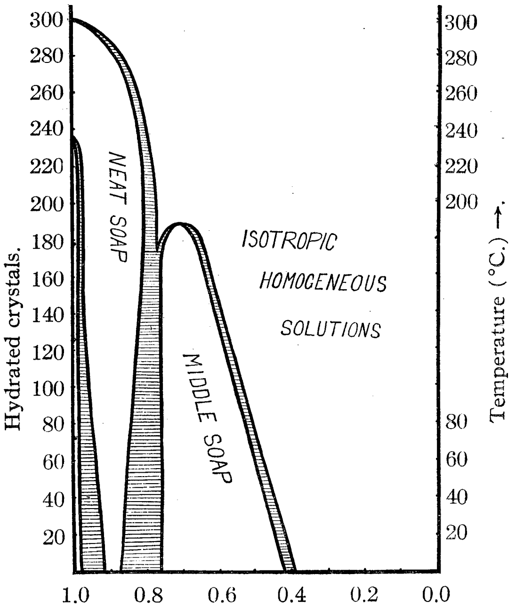

Fig. 1.—Equilibrium diagram for the two-component system potassium oleate–water (from McBain and Elford[6]).

In the middle of the isotropic region some soaps become highly viscous or set to an isotropic jelly.[15] This is not a separate phase and has no separate boundary. The jelly is clear, transparent and elastic, and may flow slowly. It is unfortunate that the term "Seifen-Gallerte" has been employed to designate a wholly different opaque mixture of phases leaving no German term to indicate the true soap jellies. Soap jellies,[15] like middle soap,[4] were previously unknown.

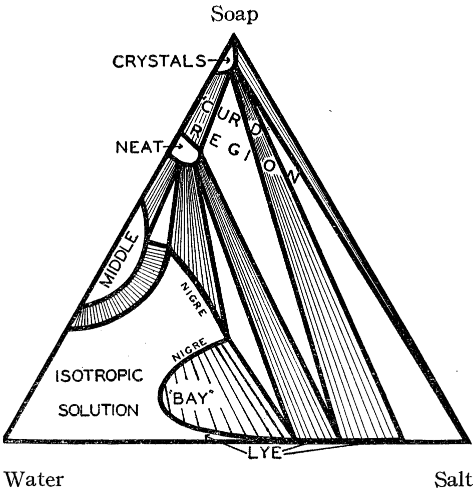

Fig. 2.—Schematic equilibrium diagram for a system soap–salt–water near 100°.

2. Neat Soap.—Neat soap is a doubly refracting clear or translucent liquid crystalline soap phase. It includes the soap boilers' fitted and settled soap (while hot), or "geschliffene Kernseife," "Kernseife auf Leimniederschlag," "abgesetzte Kernseife," "klare Seife," or "glatte Kernseife." Curd soap, or "Kernseife auf Unterlauge," is, when hot, the same phase, neat soap; except where the concentration of electrolyte is so high as to cause separation of curd fibers, which anyway appear on cooling (see below).

3. Middle Soap.—This is another conic anisotropic liquid or clear doubly refracting liquid crystalline phase, immiscible with neat soap, and of lower soap content. It sometimes has been mistakenly confused with "Leimniederschlag" or nigre which is wholly different.

4. Crystalline Phases. A. Lamellar Crystals.—These very thin six-sided transparent colorless crystals, giving a highly developed X-ray pattern, occur sometimes with sodium soaps, or sediments of acid soaps, but more frequently with potassium, ammonium and hydrogen soaps, forming the fig in soft soaps. Since they gen-

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(14) A similar bay is found for gelatin, F. Kellogg and J. W. McBain, *J. Gen. Physiol.*, **12**, 1 (1928). A diagram rather similar to Fig. 2 is also obtained for serum globulin with pseudoglobulin and euglobulin occupying the positions of neat and middle soap; J. W. McBain and E. Jameson, *Trans. Faraday Soc.*, **26**, 768 (1930).

(15) M. E. Laing and J. W. McBain, *J. Chem. Soc.*, **117**, 1506 (1920); *Kolloid-Z.*, **35**, 18 (1924).

erally are not found as a stable phase in the case of sodium soaps they do not appear on any of the phase-rule diagrams in this or the following paper.

B. Curd Fibers.—This second crystalline phase, showing with X-rays[16] a three-dimensional spacing, is the same as the *curd phase* of Vold and Ferguson.[17] It is the common crystalline form of sodium soaps and is the phase which is referred to as hydrated crystals on many of the diagrams. They are white fibers, "Kernfasern," often several centimeters long, but usually consisting of bundles of fibers which are ultramicroscopic except in length. They have been photographed in the ultramicroscope by Zsigmondy and Bachmann[18] and by McBain, Darke and Salmon.[19] Curd fibers may be anhydrous but usually contain water. It is not certain whether they form definite hydrates or are of continuously variable composition. Although submicroscopic fibers may be present, this crystalline phase is sometimes granular in appearance rather than fibrous.

Soap Systems: Multiphase Equilibria

According to the phase rule, in any three component system, three liquid or solid phases may coexist at any one temperature, with vapor, as is shown by the triangles within Fig. 2, whose corners represent the phases in contact; at least one of these four phases will be of continuously variable composition or concentration with change in temperature. Ostwald and Erbring[12] have mistakenly regarded the coexistence of three condensed phases over a temperature range as a disproof of the applicability of the phase rule. The coexistence of pairs of phases, both of variable composition at any one temperature, is likewise shown in Fig. 2 in the areas shaded with tie lines whose ends connect the phases in contact. Five phases of fixed composition are required for any invariant three component system.

Soap curd, or simply **curd** (not to be confused with commercial curd soap boiled on lye, especially not with curd fibers) is a mixture of phases which occurs in the curd region indicated on Fig. 2, and consists of a white, more or less opaque, mass of solid containing curd fibers, with or without solution or liquid crystalline material. Dry curd consists entirely of curd fibers. Curd has been variously designated "geronnener Kern," "kristallines hydratisiertes Gerinnsel," "Gerinnsel," "Koagel," "Kernseife," or "Seifengel"; it is not "Kernseife," which is neat soap. The formation of curd has been called "Erstarrung" or "Gelatinierung," which has been confusing because gelatinization is usually reserved for the formation of true jellies.

Curiously, McBain's suggestion that soap curd may consist of a mixture of definite hydrates of crystalline curd fibers has been regarded[12] (see also Lederer[13]) as evidence that the phase rule does not apply to soap systems. It is supposed that the water content of curd fibers varies continuously, with the *non sequitur* that McBain's suggestion leads to the conception of curd fibers as consisting of an infinite number of phases. The correct alternative is a single phase of continuously variable composition. The confusion may be due to failure to distinguish between curd and curd fibers, the former being the heterogeneous masses indicated in Fig. 2 in the curd region and the latter consisting either of a few definite crystalline hydrates or of one or two series of crystals containing variable amounts of water, as in the zeolites.

Summary

1. It is shown that the phase rule is applicable in its usual form to thermodynamically stable colloid systems in true equilibrium.

2. It is pointed out that the phase rule does in fact describe the actual behavior of soap systems.

3. Since reported discrepancies appear to have been due to misunderstanding of the phases and systems discussed, these are listed and defined.

STANFORD UNIVERSITY, CALIF. RECEIVED APRIL 12, 1938

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[16] S. H. Piper, *J. Chem. Soc.*, 234 (1929); P. A. Thiessen and J. Stauff, *Z. physik. Chem.*, **A176**, 397 (1936); P. A. Thiessen and R. Spychalski, *ibid.*, **A156**, 435 (1931).

[17] R. D. Vold and R. H. Ferguson, communication submitted to THIS JOURNAL.

[18] R. Zsigmondy and W. Bachmann, *Kolloid-Z.*, **11**, 152 (1912).

[19] W. F. Darke, J. W. McBain and C. S. Salmon, *Proc. Roy. Soc.* (London), **A98**, 395 (1921).

[Contribution from the Department of Chemistry, Stanford University]

Phase Rule Studies of Soap.
II. The System Sodium Laurate–Sodium Chloride–Water

By J. W. McBain, G. C. Brock, R. D. Vold and M. J. Vold

In the preceding paper a review has been made of existing phase rule studies of soap systems. This paper, extending the work begun by one of us in collaboration with A. J. Burnett[1] adds the system sodium laurate–sodium chloride–water to the list of those whose behavior has been investigated over a wide range of temperature and composition. In the present work emphasis has been placed on verifying the strict applicability of the phase rule and on ascertaining the experimental conditions necessary for establishing true reversible equilibrium.

Experimental Procedure

Three different standard methods have been employed. The first, the synthetic method, consists of observing the temperatures at which phase changes occur in systems of known composition. The second, the delimiting method, is an isothermal procedure having the consequent advantage that observations on the same tube can be made at intervals over a period of time. It consists of preparing, by trial and error, pairs of systems whose compositions lie very close together, one on each side of the boundary to be determined, and placing the boundary between them. The third method consists of analyzing the separated phases.

The sodium laurate used was a special preparation made for us by Kahlbaum (it contained less than 0.3% excess fatty acid). The soap was dried in an air oven at 105° from time to time and periodic checks made of its water content, which was always taken into account in making up tubes. Kahlbaum dry sodium chloride "for analysis" was used throughout. The water was freshly distilled, and in the case of dilute systems special precautions were taken to exclude carbon dioxide.

In all cases the calculated quantities of salt, water and soap, in the order named, were weighed into heavy-walled Pyrex glass tubes which were sealed off immediately to prevent changes in composition.

For application of the synthetic method the following procedure was adopted. The tube was first heated to a temperature such that its contents formed a homogeneous isotropic solution. A "Mazola" oil-bath was employed for temperatures up to 230°. Temperature was measured by means of a calibrated mercury thermometer. Above 230° an electrically heated oven provided with mica windows was used. Temperature was measured by means of a calibrated thermocouple pyrometer. Then the tube was allowed to cool slowly and the temperature (T_i) recorded at which the first turbidity appeared due to the formation of droplets of a second phase. Finally, the tube was cooled to room temperature and the temperature (T_c) recorded at which, on slow reheating, the last trace of crystal or curd fibers just disappeared.

For application of the delimiting method, the following procedure was found to be most desirable. Spurious results that may be obtained by superficially innocent variations of this procedure are described later. First the tube was heated to homogeneity as described under the synthetic method. It was then cooled to the desired temperature and allowed to stand for a few days, undisturbed except for periodic gentle mixing of the separated phases. The number and nature of the phases present was determined by inspection.

For the analytical work larger samples were used; consequently, because of the increased danger of explosion, these tubes were not heated to homogeneity. The tubes were allowed to stand at 90° for three months. Since the results obtained were in good agreement with those obtained by the other two methods, we are confident that equilibrium was reached. The analyses were carried out in the following manner. A tube was removed from the thermostat and quenched by immersion up to the level of the soap sample in a salt–ice–water freezing mixture. Each of the separated phases was analyzed for soap content by decomposition with a known amount of sulfuric acid, extraction with ether and titration with sodium hydroxide solution of the weighed lauric acid recovered from the ether extract, as well as back titration of the acid in the aqueous layer. Salt content was determined by titrating, with silver nitrate, the neutralized aqueous layer from which the fatty acid had been extracted.

The System Sodium Laurate–Water

In the two component system sodium laurate–water, the observations of temperatures at which phase changes occur can be plotted directly on a temperature–composition diagram. The data obtained are recorded in Table I and Fig. 1. Curve ABCD is drawn through points representing the upper temperature limit of existence of liquid crystalline soap phases (T_i). Curve EFGHDJO is drawn through points representing the upper temperature limit of the existence of crystalline soap (T_c).

At all points above the curve ABCDJ the soap system consists of homogeneous isotropic solution. In the composition range from F to G and also that from H to D, the temperature of disappearance of crystalline soap is constant. Consequently, by direct application of the phase rule, four phases are present in each of these regions. These phases are crystalline soap, middle soap,

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[1] J. W. McBain and A. J. Burnett, *J. Chem. Soc.*, **121**, 1320 (1922).

TABLE I

THE TWO COMPONENT SYSTEM SODIUM LAURATE–WATER

NaL wt. %	T_i	T_c	NaL wt. %	T_i	T_c
2.17	—	24	43.44	145	51
2.68	—	25	44.31	144	51
2.87	—	26	46.19	149	54
3.53	—	28	46.75	149	55
5.20	—	32	49.39	139	57
10.89	—	38	51.12	141	59
18.77	—	41.5	51.29	153	60
28.77	—	42	53.21	182	61
31.19	—	42	57.34	236	61.5
31.91	—	42	58.40	237	62.5
32.69	—	42	60.60	242	66
35.09	85	44	60.89	247	66
36.80	100	44	62.30	266	—
42.50	142	50	71.16	290	76
43.63	144	51	100	310	226

neat soap and vapor in the case of region FG; and crystalline soap, middle soap, isotropic solution and vapor in the case of region HD.

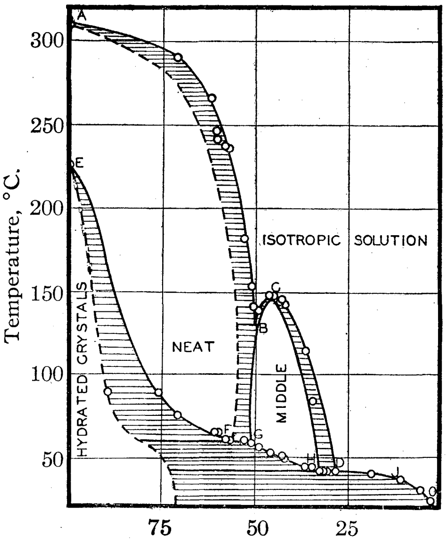

Fig. 1.—The system sodium laurate–water.

These observations make the further course of the diagram clear even though the boundaries that have not been quantitatively determined throughout are drawn with dashed lines. No conclusion concerning the constitution of the crystalline form or forms can be drawn from the work included in the present communication, but it is a definite result from vapor pressure studies at 90° (which will be communicated shortly) that it does not consist of anhydrous sodium laurate. Further vapor pressure measurements designed to ascertain the number and nature of the crystalline phases are now under way in this laboratory. Meanwhile, to facilitate interpretation of the diagram, a tentative boundary has been drawn in (dotted line, Fig. 1).

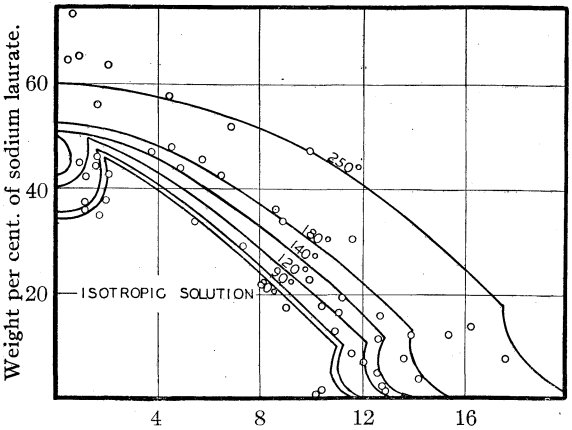

Fig. 2.—The boundaries of the field of aqueous isotropic solutions at definite temperatures (curves), as deduced from T_i determinations (circles) made at intermediate temperatures.

The phase behavior of sodium laurate and water is entirely similar to that of other soap systems.[2] The nature of the phases and the various equilibria have been described in these earlier communications. At point C middle soap is in equilibrium with an isotropic solution of the same composition (NaL + 14.4 H_2O, or 3.85 N_W solution). This point does not indicate compound formation; it has the same nature as a maximum point of

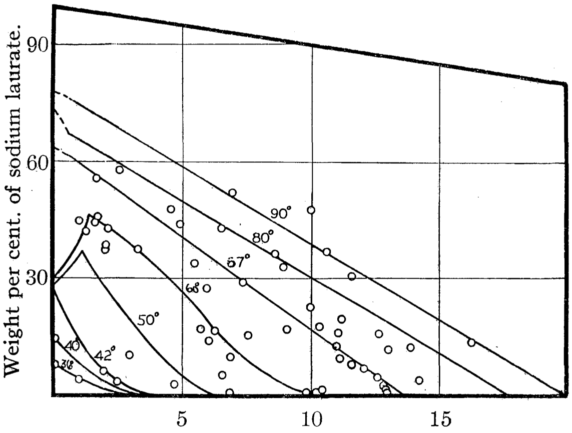

Fig. 3.—The limiting solubilities of hydrated crystalline soap at definite temperatures (curves), as deduced from the T_c determinations (circles) made at intermediate temperatures.

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[2] McBain, Lazarus and Pitter, *Z. physik. Chem.*, **A147**, 87 (1930); McBain and Elford, *J. Chem. Soc.*, 421 (1926); McBain and Field, *J. Phys. Chem.*, **30**, 1545 (1926).

tangency of an ordinary solidus and liquidus curve.[3]

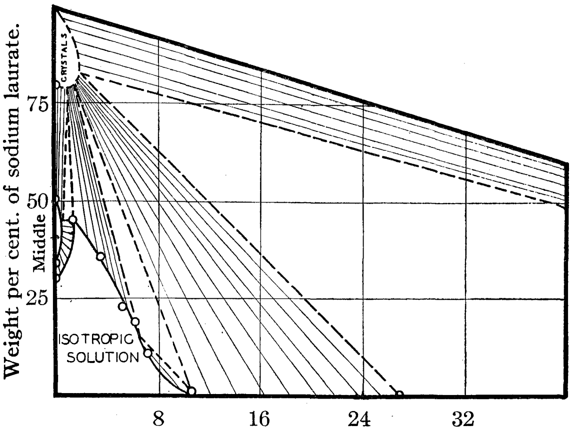

Fig. 4.—The system NaL–NaCl–H_2O: equilibria at 60°.

The System Sodium Laurate–Sodium Chloride–Water.—Typical isothermal diagrams, horizontal sections of the right triangular prism necessary for complete representation of the temperature dependence of the phase behavior of a ternary system, are given in Figs. 4 to 9. These diagrams are derived from the data of Tables II and III.

Table II

The System Sodium Laurate–Sodium Chloride–Water. Temperatures at which Isotropic Solution Separates a Liquid Crystalline or a Second Liquid Phase

Composition NaL wt. %	Composition NaCl wt. %	T_i
A. Middle Soap is Formed		
37.78	2.00	58
42.56	2.09	76
42.74	2.09	77
37.40	1.15	92
45.89	1.66	92
44.37	1.54	107
42.22	1.20	118
44.90	0.95	127
34.7	1.72	51
B. "Lye" is Formed		
1.58	10.41	65
9.58	11.11	67
16.90	9.04	71
0.63	10.20	76
6.73	12.00	113
7.97	11.53	93
4.84	12.54	128
1.35	12.89	132
2.14	12.76	133
7.56	13.6	160
11.71	12.99	160
3.73	14.20	161
12.13	13.89	183
12.29	15.36	208
C. Neat Soap is Formed		
33.72	5.48	70
29.11	7.37	106
22.66	9.96	130
17.65	10.34	108
15.81	12.67	168
16.29	11.01	120
19.39	11.20	137
44.04	4.90	171
46.94	3.76	179
33.88	8.92	175
42.52	6.51	185
47.96	4.52	192
36.12	8.61	198
30.18	11.57	198
12.87	16.28	226
7.55	17.65	226
51.91	6.91	246
55.85	1.64	247
47.44	9.92	250
57.78	4.46	252
63.68	2.02	267
64.72	0.46	275
65.13	0.81	275
73.35	0.84	290
78.81	1.21	296
79.34	0.68	295
12.59	10.97	93

Table III

Three Component System Sodium Laurate–Sodium Chloride–Water. Temperatures at which Soap Crystals or Curd Fibers Completely Dissolve

Composition NaL wt. %	Composition NaCl wt. %	T_c
A. Isotropic Solution Remains		
0.69	12.93	61
1.35	12.89	65
0.63	10.20	58
0.75	9.85	56
0.66	6.85	52
1.58	10.41	59
4.35	0.95	36
6.18	1.91	42
3.41	2.81	43
10.17	2.93	46
2.89	4.72	48
6.57	5.33	50
17.06	5.73	57
14.97	6.03	57
16.75	6.26	58
27.31	5.97	63
9.90	6.91	58
37.91	3.25	59
B. Middle Soap Remains		
37.6	1.10	58
37.4	1.15	50
42.20	1.20	54
44.37	1.54	59
44.90	0.95	55
C. Middle Soap and Nigre Remain		
37.44	1.98	55
45.89	1.66	59
38.78	2.00	56
42.56	2.09	58
D. Neat Soap and "Lye" Remain		
2.04	12.76	66
55.85	1.64	66
4.84	12.54	67
6.73	12.00	67
7.97	11.53	67
12.59	10.97	72
7.56	13.60	73
29.11	7.37	74
44.04	4.90	74
47.96	4.52	75
19.39	11.20	78
22.66	9.96	77
11.71	12.99	77
12.13	13.89	78
15.81	12.67	78
16.29	11.01	78
3.73	14.20	78
42.52	6.51	79
32.88	8.92	80
36.12	8.61	84
30.18	11.57	87
12.87	16.28	91
17.65	10.34	76
57.78	2.52	180
51.91	6.91	198
47.44	9.92	209
33.72	5.48	64
9.58	11.11	64
16.90	9.04	66

Table II gives the temperatures, T_i, at which, on cooling, tubes having the indicated composition first separated a second phase. The table has been subdivided according to the nature of the separating phases. The data in this table determine the boundary of the field of isotropic solution except at temperatures and compositions such that the isotropic solution is in equilibrium with a crystalline soap phase. In Fig. 2 all these data have been plotted on a single triangular diagram.[4] The number of points is sufficient to permit drawing in the isotherms. Since such a procedure in-

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(3) A. Findlay, "The Phase Rule," Longmans, Green and Co., New York, N. Y., seventh edition, 1931, p. 120.

(4) The right triangle used in place of the more customary equilateral triangle retains all the geometrical properties of the latter except that the water content is derived by subtracting from 100 the sum of the percentages of soap and salt.

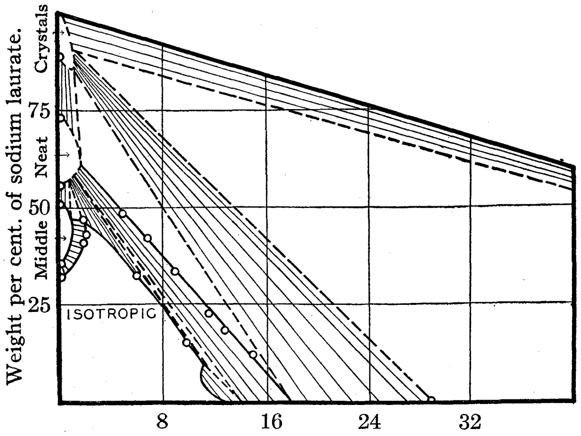

Fig. 5.—The system NaL–NaCl–H_2O: equilibria at 80°.

volves a certain degree of arbitrary choice, as does any purely graphical method, a uniform method of extrapolation was devised and used in the construction of the isotherms appearing in Fig. 2. A given isotherm is made to pass as closely as possible through all points obtained by linear interpolation or extrapolation from the compositions of pairs of points found to lie on the same boundary, although at somewhat different temperatures. For example, as is indicated in Fig. 2, a tube containing 12.5% soap and 11% salt separates neat soap at 93°; a tube containing 17% soap and 9.1% salt separates neat soap at 71°; consequently the neat–nigre boundary at 80° passes through the point 15.2% soap, 9.9% salt. Even where the experimental points are quite widely separated, the isotherms can be drawn in correctly. For example, it can be seen that a nigre–lye bay must exist in this system even at 250°.

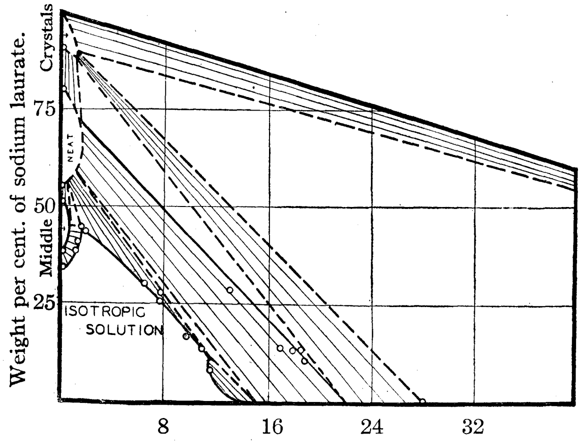

Fig. 6.—The system NaL–NaCl–H_2O: equilibria at 100°.

The course of the neat–nigre boundary at salt contents up to 9%, which is accurately determined by the experimental points, precludes the possibility of nigre's containing, for example, 18% each of salt and soap existing in equilibrium with a neat soap of any composition whatsoever, since the line corresponding to such an equilibrium cannot reach the soap axis below 100% soap without cutting across the established field of homogeneous solution.

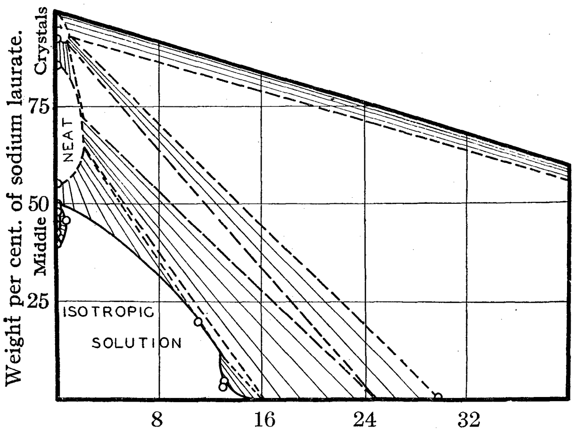

Fig. 7.—The system NaL–NaCl–H_2O: equilibria at 140°.

Table III gives the temperatures, T_c, at which, on slow heating, the last trace of crystal just dissolves in systems of indicated composition; the points have been sorted according to the number and nature of the phases remaining. All these data have been plotted on a single triangular diagram in Fig. 3. The isotherms are of three types. Below 42° the solubility isotherms are identically the isotropic solution boundaries. Above 61° the

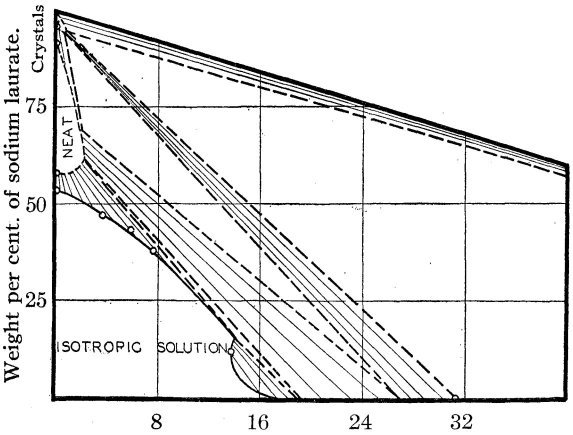

Fig. 8.—The system NaL–NaCl–H_2O: equilibria at 180°.

solubility isotherms trace out the neat–lye edge of the triangle, hydrated crystal–neat soap–lye, and a part of the neat soap boundary. At temperatures between 42 and 61° the crystalline soap phase dissolves to form either middle soap or middle soap and isotropic solution. The isotherms were constructed in the same manner as those of Fig. 2.

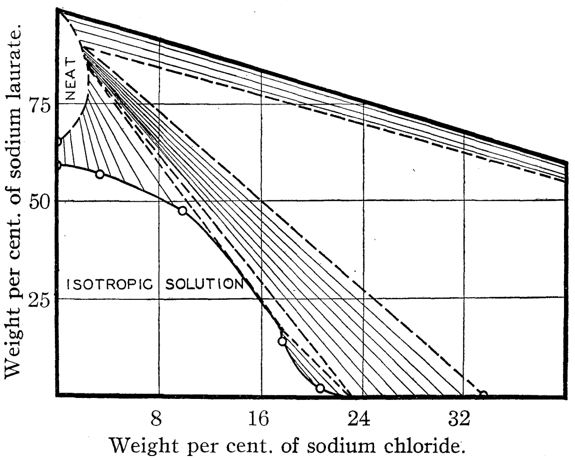

Fig. 9.—The system NaL–NaCl–H_2O: equilibria at 250°.

On the basis of the data derived from Tables II and III, the diagrams appearing in Figs. 4 to 9 were constructed. Boundaries that have not been delimited experimentally are dotted in. The authors wish to emphasize the tentative nature of the boundaries given for the crystalline soap region. They are based entirely on analogy with the course of this boundary in the case of sodium palmitate at 90°[5] and the determination by McBain and Salmon[6] of the water content at the apex of the triangle, salt–lye–crystalline soap, at 90°.

The phase behavior of the system at 90° is given in Fig. 10. For this one temperature, the exact courses of the crystalline soap boundary and upper neat soap boundary are the only uncertainties. The additional data available at this temperature are summarized in Tables IV and V. The results of the delimiting experiments fix the position of the triangle, neat–nigre–lye. They also substantiate the validity of the neat–nigre boundary obtained by the synthetic method. The analytical results confirm the correctness of the composition of lye in the triangle, neat–nigre–lye, found using the delimiting method, and also establish the directions of the tie lines in the neat–lye region. The compositions of the two phases and that of the total system lie in each case on a straight line, as is required if the analyses are accurate; the slope of

Table IV

Results of Delimiting Experiments at 90°

Composition NaL wt. %	Composition NaCl wt. %	Phases present at equilibrium
5.01	10.2	Nigre
9.95	11.1	Nigre
2.92	10.6	Nigre
2.96	10.8	Nigre
14.0	10.2	Nigre
20.0	9.10	Nigre
5.01	11.02	Nigre and lye
10.1	11.3	Nigre and lye
2.96	12.0	Nigre and lye
3.02	12.45	Nigre and lye
2.96	12.8	Nigre and lye
4.87	12.30	Nigre and lye
7.53	11.92	Nigre and lye
7.47	11.52	Nigre and lye
20.0	9.42	Neat and nigre
28.0	7.51	Neat and nigre
14.1	12.6	Neat and lye
14.1	12.78	Neat and lye
14.1	12.93	Neat and lye
14.0	12.0	Neat and lye
14.0	12.30	Neat and lye
14.0	11.51	Neat and lye
9.92	12.33	Neat and lye
3.01	13.6	Neat and lye
7.48	12.6	Neat and lye
14.0	11.02	Neat, nigre and lye
9.95	11.45	Neat, nigre and lye
9.95	11.70	Neat, nigre and lye
9.97	12.0	Neat, nigre and lye
7.50	12.20	Neat, nigre and lye
7.45	12.35	Neat, nigre and lye
13.95	10.8	Neat, nigre and lye
28.0	8.00	Neat, nigre and lye

Table V

Results of Analysis of Separated Phases

Total system NaL wt. %	Total system NaCl wt. %	Neat soap layer[a] NaL wt. %	Neat soap layer[a] NaCl wt. %	Lye layer NaCl wt. %
14.0	11.51	52.2	3.24	14.2
14.0	12.01	51.3	3.60	15.15
14.10	12.78	53.9	3.89	15.90
14.05	12.93	53.8	3.86	16.17
14.0	13.4	65.4	1.69	16.69
14.0	13.9	68.3	1.23	17.28
14.0	14.4	65.9	1.83	17.78
14.0	15.3	68.5	1.52	18.79
14.02[b]	11.02	...	...	14.07

[a] These points lie on the tie-lines but usually not on the neat soap boundary because of incomplete separation of phases. [b] This tube contained 3 layers, neat, nigre and lye. Only the lye layer could be obtained free from contamination. In addition to salt, it was found to contain only 0.2% soap.

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(5) R. D. Vold and R. H. Ferguson, to be published.

(6) J. W. McBain and C. S. Salmon, *J. Chem. Soc.*, **119**, 1374 (1921).

the tie lines is consistent with the slope of the neat–lye edges of the triangles, neat–nigre–lye and neat–crystalline soap–lye.

The work at 90° shows how well results obtained by entirely independent experimental methods fit together in complete harmony on a standard phase rule diagram, and gives further weight to the assertion[7] that the phase rule does in fact apply to soap systems.

Experimental Tests of the Applicability of the Phase Rule.—We have emphasized[7] that the applicability of the phase rule to any system is conditioned by whether or not the state of the system is completely fixed by temperature, pressure and composition, independent of time and of the previous history of the particular specimen examined. The experiments of Ostwald and Erbring,[8] of Lester Smith,[9] and of Ferguson,[10] as well as some results obtained in this Laboratory, had led to the supposition that such a reversible equilibrium might not be realizable in all soap systems. The work of Smith was concerned with metastable equilibria that exist in systems supersaturated with respect to curd fibers. Both Ostwald and Erbring and Ferguson were concerned with the nigre–lye bay and the triangle neat–nigre–lye at temperatures around 90°. The following experiments also deal with these latter regions.

Experiment 1.—Salt, water, and soap were weighed into tubes in the order named, the salt being all dissolved before the soap was added. The tubes were then sealed off, mixed thoroughly and suspended in a thermostat at 90°. After three hours, during which they were twice mixed gently, the nature of the phases present was entirely in accord with the equilibrium diagram (Fig. 10). The tubes were then allowed to stand undisturbed, except for periodic momentary removal from the thermostat for observation, for a period of three weeks. During this period the volume of the nigre layer in some systems lying within the triangle changed gradually, and a layer of neat soap formed on the surface of all systems lying within the nigre–lye two phase region. Their final condition could not be made to harmonize with any equilibrium phase diagram. Hence further experiments were planned to elucidate the behavior.

Experiment 2.—Our diagram for the phase behavior of the system sodium laurate–sodium chloride–water at 100° showed that Tube No. 14 (Table VI) should consist of homogeneous nigre. At 90° it consisted initially of nigre over lye and had acquired a small surface layer of neat soap on standing for three weeks. It was found that the neat soap layer persisted for at least a day at 100°, but that it could be destroyed by gentle mixing with the nigre and, once destroyed, did not form again at 100°.

Experiment 3.—The lesson of Experiment 2, that the highly viscous neat soap, once formed, can persist over long periods, suggested that the changes observed in Experiment 1 might have been due to the formation of a small amount of neat soap from nigre in the brief interval during which the tubes were removed from the thermostat for observation, with the gradual accumulation into a visible layer of the neat soap formed during successive observations. All tubes were therefore subjected to periodic gentle mixing carried out with the tubes out of the thermostat for not longer than ten seconds. The neat soap layers that had formed disappeared, and all the tubes returned to their original condition. No further change in the nature or relative volumes of the phases took place over a period of ten days.

It appears that neat soap forms easily from nigre, and disappears only with difficulty. This single simple fact may be in large measure responsible for the results reported above,[8,10] to the effect that variations with time occur and that results of analysis of separated phases are not in accord with the boundary determined by the delimiting method.

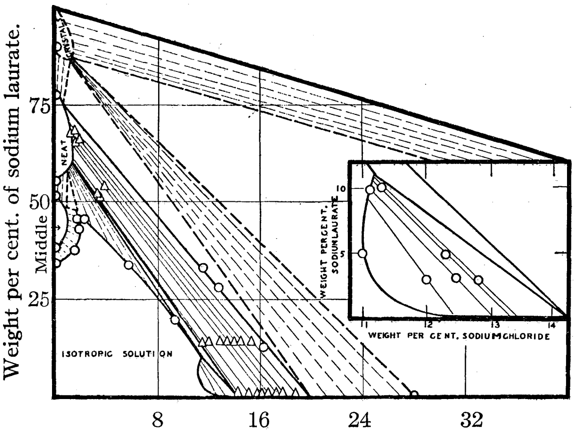

Fig. 10.—The system NaL–NaCl–H_2O: equilibria at 90°. (○), Points derived from the data of Tables I, II and III. (△), Points from Table V. Insert: the nigre–lye bay. Tie lines plotted from Table VI.

Experiment 4.—The technique described in Experiment 3 as "gentle mixing" was adopted primarily to minimize the formation of foam. However, the final equilibrium state is completely independent of the mechanical treatment of the sample as long as adequate mixing is achieved, as is proved by the following result. Gentle mixing was replaced by violent vertical shaking which produced complete emulsification of the separated phases in each other and filled the tubes with a macroscopically homogeneous foamy mass. Although there were considerable differences in the rates of settling out of different phases, every tube returned within twenty-four hours to the same state[11] as

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[7] J. W. McBain, R. D. Vold and M. J. Vold, THIS JOURNAL, **60**, 1866 (1938).

[8] Wo. Ostwald and H. Erbring, *Kolloidchem. Beihefte*, **31**, 291 (1930).

[9] E. Lester Smith, *J. Phys. Chem.*, **36**, 2455 (1932).

[10] R. H. Ferguson, private communication.

[11] In tubes such as No. 14 containing nigre nearly saturated with respect to neat soap, the foam proved very persistent. When it did finally collapse, a small ring of neat soap was deposited on the glass above the nigre meniscus. This trace of neat soap could be dissolved in the nigre by patient gentle agitation.

was reached under "gentle mixing" conditions both with respect to the phases present and their relative volumes.

Experiment 5.—It was demonstrated that in every tube (23 in all) the same final state was reached on cooling to 90° from such a temperature (160°) that the contents had formed a single homogeneous isotropic liquid, as was reached on heating to 90° from room temperature.

Discussion

The isothermal diagrams shown in Figs. 4 to 10 are for representative temperatures over the complete range from 60° to the melting point of anhydrous sodium laurate. Similar diagrams at any desired temperatures could be drawn on the basis of the data given in Tables II and III. The changes in phase behavior that occur as the temperature is raised have been described fully[2a] for the case of sodium palmitate. The behavior of sodium laurate is entirely similar as can be seen directly from the diagrams.

In experiments 1 to 5 the fact that the number and relative volumes of the separated phases was determined only by temperature and composition was regarded as sufficient proof of the applicability of the phase rule to this portion of the system. However, the measurements of relative heights of the different phases can be used in an approximate calculation verifying in further detail the conformity of the observed behavior to the requirements of the phase rule.

In the two phase "bay" the relative weights of the nigre and lye are inversely proportional to the distances measured along the tie line from the point representing the total composition of the system. Consequently, since the phases have nearly the same density, the relative volumes of nigre and lye can be used to deduce the direction of the tie lines in this region. Systems no. 14 and no. 23 happen to lie on nearly the same tie line. That the relative volumes of nigre and lye are in accord with the number calculated from the delimiting curve can be taken as verification of conformity with the requirement of the phase rule that systems lying on the same tie line must separate into phases of the same composition. An enlarged section of the "bay" is inserted in Fig. 10, and the numerical data on which the tie lines are based appear in Table VI.

Table VI

Tie Lines in the Nigre–Lye Bay

No.	Total system NaL wt. %	Total system NaCl wt. %	Nigre (A) NaL wt. %	Nigre (A) NaCl wt. %	Lye (B) NaCl wt. %	Wt. A / Wt. B Calcd.	Vol. A[a] / Vol. B Obsd.
14	10.0	11.3	10.9	11.13	13.36	12.5	12
23	3.0	12.80	10.9	11.13	13.36	0.34	0.25
R6	4.9	12.30	10.8	11.12	13.23	.81	.68
22	3.0	12.45	10.3	11.10	12.96	.39	.34
21	3.0	12.00	9.0	11.06	12.38	.43	.45

[a] The relative volumes of the phases were estimated by measuring their heights in the tube.

From any point in a three-phase triangle, such as neat–nigre–lye, the relative weights of the three phases can be calculated from the compositions of the corners. Since the neat–nigre–lye triangle is very narrow, the values of the relative weights are extraordinarily sensitive to very small changes in composition. Nevertheless, these calculated relative weights are in accord within the limits of experimental error (±0.1% in salt content) with the relative volumes observed, as can be seen in Table VII.

Table VII

Comparison of Calculated and Observed Volumes[a] of Neat, Nigre and Lye[b]

Total system NaL wt. %	Total system NaCl wt. %	Vol. neat Calcd.	Vol. neat Obsd.	Vol. nigre Calcd.	Vol. nigre Obsd.	Vol. lye Calcd.	Vol. lye Obsd.
10.0	11.45	0.024	Trace	0.88	0.78	0.10	0.22
10.0	11.7	.047	0.068	.67	.53	.27	.41
10.0	12.0	.15	.12	.01	.17	.83	.71
14.0	11.0	.18	.15	.27	.32	.54	.53
7.5	12.2	.024	.07	.51	.34	.46	.59
7.5	12.35	.071	.10	.26	.20	.67	.70

[a] The relative volumes of the phases were estimated by measuring their heights in the tube.

[b] The compositions of the triangle corners are (a) neat: 60.0% sodium laurate, 1.50% sodium chloride, (b) nigre: 11.15% sodium laurate, 11.15% sodium chloride, (c) lye: 0.20% sodium laurate, 14.07% sodium chloride.

Summary

1. Diagrams have been constructed showing the phase behavior of the two component system, sodium laurate–water, and of the three component system, sodium laurate–sodium chloride–water, at various representative temperatures from 60° to the melting point of anhydrous sodium laurate (310°). Data are tabulated that make possible construction of the diagram at any intermediate temperature.

2. Results obtained by synthetic, delimiting and analytical methods are in quantitative agreement.

3. It has been shown experimentally that true reversible equilibrium independent of time is reached in this system, and that this equilibrium is described exactly by the phase rule.

Stanford University, Calif. Received April 12, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HOWARD UNIVERSITY]

Kinetics of the Pyrolysis of Isobutyl Iodide

BY J. LESLIE JONES

This work concerns the kinetics of the thermal decomposition of gaseous isobutyl iodide in the temperature range of 550 to 600°K. Jones and Ogg[1] investigated the pyrolysis of *n*-propyl iodide and *n*-butyl iodide in the temperature range of 584 to 627°K. They found that the rate-determining step could be represented in the case of *n*-propyl iodide by the equation

$$-\frac{d(C_3H_7I)}{dt} = k(C_3H_7I)(I_2)^{1/2} \qquad (1)$$

The kinetics of the decomposition of the *n*-butyl iodide was qualitatively the same but could not be treated quantitatively. The same authors[2] found that the rate of disappearance of isopropyl iodide was governed by a unimolecular rate expression

$$-\frac{d(C_3H_7I)}{dt} = k(C_3H_7I) \qquad (2)$$

Ogg[3] studied the thermal decomposition of gaseous *s*-butyl iodide in the temperature range 511 to 549°K. He found that the results were best fitted as a combination of a unimolecular reaction plus an iodine catalyzed decomposition of the iodide

$$-\frac{d(C_4H_9I)}{dt} = k_1(C_4H_9I) + k_2(C_4H_9I)(I_2)^{1/2} \quad (3)$$

In view of the varying rate determining equations found for the various homologs, it seemed profitable to investigate additional members of the series with the view of correlating the possible mechanisms involved in the several decompositions. The possibility of certain reactions of free radicals has been strengthened by this generalization of mechanisms. Much evidence indicates that the dissociation energy of the C–I linkage is approximately equal to the activation energy of the above unimolecular reaction,[4] *e. g.*, 43,000 cal.

Experimental Section

The isobutyl iodide employed was an Eastman product. It was dried over calcium chloride and phosphorus pentoxide, then distilled *in vacuo*. The product remained colorless.

The apparatus and procedure employed were described in a previous publication.[1] A slight change was made in this apparatus, substituting a small bore greased stopcock for the Bodenstein greaseless valve. The capillary tubing leading out of the thermostat to the stopcock was heated electrically to prevent condensation of iodine. There was apparently no effect on the rate of decomposition of the alkyl iodide due to this change in apparatus.

Homogeneity of the Thermal Decomposition.—In order to test the homogeneity of the reaction the surface–volume ratio of the system was changed. The major number of experiments were carried out in a 500-cc. Pyrex bulb. Two sets of rate measurements were made in a 280-cc. Pyrex bulb packed with Pyrex glass tubing. The bulbs had surface–volume ratios of 0.63 cm.$^{-1}$ and 8.8 cm.$^{-1}$, respectively. No increase in the rate of reaction was found for the experiments carried out in the packed bulb. As will be shown later, the rate-determining step in the decomposition is of the one-half order with respect to iodine; therefore the agreement of the rate constants for the packed bulb with those in the unpacked bulb indicates the absence of appreciable wall reaction. This result is in agreement with the investigations previously cited for the homologous alkyl iodides.[1,3]

Experimental Results

Nature of the Over-all Reaction.—Glass and Hinshelwood[5] made two runs on the decomposition of isopropyl iodide and analyzed the products of complete reaction. They found that the reaction proceeded in accordance with the equation

$$2\,C_3H_7I \longrightarrow C_3H_8 + C_3H_6 + I_2 \qquad (4)$$

This was proved by a determination of the iodine formed in the reaction and an analysis of the permanent gases. The ratio of final to initial pressure, P_∞/P_0, was 1.54 at 351° and 1.45 at 301°. The ratio of P_∞/P_0 was 1.47 for *s*-butyl iodide, 1.55 for *n*-propyl iodide and 1.49 for isopropyl iodide. The present work yielded 1.55 as the value of P_∞/P_0 for isobutyl iodide. There was no apparent trend of the ratio with temperature, although it was difficult to determine accurately the values of P_0 at the highest temperatures employed.

No gases were formed which were not condensable in liquid air, thus eliminating the possibility of appreciable amounts of methane and hydrogen as products. The amount of iodine formed on complete decomposition was determined by two methods which checked with the above equation. The first method was the direct titration of the

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[1] Jones and Ogg, THIS JOURNAL, **59**, 1931 (1937).

[2] Jones and Ogg, *ibid.*, **59**, 1939 (1937).

[3] Ogg, *Trans. Faraday Soc.*, **31**, 482 (1934).

[4] See also Ogg, THIS JOURNAL, **56**, 532 (1934).

[5] Glass and Hinshelwood, *J. Chem. Soc.*, 1817 (1929).

iodine formed while the second involved the condensation of all products in the side-arm of the reaction vessel by liquid air, then allowing the side-arm to warm to room temperature during evacuation of the reaction vessel. Thus the butylenes and butanes were removed from the vessel, but the iodine, due to its low vapor pressure, remained condensed in the side-arm. The stopcock was closed and the iodine vaporized. Various experiments were frozen out before completion and tested for hydrogen iodide. In most cases none was found, but a few per cent. at most. If the reaction mixtures were allowed to stand for several hours after practical completion, hydrogen iodide formed to the extent of 5 to 10% of the iodine.

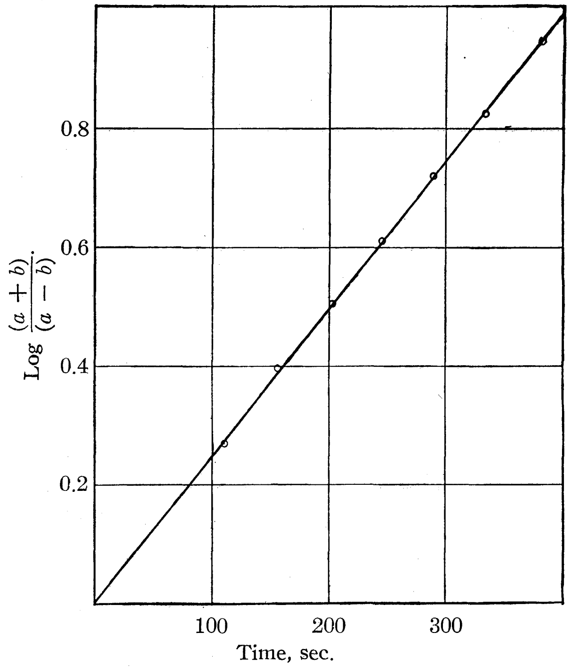

Fig. 1.—Run 24, P_0 = 42.0 mm. T = 319.5°.

All evidence points to the same over-all reaction for the decomposition of *n*-propyl iodide, isopropyl iodide, *n*-butyl iodide, *s*-butyl iodide and isobutyl iodide. This is quite remarkable in view of the fact that the rate determining step varies from case to case.

The Rate-Determining Step of the Thermal Decomposition of Isobutyl Iodide.—A rate expression fitting the data was obtained by testing various empirical equations which seemed likely. The data obtained fitted most closely the simple expression

$$-\frac{d(C_4H_9I)}{dt} = k(C_4H_9I)(I_2)^{1/2} \qquad (5)$$

The pressure of isobutyl iodide at any time t was given by

$$(C_4H_9I) = \frac{1.55\ P_0 - P_t}{0.55} \qquad (6)$$

and in the absence of initial iodine concentration

$$(I_2) = \left(\frac{0.50}{0.55}\right)(P_t - P_0) \qquad (7)$$

if it was assumed that all iodine was present as butyl iodide or free iodine. On integration and evaluation of the integration constant, the rate constant k was given by

$$k = \frac{1}{0.953(0.55)P_0^{1/2}t} \ln \left\{\frac{(0.55P_0)^{1/2} + (P_t - P_0)^{1/2}}{(0.55P_0)^{1/2} - (P_t - P_0)^{1/2}}\right\} \qquad (8)$$

The rate constants were determined by plotting the value of the logarithmic factor of equation (8) against the time. However, the slope of the line was not constant initially, generally being greater over the first 10%. A typical example is given in Fig. 1, where a well-fitting straight line was obtained after the first 10% decomposition. It was noted that the slope of the initial section of the curves fell off more rapidly with increasing temperature and in the majority of experiments well fitting straight lines were obtained after not

TABLE I

Run	Temp., °K.	P_0, mm.	$k \times 10^4$ mm. $^{-1/2}$ sec. $^{-1}$	k(mole/cc.) $^{-1/2}$ sec. $^{-1}$.	Log k
20	548.5	23.4	1.43	0.834	−0.0788
23	550.2	34.8	1.09	.639	− .195
22	550.2	54.9	1.18	.692	− .160
28[a]	556.7	28.5	1.19	.702	− .154
29[a]	556.7	100.0	1.09	.642	− .193
14	560.1	102.3	1.75	1.03	.0128
17	560.7	89.8	1.74	1.03	.0128
19	561.1	96.0	2.37	1.40	.146
13	563.1	62.5	2.19	1.30	.114
18	563.1	63.7	2.65	1.57	.196
15	564.4	27.5	3.51	2.08	.318
16	564.6	63.3	2.27	1.35	.130
5	577.0	53.7	4.99	3.01	.479
6	577.0	110.0	5.07	3.06	.486
4	577.3	74.8	6.10	3.68	.566
3	579.8	28.4	6.65	4.01	.603
2	579.8	58.0	6.57	3.97	.599
10	580.2	93.4	6.88	4.14	.617
7	581.3	40.1	7.82	4.71	.673
11	582.4	79.4	6.57	3.96	.598
12	583.3	77.7	7.22	4.36	.640
9	584.3	136.0	6.49	3.92	.593
8	585.9	82.3	7.92	4.79	.680
24	592.6	42.0	12.4	7.54	.877
26	592.8	25.5	13.2	8.03	.905
25	593.6	33.8	13.1	7.96	.901
27	594.4	132.0	12.0	7.31	.864

[a] Runs in packed flask.

more than 10% decomposition. The ordinate intercepts tended toward zero with increasing temperature, indicating that the initial rate determining step has a lower activation energy than the slow reaction predominating after 10% decomposition. Those experiments at the higher temperatures and pressures had zero intercepts. There was no definite trend to the values of k with increasing initial pressure. The experimental values of k are listed in Table I. All results have been included with the exception of the first experiment.

To obtain the activation energy for the rate-determining step, the term (log k) was plotted against $1/T$ and the best fitting straight line drawn through the experimental points (Fig. 2). The activation energy was 37,800 cal./mole with an estimated accuracy of ±2000 cal./mole.

Discussion

As in the case of n-propyl iodide the rate-determining expression (5) may be written as

$$-\frac{d(C_4H_9I)}{dt} = k_1K_{I_2}^{1/2}(C_4H_9I)(I) \qquad (9)$$

where K_{I_2} is the equilibrium constant for the dissociation of iodine. Two probable mechanisms based upon equation (9) can be rejected as contradictory to experimental facts. The mechanisms are

MECHANISM (a)

$C_4H_9I + I \longrightarrow C_4H_8I + HI$ (slow) (a-1)
$C_4H_8I \longrightarrow C_4H_8 + I$ (a-2)
$C_4H_9I + HI \longrightarrow C_4H_{10} + I_2$ (a-3)
$2I + M \longrightarrow I_2 + M$ (a-4)

MECHANISM (b)

$C_4H_9I + I \longrightarrow C_4H_9 + I_2$ (b-1)
$C_4H_9 + I_2 \longrightarrow C_4H_8 + HI + I$ (b-2)
$HI + C_4H_9I \longrightarrow C_4H_{10} + I_2$ (b-3)
$2I + M \longrightarrow I_2 + M$ (b-4)

In each case these mechanisms are intended to represent the main reaction occurring after about 10% decomposition of the alkyl iodide. In each mechanism reactions (a-1) and (b-1) are the slow rate-determining steps, accounting for the dependence of the experimental rate upon the square root of the iodine concentration.

Consideration of reaction (a-3) or (b-3) indicates that both of these mechanisms are probably invalid. Ogg[4] studied the reaction for the case of methyl, ethyl and n-propyl iodides. He found that the rate of reaction decreased in going from the ethyl iodide to the n-propyl iodide, hence the rate of reaction in the case of isobutyl iodide would be slower. If Ogg's value of the bimolecular constant (his k value) is corrected by a factor of 10^{-1}, the error arising in conversion of the concentration units from mm. to (mole/cc.), the value of the absolute rate of the reaction (a-3) or (b-3) may be calculated. Since the rate of the reaction for the case of ethyl iodide is approximately 0.43 that of n-propyl iodide, it will be assumed that the rate of the corresponding reaction for isobutyl iodide is 0.43 the rate of the reaction for n-propyl iodide. At 550°K. the rate constant for n-propyl iodide is 37.6 (mole/cc.)$^{-1}$ sec.$^{-1}$. Assuming an alkyl iodide concentration of 40 mm. and a hydrogen iodide pressure of 10 mm., the absolute rate of n-propyl iodide disappearance is 1.28×10^{-11} mole/cc./sec. At 550°K. the value of k for isobutyl iodide is 0.637 (mole/cc.)$^{-1/2}$ sec.$^{-1}$. Assuming an alkyl iodide concentration of 40 mm. and an iodine concentration of 10 mm., the absolute rate of disappearance of isobutyl iodide is 3.95×10^{-10} mole/cc./sec. Hence one may consider the experimental rate of disappearance of isobutyl iodide as 72 times the rates of disappearance as calculated for reaction (a-3) or (b-3). Assuming the same concentration values at 585°K., the absolute rate of reaction (a-3) for n-propyl iodide is 5.18×10^{-11} mole/cc./sec. and the experimental rate of disap-

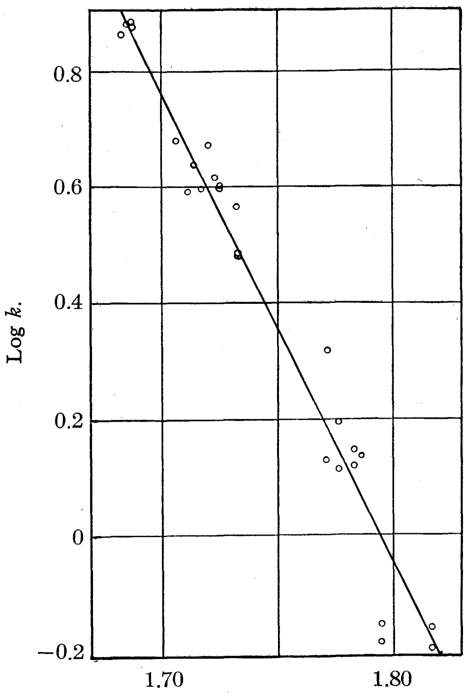

Fig. 2.

pearance of isobutyl iodide is 2.86×10^{-9} mole/cc./sec. Therefore, at 585°K. the experimental rate of disappearance of isobutyl iodide is 127 times the rate of disappearance as calculated for the reaction (a-3) or (b-3).

Evidence[2,4] indicates that the energy required to break the C–I linkage is 43 kcal., and the heat of dissociation of hydrogen iodide is 70.7 kcal. The reverse of reaction (a-1) (for *n*-propyl iodide) is thought to possess an activation energy[3] of 14 kcal. These data yield a value of the carbon–hydrogen linkage of 74.7 kcal. This value is quite low in comparison with the value of 94.5 kcal. calculated by Kistiakowsky and Gershinowitz[6] from the dissociation of cyanogen into cyanide radicals. Such a low value for the C–H bond does not seem plausible even in the possible case of a secondary hydrogen linkage. This constitutes a second serious objection to mechanism (a).

MECHANISM (c)

$$\begin{aligned} C_4H_9I + I &\longrightarrow C_4H_9 + I_2 && \text{(c-1)} \\ C_4H_9 + C_4H_9I &\longrightarrow C_4H_{10} + C_4H_8I && \text{(c-2)} \\ C_4H_8I &\longrightarrow C_4H_8 + I && \text{(c-3)} \\ 2I + M &\longrightarrow I_2 + M && \text{(c-4)} \end{aligned}$$

This mechanism is quite probably the one which prevails in the decomposition of *s*-butyl iodide (with the addition of a simple unimolecular rate determining step). The absolute rate of the iodine atom catalyzed reaction for *s*-butyl iodide at 549°*K*. and the previous concentration units is 1.86×10^{-10} mole/cc./sec. Compare this with the experimental absolute rate of disappearance of isobutyl iodide, *e. g.*, 3.95×10^{-10} mole/cc./sec. at 550°K. The structure of isobutyl iodide with regard to the carbon–iodine bond is similar to the normal alkyl iodide. In the case of *n*-propyl iodide[4] the reaction between free propyl radical and iodine molecule is more rapid than reaction (c-2). Hence, on the basis of the similar rate-determining steps one can rule out this mechanism as it is also improbable for *n*-propyl iodide.

Mechanism (d).—A mechanism was presented in the paper on *n*-propyl iodide which adequately described the decomposition. This mechanism may be generalized to account for the pyrolysis of isobutyl iodide.

The reaction rate constant is comparatively high for the first 10% decomposition, decreasing meanwhile to give a constant value over the remainder of the pyrolysis. Comparison of the unimolecular rate data for *s*-butyl iodide and *n*-propyl iodide yields some interesting results. At 550°K. and the given concentration units, the absolute rate of disappearance of *s*-butyl iodide is 2.42×10^{-10} mole/cc./sec. and for *n*-propyl iodide 2.62×10^{-10} mole/cc./sec. On this basis one can account for the rate of the initial decomposition of isobutyl iodide by the mechanism proposed for *n*-propyl iodide, *e. g.*

$$\begin{aligned} C_4H_9I &\longrightarrow C_4H_9 + I && \text{(d-1)} \\ C_4H_9 + C_4H_9I &\longrightarrow C_4H_{10} + C_4H_8 + I && \text{(d-2)} \end{aligned}$$

Reaction (d-2) is a comparatively slow reaction, the rate constant of the reaction of the free radical with iodine molecule probably being larger.

Due to the reaction between *n*-propyl radicals and iodine molecules the equilibrium (d-3) is established quite rapidly. On this basis the main mechanism is

$$\begin{aligned} i\text{-}C_4H_9I &\rightleftarrows i\text{-}C_4H_9 + {}^1/_2\, I_2\text{(equil.)} && \text{(d-4)} \\ i\text{-}C_4H_4 + I_2 &\longrightarrow \underline{\underline{C_4H_9I}} + I\text{(slow)} && \text{(d-5)} \\ i\text{-}C_4H_9 + \underline{\underline{C_4H_9I}} &\longrightarrow C_4H_{10} + C_4H_8 + I\text{(rapid)} && \text{(d-6)} \\ 2I + M &\longrightarrow I_2 + M \end{aligned}$$

The formula $\underline{\underline{C_4H_9I}}$ represents an activated molecule whose spatial configuration is not necessarily that of isobutyl iodide. This activated molecule reacts with an isobutyl radical, simultaneously losing a hydrogen atom and an iodine atom to form butene. Calculations below indicate that reaction (d-4) has a steric factor of about 10^{-4}. This factor can represent the infrequent occurrence of the proper internal phase conditions necessary for the formation of the activated molecule which has the opportunity of colliding with an isobutyl radical. In the case of *n*-propyl iodide it was considered[1] that the slow step (d-4) resulted in the formation of isopropyl iodide whose rate of decomposition is known[2] to be faster than that of *n*-propyl iodide. Calculations which are presented above indicate that the absolute rate of decomposition of *s*-butyl iodide is less than that of isobutyl iodide; hence, *s*-butyl iodide could not be a possible isomerization product of isobutyl iodide. In addition the isomerization would involve a shift of a carbon atom, a process requiring high activation energy. Isomerization to *t*-butyl iodide would require only the shift of a hydrogen atom; however, *t*-butyl iodide decomposes[7] to form isobutylene and hydrogen iodide and the hydrogen iodide would accumulate in concentrations greater than the experimental values.

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[6] Kistiakowsky and Gershinowitz, *J. Chem. Phys.*, **1**, 432 (1933).

[7] Jones and Ogg, THIS JOURNAL, **59**, 1942 (1937).

Some interesting calculations can be made concerning the rate of reaction (d-5). Since the equilibrium constant K for (d-4) is

$$\frac{(I_2)^{1/2}(i\text{-}C_4H_9)}{(i\text{-}C_4H_9I)} = K$$

then

$$-\frac{d(i\text{-}C_4H_9I)}{dt} = k_5(i\text{-}C_4H_9)(I_2) = k_5K(i\text{-}C_4H_9I)(I_2)^{1/2}$$

The experimental value k is equal to k_5K. As the equilibrium constant K is given by $K = e^{\Delta S^0/R}\,e^{-Q/RT}$, where ΔS^0 is the standard entropy change for reaction (d-4), the rate constant k_5 can be calculated if the entropies of the compounds involved in the reaction are known.

The value of ΔS^0 is calculated at 570°K. The entropy of the iodine molecule at 570°K. (62.53 e. u.) is calculated from the spectroscopic data of Murphy[8] and the Sackur–Tetrode equation. As an approximation, the entropy of the isobutyl radical is taken to be that of isobutane, the data of Pitzer[9] being used to calculate the translational plus rotational entropy of the molecule. The value is 65.64 e. u. at 570°K. Since the calculation of ΔS^0 is primarily concerned with the breaking of the carbon–iodine bond, it will be assumed that the remaining vibrational entropy of isobutyl iodide and isobutyl radical will cancel in the reaction. Hence, only the vibrational entropy ascribed to the carbon–iodine bond is calculated,[10] using 503 and 260 cm.$^{-1}$ (doubly degenerate) as the proper frequencies. The total value of the vibrational entropy ascribed to the bond is 4.41 e. u. The rotational and translational entropy of isobutyl iodide is calculated as 74.01 e. u. where the moments of inertia are taken as 9.0×10^{-39}, 61.0×10^{-38} and 61.0×10^{-38} g. cm.^{2}.

The value of ΔS^0 is 15.52 e. u. at 570°K. and the value of $e^{\Delta S^0/R}$ is 2.48×10^3. The data of Murphy give the heat of dissociation of iodine at 570°K. as 36.65 kcal./mole. The probable heat of dissociation of the primary carbon–iodine bond is 43 kcal. Hence, the value of the heat of reaction Q for the equilibrium (d-4) is 24.7 kcal. So

$$K = 2.48 \times 10^3 e^{-24,700/RT}\ (\text{mole/cc.})^{1/2}$$

The critical increment E_5 for the reaction (d-4) is related to the true activation energy Q_5 by the relation $E_5 = Q_5 + {}^1/_2RT$ (simple bimolecular reaction theory). As E_5 is 13.1 kcal./mole, Q_5 is 12.5 kcal./mole. The temperature dependent equation for k_5 is given by $k_5 = 3.39 \times 10^9\ T^{1/2}e^{-12,500/RT}$ (mole)$^{-1}$/(cc.) sec.$^{-1}$. This equation gives an effective collision diameter of 9.1×10^{-10} cm. Assuming a "true collision diameter" of 6×10^{-8} cm., this corresponds to a steric factor of approximately 2.3×10^{-4}. This value of the steric factor is probably accurate to a factor of 10^2.

On the basis of the above experimental data the reaction

$$i\text{-}C_4H_9 + I_2 \longrightarrow i\text{-}C_4H_9I + I$$

may be considered to have the same activation energy as (d-5). Previous work indicates that the reaction

$$s\text{-}C_4H_9 + I_2 \longrightarrow s\text{-}C_4H_9I + I$$

has an activation energy of 14.2 kcal. and the reaction

$$C_2H_4I + I_2 \longrightarrow C_2H_4I_2 + I$$

has an activation energy of 11.2 kcal. On the basis of the above discussion the reaction

$$n\text{-}C_3H_7 + I_2 \longrightarrow n\text{-}C_3H_7I + I$$

has an activation energy of 12.6 kcal.

On the whole a consistent interpretation can be given to the thermal decomposition of the alkyl iodides based upon a large amount of experimental data. It is felt that the work indicates that the reactions of free radicals require appreciable activation energy, in accord with other existing experimental evidence. At the present there is no evidence which indicates that the strength of the primary carbon–iodine bond is not approximately 43 kcal.

Summary

An experimental study is presented on the kinetics of the thermal decomposition of gaseous isobutyl iodide in the temperature range of 550 to 600°K. The rate of disappearance of isobutyl iodide is expressed by

$$-\frac{d(C_4H_9I)}{dt} = k(C_4H_9I)(I_2)^{1/2}$$

Several proposed mechanisms are shown to be invalid. A mechanism consistent with the experimental data and also explaining the decomposition of n-propyl iodide is in the main

$$i\text{-}C_4H_9I \rightleftarrows i\text{-}C_4H_9 + {}^1/_2\ I_2(\text{equil.}) \qquad (\text{d-4})$$
$$i\text{-}C_4H_9 + I_2 \longrightarrow \underline{\underline{C_4H_9I}} + I(\text{slow}) \qquad (\text{d-5})$$
$$i\text{-}C_4H_9 + \underline{\underline{C_4H_9I}} \longrightarrow \overline{C_4H_9} + C_4H_{10} + I(\text{fast}) \qquad (\text{d-6})$$
$$2I + M \longrightarrow I_2 + M$$

The equilibrium constant K for reaction (d-4) is

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(8) Murphy, *J. Chem. Phys.*, **4**, 344 (1936); Tolman, "Statistical Mechanics as Applied to Physics and Chemistry," Chemical Catalog Co., New York, N. Y., 1927.

(9) Pitzer, *J. Chem. Phys.*, **5**, 473 (1937).

(10) Halford, *ibid.*, **2**, 694 (1934); Mayer, Brunauer and Mayer, THIS JOURNAL, **55**, 37 (1933).

calculated from certain assumptions and spectroscopic data; the rate constant k_5 for reaction (d-5) also has been calculated.

WASHINGTON, D. C. RECEIVED APRIL 18, 1938

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

The Synthesis of Disubstituted Acetylenes

BY JOHN R. JOHNSON, A. M. SCHWARTZ AND THOMAS L. JACOBS

In pursuing an investigation of the reactions of certain acetylenic systems, a number of disubstituted propynes of the type R—C≡C—CH$_2$—R′ were required. The present paper reports a study of synthetic methods for the preparation of pure individuals of known structure.

The alkylation of monosubstituted acetylenes was investigated as a promising preparative method. Nef[1] reported the methylation of phenylacetylene by heating it with methyl iodide and potassium hydroxide, and Morgan[2] effected ethylation of phenylacetylene by heating the sodium derivative with ethyl iodide. Both reactions were carried out in sealed tubes at relatively high temperature (140°) and the yields were low. Preliminary studies of these methods indicated that neither would be satisfactory for preparative purposes. In attempting to employ the method of Morgan, it was found that the sodium derivatives of typical alkyl- and arylacetylenes were surprisingly inert toward alkyl halides. At temperatures sufficiently high to bring about a reaction, vigorous deep-seated decomposition occurred. The substituted acetylides are evidently much less reactive than the monosodium derivative of acetylene itself, which reacts smoothly with alkyl halides at low temperatures.[3] Attempts to effect metathetical reactions between alkyl halides and other metallic derivatives of monosubstituted acetylenes (such as the bromomagnesium, cuprous, silver, and mercuric compounds), in a variety of solvent media, were also unsuccessful.[4]

In an investigation of the action of alkyl *p*-toluenesulfonates on organomagnesium halides, Gilman and Beaber[5] reported the synthesis of β-chloroethylphenylacetylene from the bromomagnesium derivative of phenylacetylene and β-chloroethyl *p*-toluenesulfonate. We have employed their method with excellent results for the preparation of several alkyl derivatives of phenylacetylene. However, the modification of Truchet,[6] in which the sodium derivatives of the acetylenes are used, is advantageous in one respect. When the organomagnesium halide is used, two moles of the sulfonic ester is consumed in producing one equivalent of the alkylated acetylene, since one mole of the ester is converted to the corresponding alkyl bromide (reaction I);[7] but with the sodium acetylides only one equivalent of the sulfonic ester is required (reaction II).

$$\mathrm{R{-}C{\equiv}C{-}MgBr + 2R'{-}OSO_2{-}C_7H_7 \longrightarrow R{-}C{\equiv}C{-}R' + R'{-}Br + Mg(OSO_2{-}C_7H_7)_2} \quad \text{(I)}$$

$$\mathrm{R{-}C{\equiv}C{-}Na + R'{-}OSO_2{-}C_7H_7 \longrightarrow R{-}C{\equiv}C{-}R' + NaOSO_2C_7H_7} \quad \text{(II)}$$

The sodium derivatives were used with satisfactory results for the alkylation of phenylacetylene and *n*-octylacetylene, to obtain the following disubstituted acetylenes: ethyl-, *n*-butyl-, and γ-chloropropylphenylacetylene; ethyl- and γ-chloropropyl-*n*-octylacetylene. The sodium derivatives appeared to be particularly advantageous in the aliphatic series, but there are certain limitations. Attempts to effect syntheses using phenylethynylsodium and benzyl or β-chloroethyl *p*-toluenesulfonate were unsuccessful. In these instances, however, the desired compounds were obtained by the use of phenylethynylmagnesium bromide.

The structures of the disubstituted acetylenes were checked by several methods. In some instances oxidation with aqueous potassium permanganate was employed and the resulting acids

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(1) Nef, *Ann.*, **310**, 333 (1900).

(2) Morgan, *J. Chem. Soc.*, **29**, 162 (1876).

(3) Picon, *Compt. rend.*, **169**, 32 (1919).

(4) A few exceptionally active halides do react with phenylethynylmagnesium bromide to give substituted phenylacetylenes; *e. g.*, allyl bromide [Grignard and Lapayre, *ibid.*, **192**, 250 (1931)], benzohydryl bromide [Wieland and Kloss, *Ann.*, **470**, 217 (1928)], α-furfuryl chloride [Gilman, Van Ess and Burtner, THIS JOURNAL, **55**, 3461 (1933)].

(5) Gilman and Beaber, *ibid.*, **45**, 839 (1923).

(6) Truchet, *Compt. rend.*, **191**, 854 (1930); *Ann. chim.*, [10] **16**, 309 (1931).

(7) Marvel and Rossander, THIS JOURNAL, **50**, 1491 (1928). The correctness of this equation was confirmed in the present work by the isolation of ethylene chlorobromide and benzyl bromide from the reactions in which β-chloroethyl and benzyl *p*-toluenesulfonates were used.

were identified; in others, the hydrocarbons were hydrated with mercuric sulfate and sulfuric acid to the corresponding ketones. The halogenated hydrocarbons were identified by replacement of the halogen atom by carboxyl, by way of the nitrile, and oxidation of the resulting acetylenic acid.

$$\begin{aligned}&\mathrm{R{-}C{\equiv}C{-}(CH_2)_{\mathit{n}}{-}Cl} \longrightarrow \\ &\mathrm{R{-}C{\equiv}C{-}(CH_2)_{\mathit{n}}{-}C{\equiv}N} \longrightarrow \mathrm{R{-}C{\equiv}C{-}(CH_2)_{\mathit{n}}{-}CO_2H} \\ &\mathrm{R{-}C{\equiv}C{-}(CH_2)_{\mathit{n}}{-}COOH} + \mathrm{H_2O} + 3[\mathrm{O}] \longrightarrow \\ &\qquad\qquad \mathrm{R{-}COOH} + \mathrm{HOOC{-}(CH_2)_{\mathit{n}}{-}COOH}\end{aligned}$$

In all cases the compounds behaved like pure individuals and the structures corresponded with those anticipated.

Experimental

Ethylphenylacetylene (1-Phenylbutyne-1).—In a three-necked flask fitted with a mechanical stirrer, reflux condenser and separatory funnel, were placed 75 cc. of anhydrous ether and 4.6 g. (0.2 mole) of clean sodium wire. With vigorous stirring, 21 g. (0.2 mole) of phenylacetylene was added slowly. The reaction started spontaneously and the phenylacetylene was added at such a rate that the ether refluxed gently. The mixture was refluxed for two hours and the ether was then removed completely by warming on a steam-bath. The solid phenylethynylsodium was covered with 75 cc. of anhydrous di-*n*-butyl ether, the mixture was warmed to 60°, and 40 g. (0.2 mole) of freshly distilled ethyl *p*-toluenesulfonate was added dropwise, while stirring vigorously. A spontaneous exothermic reaction occurred and the temperature was maintained below 70° by external cooling. After two hours at 60–70°, the reaction mixture was cooled and treated with a large volume of water. The upper layer was separated, washed with dilute hydrochloric acid and finally with water. After drying, the product was fractionated under reduced pressure. After removal of a small quantity of unreacted phenylacetylene and of di-*n*-butyl ether, the ethylphenylacetylene distilled sharply at 82–83° (5 mm.). After redistillation the product weighed 20 g. (77% yield); b. p. 82° at 5 mm., d^{20}_{4} 0.9210.

This preparation was also carried out using toluene as the reaction medium; in this modification the phenylethynylsodium was prepared directly in toluene. Using the quantities of reactants given above, about 5 g. of phenylacetylene was recovered and 18–20 g. of ethylphenylacetylene was obtained.

The structure of this compound was checked by hydration to *n*-butyrophenone. Five grams of the hydrocarbon in 15 cc. of ethyl alcohol was treated with 2 g. of mercuric oxide, and 15 g. (8 cc.) of concd. sulfuric acid was added dropwise with shaking. After cooling to 20°, the mixture was poured into water and the product extracted with ether. The resulting ketone distilled at 220–223° (740 mm.), and was identified as *n*-butyrophenone through the oxime, m. p. 47°, and the semicarbazone, m. p. 187–188°.

β-Chloroethylphenylacetylene (1-Phenyl-4-chlorobutyne-1).[5]—An ethereal solution of phenylethynylmagnesium bromide was prepared by refluxing 21 g. (0.2 mole) of phenylacetylene with slightly more than the calculated quantity of ethylmagnesium bromide (in approximately molar solution). The resulting solution was added dropwise, with vigorous stirring, to 94 g. (0.4 mole) of β-chloroethyl *p*-toluenesulfonate. The mixture was refluxed gently for eight hours and after cooling was decomposed by iced hydrochloric acid. The ethereal layer was separated and washed successively with water, sodium bicarbonate solution, and water. After drying over calcium chloride the ether was removed and the residue was fractionated under reduced pressure. A large fraction which distilled below 50° at 25 mm., was refractionated at atmospheric pressure and gave 5 g. of phenylacetylene and 25 g. of ethylene chlorobromide (86% of the calculated amount). The remainder gave 15 g. (46% yield) of β-chloroethylphenylacetylene: colorless liquid, b. p. 95° (3 mm.); d^{20}_{4} 1.0763, n^{20}_{D} 1.5724, n^{20}_{C} 1.5657, n^{20}_{F} 1.5882; MR_{D} calcd., 47.6, obsd. 50.52.

Anal. Calcd. for $C_{10}H_9Cl$:Cl, 21.58. Found: Cl, 21.52, 21.56.

This compound was not obtained when phenylethynylsodium was used in place of phenylethynylmagnesium bromide. In this case the phenylacetylene was recovered unchanged after the reaction mixture was hydrolyzed, but none of the sulfonic ester was recovered.

γ-Chloropropylphenylacetylene (1-Phenyl-5-chloropentyne-1).—This substance was prepared according to the procedure given under ethylphenylacetylene, using 50 g. (0.2 mole) of γ-chloropropyl *p*-toluenesulfonate instead of the ethyl ester. The yield of purified product was 27 g. (75% yield). When toluene was used as the reaction medium, a large quantity of phenylacetylene was recovered and only 9 g. (25% yield) of the disubstituted acetylene was obtained.

A redistilled specimen of γ-chloropropylphenylacetylene had the following constants: b. p. 125–127° (4 mm.); d^{20}_{4} 1.0576, n^{20}_{D} 1.5615, n^{20}_{C} 1.5555, n^{20}_{F} 1.5761; MR_{D} calcd., 52.2, obsd. 54.70.

Anal. Calcd. for $C_{11}H_{11}Cl$: Cl, 19.88. Found: Cl, 19.76, 19.84.

The structure of this compound was checked by conversion to 6-phenyl-5-hexynoic acid, and oxidation of the latter to benzoic and glutaric acids. A solution of 5 g. of the chloropropylphenylacetylene in 50 cc. of 90% alcohol was refluxed with 10 g. of pulverized potassium cyanide for thirty hours. After cooling, the mixture was poured into a large volume of water and the oily layer of nitrile was separated. This was refluxed with an excess of 10% potassium hydroxide solution until no oily drops remained. After cooling, the solution was poured into an excess of iced hydrochloric acid, whereupon the acetylenic acid separated as an oil. The latter was extracted with ether and the solvent was distilled off. No attempt was made to purify the intermediate acid. The crude acid was allowed to stand for twenty-four hours at room temperature with a slight excess of 1% aqueous potassium permanganate, with occasional shaking. Oxidation occurred readily and a clear colorless solution was obtained after filtering off the manganese dioxide. The solution was concentrated to a small volume and poured into an excess of iced acid. An oily mixture of acids was precipitated, from which benzoic and glutaric acids were isolated by repeated partition between ether and water. Benzoic acid was identified by a mixed melting point with an authentic specimen. The glutaric acid melted at 97–98°; neutralization equivalent, 68 (calcd., 66); anilide, m. p. 218–219°.

***n*-Butylphenylacetylene (1-Phenylhexyne-1).**—Phenylethynylsodium was prepared by adding slowly 51 g. (0.5 mole) of phenylacetylene to 11.5 g. (0.5 gram atom) of sodium wire in toluene at 35–40°. Higher temperatures must be avoided or the sodium derivative is converted to a gelatinous mass in the presence of toluene. To the suspension of the sodium derivative, 114 g. (0.5 mole) of *n*-butyl *p*-toluenesulfonate was added slowly, with stirring, while the temperature was maintained at 70°. The reaction mixture was treated in the usual way and the product was fractionated through a 30-cm. heated Vigreux column under reduced pressure. A small amount of phenylacetylene was recovered and 51–55 g. (65–70% yield) of *n*-butylphenylacetylene was obtained. The redistilled product had the following constants: b. p. 94–95° at 4 mm. (bath 110–115°), 109–110° at 12 mm. (bath 129–133°); d^{20}_4 0.9024; n^{20}_C 1.5292, n^{20}_D 1.5347, n^{20}_F 1.5485, n^{20}_G 1.561; *MR*D calcd., 52.0, obsd. 54.8.

On hydration in the usual way there was obtained *n*-amyl phenyl ketone (*n*-caprophenone), m. p. 24°, b. p. 137–139° (15 mm.); the semicarbazone of the ketone, after one crystallization from 50% alcohol, melted at 131.5–132° (reported, 127–128° and 131–132°).[8]

Ethyl-*n*-octylacetylene (Dodecyne-3).—Twenty-eight grams (0.2 mole) of pure *n*-octylacetylene[9] in 80 cc. of di-*n*-butyl ether was treated with 8 g. (0.2 mole) of sodamide, previously pulverized under di-*n*-butyl ether. The mixture was heated at 100° for two hours, with stirring, to complete the formation of the sodium derivative, and after cooling to 60° was treated dropwise with 40 g. (0.2 mole) of ethyl *p*-toluenesulfonate. The reaction mixture was heated at 70° for three hours, cooled and treated with cold water. The product was isolated by fractionation under reduced pressure. There was obtained 21 g. (63% yield) of ethyl-*n*-octylacetylene, b. p. 95° (12 mm.); d^{20}_4 0.7871, n^{20}_D 1.44415, n^{20}_C 1.44236, n^{20}_F 1.45162; *MR*D calcd., 55.6, obsd. 55.65.

Anal. Calcd. for $C_{12}H_{22}$: C, 86.65; H, 13.35. Found: C, 86.59, 86.63; H, 13.33, 13.35.

The structure of this hydrocarbon was checked by oxidation with 1% aqueous potassium permanganate, as described above, which gave propionic and pelargonic acids. The former boiled at 138°, and gave propionanilide, m. p. 105°; this anilide showed no depression of the m. p. when mixed with an authentic sample of propionanilide. Pelargonic acid was identified by formation of the amide, m. p. 90°, which showed no depression when mixed with the amide obtained from a sample of synthetic pelargonic acid.

3-Chloropropyl-*n*-octylacetylene (1-Chlorotridecyne-4).—This compound was prepared according to the directions given for ethyl-*n*-octylacetylene, using 50 g. (0.2 mole) of γ-chloropropyl *p*-toluenesulfonate in place of the ethyl ester. The yield of purified product was 65% of the theoretical. A redistilled sample of 3-chloropropyl-*n*-octylacetylene had the following constants: b. p. 123–124° (3 mm.), d^{20}_4 0.9275, n^{20}_D 1.47073, n^{20}_C 1.46810, n^{20}_F 1.47749; *MR*D calcd., 65.1, obsd. 65.0.

Anal. Calcd. for $C_{13}H_{23}Cl$: Cl, 16.54. Found: Cl, 16.40, 16.48.

The structure of this compound was checked by conversion to 4-tetradecynoic acid, and oxidation of the latter with 1% aqueous permanganate, following the procedure given under γ-chloropropylphenylacetylene. There were obtained pelargonic and glutaric acids, which were identified as described above.

Summary

A study has been made of the alkylation of metallic derivatives of monosubstituted acetylenes. The action of alkyl *p*-toluenesulfonates on the sodium or bromomagnesium derivatives of alkyl or arylacetylenes has been found to be a satisfactory procedure for the preparation of a variety of disubstituted acetylenes.

ITHACA, N. Y. RECEIVED APRIL 25, 1938

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[8] Truchet (ref. 6b, p. 400) reported that the semicarbazone of the ketone obtained by hydration of *n*-butylphenylacetylene melted at 164–165°, in agreement with the reported value for the semicarbazone of *n-amylacetophenone*. This is evidently an error since the acetylene in question should yield the lower homolog, *n*-butylacetophenone, as we have found.

[9] Johnson and McEwen, THIS JOURNAL, **48**, 473 (1926).

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

A Study of Propyne-Allene Tautomerism. 1,3-Diphenylpropyne (Benzylphenylacetylene) and Related Compounds

BY JOHN R. JOHNSON, THOMAS L. JACOBS AND A. M. SCHWARTZ

The best known examples of prototropic triad systems are those involving a double bond, and the tautomeric change can be expressed by a simple general equation

$$\mathrm{H{-}X{-}Y{=}Z} \rightleftarrows \mathrm{X{=}Y{-}Z{-}H}$$

in which X, Y and Z represent atoms of carbon, nitrogen or oxygen (occasionally, sulfur). Analogous prototropic systems containing a triple bond are encountered less frequently and have not been studied extensively. These may be represented by means of two general equations, corresponding to the presence of one or two mobile protons in the particular system.[1]

$$\mathrm{H{-}X{-}Y{\equiv}Z} \rightleftarrows \mathrm{X{=}Y{=}Z{-}H}$$

$$\mathrm{H_2X{-}Y{\equiv}Z} \rightleftarrows \mathrm{H{-}X{=}Y{=}Z{-}H} \rightleftarrows \mathrm{X{\equiv}Y{-}ZH_2}$$

This type of prototropic system is of particular interest in view of the circumstance that one of the tautomeric forms is a 1,2-dienoid structure of the allene or ketene type.

The existence of proton mobility in the system $\mathrm{R{-}CH_2{-}C{\equiv}N}$ is well recognized, and the metallic derivatives of these compounds exist largely in the ketene-imine form. The reverse change is demonstrated by the observation that the Hofmann degradation of phenylpropiolic amide ($\mathrm{C_6H_5{-}C{\equiv}C{-}CO{-}NH_2}$), which would be expected to produce phenylethynylamine, actually yields benzyl cyanide.[2]

$$\underset{\text{ethynylamine}}{\mathrm{C_6H_5{-}C{\equiv}C{-}NH_2}} \longrightarrow \underset{\text{ketene-imine}}{\mathrm{C_6H_5{-}CH{=}C{=}NH}} \longrightarrow \underset{\text{nitrile}}{\mathrm{C_6H_5{-}CH_2{-}C{\equiv}N}}$$

The present investigation deals with the preparation and reactions of several 1,3-diarylpropynes, which contain a potentially prototropic system of the type $\mathrm{C_6H_5{-}CH_2{-}C{\equiv}C{-}C_6H_5}$. This system is related structurally to the arylpropynes studied by Bourguel,[3] and to certain trisubstituted propynes that have been observed to undergo propyne–allene transformations.[4]

The first compound chosen for study was the parent structure itself, 1,3-diphenylpropyne (benzylphenylacetylene). Owing to the identity of the terminal substituents in this particular compound, the possible prototropic change involves only two individuals: 1,3-diphenylpropyne (I) and 1,3-diphenylallene (II).

$$\underset{\text{I}}{\mathrm{C_6H_5{-}CH_2{-}C{\equiv}C{-}C_6H_5}} \qquad \underset{\text{II}}{\mathrm{C_6H_5{-}CH{=}C{=}CH{-}C_6H_5}}$$

The desired disubstituted acetylene could not be prepared by the action of benzyl halides on sodium phenylacetylide but was finally obtained by the reaction of phenylethynylmagnesium bromide with an excess of benzyl *p*-toluenesulfonate.[5] Subsequently, another specimen of the hydrocarbon was prepared by the interaction of phenylmagnesium bromide and phenylpropargyl bromide, according to the general method of Lai,[6] and this sample was found to be identical with the other.

1,3-Diphenylpropyne reacted with two atoms of bromine or iodine (in carbon tetrachloride solutions) to give a dihalide, and underwent autoxidation slowly in the air. The hydrocarbon was unaffected by heating with metallic sodium in an inert medium and gave a negative result in the Zerewitinoff test for active hydrogen,[7] using ethylmagnesium bromide in di-*n*-butyl ether.

To obtain evidence bearing upon the subject of propyne–allene tautomerism, the hydrocarbon was hydrated to a ketone by means of sulfuric acid and mercuric oxide, and was subjected to oxidation. The product of hydration proved to be benzylacetophenone (1,3-diphenyl-1-propanone), which would be expected from the acetylenic form since all of the known alkyl phenylacetylenes produce ketones of the type $\mathrm{C_6H_5{-}CO{-}CH_2{-}R}$ upon hydration. None of the isomeric compound, dibenzyl ketone, which might have been produced from 1,3-diphenylallene, could be detected in the reaction product. The fact that the hydrocarbon does not polymerize readily may

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[1] These *prototropic* transpositions are the counterpart of the analogous *anionotropic* changes of the type: $\mathrm{R_2CBr{-}C{\equiv}CR} \longrightarrow \mathrm{R_2C{=}C{=}CRBr}$, and $\mathrm{R_2COH{-}C{\equiv}CR} \longrightarrow \mathrm{R_2C{=}CH{-}CO{-}R}$.

[2] Rinkes, *Rec. trav. chim.*, **39**, 704 (1920).

[3] Bourguel, *Compt. rend.*, **192**, 686 (1931); Bourguel and Piaux, *Bull. soc. chim.*, [4] **51**, 1042 (1932).

[4] Stampfli and Marvel, THIS JOURNAL, **53**, 4057 (1931); Ford, Thompson and Marvel, *ibid.*, **57**, 2619 (1935).

[5] Johnson, Schwartz and Jacobs, *ibid.*, **60**, 1882 (1938).

[6] Lai, *Bull. soc. chim.*, [4] **53**, 687, 1533, 1537 (1933).

[7] It is of interest to note that Grignard and Lapayre [*Compt. rend.*, **192**, 250 (1931)] obtained a positive Zerewitinoff test with compounds of the type $\mathrm{R{-}C{\equiv}C{-}CH_2{-}C{\equiv}C{-}R}$, and other related structures.

be taken as further evidence against the allene structure, since allenes of this general type are known to form dimers with great ease.[4]

Oxidation of the hydrocarbon with cold 1% potassium permanganate solution gave a large amount of benzoic acid (0.96 equivalent) and a much smaller quantity of phenylacetic acid (0.15 equivalent). Ozonation of the hydrocarbon and hydrolysis of the ozonide gave benzoic acid (1.2 equivalents) and phenylacetic acid (0.10 equivalent). Treatment of the ozonide with aqueous potassium iodide, followed by sodium thiosulfate, gave benzyl phenyl diketone in 25% of the theoretical yield.[8] The allene form would have been expected to give benzaldehyde upon ozonolysis, but it is not certain that a small quantity of benzaldehyde would have survived the experimental procedure.

The chemical evidence indicates that 1,3-diphenylpropyne exists largely, if not entirely, in the acetylene form but the possibility of a small proportion of the allene form is not excluded. Conclusive evidence on this point was obtained through the study of a pair of isomeric derivatives of 1,3-diphenylpropyne, in which the terminal aryl groups were not identical. Owing to the circumstance that both of the isomeric propynes (III and V) would give rise to the same allene (IV), it is evident that active prototropy in the system would result in an interconversion of the two propynes. Prototropic change in the 1,3-diarylpropenes and 1,3-diarylmethylene-azomethines has been investigated in this way by Ingold and his collaborators,[9] who found that isomeric diarylpropenes possessing structures VI and VII existed as separate static individuals.

$$BrC_6H_4—CH_2—C{\equiv}C—C_6H_5$$

III

$$BrC_6H_4—CH{=}C{=}CH—C_6H_5$$

IV

$$BrC_6H_4—C{\equiv}C—CH_2—C_6H_5$$

V

$$CH_3O—C_6H_4—CH_2—CH{=}CH—C_6H_5$$

VI

$$CH_3O—C_6H_4—CH{=}CH—CH_2—C_6H_5$$

VII

Each gave rise only to its own oxidation products but interconversion (equilibration) could be effected by heating with alcoholic sodium ethoxide at 85°.[10]

The compounds chosen for the present study were *p*-bromobenzylphenylacetylene (III) and benzyl-*p*-bromophenylacetylene (V). If interconversion did not occur, the former should result from the interaction of *p*-bromobenzyl *p*-toluenesulfonate and phenylethynylmagnesium bromide (reaction A) and the latter from benzyl *p*-toluenesulfonate and *p*-bromophenylethynylmagnesium bromide (reaction B).

$$\text{(A)}\quad 2BrC_6H_4CH_2—OSO_2T + C_6H_5C{\equiv}C—MgBr \longrightarrow \underset{\text{III}}{BrC_6H_4CH_2—C{\equiv}C—C_6H_5} + BrC_6H_4CH_2Br + Mg(OSO_2T)_2$$

$$\text{(B)}\quad 2C_6H_5CH_2—OSO_2T + BrC_6H_4C{\equiv}C—MgBr \longrightarrow \underset{\text{V}}{C_6H_5CH_2—C{\equiv}C—C_6H_4Br} + C_6H_5CH_2Br + Mg(OSO_2T)_2$$

The two syntheses were carried out successfully, and the products were examined carefully to establish their constitution and to discover whether interconversion had occurred.

The compound (III) obtained by reaction A was a crystalline solid which melted at 42–44°. It gave a dibromide, m. p. 108–108.5°, and on hydration produced a ketone which was shown to be *p*-bromobenzylacetophenone, m. p. 68.5–69°. The isomer (V) obtained by reaction B was a liquid that could not be crystallized. Its dibromide melted at 87°, and the ketone obtained by hydration was identified as benzyl-*p*-bromoacetophenone, m. p. 98–99°. The structure of the isomeric ketones was established by the synthesis of authentic specimens, and mixed melting point determinations with the ketones and with suitable derivatives.

$$\text{III} \xrightarrow[HgO]{H_2SO_4} BrC_6H_4CH_2CH_2COC_6H_5$$

$$\text{V} \xrightarrow[HgO]{H_2SO_4} C_6H_5CH_2CH_2COC_6H_4Br$$

The chemical evidence therefore indicates that the three-carbon system of the simple 1,3-diarylpropynes is not actively prototropic, and that these compounds are distinct individuals which do not exist in dynamic equilibrium with the isomeric allenes. Proton mobility in the 1,3-diarylpropyne system is evidently quite low, since the isomeric bromodiphenylpropynes were not interconverted by contact with a Grignard re-

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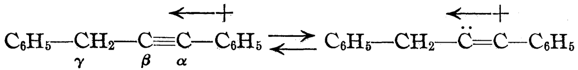
(8) Jacobs, THIS JOURNAL, **58**, 2272 (1936).

(9) For an excellent survey of this subject, and a discussion of electronic theories of tautomeric change, see J. W. Baker, "Tautomerism," George Routledge and Sons, Ltd., London, 1934.

(10) Ingold and Piggott, *J. Chem. Soc.*, **121**, 2381 (1922); Ingold and Shoppee, *ibid.*, 447 (1929). See also Shoppee, *ibid.*, 968 (1930); 1225 (1931).

agent nor with hot aqueous potassium hydroxide solution.

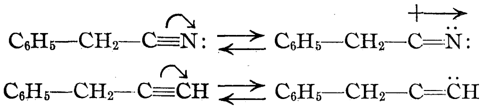
A consideration of structural features of the 1,3-diarylpropyne system, on the basis of current electronic theories of tautomeric change,[9] affords a suitable explanation of the observed low proton mobility. The ability of the aryl group at C_α to facilitate dynamic electron release toward the acetylenic system, leads to the inference that the significant activation of the molecule involves withdrawal of an electron pair of the multiple bond by the central atom (C_β). This view is in agreement with the fact that hydration of arylacetylenes to ketones invariably leads to a combination of protons at C_β and oxygen at C_α.



$$C_6H_5—\underset{\gamma}{CH_2}—\overset{\longleftarrow +}{\underset{\beta\quad\alpha}{C\equiv C}}—C_6H_5 \rightleftarrows C_6H_5—CH_2—\overset{\longleftarrow +}{\ddot{C}=C}—C_6H_5$$

active configuration

The direction of this displacement is favorable for the transfer of an anion from C_γ to C_α but is definitely unfavorable for the shift of a proton to C_α, since the increased electron density at C_γ tends to hold the available protons more firmly *and* the active configuration fails to provide an unshared electron pair at C_α to serve as a seat for available protons. This view of the 1,3-diarylpropynes is supported by comparison with benzyl cyanide and 3-phenyl-1-propyne.



$$C_6H_5—CH_2—C\overset{\curvearrowright}{\equiv N}: \rightleftarrows C_6H_5—CH_2—\overset{+\longrightarrow}{C=\ddot{N}}:$$
$$C_6H_5—CH_2—C\overset{\curvearrowright}{\equiv CH} \rightleftarrows C_6H_5—CH_2—C=\ddot{C}H$$

In these structures the activation involves electron withdrawal from C_β and results in a configuration that is favorable for prototropic change.[11] The decrease of electron density at C_γ increases the proton escaping tendency, and an unshared electron-pair is available to furnish a proton-seat at the α-position; consequently these systems are relatively mobile.

The behavior of the 1,3-diarylpropynes indicates that they are less mobile than benzyl cyanide or 3-phenyl-1-propyne, and that the group $—C\equiv C—C_6H_5$ has less activating effect on a methylene group than $—C\equiv N$ or $—C\equiv CH$.

Experimental

Benzylphenylacetylene (1,3-Diphenylpropyne)

Preparation.—An ethereal solution of 0.6 mole of phenylethynylmagnesium bromide was added dropwise, with stirring, to a gently refluxing solution of 330 g. (1.25 moles) of benzyl *p*-toluenesulfonate in 900 cc. of absolute ether. After the addition was completed (about two and one-half hours), the mixture was refluxed gently for six hours and hydrolyzed with cold dilute hydrochloric acid. The ethereal layer was washed with water, sodium carbonate, and finally with water. After removal of the solvent the residual oil was treated with 15% aqueous potassium hydroxide solution and the whole subjected to steam distillation. The distillate, containing benzyl bromide and benzyl alcohol, was discarded. The residual oil was taken up in ether, washed thoroughly with water, dried over anhydrous potassium carbonate, and distilled in an atmosphere of nitrogen. There was obtained 84 g. (72% yield) of benzylphenylacetylene, b. p. 150–160° (4 mm.). Redistillation gave a pale yellow, highly refringent liquid; b. p. 128–129° (1–2 mm.), $d^{20}{}_4$ 1.0273, $n^{20}{}_D$ 1.5946, $n^{20}{}_C$ 1.5881, $n^{20}{}_F$ 1.6113; *MR*D, calcd. 62.2, obsd. 63.5.

Anal. Calcd. for $C_{15}H_{12}$: C, 93.7; H, 6.3. Found: C, 93.68, 93.50; H, 6.44, 6.45.

Benzylphenylacetylene was prepared also by the general procedure of Lai,[6] but this method is much less convenient. A filtered solution of 0.32 mole of phenylmagnesium bromide was added dropwise over a period of two hours to a stirred solution of 62.5 g. (0.32 mole) of phenylpropargyl bromide in 150 cc. of absolute ether. The mixture was refluxed for three hours and hydrolyzed with cold dilute hydrochloric acid. Repeated fractionation under reduced pressure, under nitrogen, gave 14 g. (27% yield) of benzylphenylacetylene; b. p. 134–135° (1–2 mm.), $d^{20}{}_4$ 1.0408, $n^{20}{}_D$ 1.607. This specimen, although slightly less pure, was substantially identical with that obtained by the first method. Both samples gave the same ketone, benzylacetophenone, when subjected to hydration with sulfuric acid and mercuric oxide.

Benzylphenylacetylene absorbs oxygen slowly from the air but no definite product was isolated. Oxidation of 5 g. of the acetylene with cold 1% aqueous potassium permanganate solution gave 3.0 g. (48%) of benzoic acid and 0.5 g. (15% yield) of phenylacetic acid. Details of the ozonization experiments have been reported.[8]

Hydration to Benzylacetophenone (1,3-Diphenyl-1-propanone).—Two grams of mercuric oxide was mixed with a solution of 5 g. of benzylphenylacetylene in 10 cc. of 95% ethyl alcohol, and 15 g. (8 cc.) of cold concd. sulfuric acid was added slowly with shaking. The hot solution was allowed to cool to 20° and poured into a large volume of cold water. The resulting ketone, after two crystallizations from ethyl alcohol, weighed 3 g. (50% yield) and melted at 72–73°; the oxime melted at 82–83°. Benzylacetophenone is reported to melt at 72–73°, and its oxime at 82°.

Conversion to the Dibromide (1,2-Dibromo-1,3-diphenyl-1-propene).—A solution of 3 g. of the acetylene in 10 cc. of carbon tetrachloride was treated with a solution of 1 g. of bromine. Evaporation gave a mass of white needles; after crystallization from methyl alcohol and from petroleum ether, the product melted at 60°.

Anal. Calcd. for $C_{15}H_{12}Br_2$: Br, 45.41. Found: Br, 45.38, 45.41.

The acetylene readily absorbed two atoms of iodine in carbon tetrachloride solution but the resulting product was a viscous oil which could not be induced to crystallize.

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(11) The predicted direction of electron displacement is confirmed by the fact that hydration of benzyl cyanide and 3-phenyl-1-propyne yields, respectively, phenylacetamide and phenylacetone.

Benzyl-*p*-bromophenylacetylene

Preparation.—*p*-Bromophenylacetylene was obtained conveniently from *p*-bromoacetophenone by the procedure of Dufraisse and Desquesnes.[12] The product boiled at 71–72° (3 mm.) and melted at 62–63°.

p-Bromophenylacetylene (64 g., 0.35 mole) was converted to the bromomagnesium derivative by warming with a slight excess of ethylmagnesium bromide, and the resulting homogeneous solution was added slowly to an excess (185 g., 0.7 mole) of benzyl *p*-toluenesulfonate in ether solution. The procedure was essentially the same as that employed for benzylphenylacetylene. There was obtained 25 g. (26% yield) of crude benzyl-*p*-bromophenylacetylene, b. p. 170–180° (3 mm.); redistillation gave a pale yellow liquid, b. p. 175–180° (3 mm.). The product was characterized by means of the solid dibromide, and by hydration to a solid ketone.

A solution of 2 g. of the acetylene in 10 cc. of carbon tetrachloride was treated with slightly more than two equivalents of bromine in the same solvent. The solvent was evaporated at 20° and the crude product recrystallized from ethyl alcohol. There was obtained 2 g. (63% yield) of the dibromide; white needles, m. p. 87°.

Anal. Calcd. for $C_{15}H_{11}Br_3$: Br, 55.66. Found: Br, 55.70, 55.71.

Hydration to Benzyl-*p*-bromoacetophenone.—In the usual way 5 g. of benzyl-*p*-bromophenylacetylene was treated with sulfuric acid and mercuric oxide, in the presence of ethyl alcohol. The resulting ketone after crystallization from ethyl alcohol weighed 2 g.; white leaflets, m. p. 98–99°. The semicarbazone of the ketone crystallized from alcohol in white needles, m. p. 163–164°. The ketone formed an oxime which crystallized readily from alcohol but showed a wide melting range; m. p. 115–125°. The ketone produced in the hydration reaction was shown to be the expected compound, benzyl-*p*-bromoacetophenone, by direct comparison with an authentic specimen, as described below.

Synthesis of Benzyl-*p*-bromoacetophenone.—A solution of 18.2 g. (0.1 mole) of pure *p*-bromobenzonitrile in absolute ether was added with stirring to a solution of 2-phenyl ethylmagnesium bromide (0.1 mole) and the mixture was refluxed gently for three hours. The reaction mixture was treated with a large excess of cold 15% sulfuric acid and the ether was distilled off without separating the aqueous acidic layer. The oily reaction product crystallized on cooling and after recrystallization from ethyl alcohol formed glistening white plates, m. p. 98–99°. The melting point was not changed by admixture with the ketone obtained by hydration of benzyl-*p*-bromophenylacetylene.

Anal. Calcd. for $C_{15}H_{13}OBr$: Br, 27.67. Found: Br, 27.62, 27.65.

The semicarbazone of the synthetic ketone melted at 164–165°, and showed no depression when mixed with the specimen obtained from the acetylene.

p-Bromobenzylphenylacetylene

Preparation.—A mixture of 54 g. (0.3 mole) of pure *p*-bromobenzyl alcohol (m. p. 77–78°), 54.5 g. (0.3 mole) of redistilled and recrystallized *p*-toluenesulfonyl chloride, and 500 cc. of anhydrous ether was cooled to −10° and treated with 24 g. (0.43 mole) of finely powdered potassium hydroxide, in small portions and with good stirring. The mixture was stirred vigorously for several hours, removed from the cooling bath, and treated with water. The ethereal layer was washed with water, dried over anhydrous potassium carbonate, and concentrated under reduced pressure. The crude *p*-bromobenzyl *p*-toluenesulfonate was precipitated by the addition of petroleum ether and was purified by recrystallization from ether and petroleum ether. The purified product (55% yield) formed large transparent plates, m. p. 74–75°.

An ethereal solution of 79.5 g. (0.23 mole) of *p*-bromobenzyl *p*-toluenesulfonate was treated with 0.115 mole of phenylethynylmagnesium bromide, and the reaction and purification were carried out as described for benzylphenylacetylene. There was obtained 15.5 g. (50% yield) of a pale yellow liquid boiling at 167–171° (1–2 mm.). Redistillation gave 12.5 g. of pure *p*-bromobenzylphenylacetylene; b. p. 166–169° (1–2 mm.), m. p. 42–44°.

Anal. Calcd. for $C_{15}H_{11}Br$: Br, 29.49. Found: Br, 29.88, 30.05.

Treatment of the acetylene with two equivalents of bromine in carbon tetrachloride gave a crystalline dibromide, which melted at 108–108.5° after two crystallizations from ethyl alcohol.

Hydration to *p*-Bromobenzylacetophenone.—To a solution of 5.8 g. of *p*-bromobenzylphenylacetylene in 10 cc. of ethyl alcohol, 2 g. of yellow mercuric oxide was added and 15 g. (8 cc.) of concd. sulfuric acid was introduced dropwise, with cooling and stirring, over a period of ten minutes. The temperature of the flask was raised to 50° for thirty minutes and finally to 95° for fifteen minutes. The reaction mixture was cooled and poured into 250 cc. of cold water. The crude ketone (5.2 g.) was recrystallized from ethyl alcohol and finally from methyl alcohol; m. p. 68.5–69°. The semicarbazone melted at 161–162°. A mixture of this compound with the semicarbazone of the isomeric ketone from benzyl-*p*-bromophenylacetylene, m. p. 163–164°, was found to melt at 133–142°.

The identity of the product of hydration of *p*-bromobenzylphenylacetylene was established by comparison of the ketone and of its semicarbazone with a synthetic specimen of *p*-bromobenzylacetophenone and its semicarbazone.

Synthesis of *p*-Bromobenzylacetophenone.—Several methods were investigated before a satisfactory synthesis of this ketone was found. The preparation was finally effected in an unequivocal manner by the interaction of *p*-bromophenylpropionyl chloride and diphenylzinc. We are greatly indebted to Mr. Stephen Hubard for carrying out the following preparations.

β-Phenylpropionic acid was brominated according to the general directions of Göring[13] and the mixture of brominated products was crystallized three times from 50% alcohol and once from a 1:1 mixture of benzene and petroleum ether. The resulting *p*-bromophenylpropionic acid melted at 131.5–134° (reported, 135°). The constitution of the acid was confirmed by oxidation with aqueous

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[12] Dufraisse and Desquesnes, *Bull. soc. chim.*, [4] **49**, 1880 (1931).

[13] Göring, *Chem. Centr.*, (3) **8**, 795 (1877); Glaser, *Ann.*, **143**, 341 (1867).

potassium permanganate, which produced *p*-bromobenzoic acid, m. p. 245–246.5°.

Twenty-five grams of *p*-bromophenylpropionic acid was refluxed gently for five hours with four equivalents of thionyl chloride, and the excess of thionyl chloride was removed by distillation. The residual acid chloride was taken up in 75 cc. of benzene and the solution was added slowly, with stirring, to an excess of diphenylzinc. The latter was prepared by the addition of 27 g. (0.2 mole) of anhydrous zinc chloride in 25 cc. of absolute ether, to 0.45 mole of phenylmagnesium bromide.[14] After the reaction had been completed the mixture was hydrolyzed with dilute acid; the benzene–ether layer was separated, washed with dilute alkali, and finally with water. After removal of the solvent the crude product was recrystallized from ethyl alcohol, and finally from methyl alcohol. The purified ketone formed white needles, m. p. 68–69°. This material was identical with a small sample of the ketone which had been obtained by treating the sodium derivative of ethyl benzoylacetate with *p*-bromobenzyl bromide and saponifying the resulting ethyl benzoyl-*p*-bromobenzylacetate.

Anal. Calcd. for $C_{15}H_{13}OBr$: C, 62.30; H, 4.50. Found: C, 61.89; H, 4.78.

The semicarbazone of the synthetic ketone melted at 160–161.5°, and the 2,4-dinitrophenylhydrazone at 67–67.5°. The synthetic ketone and its semicarbazone showed no depression of the melting point when mixed with the specimens obtained from *p*-bromobenzylphenylacetylene.

Summary

1,3-Diphenylpropyne (benzylphenylacetylene) and two isomeric bromo derivatives have been prepared, and their chemical reactions investigated.

It has been shown that active prototropy of the propyne–allene type does not occur in these compounds, and that the 1,3-diarylpropynes exhibit low proton mobility.

Comparison with benzyl cyanide and 3-phenyl-1-propyne indicates that the phenylethynyl group has less activating effect than —C≡N or —C≡CH, which is in agreement with the anticipated order.

ITHACA, N. Y. RECEIVED APRIL 25, 1938

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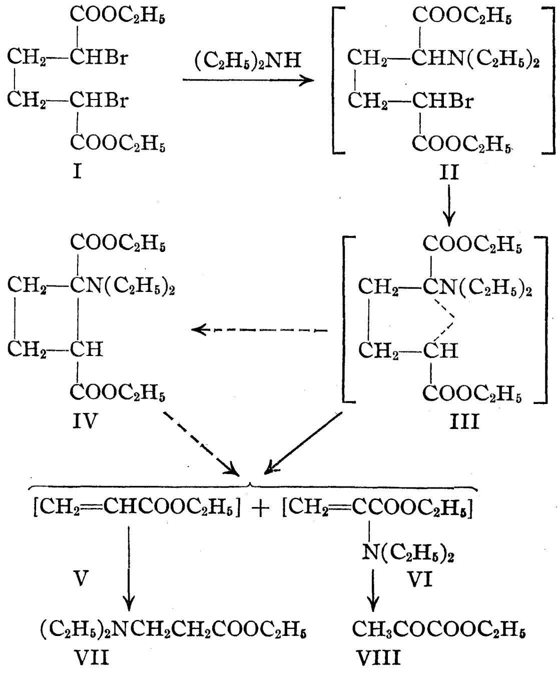
[14] Job and Reich, *Bull. soc. chim.*, [4] **33**, 1428 (1923).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

The Mechanism of the Cleavage of Ethyl α,α'-Dibromoadipate by Diethylamine

BY REYNOLD C. FUSON AND WM. E. LUNDQUIST

The cleavage of ethyl α,α'-dibromoadipate (I) by secondary amines, discovered by von Braun, Leistner and Münch,[1] may be interpreted in the light of Criegee's recently proposed theory of chain cleavages.[2] This postulate suggests that the cleavage may be explained by the formation of a 1,4-biradical. According to Criegee such radicals may stabilize themselves in two ways: (1) by closure to a four-membered ring or (2) by chain fission between atoms 2 and 3 to give two molecules of olefinic character. Applied to the cleavage of ethyl α,α'-dibromoadipate (I) by diethylamine this theory suggests that the biradical (III) may be produced from the intermediate bromoamino ester (II) by the loss of hydrogen bromide. The biradical might be expected to decompose to give ethyl acrylate (V) and ethyl α-diethylaminoacrylate (VI). The products actually isolated were ethyl β-diethylaminopropionate (VII) and ethyl pyruvate (VIII)—compounds which may be regarded as transformation products of V and VI, respectively. The formation of these compounds constitutes an example of the second mode of stabilization of the biradical.



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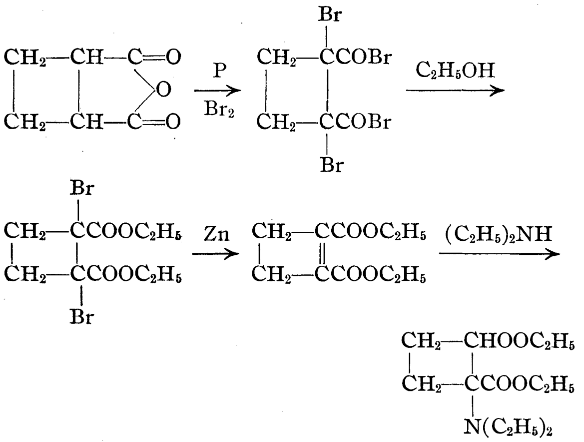
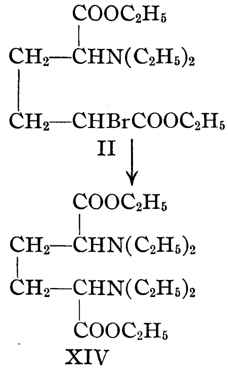
[1] Von Braun, Leistner and Münch, *Ber.*, **59**, 1950 (1926).

[2] Criegee, *ibid.*, **68B**, 665 (1935).

If the biradical stabilized itself by the first mode, *i. e.*, by closure to a four-membered ring, the product would be ethyl 1-diethylamino-1,2-cyclobutanedicarboxylate (IV). Although none of this compound was isolated, it was important to determine whether it might be a possible intermediate in the cleavage as was suggested by Fuson[3] in 1928. We have made this compound (IV), and have tested its thermal stability. The synthesis was carried out by the following sequence of transformations



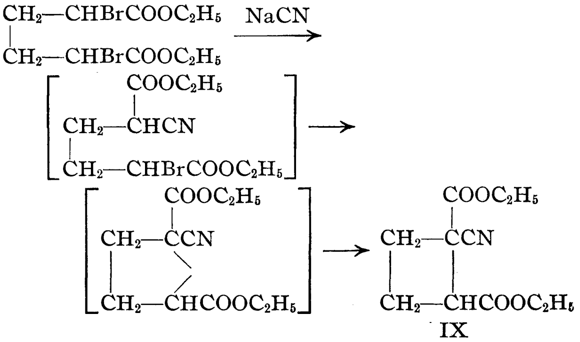
The amino ester was analyzed, and its molecular refraction and parachor were determined as a check on its identity. Its picrate was also prepared and characterized. The amino ester was found to be stable toward aqueous acid and alkali and could be distilled under diminished pressure without decomposition. It is therefore extremely unlikely that it is an intermediate in the cleavage of ethyl α,α'-dibromoadipate by diethylamine. This conclusion lends support to Criegee's theory.



II

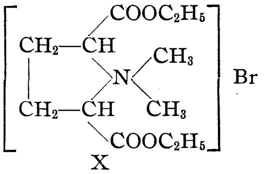
XIV

It is interesting to note that on the strength of his original theory—a theory which is no longer tenable—Fuson predicted that ethyl α,α'-dibromoadipate should react with sodium cyanide to give a cyclobutane derivative, and experiments showed that good yields of a stable cyclized product (IX) could be obtained.[4] This formation of a four-membered ring appears to be an example of the stabilization of a 1,4-biradical by ring closure. Thus the reactions of ethyl α,α'-dibromoadipate with sodium cyanide and diethylamine may be interpreted as examples of two ways in which 1,4-biradicals can stabilize themselves.

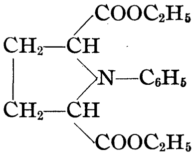


IX

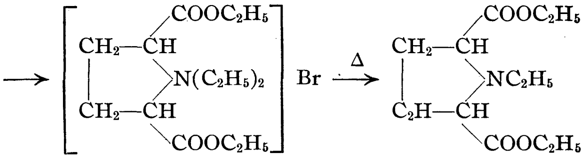
It might be expected that ethyl α-bromo-α'-diethylaminoadipate (II), postulated as the first product of the reaction, would tend to form the corresponding pyrrolidinium bromide. Ethyl α,α'-dibromoadipate reacts with dimethylamine in alcohol to give a pyrrolidinium bromide (X),[5] and with aniline,[6] ethylaniline,[7] and diethylaniline[8] at 100° or above to give ethyl 1-phenyl-2,5-pyrrolidinedicarboxylate (XI). The work of Menschutkin[9] on the velocity of the reaction of triethylamine with ethyl iodide in various solvents suggests that ethyl α,α'-dibromoadipate might be converted to a pyrrolidine derivative (XII) if the treatment with diethylamine were carried out in a suitable solvent.



X



XI



XII

XIII

The reaction was therefore repeated using acetone, ethyl alcohol and benzene as diluents in

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[3] Fuson, This Journal, **50**, 1444 (1928).

[4] Fuson and Kao, *ibid.*, **51**, 1536 (1929).

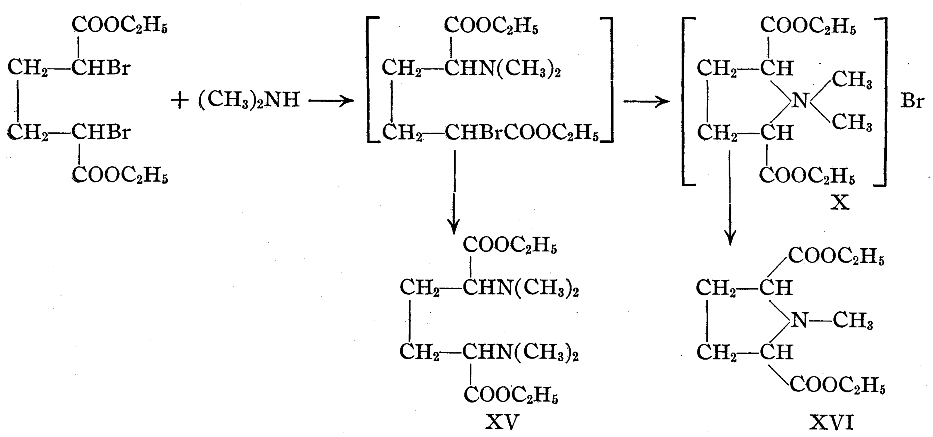
[5] Fuson and Connor, *ibid.*, **52**, 2985 (1930).

[6] Von Braun and Seemann, *Ber.*, **56B**, 1840 (1923).

[7] Le Sueur, *J. Chem. Soc.*, **95**, 273 (1909).

[8] Le Sueur and Haas, *ibid.*, **97**, 173 (1910).

[9] Menschutkin, *Z. physik. Chem.*, **6**, 41 (1890).



comparable runs. The ethyl alcohol and acetone would be expected to hasten the formation of the intermediate, II, and the further reaction of II with more diethylamine to give the diamino product (XIV) or with itself by ring closure to give the quaternary pyrrolidinium salt (XII). The reaction in benzene would be expected to proceed in much the same manner as if there were no solvent;[10] that is, cleavage should result. It was found that the solvents had the expected effect. In ethyl alcohol the pyrrolidine derivative (XII) was formed with no evidence of any cleavage. In acetone the pyrrolidine derivative was also obtained but there was evidence of a small amount of cleavage. In benzene only a small amount of pyrrolidine was formed and both of the cleavage products (VII and VIII) were found. The salt, XII, was not isolated as such but rather as its thermal decomposition product, XIII.

The effect of solvents on the course of the reaction between diethylamine and ethyl α,α'-dibromoadipate made it seem necessary to reinvestigate the reaction of the ester with dimethylamine. It had been carried out in benzene solution by von Braun and Münch[11] who obtained a 20% yield of ethyl α,α'-tetramethyldiaminoadipate (XV). Fuson and Connor[5] using alcohol obtained small amounts of the diamino ester (XV) and the pyrrolidinium bromide (X). To favor cleavage the reaction was carried out rapidly and without a solvent. Dimethylamine and ethyl α,α'-dibromoadipate were heated in a sealed tube on a steam-bath for one-half hour and the crude reaction product was distilled. In this way there was obtained a 35% yield of ethyl 1-methyl-2,5-pyrrolidinedicarboxylate (XVI) with no evidence of any cleavage products.

Experimental

Ethyl 1-Diethylamino-1,2-cyclobutanedicarboxylate.—The anhydride of 1,2-cyclobutanedicarboxylic acid[12] was treated with bromine and red phosphorus[13] and then with ethyl alcohol to produce ethyl 1,2-dibromo-1,2-cyclobutanedicarboxylate. Dehalogenation with zinc in ether[14] gave ethyl Δ'-1,2-cyclobutenedicarboxylate.[15] The properties found for this substance are: b. p. 92–94° (2 mm.); $n^{20}\text{D}$ 1.4610; $d^{20}{}_4$ 1.081; γ^{20} 33.8 dynes/cm.;[16] $M\text{D}$ 50.3; P, 442.1. Calcd. for $C_{10}H_{14}O_4$: $M\text{D}$ 49.51;[17] P, 442.2.[18]

Diethylamine was added to this unsaturated material by the method of Körner and Menozzi.[19] Two grams of ethyl Δ'-1,2-cyclobutenedicarboxylate, 2 g. of diethylamine, and 5 cc. of absolute alcohol were heated at 100° in a sealed tube for five hours. The alcohol and excess diethylamine were removed by distillation, and the amine was then dissolved in ether leaving the amide behind. The amine was extracted from the ether with cold dilute sulfuric acid, and the aqueous solution was washed well with ether. Sodium hydroxide liberated an oil which was removed by ether extraction. The ethereal solution was washed well with water to remove much of the coloring matter, and was then dried with magnesium sulfate. Removal of the ether left a red oil which distilled under diminished pressure to give a clear colorless oil; b. p. 100–101° (2 mm.); $n^{20}\text{D}$ 1.4540; $d^{20}{}_4$ 1.016; γ^{20} 29.7 dynes/cm.[16]

Anal. Calcd. for $C_{14}H_{25}O_4N$: C, 61.97; H, 9.28; $M\text{D}$ 72.56;[17] P, 638.8.[18] Found: C, 62.25, 62.25; H, 9.43, 9.27; $M\text{D}$ 72.3; P, 623.4.

The picrate of the amine was prepared by adding 1 g. of ethyl 1-diethylamino-1,2-cyclobutanedicarboxylate to a saturated solution of 1 g. of picric acid in ethyl alcohol. The yellow crystals which soon appeared were recrystal-

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(10) Moelwyn-Hughes and Hinshelwood, *J. Chem. Soc.*, 230 (1932).

(11) Von Braun and Münch, *Ber.*, **59B**, 1941 (1926).

(12) Ellingboe and Fuson, THIS JOURNAL, **56**, 1774 (1934).

(13) Perkin, *J. Chem. Soc.*, **65**, 950 (1894).

(14) Michael and Schulthess, *J. prakt. Chem.*, [2] **43**, 587 (1891).

(15) Kon and Nandi, *J. Chem. Soc.*, 1628 (1933).

(16) Surface tension measurements were made by the capillary rise method.

(17) Calculated from values found in Gilman "Organic Chemistry," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1938, p. 1739.

(18) Calculated from Sugden's values found in Gilman, ref. 17, p. 1733.

(19) Körner and Menozzi, *Atti accad. Lincei*, Rome, V, **5**, I, 456 (1896).

lized several times from ethyl alcohol; m. p. 125–130.5°. The crystals are sensitive to direct sunlight.

Anal. Calcd. for $C_{20}H_{28}O_{11}N_4$: C, 48.00; H, 5.64; N, 11.20. Found: C, 47.96; H, 5.67; N, 11.22.

Ethyl 1-Ethyl-2,5-pyrrolidinedicarboxylate.—This substance was prepared by the method of von Braun and Seemann.[6] Thirty-six grams (0.1 mole) of ethyl *meso*-α,α'-dibromoadipate and 50 g. of dry benzene containing 13.5 g. (0.3 mole) of ethylamine were placed in a sealed tube. The tube soon became warm, and ethylamine hydrobromide began to separate. After standing at room temperature for twenty-four hours the bomb was warmed in a steam-bath for four hours. It was then cooled and the solution was filtered to remove ethylamine hydrobromide. The filtrate was diluted with ether and was extracted with an excess of cold dilute sulfuric acid to remove the basic fraction. The aqueous solution was washed with ether and was then made alkaline with sodium bicarbonate. The oil which separated was removed by ether extraction, the ethereal solution was washed with water and dried, and the ether was removed by distillation. Vacuum distillation of the residual oil gave 7 g. (30% of the theoretical amount) of a colorless oil, b. p. 108–114° (2 mm.). Redistillation gave a fraction boiling at 108–109° (2 mm.); $n^{20}\text{D}$ 1.4508; d^{20}_4 1.052; γ^{20} 32.5 dynes/cm.[16]

Anal. Calcd. for $C_{12}H_{21}O_4N$: C, 59.24; H, 8.70; *M*D 62.84;[17] *P*, 557.7.[18] Found: C, 59.33, 59.34; H, 8.56, 8.63; *M*D 62.2; *P*, 552.2.

The chloroplatinate of the pyrrolidine was prepared by treating 0.8 g. of ethyl 1-ethyl-2,5-pyrrolidinedicarboxylate with 0.7 g. of platinic chloride and 1 cc. of concd. hydrochloric acid in 20 cc. of ethyl acetate. The product was recrystallized from a mixture of equal volumes of ethyl alcohol and ethyl acetate to obtain pale orange crystals; m. p. 133.5–135.5°.

Anal. Calcd. for $(C_{12}H_{21}O_4N)_2\cdot H_2PtCl_6$: Pt, 21.77. Found: Pt, 21.70, 21.70.

Reaction of Diethylamine with Ethyl α,α'-Dibromoadipate. Reaction in Alcohol.—Thirty-six grams of ethyl α,α'-dibromoadipate and 60 cc. of diethylamine were added to 150 cc. of 95% ethyl alcohol and the mixture was allowed to stand at room temperature. At the end of one day all of the dibromo ester had not dissolved so the mixture was warmed until solution was complete. The solution was then let stand at room temperature for an additional forty hours. The solvent and excess diethylamine were removed from the solution by distillation through a 12-in. (30-cm.) Widmer column, and the residue was then heated under diminished pressure to liberate as much material as possible from the diethylamine hydrobromide. The crude distillate obtained in this way was redistilled to obtain 6.5 g. (27% of the theoretical amount) of ethyl 1-ethyl-2,5-pyrrolidinedicarboxylate, boiling at 113–114° (3 mm.).

Reaction in Acetone.—Thirty-six grams of ethyl α,α'-dibromoadipate and 60 cc. of diethylamine were dissolved in a mixture of 145 cc. of acetone and 5 cc. of water, and the solution was allowed to stand at room temperature for two days. The solvent was then removed by distillation and the residue was distilled under reduced pressure. The crude distillate obtained was redistilled to get about 0.5 cc. of a product boiling at 90–95° (18 mm.) and 3 cc. of ethyl 1-ethyl-2,5-pyrrolidinedicarboxylate, boiling at 143–145° (18 mm.).

Reaction in Benzene.—Thirty-six grams of ethyl α,α'-dibromoadipate and 60 cc. of diethylamine were dissolved in 150 cc. of benzene and the solution was allowed to stand at room temperature for sixty hours. It was then filtered to obtain 30 g. of crude diethylamine hydrobromide (the theory calls for 30.8 g. of diethylamine hydrobromide). The diethylamine and benzene were removed from the filtrate by fractional distillation through a 12-in. (30 cm.) Widmer column. The residue was then distilled under diminished pressure to obtain 7 g. of a product boiling at 83–88° at 16 mm. pressure. This was allowed to stand with a slight excess of cold dilute hydrochloric acid for an hour, and it was then extracted with ether. Evaporation of the ether from this extract left a small quantity of an oil which was shown to be ethyl pyruvate by conversion to its phenylhydrazone.

The acid solution was made alkaline with sodium hydroxide and the liberated amine was removed by extraction with ether. The ether solution was dried and the ether was removed by distillation. The residual oil was distilled under diminished pressure to give 3.5 g. (20% of the theoretical) of ethyl β-diethylaminopropionate boiling at 85–86° (15 mm.); $n^{20}\text{D}$ 1.4268.

The crude diethylamine hydrobromide was heated under reduced pressure to yield a small amount of an oil which on redistillation gave about 0.5 cc. of ethyl 1-ethyl-2,5-pyrrolidinedicarboxylate boiling at 110° (2–3 mm.).

Reaction of Dimethylamine with Ethyl α,α'-Dibromoadipate.—Eighteen grams of ethyl α,α'-dibromoadipate was placed in a glass tube and the tube was cooled in a dry ice–acetone bath. Dimethylamine, prepared by dropping a commercial aqueous solution on solid potassium hydroxide and dried by passing the gas over solid potassium hydroxide, was condensed and added to the tube until the weight of the tube had increased by 13.5 g. The tube was then sealed and allowed to warm up to room temperature. A spontaneous reaction occurred and after fifteen minutes the tube had become hot. It was heated for an additional half hour in a steam-bath, cooled and opened. The excess dimethylamine quickly vaporized and the remainder of the product was then distilled under diminished pressure. Redistillation of the crude product obtained gave 4 g. (35% of the theoretical) of ethyl 1-methyl-2,5-pyrrolidinedicarboxylate boiling at 138–141° (20 mm.). This when redistilled had the following properties: b. p. 114–115° (4 mm.), $n^{20}\text{D}$ 1.4515, d^{20}_4 1.072.

Summary

Ethyl 1-diethylamino-1,2-cyclobutanedicarboxylate has been prepared and found to be stable at ordinary temperatures. It is therefore concluded that this ester cannot be an intermediate in the cleavage of ethyl α,α'-dibromoadipate by diethylamine.

The reaction of diethylamine α,α'-dibromoadipate has been carried out using ethyl alcohol, acetone and benzene as solvents in comparable

runs. It has been found that the solvent affects the course of the reaction; ethyl 1-ethyl-2,5-pyrrolidinedicarboxylate is produced in these solvents. It is therefore concluded that 1,1-diethyl-2,5-dicarbethoxypyrrolidinium bromide cannot be an intermediate in the cleavage.

The 1,4-biradical theory of Criegee offers a satisfactory explanation of the facts.

The reaction of dimethylamine and ethyl α,α'-dibromoadipate carried out without a solvent gives a 35% yield of ethyl 1-methyl-2,5-pyrrolidinedicarboxylate with no evidence of any cleavage.

URBANA, ILLINOIS RECEIVED MAY 2, 1938

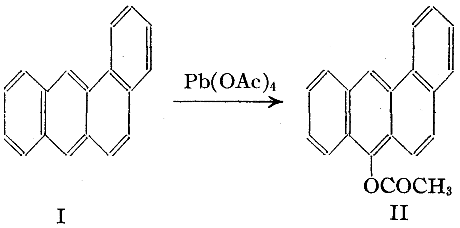
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Substitution Reactions and Meso Derivatives of 1,2-Benzanthracene

BY LOUIS F. FIESER AND E. B. HERSHBERG[1]

Among various miscellaneous observations reported in this paper is a study of the action of lead tetraacetate on 1,2-benzanthracene and two related carcinogenic hydrocarbons. The idea of investigating the action of this oxidizing agent on polynuclear aromatic hydrocarbons was suggested by an observation of K. H. Meyer[2] which heretofore has attracted little attention. Schulze[3] at an early date had investigated the action of lead dioxide on anthracene in acetic acid solution, but it remained for Meyer to interpret the reaction correctly and to show that with two moles of oxidizing agent the chief product is hydroxyanthrone acetate. Using one mole of lead dioxide, Meyer obtained anthranyl acetate in 40–50% yield and noted that this was the first instance of the direct oxidation of a hydrocarbon to a phenol derivative. It occurred to us that this method of hydroxylation might have preparative value, that it might afford a useful method of probing for centers of reactivity in polynuclear compounds, and that the reaction would form an interesting model for a possible hydroxylation of carcinogenic hydrocarbons introduced into the animal organism.

In trial experiments lead tetraacetate was found to act as well as lead dioxide and it is a generally superior reagent. The reaction of one mole of lead tetraacetate with 1,2-benzanthracene in glacial acetic acid is complete after short heating on the steam-bath, and the purified reaction product, isolated in 52% yield, was found to be identical with synthetic 1,2-benzanthranyl-10-acetate[4] (II). The chief point of attack in the oxidation therefore is at the less hindered meso position 10.



I II

Little previous work has been done on the orientation of 1,2-benzanthracene in monosubstitutions. Cook and Hewett[5] found that the chief product of the Friedel and Crafts reaction with acetyl chloride at a low temperature is a meso ketone, but a distinction between the 9- and 10-positions was not made. With oxalyl chloride, Dansi[6] obtained besides a diketone a small amount of an acidic substance regarded as 1,2-benzanthracene-10-carboxylic acid. Barnett and Matthews[7] prepared a mononitro compound which they regarded as a 9- or 10-derivative, but they did not investigate the structure. We prepared a sample of the nitro compound by their method and reduced it to the amine. The same amine was obtained in good yield from 1,2-benz-10-anthranol[4] by the Bucherer reaction, from which it is evident that the nitration product prepared by Barnett and Matthews is 10-nitro-1,2-benzanthracene. The nitration of the hydrocarbon thus follows the same course as the oxidation with lead tetraacetate. Since 10-substituted derivatives of 1,2-benzanthracene are of particular interest in connection with the problem of carcinogenesis, it is significant that such compounds are available by the route of direct substitution reac-

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[1] Research Fellow on funds from the National Cancer Institute and the Ely Lilly Company.

[2] K. H. Meyer, *Ann.*, **379**, 73 (1911).

[3] Schulze, *Ber.*, **18**, 3036 (1885).

[4] Fieser and Hershberg, THIS JOURNAL, **59**, 1028 (1937).

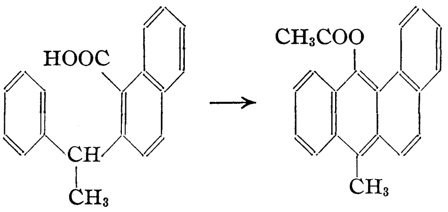
[5] Cook and Hewett, *J. Chem. Soc.*, 1408 (1933).

[6] Dansi, *Gazz. chim ital.*, **67**, 85 (1937).

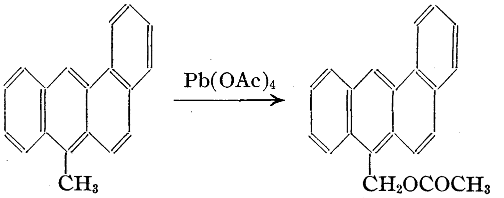
[7] Barnett and Matthews, *Chem. News*, **130**, 339 (1925).

tions.[8] Two additional 10-derivatives described in the Experimental Part are 3,10-dimethoxy-1,2-benzanthracene, prepared by methylation of the MgBr-salt of the corresponding 10-hydroxy compound, and a glycol dibenzoate resulting from the action of the silver benzoate–iodine compound[9] on 10-allyl-1,2-benzanthracene.

Lead tetraacetate reacts somewhat less smoothly with 10-methyl-1,2-benzanthracene than with the parent hydrocarbon, but a crystalline reaction product (m. p. 151°) was isolated in a pure condition if in rather low yield. The substance has the composition of a monoacetoxy compound, and it seemed possible that oxidation had occurred in the available meso position 9. The hitherto unknown 9-acetoxy-10-methyl-1,2-benzanthracene (IV) was therefore synthesized for comparison by the acetylative cyclization[4] of the previously described[10] acid III with zinc chloride catalyst in acetic acid–anhydride, but the synthetic acetate (m. p. 154°), gave a marked depression when mixed with the product of oxidation. We next prepared the 3-acetoxy derivative of 10-methyl-1,2-benzanthracene, since a sample of the hydroxy compound was available from earlier work,[4] but this acetate melted much higher (215°) than the compound in question. The substance was finally identified as 10-acetoxymethyl-1,2-benzanthracene (VI) by direct comparison with a sample of this substance kindly provided by Professor J. von Braun, who in unpublished work has prepared the acetoxy compound by a method leaving no doubt as to the structure. The oxidation of an alkyl side chain is not without parallel, for Dimroth and Schweizer[11] obtained benzyl acetate in about 12% yield on refluxing toluene with lead tetraacetate for four hours, and Criegee[12] found that tetralin is converted by the reagent into the 1-acetoxy derivative (one hour). The oxidation of the hydrocarbon V is complete after fifteen minutes, but whether or not this indicates a special reactivity of the 10-methyl group cannot be determined until more data are available. At all events it is very surprising that the methyl group is attacked in preference to oxidation at the free meso position. In comparison with the meso reactivity of anthracene, and that manifested at the 10-position in 1,2-benzanthracene, the 9-position of the hydrocarbon in question appears to be definitely inert. We are inclined to attribute this effect to steric hindrance, and it may be noted that the 9-position of 1,2-benzanthracene corresponds to position 4 in the phenanthrenoid system present in the molecule and that there are definite indications of hindrance at this position in phenanthrene.[13] While 4-substitution is not unknown,[14] it is extremely rare.



III IV



V VI

In 1,2,5,6-dibenzanthracene both meso positions should be subject to any blocking effect which may be exerted by an angular ring and, in line with the expectations from the behavior of 10-methyl-1,2-benzanthracene, it was found that the tetracyclic hydrocarbon is more resistant to attack by lead tetraacetate than 1,2-benzanthracene. From the reaction of the pure, colorless hydrocarbon with one mole of reagent we invariably recovered some unchanged material, and no homogeneous reaction product was isolated. In the course of the experiments it was observed that the yellow chrysogen (1,2,6,7-dibenzanthracene[15,16]) present in crude 1,2,5,6-dibenzanthracene is oxidized more readily than this hydrocarbon by lead tetraacetate and converted into more soluble products. This suggested a method for the purification of the widely used carcinogenic hydrocarbon which has been found very convenient and efficient. The yellow material

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[8] Dr. J. L. Hartwell of this Laboratory has prepared 1,2-benzanthracene-10-aldehyde, m. p. 147.3–148°, corr., by direct substitution.

[9] Prévost, *Compt. rend.*, **196**, 1129 (1933); **197**, 1661 (1933); Hershberg, *Helv. Chim. Acta*, **17**, 351 (1934).

[10] Fieser and Newman, THIS JOURNAL, **58**, 2376 (1936).

[11] Dimroth and Schweizer, *Ber.*, **56**, 1375 (1923).

[12] Criegee, *Ann.*, **481**, 263 (1930).

[13] Fieser, "The Chemistry of Natural Products Related to Phenanthrene," 2d ed., Reinhold Publishing Corp., New York, N. Y., 1937, pp. 13–14.

[14] Bachmann and Kloetzel, THIS JOURNAL, **59**, 2207 (1937).

[15] Cook, *et al.*, *Proc. Roy. Soc.* (London), **B111**, 469 (1932).

[16] Winterstein and Schön, *Z. physiol. Chem.*, **230**, 146 (1934).

is refluxed for a short time in benzene–acetic acid with about 0.1 mole of lead tetraacetate, and after concentrating and cooling the solution there is obtained very satisfactory, colorless 1,2,5,6-dibenzanthracene in over 80% yield. In our experience this method is considerably more rapid and sparing of material than preferential sulfonation of the chrysogen,[17] reaction with maleic anhydride,[15,18] or chromatographic adsorption.[16]

The lead tetraacetate reaction offers promise of providing information of value concerning the reactivity of various types of polynuclear aromatic hydrocarbons, with or without side chains and alicyclic rings, and the investigation of the reaction is being extended. The conversion of 3,4-benzpyrene and methylcholanthrene into monoacetoxy derivatives, m. p. 208.5–209°, corr., and m. p. 179.5–180.5°, corr., will be described at a later date.

In connection with the acetylative cyclization of the acid III, mentioned above, to an enol acetate (IV), the present paper reports a few additional observations concerning the application of this method[4] of ring closure. The most novel result is the cyclization of γ-(3-acenaphthyl)-butyric acid[19] by the catalytic method to 1-keto-1,2,3,4-tetrahydro-8,9-acephenanthrene[18] in 78% yield. Reference is also made below to a dimolecular product previously obtained[4] from 1,2-benz-10-anthranol.

Experimental Part[20]

Oxidation of 1,2-Benzanthracene.—A solution of 0.5 g. of colorless 1,2-benzanthracene and 1.5 g. of lead tetraacetate in 20 cc. of glacial acetic acid (distilled from permanganate) was warmed on the steam-bath for fifteen minutes and diluted with water to the point of saturation. On cooling there was obtained 0.43 g. (69%) of crude **1,2-benz-10-anthranyl acetate,** m. p. 130–140°, which yielded 0.33 g. (52%) of pure material, m. p. 160–163°, on crystallization from benzene–ligroin. This did not depress the melting point of the previously described sample.[4]

10-Acetoxymethyl-1,2-benzanthracene (VI).—The reaction was conducted as above at the steam-bath temperature, using 1.2 g. of 10-methyl-1,2-benzanthracene in 50 cc. of glacial acetic acid and 2.2 g. of lead tetraacetate in 50 cc. of this solvent. After fifteen minutes the solution was cooled well and diluted with two volumes of ice water. The precipitated material was collected and washed in the cold (otherwise it becomes gummy), dried in vacuum at 50°, and taken into ether–petroleum ether. An amorphous solid was obtained after concentrating the solution, and on three crystallizations from methanol the product formed pale greenish-yellow needles, m. p. 150.5–151.5°; yield, 0.25 g. (17%).

Anal. Calcd. for $C_{21}H_{16}O_2$: C, 83.98; H, 5.37. Found: C, 83.95; H, 5.53.

The substance did not depress the melting point of a sample of 10-acetoxymethyl-1,2-benzanthracene (of nearly identical m. p.) obtained from Professor J. von Braun.

Cyclization Experiments.—Following the exact procedure described[4] for the cyclization of 2-(α-naphthylmethyl)-benzoic acid, *o*-benzylbenzoic acid gave satisfactory **anthranyl-10-acetate** in 73% yield. It was not found easy to obtain material of constant melting point either from this source or from a sample prepared from anthrone; the best material melted at 134.5–135.5°. With 2-(4′-methyl-1′-naphthylmethyl)-benzoic acid[21] (5 g.), the amount of acetic anhydride was cut in half and the time of heating extended to one and one-half hours; the yield of **3-methoxy-10-acetoxy-1,2-benzanthracene,**[21] m. p. 193–194°, was 4.15 g. (86%). Two further crystallizations from glacial acetic acid gave colorless needles, m. p. 194–194.5°. Using the standard procedure,[4] γ-(3-acenaphthyl)-butyric acid[19] was converted in 78% yield into **1-keto-1′,2′,3′,4′-tetrahydro-8,9-acephenanthrene,**[19] m. p. 143–145°, and 2-(α-methylbenzyl)-1-naphthoic acid[10] (III) afforded **9-acetoxy-10-methyl-1,2-benzanthracene** (see below), m. p. 152.5–153.5°, in 95% yield.

9-Acetoxy-10-methyl-1,2-benzanthracene (IV).—Recrystallization of the cyclization product just mentioned from methanol gave small, colorless prisms, m. p. 153.5–154°. When mixed with 10-acetoxymethyl-1,2-benzanthracene the m. p. was depressed to 130–133°.

Anal. Calcd. for $C_{21}H_{16}O_2$: C, 83.98; H, 5.37. Found: C, 83.77; H, 5.33.

3-Acetoxy-10-methyl-1,2-benzanthracene.—The free hydroxy compound[4] was refluxed with acetic anhydride and fused sodium acetate and the product crystallized from methanol. It formed pale yellow prisms, m. p. 214–215°.

Anal. Calcd. for $C_{21}H_{16}O_2$: C, 83.98; H, 5.37. Found: C, 83.55; H, 5.49.

3,10-Dimethoxy-1,2-benzanthracene.—A mixture of 2.5 g. of 3-acetoxy-10-methyl-1,2-benzanthracene in 50 cc. of benzene and the Grignard reagent from 4.3 g. of *n*-butyl bromide in ether was refluxed for one hour, treated with 12 g. of dimethyl sulfate in 50 cc. of benzene, and refluxed for three hours. After hydrolysis with dilute acid a benzene solution of the product was passed through a tower of alumina to remove any hydroxy compound escaping methylation and the filtrate was evaporated. The residual material was very soluble in methanol or petroleum ether (b. p. 20–40°) and from the latter solvent it separated as transparent yellow cubes, m. p. 84–87°; yield, 1.2 g. (53%). This appeared to be a metastable form of the compound, for on being rubbed it changed to an opaque solid considerably less soluble than before. On recrystallization from ligroin (b. p. 60–70°) there was obtained 0.95 g. of light yellow, diamond-shaped prisms, m. p. 145–146.5°. Two more crystallizations from this solvent and one from methanol brought the melting point to 146–146.5°.

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(17) Cook, *J. Chem. Soc.*, 487 (1931).

(18) Cook, *ibid.*, 3273 (1931).

(19) Fieser and Peters, THIS JOURNAL, **54**, 4373 (1932).

(20) All melting points are corrected. Analyses by Mrs. G. M. Wellwood, Mrs. Verna R. Keevil, and the Arlington Laboratories.

(21) Fieser and Dietz, THIS JOURNAL, **51**, 3141 (1929).

Anal. Calcd. for $C_{20}H_{16}O_2$: C, 83.31; H, 5.60. Found: C, 83.08; H, 5.80.

9-Methoxy-10-methyl-1,2-benzanthracene.—This was prepared from the acetoxy compound IV (0.85 g.) by cleavage with the Grignard reagent from *n*-butyl bromide (1.95 g.) and methylation (8 cc. of dimethyl sulfate, several hours), as above, except that at the end of the reaction the mixture was treated with alkali and stirred for two hours and then acidified. From the benzene solution there was obtained material which after one crystallization from methanol melted at 143–144°; yield, 0.46 g. (60%). The substance formed thin, pale greenish-yellow, square plates and recrystallization did not alter the melting point.

Anal. Calcd. for $C_{20}H_{16}O$: C, 88.20; H, 5.92. Found: C, 88.11; H, 6.00.

Purification of Yellow 1,2,5,6-Dibenzanthracene.—A warm solution of 0.6 g. of lead tetraacetate in 150 cc. of glacial acetic acid was added in small portions to a solution of 3 g. of bright yellow commercial hydrocarbon in 150 cc. of benzene. The addition must be made slowly to prevent precipitation of the hydrocarbon. After refluxing for one-half hour, the solution was concentrated in the course of one hour to a volume of about 100 cc. and allowed to cool. There was obtained 2.5 g. (83%) of 1,2,5,6-dibenzanthracene in the form of colorless leaflets melting at 265–266° and having a blue fluorescence in ultraviolet light. In other experiments in this Laboratory with larger amounts of a new lot of crude hydrocarbon the recovery has been somewhat lower. On comparing samples of hydrocarbon purified and recrystallized in various ways, the best material was found to melt at 266–266.5°.

10-Amino-1,2-benzanthracene. (a) **From the Nitro Compound.**—The hydrocarbon (4.6 g.) was nitrated at room temperature according to Barnett and Matthews[7] and the crude product (2 g.) crystallized twice from alcohol (100 cc. per g.). There was obtained 1.38 g. (25%) of **10-nitro-1,2-benzanthracene,** m. p. 164–165°.

Hydrogenation of the nitro compound (1.26 g.) in ethyl acetate (75 cc.) was conducted in the presence of Adams catalyst (25 mg.), and the filtered solution was concentrated and treated with ligroin. The solid which separated afforded on recrystallization from ether–ligroin 0.6 g. (54%) of the amine in the form of yellow leaflets, m. p. 174–175°. This did not depress the melting point of the analytical sample described in the next section.

(b) **From the Hydroxy Compound.**—A mixture of 0.5 g. of 1,2-benz-10-anthranol, 5 cc. of concentrated ammonia solution, 2.5 g. of sodium bisulfite in 5 cc. of water, and 2 cc. of dioxane was heated in a sealed tube at 150° for fifty hours. After dilution with water the precipitated solid was dried in vacuum and crystallized from ether–ligroin, giving in all 0.37 g. (74%) of product melting in the range 163–168°. Three more crystallizations gave material melting constantly at 174.5–175.5°. Depending on the relative proportions of ether and ligroin, the amine separated as yellow leaflets or as long yellow needles.

Anal. Calcd. for $C_{18}H_{13}N$: N, 5.76. Found: N, 6.00.

3-(1,2-Benz-10-anthryl)-1,2-propylene Glycol Dibenzoate.—A mixture of 0.93 g. of 10-allyl-1,2-benzanthracene, 1.59 g. of silver benzoate, and 0.88 g. of iodine in 25 cc. of dry benzene was refluxed for fifteen hours on the steam-bath, the solution was filtered. concentrated, and treated with ligroin. This gave 1.5 g. (85%) of satisfactory material, m. p. 148–151°. Two further crystallizations from benzene gave clusters of fluffy, colorless needles, m. p. 152.5–153.5°.

Anal. Calcd. for $C_{35}H_{26}O_4$: C, 82.33; H, 5.13. Found: C, 82.44; H, 5.03.

?-Chloro-1,2-benz-10-anthrone(ol?).—A suspension of 1 g. of powdered 1,2-benz-10-anthranol in 10 cc. of dry ether was treated with 0.6 cc. of *t*-butyl hypochlorite and shaken for about ten minutes, when the orange solid had been converted into a yellow microcrystalline product. Collected and washed with ether, in which it is practically insoluble, the material weighed 0.87 g. (76%) and melted at about 125–130° with decomposition. After three crystallizations from ethyl acetate it melted constantly at 197–198°, dec., when inserted in a bath at 193° and heated rapidly. The substance contains chlorine and forms colorless, highly refractive prisms. It becomes yellow on storage or on being heated.

Anal. Calcd. for $C_{18}H_{18}OCl$: C, 77.58; H, 3.98. Found: C, 77.37; H, 3.94.

Dimolecular Product from 1,2-Benz-10-anthranol.[22]—The above chloro compound was converted on attempted crystallization from methanol into a sparingly soluble chlorine-free product. The same substance was obtained on shaking a suspension of 0.5 g. of 1,2-benz-10-anthranol in 20 cc. of methanol with 0.3 cc. of *t*-butyl hypochlorite for fifteen minutes and boiling the mixture for five minutes. The sparingly soluble material which precipitated (0.25 g.) on crystallization from acetic acid and from toluene formed fine, colorless needles, m. p. 261–263°, dec.

Anal. Calcd. for $C_{36}H_{24}O_2$: C, 88.49; H, 4.94. Found: C, 88.23; H, 4.73.

The substance gave no depression when mixed with the "condensation product" (m. p. 265–267°, dec.) previously described. The present method of preparation suggests that the substance is an oxidation product, and the composition, particularly as indicated by the earlier analyses, appears to be approximately that of a dianthrone (calcd. for $C_{36}H_{22}O_2$: C, 88.86; H, 4.56).

Summary

1,2-Benzanthracene reacts with lead tetraacetate to give the 10-acetoxy derivative, while with 10-methyl-1,2-benzanthracene the reagent attacks the methyl group and the product is 10-acetoxymethyl-1,2-benzanthracene. A very simple and effective method of removing the yellow impurity accompanying 1,2,5,6-dibenzanthrene prepared by the Elbs reaction consists in preferential oxidation with lead tetraacetate.

Various miscellaneous *meso*-substituted derivatives of 1,2-benzanthracene are described in this paper, and it is shown that nitration of the hydrocarbon gives the 10-nitro compound.

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[22] Ref. 4, pp. 1034–1035.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. XLI. Reduction of Naphtholic Steroids to Phenolic Steroids. Equilenin

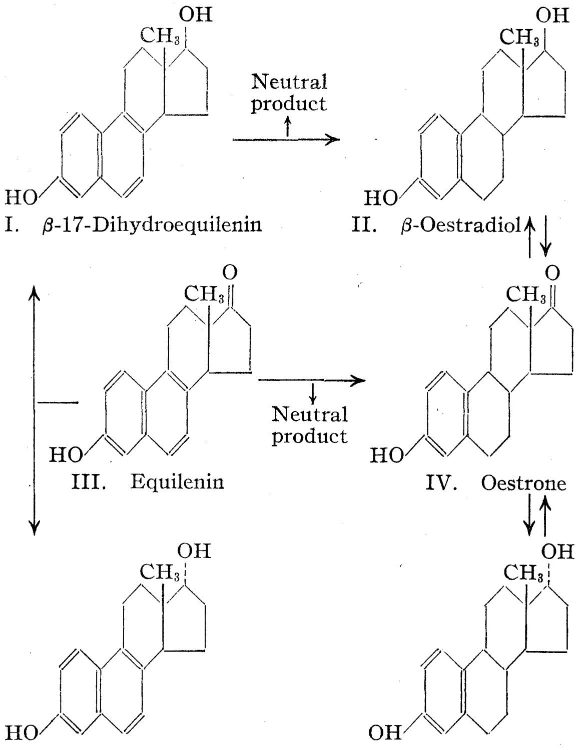
BY RUSSELL E. MARKER

Some time ago we reported the preparation of oestrone from ergosterol.[1] Although no details of the synthesis could be included in that short note, we felt that since the entire synthesis had been checked by two of us, and since the oestrone was shown to be identical in all respects with the natural hormone, no doubt could exist as to the validity of our preparation. However, soon after the appearance of our note, Windaus and Deppe[2] reported that they had been unable to duplicate our preparation of the phenolic tetrahydrodehydroneoergosterol by the reduction of dehydroneoergosterol with sodium and amyl alcohol; in fact, they claimed to find almost no phenolic products in the reduction mixture. As a result of this paper, a number of authors[3–6] have questioned our claim to have prepared synthetic oestrone.

We are now prepared to present a series of papers showing that, contrary to the claims of Windaus and Deppe, β-naphtholic steroids can be reduced to give substantial yields of phenolic steroids as well as larger amounts of neutral steroids. These reductions, which have been carried out by the same general procedure as that used to prepare the phenolic steroid used in our synthesis of oestrone, are actually an extension of the classic studies of Bamberger and co-workers,[7] studies which apparently were overlooked by Windaus.

In this paper we shall describe the reduction of equilenin and of the isomeric 17-dihydroequilenins. The accompanying chart shows the transformation involved.

Since the products sought for in the reduction experiments included oestrone derivatives, great care was taken to purify the equilenin used in this work. Equilenin, m. p. 252°, obtained by repeated crystallizations was first converted into its picrate, and then into its benzoate. Hydrolysis of the equilenin benzoate after repeated recrystallization finally gave equilenin, m. p. 257–258°, $[\alpha]^{25}\text{D} + 89°$, of very high purity.



I. β-17-Dihydroequilenin II. β-Oestradiol III. Equilenin IV. Oestrone V. α-17-Dihydroequilenin VI. α-Oestradiol

We have reported in a short note[8] that when equilenin is reduced with aluminum isopropylate and isopropyl alcohol, a mixture of α- and β-17-dihydroequilenins is formed. The β-17-dihydroequilenin, m. p. 215°, has been isolated as one component of the δ-follicular hormone, from mares' pregnancy urine, by Wintersteiner, Schwenk, Hirschmann and Whitman.[9] Since this substance does not precipitate with digitonin they suggested that it is configurationally related to β-oestradiol, for the latter, unlike α-oestradiol, also does not precipitate digitonin. Since Wintersteiner[10] has also suggested, on the basis of a com-

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[1] Marker, Kamm, Oakwood and Laucius, THIS JOURNAL, **58**, 1503 (1936).

[2] Windaus and Deppe, *Ber.*, **70**, 76 (1937).

[3] Marrian, "The Chemistry of the Oestrogenic Hormones," in "Ergebnisse der Vitamin und Hormon-forschung," Ruzicka and Stepp, Akademische Verlagsgesellschaft m. b. H., Leipzig, pp. 446 ff.

[4] Remesov, *Rec. trav. chim.*, **56**, 1093 (1937).

[5] Strain, "The Sterols and Related Compounds," in Gilman's "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1938, Chap. 15, pp. 1316 ff.

[6] Freedman, "Sterols and Related Compounds," Chemical Pub. Co., New York, N. Y., 1938.

[7] For example, Bamberger and Kitschelt, *Ber.*, **23**, 885–7 (1890), obtained *ar*-tetrahydro-β-naphthol by the reduction of β-naphthol with sodium and amyl alcohol (8% yield of purified product).

[8] Marker, Kamm, Oakwood and Tendick, THIS JOURNAL, **59**, 768 (1937).

[9] Wintersteiner, Schwenk, Hirschmann and Whitman, *ibid.*, **58**, 2652 (1936).

[10] Wintersteiner, *ibid.*, **59**, 765 (1937).

parison of physiological activities and melting points, that α-oestradiol and α-testosterone (*trans*-testosterone) are configurationally related, it follows that Wintersteiner's β-17-dihydroequilenin, m. p. 215–217°, has the structure I. We find that our β-17-dihydroequilenin, m. p. 215°, has the same properties as the natural hormone isolated by Wintersteiner; it forms a monobenzoate, m. p. 204°, and does not precipitate with digitonin. The less soluble α-17-dihydroequilenin, m. p. 248°, (V) forms a monobenzoate, m. p. 215°, and a diacetate, m. p. 124°. However, in contrast to the behavior of α-oestradiol, α-17-dihydroequilenin does not precipitate with digitonin. Tests[11] show that β-17-dihydroequilenin has an oestrogenic potency of 75–100 R. U. per mg. while the α-epimer has a somewhat greater potency, 250 R. U. per mg. Thus the two epimers are about one-fortieth to one-thirtieth, and one-twelfth as active as oestrone. This relatively low physiological activity of α-17-dihydroequilenin is contrary to the predictions of Wintersteiner, who thought he had isolated, in impure form, "α-dihydroequilenin" from mares' pregnancy urine. His product had a higher melting point than β-17-dihydroequilenin, and a high oestrogenic activity. Obviously, his product was contaminated with some highly active substance, possibly α-oestradiol. It is now evident that Wintersteiner's correlation of β-17-dihydroequilenin with β-oestradiol is correct, but his arguments—the non-precipitability with digitonin and low physiological activity of this, the lower melting epimeric 17-dihydroequilenin—have little bearing on the configuration, since the higher melting α-epimer is also not precipitated by digitonin, and also shows low oestrogenic potency. In this connection it should be emphasized that assignments of configuration based on a comparison of melting points are always to be regarded as only tentative, for the melting point relationships in a given type of epimeric steroids may be reversed by the introduction of double bonds. Thus while the melting points of *epi*-stigmastanol, *epi*-cholestanol, and similar *epi*-saturated steroids are considerably higher than for the corresponding β-epimers, this relationship is reversed in steroids of the type of cholesterol, sitosterol and stigmasterol, where the *epi*-forms melt somewhat lower than the β-forms. In most cases valid correlations of configurations can be made today only by actual chemical interconversions.

Accordingly, to establish the relationship of the 17-dihydroequilenin to the oestradiols, and to provide additional examples of the reduction of naphtholic steroids to phenolic steroids, the 17-dihydroequilenins were treated with sodium in boiling amyl alcohol according to the procedure developed by Bamberger[7] and used by us in the preparation of oestrone from dehydroneoergosterol.[1] By this method α-dihydroequilenin gave α-oestradiol, m. p. 176°, as proved by comparison of the product and its benzoate with authentic α-oestradiol and its monobenzoate. In addition, a small amount of another phenolic substance, m. p. 151–154°, was isolated in an impure state. The non-phenolic fraction from the reduction constituted the major portion of the reaction products, and yielded a substance of m. p. 172°, which will be described in a subsequent paper. Similarly, the reduction of β-17-dihydroequilenin yielded, besides larger quantities of non-phenolic material, β-oestradiol. The mother liquors, after conversion to the monobenzoate, on oxidation yielded oestrone monobenzoate. From the mother liquors of this experiment and a similar experiment using the α-epimer, a phenolic ketone, m. p. 222–225°, which analyzed for four double bonds was obtained. This may be equilin or one of its isomers. When equilenin was reduced with sodium in amyl alcohol, and the phenolic reduction product benzoylated and oxidized, oestrone benzoate was obtained.

In connection with the reduction of equilenin it should be noted that David[12] found that the action of sodium in amyl alcohol gave an oil of high oestrogenic potency. Since the 17-dihydroequilenins have very little potency it seems likely that he had also obtained reduction to phenolic substances, oestradiols, which gave his oil its high activity.

The details of our preparation of oestrone, which have been repeated many times in this Laboratory by different workers, will be reported as the last paper of this series on the reduction of naphtholic steroids.

I wish to thank Dr. Oliver Kamm and Parke, Davis & Company for their generous help and assistance in various phases of this work. I also express my thanks to Drs. Elmer J. Lawson, Eugene L. Wittle, Thomas S. Oakwood, Harry

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[11] Unpublished results from the laboratories of Parke, Davis & Co.

[12] David, *Acta brevia Neerland*, **4**, 63 (1934).

M. Crooks, Ewald Rohrmann, Frank H. Tendick and David M. Jones.

Experimental

Purification of Equilenin.—The equilenin used in this work was separated from oestrone as well as possible by crystallization to give a product melting at 252°. Five grams of this product was dissolved in benzene and an equal volume of benzene saturated with picric acid was added. The solution was evaporated to one-half volume and let stand overnight in a refrigerator. The red picrate was filtered and recrystallized from a benzene solution saturated with picric acid. The picrate was dissolved in ether and shaken with ammonia diluted with an equal volume of water until it was washed free of picric acid. The ether was evaporated and the residue after one crystallization from 60% alcohol was shaken with 300 cc. of a 10% sodium hydroxide solution. At intervals benzoyl chloride was added until an excess was present. The insoluble benzoate was filtered, washed with water and recrystallized from ethanol to a melting point of 225°. This gave a depression in melting point when mixed with oestrone benzoate, m. p. 215°.

The purified equilenin benzoate was dissolved in ethanol and hydrolyzed by refluxing with an excess of potassium hydroxide for one hour. The equilenin was recrystallized from ethanol and then melted at 257–258° (uncorr.), $[\alpha]^{25}_{D}$ +89°.

The Dihydroequilenins.—To a solution of 4 g. of purified equilenin in 70 cc. of dry isopropyl alcohol was added 4 g. of powdered aluminum isopropylate. The mixture was refluxed for five hours and then concentrated to 20 cc. by slow distillation over a five-hour period. While the mixture was still warm, 2 g. of potassium hydroxide dissolved in 60 cc. of methanol was added. The mixture was let stand for thirty minutes, and then was poured into water and acidified with hydrochloric acid. The product was extracted with ether, the solvent removed and the residue crystallized from 100 cc. of 80% ethanol. After three crystallizations a constant melting point of 248° was reached which did not increase upon further crystallization. When mixed with equilenin it gave a depression in melting point to 215°. This compound is designated as α-dihydroequilenin.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.5; H, 7.5. Found: C, 80.3; H, 7.6.

Diacetate of α-Dihydroequilenin.—α-Dihydroequilenin (100 mg.) was refluxed for thirty minutes with 5 cc. of acetic anhydride. After removal of the excess acetic anhydride, the residue was crystallized from 50% ethanol to give needles melting at 124°.

Anal. Calcd. for $C_{22}H_{24}O_4$: C, 74.9; H, 6.9. Found: C, 74.8; H, 7.0.

Monobenzoate of α-Dihydroequilenin.—α-Dihydroequilenin (25 mg.) was shaken with 6 cc. of 10% sodium hydroxide solution and an excess of benzoyl chloride for twenty minutes. The benzoate was filtered and recrystallized from ethanol; m. p. 215°.

Anal. Calcd. for $C_{25}H_{24}O_3$: C, 80.4; H, 6.7. Found: C, 80.5; H, 6.7.

β-Dihydroequilenin (δ-Follicular Hormone).—The mother liquor from the crystallization of α-dihydroequilenin was diluted while hot with water until a concentration of 50% alcohol was reached. It was allowed to cool slowly to room temperature for one hour, and the precipitate filtered. This consisted chiefly of some additional α-dihydroequilenin. The filtrate was cooled in a freezing mixture of ice and hydrochloric acid. The product was filtered and recrystallized from 50% ethanol to give a product melting at 215°, which gave a depression in melting point to 180° when mixed with α-dihydroequilenin.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.5; H, 7.5. Found: C, 80.4; H, 7.7.

Monobenzoate of β-Dihydroequilenin.—This was prepared in a way similar to that described for the α-form. It was crystallized from alcohol to a constant melting point of 204°.

Anal. Calcd. for $C_{25}H_{24}O_3$: C, 80.4; H, 6.7. Found: C, 80.4; H, 6.7.

Reduction of α-Dihydroequilenin by Sodium in Amyl Alcohol.—To a solution of 1 g. of α-dihydroequilenin, m. p. 248°, dissolved in 100 cc. of *n*-amyl alcohol (dry) was added 8 g. of sodium. The amyl alcohol was refluxed until the sodium had dissolved (two hours). Water was added, and the alkaline solution was acidified with hydrochloric acid. The product was extracted with ether, and the solvent removed *in vacuo*. The residue was dissolved in ether and the ethereal solution was washed well six times with 100-cc. portions of 2% sodium hydroxide solution. The alkaline solution was acidified and extracted with ether. The ether was evaporated and the phenolic residue was sublimed in a high vacuum at 175° bath temperature. The sublimate weighed 194 mg. A small amount of tarry phenolic material did not sublime. The sublimate was crystallized from dilute ethanol to give a product melting at 176°. This was purified only with difficulty as there was present a second phenolic product which could not be crystallized beyond 151–154° (unsharply) because of the small amount of product and some difficulty of separation. This product is being investigated further. The 176° product gave no depression in melting point when mixed with oestradiol, m. p. 178°.

The total product was converted to its monobenzoate by shaking with sodium hydroxide solution and benzoyl chloride. The product after crystallization from dilute ethanol melted at 194°. When mixed with the monobenzoate of α-dihydrooestrone it gave no depression in melting point; yield 41 mg.

Anal. Calcd. for $C_{25}H_{28}O_3$: C, 79.5; H, 7.5. Found: C, 79.5; H, 7.5.

The neutral fraction from the reduction which was not extractable with alkali from an ethereal solution was recrystallized from acetone–water to give a product melting at 172°. A study of this compound will be reported later.

Reduction of β-Dihydroequilenin with Sodium in Amyl Alcohol.—One gram of β-dihydroequilenin was reduced with sodium in amyl alcohol as described for the α-compound. The phenolic material was removed by shaking an ethereal solution of the reduced product with 2% sodium hydroxide. This phenolic fraction was sublimed in high vacuum at 175° (bath temp.) to give 205 mg. of sublimate.

As there was present in the sublimate a product other than β-dihydrooestrone, separation by direct crystallization could not be accomplished. The total product was converted into the benzoate by shaking with sodium hydroxide and benzoyl chloride. This was crystallized from dilute ethanol to give a substance of indefinite melting point; upon hydrolysis of this product with potassium hydroxide in ethyl alcohol a product was obtained which after crystallization from dilute ethanol gave a melting point of 215–219°. When this substance was mixed with β-dihydrooestrone, m. p. 222°, no depression in melting point was observed. Only 11 mg. of this product was obtained. It gave a depression in melting point of 24° when mixed with β-dihydroequilenin, m. p. 215°.

The total mother liquors from this product was converted again into the benzoate and this was oxidized with 40 mg. of chromic oxide in acetic acid for one hour. Water was added and the product extracted with ether and washed with water and sodium carbonate solution. After removal of the ether, the residue was dissolved in 50 cc. of ethanol and refluxed for thirty minutes with 1 g. of Girard's reagent. Water and ether were added, the layers separated and the aqueous layer heated on a steam-bath for a few minutes with an excess of hydrochloric acid. The ketonic material was extracted with ether, and the residue after removal of the ether was hydrolyzed with alcoholic potassium hydroxide. The product thus obtained was sublimed in high vacuum at 160°. From the sublimate after crystallization from ethanol was obtained 28 mg. of oestrone, m. p. 255°. When it was mixed with authentic oestrone it showed no depression in melting point.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.9; H, 8.2. Found: C, 79.9; H, 8.3.

The mother liquors of this gave a product which after several crystallizations from dilute ethanol melted unsharply at 222–225°. This gave a depression in melting point when mixed with both oestrone and equilenin. The same product was obtained by the oxidation of the mother liquors from the α-dihydrooestrone obtained from the reduction of α-dihydroequilenin. This gave an analysis for a compound more unsaturated than oestrone, and is being studied further.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.5; H, 7.5. Found: C, 80.3; H, 7.5.

Reduction of Equilenin by Sodium in Amyl Alcohol.—One gram of equilenin was reduced by sodium in amyl alcohol as described for dihydroequilenin. The phenolic product of reduction was distilled in high vacuum, giving 123 mg. of distillate. This was converted to the benzoate and oxidized by chromic acid to give 31 mg. of oestrone after hydrolysis. It melted at 250–251°, and gave no depression in melting point when mixed with oestrone.

Reduction of Oestrone Benzoate with Aluminum Isopropylate.—To a solution of 500 mg. of oestrone benzoate dissolved in 20 cc. of dry isopropyl alcohol was added 1 g. of aluminum isopropylate and the reduction was carried out as described for the reduction of equilenin. The product which was obtained was dissolved in 25 cc. of ethanol and a solution of 2 g. of digitonin in 100 cc. of 65% alcohol was added. After standing overnight, the digitonide was filtered and washed with 70% ethanol. This after drying was warmed with pyridine on a steam-bath for thirty minutes. After removal of the pyridine and digitonin the product was crystallized from dilute ethanol and then melted at 195°. Upon hydrolysis it gave oestradiol of m. p. 178°.

The mother liquors from the digitonide of the α-form were concentrated to a small volume and shaken with water and ether. The ethereal solution was filtered and concentrated. The residue was hydrolyzed with alcoholic potassium hydroxide and gave after crystallization from dilute ethanol a product melting at 222°, which was β-oestradiol as shown by mixed melting points.

Summary

The reduction of equilenin by aluminum isopropylate gives a mixture of α- and β-dihydroequilenin which can be separated readily by crystallization. The latter compound is identical with the δ-follicular hormone. Upon reduction of either isomeric dihydroequilenin by sodium in amyl alcohol about 20% of phenolic substances are formed and from the α-form is obtained α-oestradiol whereas the β-dihydroequilenin yields β-oestradiol. Both yield about 75% of nonphenolic products which are being studied.

STATE COLLEGE, PENNA. RECEIVED JUNE 15, 1938

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. XLII. The Isolation of Oestranediols from Human Non-Pregnancy Urine

BY RUSSELL E. MARKER, EWALD ROHRMANN, ELMER J. LAWSON AND EUGENE L. WITTLE

In an earlier paper in this series[1] it has been proposed that the numerous steroids present in urines and glandular extracts arise by reductive processes in the course of utilization of the sex and cortical hormones. On the basis of new experimental information to be presented in this paper, it now appears that the oestrogenic hormones suffer these same reductive processes when they are utilized as hormones in the non-pregnant woman, for from the urines of such subjects we have isolated two isomeric oestranediols.[2]

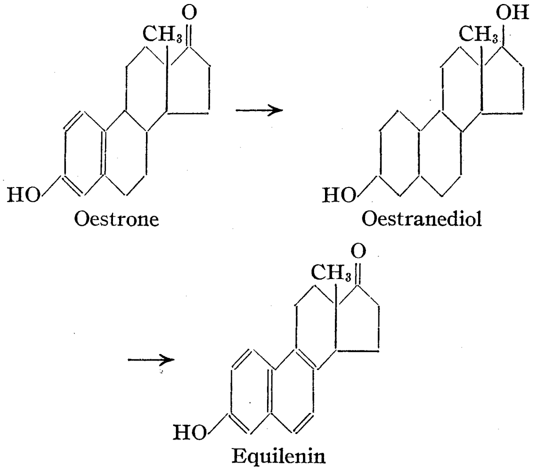

Fig. 1.

The mode of isolation of these diols was essentially the same as that described in earlier papers. Two hundred gallons (755 liters) of non-pregnancy human urine was extracted with butanol, and hydrolyzed with acid and alkali to yield a neutral fraction which was separated by means of succinic anhydride and Girard's reagent into carbinols, ketones, and inert substances. The carbinol fraction, corresponding to 40 mg. per gallon of urine, was treated with digitonin to separate the 3-βOH and 3-αOH sterols. The 3-βOH sterol fraction proved to be mainly cholesterol. From the carbinol fraction not precipitable by digitonin two alcohols, $C_{18}H_{30}O_2$, m. p. 242 and 204°, were isolated by fractional crystallization after removal of a small amount of pregnanediol. The structures of these diols as stereoisomeric oestranediols are proved by the following facts. Both diols form diacetates melting at 160° which show a decided depression in admixture. Both diols, when heated with platinum black, are dehydrogenated to give equilenin, although in poor yields because of the polymerization of the latter to equilenin red. Furthermore, the catalytic hydrogenation of oestrone in alcoholic solution containing a little hydrochloric acid[3] gives an oestranediol, m. p. 205°, identical with oestranediol-B, m. p. 204°. Since this oestranediol yields a different diketone, 170°,[3a] from the diketone, m. p. 124°, formed by oestranediol-A the two carbinols must differ at least in regard to their configuration at C_5 or C_{10}. Ample opportunity for isomerism is of course possible since the reduction of oestrone generates new asymmetric centers at C_3, C_5, and C_{10}. We have, indeed, indications of the presence of other possibly isomeric carbinols in the mother liquors from which the diols were isolated. Neither oestranediol-A, nor the less abundant and more soluble oestranediol-B, precipitates with digitonin, but this cannot be taken as indicating that these diols contain 3-αOH groups, for neither neoergosterol nor *epi*-neoergosterol form insoluble digitonides,[4] apparently, the presence of an angular methyl group at C_{10} is essential for the formation of insoluble digitonides.

The isolation of these stereoisomeric oestranediols from the urine of non-pregnant women throws considerable light on the manner of utilization of oestrone when it functions as a hormone in the organism. Large quantities of oestrone are excreted by the pregnant woman, probably because the hormone is not being utilized while the oestrus cycle is suspended. During this same period, however, no appreciable amount of progesterone is excreted for the latter is being used to control the development of pregnancy; instead large quantities of carbinols and ketones, which are reduction products of progesterone, are elimi-

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(1) Marker, THIS JOURNAL, **60**, 1725 (1938).

(2) The name oestrane for the saturated hydrocarbon related to oestrone has been suggested by Adam, Danielli, Dodd, King, Marrian, Parkes and Rosenheim, *Nature*, **132**, 205 (1933).

(3) Dirscherl, *Z. physiol. Chem.*, **239**, 53 (1936).

(3a) The value of 148° reported in Sterols XXXIV, THIS JOURNAL, **60**, 1512 (1938), should be 170°.

(4) Unpublished observations in this Laboratory.

nated. In the mature non-pregnant female, on the other hand, oestrone is being utilized to control the oestrus cycle, so almost none of this hormone is excreted in the urine;[5] instead, its reduction products, the oestranediols formed in the course of utilization of the hormone are excreted. In complete harmony with these facts is the small amount of pregnanediols in non-pregnancy urine. Furthermore, the oestranediols are not present in pregnancy urine, for their relative ease of isolation makes it highly improbable that they could have been overlooked in our extensive investigation of its steroid fraction.[6]

The presence of the oestranediols in non-pregnancy urine but not in pregnancy urine shows that they are formed, not by merely enzymatic processes, but in the actual utilization of oestrone. This view is supported by the results of some experiments on the enzymatic reduction of oestrone by the methods of Mamoli, Vercellone and Ercoli.[7] Enzyme extracts of hog ovaries, beef suprarenal glands and bull testes were mixed with oestrone and allowed to stand for thirty days. In none of these cases was any reduction product formed, the oestrone being recovered unchanged.

The investigation of steroids from non-pregnancy urine is being continued on a much larger scale. We wish to thank Dr. Oliver Kamm and Parke, Davis & Company for their generous help and assistance in various phases of this work. The micro-analyses were done by Dr. George H. Fleming of this Laboratory.

Experimental Part

Isolation of Total Sterol Fraction.—Two hundred gallons (756 liters) of human non-pregnancy urine was extracted thoroughly with butanol before hydrolysis. The aqueous portion was then hydrolyzed by heating with hydrochloric acid, and after hydrolysis this was again thoroughly extracted with butanol. The butanol was evaporated *in vacuo* from both extracts and the products worked up separately.

The product from the extraction of the non-hydrolyzed urine was heated on a steam-bath with 5 kg. of sodium hydroxide dissolved in 20 liters of water for one hour, then steam distilled until no more volatile material came over. This required six hours. The residue remaining in the flask was thoroughly extracted with ether, and the solvent evaporated. The residue was rehydrolyzed with alcoholic potassium hydroxide, and the neutral product so obtained weighed 17 g. after removal of the solvent.

The residue was dried by distillation with benzene. To this was added 25 g. of succinic anhydride and 50 cc. of pyridine and the mixture was heated for one hour on a steam-bath. Ice and ether were added and the pyridine was removed by shaking with dilute hydrochloric acid. The succinic esters were then removed from the ether solution by shaking with sodium carbonate solution. The aqueous layer was acidified and the succinic esters of the carbinols were extracted with ether. The ether was evaporated and the residue was hydrolyzed by heating with an excess of alcoholic potassium hydroxide solution. The hydrolyzed carbinol fraction weighed 8 g. after removal of the solvent. This residue was dissolved in 100 cc. of ethyl alcohol and 5 g. of Girard's reagent was added. The solution was heated for twenty minutes on a steam-bath, water was added and the product was well extracted with ether. The aqueous layer upon heating with hydrochloric acid gave only a small amount of ketones which were reserved for future investigation. The solvent was removed from the ethereal extract from the Girard's reagent treatment and the residue was dissolved in a small amount of ethyl alcohol. To this was added 250 cc. of a 2% digitonin solution in 90% ethyl alcohol, and the mixture allowed to stand overnight. The digitonide was filtered and dried. It gave 3.7 g. of digitonide which upon hydrolysis gave mainly cholesterol. The alcohol was distilled from the filtrate from the digitonide and the residue was thoroughly extracted with ether and filtered. The ether was evaporated giving a residue weighing 5 g.

The sterol fraction from the acid hydrolyzed fraction of the non-pregnancy urine was worked up to this point in a similar manner. This fraction was similar to the other in all respects, except that the cholesterol content appeared to be less. Four grams of carbinols remained after removal of the cholesterol, ketones and non-carbinol material.

Oestranediol-A.—The above sterol fractions were sublimed separately using a mercury vapor pump and the fraction subliming at 110–135° was collected over a period of twenty hours. The distillates upon cooling in acetone gave in both cases a crude crystalline product melting at 200–210° which did not depress in melting point when mixed, so the total distillates, weighing 3.9 g., were combined. This was dissolved in 15 cc. of acetone, cooled overnight in a refrigerator and then filtered. This fraction was principally pregnanediol. The filtrate was cooled in a mixture of ice and hydrochloric acid for two hours. The crystalline product was filtered and the mother liquors reserved for future investigation.

The crystalline material (1.2 g.) was recrystallized from acetone to give a substance of a constant melting point 242°; yield 295 mg. This, when pure, is quite insoluble in acetone and can also be crystallized from a mixture of benzene and ligroin. It gave a depression in melting point of 30° when mixed with pregnanediol and 25° when mixed with *allo*-pregnanediol.

Anal. Calcd. for $C_{18}H_{30}O_2$: C, 77.6; H, 10.9. Found: C, 77.4; H, 10.8.

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(5) Loews and Lange, *Klin. Wochr.*, **5**, 1038 (1926), found very little oestrogenic activity in concentrates from non-pregnancy urine.

(6) At present we have worked over the steroid fraction of over 100,000 gallons (378,000 liters) of human pregnancy urine, whereas the oestranediols are easily isolated from small amounts of non-pregnancy urine.

(7) Mamoli and Vercellone, *Z. physiol. Chem.*, **245**, 93 (1937); *Ber.*, **70B**, 470 (1937); Vercellone and Mamoli, *Z. physiol. Chem.*, **248**, 277 (1937); Ercoli and Mamoli, *Ber.*, **71**, 156 (1938); Ercoli, *Ber.*, **71**, 650 (1938).

Diacetate of Oestranediol-A.—A solution of 25 mg. of oestranediol-A in 5 cc. of acetic anhydride was refluxed for thirty minutes. The acetic anhydride was evaporated and the residue was recrystallized from methanol to a constant melting point of 160°.

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.9; H, 9.5. Found: C, 73.2; H, 9.7.

Oestranedione-A.—To a solution of 50 mg. of oestranediol-A in 20 cc. of acetic acid was added 40 mg. of chromic anhydride in 5 cc. of 90% acetic acid. After standing at room temperature for one hour, water was added and the product was extracted with ether. The ethereal solution was freed of acids by shaking with water and 2% sodium hydroxide solution, and evaporated. The residue was sublimed in high vacuum and the fraction distilling at 120° was recrystallized from 50% acetone to give 36 mg. of oestranedione-A, m. p. 124°.

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.8; H, 9.5. Found: C, 79.2; H, 9.8.

Equilenin from Oestranediol-A.—A mixture of 150 mg. of oestranediol-A and 100 mg. of platinum black was melted in a stream of nitrogen. The temperature was then lowered to 215–225° and kept there for one hour, during which time bubbles of hydrogen were given off. The product was dissolved in ether and filtered. The ether was evaporated and the residue dissolved in 10 cc. of benzene. To this was added 10 cc. of a benzene solution saturated with picric acid and the solution concentrated to 10 cc. After standing in a refrigerator overnight the red crystalline picrate was collected and dissolved in ether. The ether solution was shaken with ammonia diluted with an equal volume of water until the color of picric acid was no longer present. The ether solution was then shaken with 5% sodium hydroxide solution. The alkaline solution was acidified and the product was filtered and washed with water. It was recrystallized from 50% alcohol to give 14 mg. of a product melting at 247–249°, giving a bright red color characteristic of equilenin when melted in the presence of oxygen. It gave no depression in melting point when mixed with an authentic sample of equilenin, m. p. 256°. It gave a depression in melting point to 233° when mixed with oestrone.

Oestranediol-B.—The mother liquors from the crystallization of oestranediol-A were concentrated to about 20 cc. and cooled in a refrigerator overnight. The crystalline material was filtered and the filtrate was evaporated to about 10 cc. and cooled in ice–hydrochloric acid mixture. The crystalline product was filtered and crystallized from benzene–ligroin mixture. It was then crystallized from acetone to a constant melting point of 204°, yield 43 mg.

A sample of octahydro-oestrone was prepared by the method of Dirscherl[3] by the catalytic reduction of oestrone in alcoholic–hydrochloric acid solution using platinum oxide as a catalyst. This melted at 204–205°, and gave no depression in melting point when mixed with oestranediol-B isolated from non-pregnancy urine. Oestranediols-A and -B gave a depression in melting point when mixed with each other.

Anal. Calcd. for $C_{18}H_{30}O_2$: C, 77.6; H, 10.9. Found: C, 77.6; H, 10.8.

Diacetate of Oestranediol-B.—A solution of 25 mg. of oestranediol-B in 5 cc. of acetic anhydride was refluxed for thirty minutes. The acetic anhydride was evaporated and the residue was crystallized from methanol to a constant melting point of 160°.

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.9; H, 9.5. Found: C, 72.8; H, 9.5.

Oestranedione-B.—A solution of 30 mg. of oestranediol-B (prepared by the reduction of oestrone) was oxidized by 30 mg. of chromic anhydride as described for oestranediol-A. The product was sublimed *in vacuo* and the sublimate was recrystallized from 50% acetone to a melting point of 170°.

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.8; H, 9.5. Found: C, 79.0; H, 9.6.

Equilenin from Oestranediol-B.—One hundred and fifty mg. of oestranediol-B (from oestrone) was dehydrogenated as described for oestranediol-A. The product was isolated and purified as described before. It melted at 247° with the formation of a red color. Mixed with equilenin of known purity its melting point was raised to 250–254°. Mixed with oestrone it depressed to 230°.

Attempted Enzymatic Reduction of Oestrone.—Fresh hog ovaries were autolyzed according to the procedure used by Mamoli with stallion testes.[7] Three hundred cc. of the resulting extract (equivalent to 150 g. of ovaries) was mixed with 200 mg. of oestrone and the mixture was allowed to stand at 37° with frequent shaking for a period of thirty days. Then the mixture was extracted with ether, the solvent was evaporated to a volume of 50 cc. and washed with a 5% sodium hydroxide solution. The separated aqueous washings were then acidified with hydrochloric acid and the crystalline precipitate filtered, thoroughly washed with water and dried. The weight of the dried precipitate was 140 mg. It melted at 240–250° and showed no depression in melting point with an authentic sample of oestrone.

Similar results were obtained with extracts from suprarenal glands of beef, and bull testes.

Summary

Two stereoisomeric oestranediols have been isolated from non-pregnancy urine. The occurrence of these oestranediols in non-pregnancy urine but not in pregnancy urine indicates that they are formed by non-enzymatic reductive processes in the course of utilization of oestrone as a hormone.

STATE COLLEGE, PA. RECEIVED JUNE 15, 1938

[Contribution from the School of Chemistry and Physics of the Pennsylvania State College]

Sterols. XLIII. The 3(β)-Hydroxysteroids in Human Pregnancy Urine

By Russell E. Marker, Stephen B. Binkley, Eugene L. Wittle and Elmer J. Lawson

On the basis of a theory of the origin and interrelationships of the sex and cortical steroids[1] we have predicted the absence in glandular extracts and urines of 3(β)-hydroxy saturated steroids of the coprostanol type. The absence of this type of steroid from mare pregnancy urine already has been reported.[2] As further verification of this prediction, we are now able to report the absence of this type of steroid in human pregnancy urine. Our examination of the 3(β)-hydroxy steroid fraction from 1000 gallons (3780 liters) of human pregnancy urine has revealed the presence, in more than mere traces, of only cholesterol (4 mg. per gallon) and *allo*-pregnanediol-3(β),20(α) (1–1.5 mg. per gallon).

The carbinol fraction of 1000 gallons (3780 liters) of human pregnancy urine from which pregnanediol-3(α),20(α), and *allo*-pregnanediol-3(α),20(α) had been removed was treated with digitonin solution to isolate the 3(β)-hydroxysteroids. The 3(β)-hydroxysteroid fraction thus obtained was distilled and the fraction subliming up to a bath temperature of 170° was investigated. (The residue which did not distil, consisting of triols, tetrols and so forth, was too small to warrant investigation.) The distillate, consisting of mono- and dihydroxy steroids was separated into a saturated and unsaturated steroid fraction, making use of the fact that the unsaturated sterol dibromides do not precipitate with digitonin. Crystallization of the unsaturated sterol fraction yielded cholesterol, and an examination of the mother liquors from this showed the presence of only small amounts of other substances. Similarly, the saturated sterol fraction proved to be almost entirely *allo*-pregnanediol-3(β),20(α). To prove the absence of pregnanediol-3(β),20(α) and similar coprostanol derivatives, the sterols in the mother liquors from the isolation of *allo*-pregnanediol-3(β),20(α) were epimerized with sodium in boiling xylene, the cholestanol derivatives precipitated with digitonin, and the filtrate examined for the presence of *epi*-coprostanol type derivatives, but none were found present.

We wish to thank Dr. Oliver Kamm and Parke, Davis & Company for their generous help and assistance in various phases of this work.

Experimental Part

The carbinol fraction from 1000 gallons (3780 liters) of human pregnancy urine after removal of the preganediol, *allo*-pregnanediol and ketones was dissolved in a small amount of ethyl alcohol. To this was added a solution of 40 g. of digitonin in 2 liters of 90% ethyl alcohol. It was allowed to stand overnight; then the insoluble digitonide was filtered and washed with ethyl alcohol until colorless. After drying it weighed 38 g.

The digitonide was decomposed by heating for thirty minutes on a steam-bath with 150 cc. of pyridine and pouring into 2 liters of ether. The digitonin was filtered and the pyridine was removed by washing with hydrochloric acid. The ether was evaporated, giving a residue of 9.8 g. of sterols. This residue was sublimed *in vacuo* up to 170° using a mercury vapor pump for forty hours. Only mono- and dihydroxysterols distil up to this temperature. The distillate, weighing 7.0 g., was dissolved in 500 cc. of ethyl alcohol, cooled to 0° and enough bromine added to give a permanent yellow color. Then an excess of a 1% solution of digitonin in 90% alcohol was added. After standing overnight, the digitonide was filtered. Upon drying this weighed 6.4 g. From the filtrate was obtained, after debromination with zinc dust, 3.2 g. of cholesterol. The filtrate contained a considerable amount of cholesterol in addition to some other unsaturated steroids in smaller amounts. The insoluble digitonide was decomposed by pyridine as previously described. Upon crystallizing the liberated sterol from acetone, 0.8 g. of a product was obtained melting at 216°, which gave no depression in melting point when mixed with *allo*-pregnanediol-3(β),20(α) (m. p. 216°).

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.8; H, 11.3. Found: C, 79.9; H, 11.4.

Oxidation of this gave *allo*-pregnanedione of m. p. 200° which showed no depression in melting point when mixed with a known sample.

To see whether the filtrate from the *allo*-pregnanediol-3-(β),20(α) contained any carbinols of the pregnane series with β-OH groups in the 3-position, the residue after evaporation of the solvent was epimerized by refluxing for nine hours with 5 g. of sodium in 100 cc. of xylene. The sodium was destroyed with aqueous alcohol and the product was extracted with ether. The solvent was removed and the residue dissolved in a small amount of alcohol. An excess of digitonin in 90% alcohol was added, and after standing overnight the digitonide was filtered. The alcohol was removed from the filtrate and the residue was extracted for twenty-four hours with ether. No residue remained after evaporating the ethereal solution, showing that all of the sterols in human pregnancy urine precipi-

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(1) Marker, This Journal, **60**, 1725 (1938).

(2) Marker, Rohrman and Wittle, *ibid.*, **60**, 1561 (1938).

table by digitonin and containing one or two hydroxyl groups are either unsaturated sterols or belong to the *allo*-saturated series, with none of the regular pregnane series present.

Summary

Cholesterol and *allo*-pregnanediol-3(β),20(α) were isolated from the digitonin precipitable fraction of human pregnancy urine sterols. No mono- or dihydroxy-steroids of the pregnane configuration at C-5 with 3(β)-OH groups were found present.

STATE COLLEGE, PENNA. RECEIVED JUNE 15, 1938

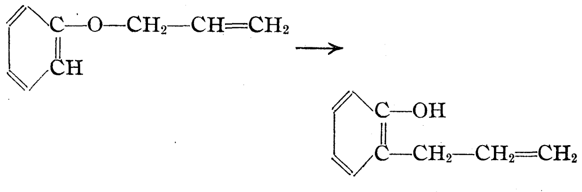
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Rearrangement of Vinyl Allyl Ethers

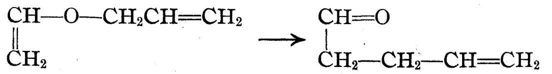
BY CHARLES D. HURD AND MAXWELL A. POLLACK

That phenyl allyl ether undergoes thermal rearrangement into *o*-allylphenol has been known for several years. Recent investigations have demonstrated the intramolecular nature of the process,[1] the inversion of the allyl group,[2] the failure of α,α-disubstituted allyl ethers to rearrange,[3] and the unusual rearrangement of γ-ethylallyl phenyl ether.[4]

That part of the aryl allyl ethers which is concerned in the rearrangement possesses the skeleton C═C—O—C—C═C



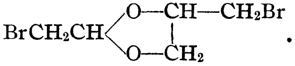
There is no previous mention in the literature of vinyl allyl ether, the simplest compound to possess this structure. It seemed important, therefore, to prepare it so that its pyrolytic behavior might be studied. If a comparable rearrangement occurred, allylacetaldehyde would be anticipated.



$$CH_2{=}CH{-}O{-}CH_2CH{=}CH_2 \longrightarrow CH(=O){-}CH_2{-}CH_2{-}CH{=}CH_2$$

The enol modification of this aldehyde, $CH_2{=}CH{-}CH_2{-}CH{=}CHOH$, would be analogous to the *o*-allylphenol.

Since neither vinyl allyl ether nor any of its simple analogs are known, several synthetical approaches were tested. One of these methods consisted in the condensation between allyl bromoacetal and sodium. A similar reaction had been employed successfully by Wislicenus[5] in the preparation of vinyl ethyl ether: $BrCH_2CH(OC_2H_5)_2 + Na \longrightarrow CH_2{=}CHOC_2H_5 + NaBr + C_2H_5ONa$, but in the present adaptation, the yield was trivial. When only one-fifth of the theoretical amount of sodium was added to the acetal, the reaction mixture became a thick brown mass, to which further addition of alkali metal proved ineffectual. No improvement was realized with xylene as solvent. Somewhat similar results were obtained by Hibbert and Hill[6] from the reaction between sodium and 3-bromo-1,2-propanediol bromoacetal,



$$BrCH_2CH\langle{}^{O-CH-CH_2Br}_{O-CH_2}$$

Another procedure tried was related to the last step in Boord's[7] synthesis of α-olefins from β-bromo ethers: $BrCH_2CHROC_2H_5 + Zn \longrightarrow CH_2{=}CHR + BrZnOC_2H_5$. Here again, however, the analogy was misleading for only slight yields of vinyl allyl ether were obtained following the action of zinc on allyl bromoacetal, $BrCH_2CH(OC_3H_5)_2$. With no solvent, very little reaction occurred below 148°, and above that temperature the violence of reaction led to the formation of a black tar. When boiling alcohol was used as a medium, it was found that the rate of reaction was very slow, only a small amount of ether being obtained in six hours.

Another approach to the synthesis of this material was based on the fact that enol ethers may be prepared by heating certain ketals in the presence of an acid catalyst.[8] When allyl acetal was heated with a trace of *p*-toluenesulfonic acid, a small amount of vinyl allyl ether was obtained, but most of the material remained unreacted.

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(1) Hurd and Schmerling, THIS JOURNAL, **59**, 107 (1937).

(2) Claisen and Tietze, *Ber.*, **58**, 275 (1925).

(3) Claisen and co-workers, *J. prakt. chem.*, **105**, 67 (1922); Hurd and Cohen, THIS JOURNAL, **53**, 1919 (1931).

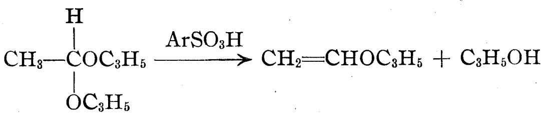
(4) Lauer and Filbert, *ibid.*, **58**, 1388 (1936).

(5) Wislicenus, *Ann.*, **192**, 106–112 (1879).

(6) Hibbert and Hill, THIS JOURNAL, **45**, 746 (1923).

(7) Dykstra, Lewis and Boord, *ibid.*, **52**, 3401 (1930).

(8) Johannissian and Akunian, *Bull. univ. etat R. S. S.-Armenie* No. **5**, 245–249 (1930); *C. A.* **25**, 921 (1931); Killian, Hennion and Nieuwland, THIS JOURNAL, **57**, 544 (1935).



$$CH_3\text{—}\overset{H}{\underset{OC_3H_5}{C}}OC_3H_5 \xrightarrow{ArSO_3H} CH_2\text{=}CHOC_3H_5 + C_3H_5OH$$

Killian, Hennion and Nieuwland were unable to obtain vinyl ethers by similar treatment of ethyl and propyl acetals.

One method which was found to be fairly serviceable involved heating allyl acetal with phosphorus pentoxide in a solvent such as quinoline or dimethylaniline.

$$CH_3CH(OC_3H_5)_2 + P_2O_5 \longrightarrow CH_2\text{=}CH\text{—}O\text{—}C_3H_5 + 2HPO_3$$

Yields of 12–19% were obtained. Claisen[9] used this general method in 1898 in preparing vinyl ethyl ether.

The best synthesis of vinyl allyl ether was found to be the reaction between β-bromoethyl allyl ether and powdered potassium hydroxide. A 51% yield was realized.

$$BrCH_2CH_2OCH_2CH\text{=}CH_2 + KOH \longrightarrow CH_2\text{=}CHOCH_2CH\text{=}CH_2 + KBr + H_2O$$

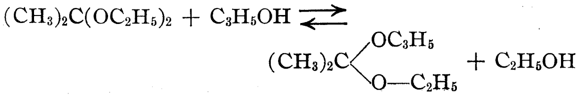
Bromoethyl allyl ether was prepared for this purpose by condensing the sodium salt of ethylene glycol with allyl bromide (77–81% yields), and treating the resulting β-hydroxyethyl allyl ether in pyridine with phosphorus tribromide.

$$HOCH_2CH_2ONa + BrCH_2CH\text{=}CH_2 \longrightarrow HOCH_2CH_2OCH_2CH\text{=}CH_2 \xrightarrow{PBr_3} BrCH_2CH_2OCH_2CH\text{=}CH_2.$$

Yields of 35–45% were obtained in this last reaction. There was considerable splitting of the ether during this treatment, which accounted for the low yield.

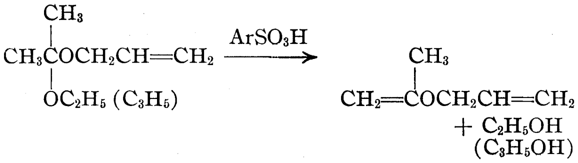
It will be recalled that the attempts to prepare vinyl allyl ether from allyl acetal were unsuccessful. A similar reaction with allyl dimethylketal, however, yielded acceptable quantities of α-methylvinyl allyl ether. For this synthesis, ethyl dimethylketal, $(CH_3)_2C(OC_2H_5)_2$, was required. It was obtained readily when acetone was condensed with ethyl orthoformate and ethyl alcohol in the presence of *p*-toluenesulfonic acid. When this ketal was heated for a few minutes with an excess of allyl alcohol and the same catalyst, an interchange of groups occurred and allyl dimethylketal was isolable from the reaction mixture in 38% yield. A smaller amount (12%) of the mixed ketal was also obtained.

$$(CH_3)_2C(OC_2H_5)_2 + 2C_3H_5OH \xrightleftharpoons{ArSO_3H} (CH_3)_2C(OC_3H_5)_2 + 2C_2H_5OH$$



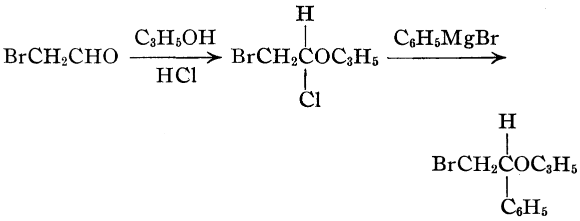
$$(CH_3)_2C(OC_2H_5)_2 + C_3H_5OH \rightleftharpoons (CH_3)_2C\begin{smallmatrix}OC_3H_5\\ O\text{—}C_2H_5\end{smallmatrix} + C_2H_5OH$$

When either of these allyl dimethylketals was distilled slowly from *p*-toluenesulfonic acid, α-methylvinyl allyl ether was obtained.



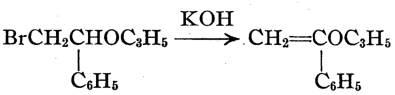
$$CH_3\overset{CH_3}{\underset{OC_2H_5\,(C_3H_5)}{C}}OCH_2CH\text{=}CH_2 \xrightarrow{ArSO_3H} CH_2\text{=}\overset{CH_3}{C}OCH_2CH\text{=}CH_2 + C_2H_5OH\ (C_3H_5OH)$$

The work of Boord and Lauer and their coworkers[10] on the preparation of vinyl ethers was adapted to this synthesis. α-Chloro-β-bromoethyl allyl ether, prepared by allowing dry hydrogen chloride and allyl alcohol to react with a mixture of bromoacetaldehyde and its trimer, was condensed with phenylmagnesium bromide. In this way, α-phenyl-β-bromoethyl allyl ether was formed.



$$BrCH_2CHO \xrightarrow[HCl]{C_3H_5OH} BrCH_2\overset{H}{\underset{Cl}{C}}OC_3H_5 \xrightarrow{C_6H_5MgBr} BrCH_2\overset{H}{\underset{C_6H_5}{C}}OC_3H_5$$

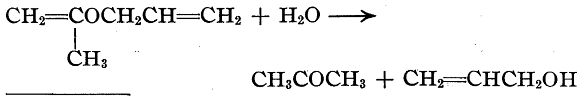
When it was heated with powdered potassium hydroxide, α-phenylvinyl allyl ether was produced.



$$BrCH_2\underset{C_6H_5}{C}HOC_3H_5 \xrightarrow{KOH} CH_2\text{=}\underset{C_6H_5}{C}OC_3H_5$$

Acid Hydrolysis of the Vinyl Ethers.—It is known[11] that allyl ethers hydrolyze readily when exposed to aqueous solution of acid. The three new vinyl ethers were also subjected to acid hydrolysis for purposes of characterization. Acetaldehyde, acetone and acetophenone were formed in turn.

$$CH_2\text{=}CHOCH_2CH\text{=}CH_2 + H_2O \xrightarrow{HCl} CH_3CHO + CH_2\text{=}CHCH_2OH$$



$$CH_2\text{=}\underset{CH_3}{C}OCH_2CH\text{=}CH_2 + H_2O \longrightarrow CH_3COCH_3 + CH_2\text{=}CHCH_2OH$$

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[9] Claisen, *Ber.*, **31**, 1021 (1898).

[10] Swallen and Boord, THIS JOURNAL, **52**, 651 (1930); Dykstra, Lewis and Boord, *ibid.*, **52**, 3396 (1930); Lauer and Spielman, *ibid.*, **53**, 1533 (1931).

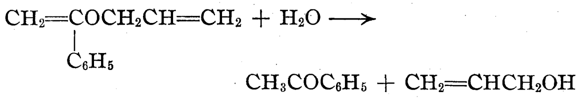
[11] Lauer and Spielman, *ibid.*, **53**, 1533 (1931).

TABLE I

PROPERTIES OF NEW COMPOUNDS

Compound	B. p., °C.	Press., mm.	n^{20}_D	d^{20}_4	Mol. ref. Found	Mol. ref. Calcd.
Vinyl allyl ether	65.0–65.2	733	1.4115	0.805	25.98	26.00
α-Methylvinyl allyl ether	87.5–88.0	745	1.4191	0.808	30.67	30.62
α-Phenylvinyl allyl ether	104–105	12	1.5402	1.007	49.91	50.34
β-Hydroxyethyl allyl ether	63–64	18–19	1.4356	0.958	27.84	27.99
β-Bromoethyl allyl ether	68.5–69.0	36	1.4668	1.336	34.22	34.23
α-Phenyl-β-bromoethyl allyl ether	129–130	12	1.5421	1.299	58.40	58.61
Allyl acetal[a]	148–149	753	1.4242	0.877	41.41	41.50
Allyl dimethylketal	61	26	1.4254	.870	45.93	46.11
Ethyl allyl dimethylketal	43–45	26	1.4090	.852	41.85	41.96
Allyl bromoacetal	102–104	23	1.4729	1.269	48.86	49.38
Allylacetaldehyde	103–104	749	1.4191	0.852	24.92	24.83

[a] Nieuwland and co-workers, THIS JOURNAL, **45**, 1552 (1923), and **52**, 2892 (1930), obtained materials with the boiling points of 162° (atm.) and 90–93° (16 mm.), n^{28}_D 1.4351, which he considered to be allyl acetal. However, in view of the discrepancies between these values and the ones found here, and the fact that no other constants or analyses were given by Nieuwland, it seems possible that the material obtained by him either was not the acetal or was a very impure sample.

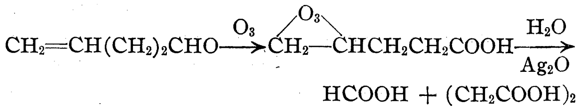


$$\mathrm{CH_2{=}\underset{\substack{|\\ C_6H_5}}{C}OCH_2CH{=}CH_2 + H_2O \longrightarrow CH_3COC_6H_5 + CH_2{=}CHCH_2OH}$$

Pyrolysis of the Ethers.—Heating in the liquid phase to 200–250° is the general method of bringing about the rearrangement of aryl allyl ethers into phenols. Whether or not vapor phase heating of vinyl allyl ether, necessitated by the low boiling point of the latter, would be comparable, could not be predicted. It was found, however, that the anticipated rearrangement into allylacetaldehyde occurred to the extent of 40–50% at 255°.

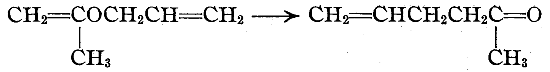
$$\mathrm{CH_2{=}CHOCH_2CH{=}CH_2 \longrightarrow CH_2{=}CHCH_2CH_2CHO}$$

No other products were formed, the remainder of the material being unchanged ether. At 215°, no rearrangement was observable. The identity of allylacetaldehyde was confirmed by analyses and by treatment with ozone, which gave rise to formic and succinic acids.



$$\mathrm{CH_2{=}CH(CH_2)_2CHO \xrightarrow{O_3} \overset{O_3}{CH_2{-}CH}CH_2CH_2COOH \xrightarrow[Ag_2O]{H_2O} HCOOH + (CH_2COOH)_2}$$

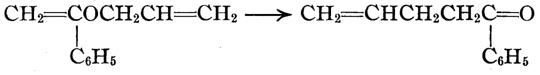
α-Methylvinyl allyl ether was found to be somewhat less stable to heat. There was practically complete conversion into allylacetone by heating in the vapor phase at 255°.



$$\mathrm{CH_2{=}\underset{\substack{|\\ CH_3}}{C}OCH_2CH{=}CH_2 \longrightarrow CH_2{=}CHCH_2CH_2\underset{\substack{|\\ CH_3}}{C}{=}O}$$

Indeed, a small amount of this ketone was isolated during the preparation of the ether, in which process the bath temperature reached 200°.

α-Phenylvinyl allyl ether appeared to be the least stable of these ethers. Mere distillation under reduced pressure (temperature below 175°) caused rearrangement into ω-allylacetophenone, and brief refluxing under atmospheric pressure brought about this reaction in a high yield.



$$\mathrm{CH_2{=}\underset{\substack{|\\ C_6H_5}}{C}OCH_2CH{=}CH_2 \longrightarrow CH_2{=}CHCH_2CH_2\underset{\substack{|\\ C_6H_5}}{C}{=}O}$$

Experimental Part

Bromoacetaldehyde.—Paraldehyde (125 g.) was brominated at −5 to −10° with bromine (360 g.) according to the directions of Hibbert and Hill.[12] The yields of the lachrymatory mixture of bromoacetaldehyde and its trimer were 39–53%.

Allyl Bromoacetal.—Seventy grams of the above bromoacetaldehyde mixture was placed in a 500-cc. three-necked flask, equipped with a mercury-sealed stirrer and a reflux condenser which was protected from moisture by a calcium chloride tube. To this were added 69 g. of allyl alcohol (b. p. 93–95°) and 0.4 cc. of 40% sulfuric acid. The resulting solution was refluxed, with constant stirring, for nine hours on the steam-bath. After cooling, it was taken up in an equal volume of ether and neutralized by shaking with a dilute sodium hydroxide solution. It was further washed with a small amount of sodium bisulfite solution, then washed with water, and dried over anhydrous sodium sulfate.

The ether solution was filtered and the ether removed under diminished pressure. The reddish-brown residual liquor was distilled under reduced pressure. Redistillation gave pure allyl bromoacetal, boiling at 102–104° at 23 mm. The material was colored slightly yellow when freshly distilled, but became colorless on standing. Constants for this compound, and for the other compounds to be described in this paper, are collected in Table I.

Anal. Calcd. for $C_8H_{13}O_2Br$: Br, 36.16. Found: Br, 35.94.

The yield obtained in this way was 20.5%. The yield

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(12) Hibbert and Hill, THIS JOURNAL, **45**, 746 (1923).

was increased to 26.4% by removal of the water formed in the reaction. An experiment using 91.5 g. of the aldehyde, 90 g. of dry allyl alcohol and 0.55 cc. of 40% sulfuric acid was carried out. During a similar heating period of nine hours, 24 cc. of an alcohol–water constant-boiling mixture was removed, while 40 cc. of the alcohol was added. On working up the products as before, 43.4 g. of the acetal was obtained. If the allyl alcohol (53% of calcd.) was added directly to the bromination product of paraldehyde as soon as the color of bromine had disappeared from the solution, the yield of the acetal was 25%. In this reaction, stirring at −5° was maintained for two and a half hours before allowing the flask to warm up to room temperature. The lower layer was separated, dissolved in ether and purified as before.

Effect of Metals on Allyl Bromoacetal

Sodium.—Small pieces of sodium were added to 9.6 g. of allyl bromoacetal at 140–145°. About four drops of water-insoluble, odoriferous liquid, $n^{20}\text{D}$ 1.4105, was collected as distillate, which was identified later as vinyl allyl ether. When only 0.4 g. of sodium was added the reaction mixture set to a brown mass from which half of the original bromoacetal was recoverable (b. p. 103–105° at 27 mm.). Additional sodium rested on the surface of the brown mass without reacting. Xylene, as diluent, did not prevent the formation of this brown sludge.

Zinc.—Little or no reaction occurred between allyl bromoacetal and zinc dust up to 148°, but at this temperature a violent exothermic reaction ensued. A black tar was the only product.

A mixture of 20 g. of allyl bromoacetal, 50 cc. of alcohol and 14.7 g. of zinc dust was heated to reflux temperatures and stirred for three hours. Then 20 cc. of distillate (A) was taken off and 20 cc. of alcohol added for another refluxing period of three hours, after which all that would distil over (B) on the steam-bath was collected. Both A and B smelled strongly of allyl vinyl ether. When A was mixed with an equal volume of water, about 0.5 cc. of it separated, $n^{20}\text{D}$ 1.4101. No separation occurred when B was diluted. Much allyl bromoacetal was recovered from the higher boiling residue.

Allyl Acetal.—Twenty grams of dry calcium chloride was dissolved in 132 g. of allyl alcohol (b. p. 93–96°) by shaking in a tightly stoppered bottle. This solution was cooled to 0° and 50 g. (1.14 moles) of cold acetaldehyde was added. The bottle was restoppered and the mixture was shaken vigorously for ten minutes, at the end of which time two layers had formed.

The mixture was allowed to stand for thirteen and one-half hours with occasional shaking, before separating the clear upper layer. This was washed with 100 cc. of distilled water in three portions. The washed oil was allowed to stand for three hours to permit more water to settle out, and was then dried over anhydrous potassium carbonate for eighteen hours. After filtering, the material was distilled. Refractionation gave a total of 110.5 g. (68.2% yield) of allyl acetal which boiled between 146–150°. Other runs gave yields of 62.4 and 64.7%. The pure material boiled at 148–149°.

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.61; H, 9.88. Found: C, 67.14, 67.37; H, 9.88, 9.95.

Decomposition of Allyl Acetal in the Presence of *p*-Toluenesulfonic Acid.—A mixture of 16 g. of allyl acetal and 0.045 g. of *p*-toluenesulfonic acid was heated to refluxing on an oil-bath. A small amount of tar appeared and the solution became red-brown in color. Subsequently, the material was heated at 105° for two and one-half hours and then at 130–140° for ten hours. During this latter heating period, 3 g. of liquid distilled over. Redistillation of this distillate gave 1.82 g. of crude vinyl allyl ether, collected between 48–98°. The usual ethereal odor was observed with this material. Its index of refraction $n^{20}\text{D}$ was 1.4107 ($n^{20}\text{D}$ for the pure ether, 1.4115). Evidence for its structure was obtained by hydrolysis of a small portion with dilute hydrochloric acid. To this resulting solution was added 5 cc. of an alcoholic solution of 2,4-dinitrophenylhydrazine. The hydrazone melted (without recrystallization) at 151–152°; mixed melting point with an authentic sample of the acetaldehyde derivative (m. p. 161–163°) was 157–158°.

Reaction between Allyl Acetal and Phosphorus Pentoxide.—Sixty grams of dimethylaniline (b. p. 190–191°) and 60 g. of phosphorus pentoxide were mixed thoroughly in a 500-cc. flask, after which 59 g. of allyl acetal was added. A 25-cm. empty Hempel column was placed on top of the flask and was connected to a condenser set for distillation. The mixture was heated slowly and kept at gentle refluxing until all of the easily-volatile material had distilled over. During this period a considerable amount of tarring occurred. The total weight of distillate was 28.8 g. Fractionation of this material through a 25-cm. Widmer column gave 6.8 g. (19.3%) of crude vinyl allyl ether (b. p. 56–70°). The other fractions consisted mainly of allyl alcohol (app. 60% of total), some allyl acetal and 1 g. of an unidentified substance boiling at 40–42°.

Other runs gave essentially the same products. The yields of vinyl allyl ether obtained in these other cases were: 15.5% (crude, using dimethylaniline as solvent) and 11.5% (pure, using quinoline as solvent). One redistillation through a good column sufficed for the purification of the ether, b. p. 65.0–65.2°.

Anal. Calcd. for C_5H_8O: C, 71.38; H, 9.59. Found: C, 71.30; H, 9.39.

β-Hydroxyethyl Allyl Ether.—To 158 g. of redistilled ethylene glycol 23.4 g. of sodium was added slowly in small pieces. After the reaction was over, the solution was heated with stirring on the steam-bath while 124 g. of allyl bromide was slowly added. The mixture was heated for two hours after the addition. The sodium bromide was filtered off and the filtrate distilled under reduced pressure. Redistillation through a 60-cm. Vigreux column gave 79.6 g. of pure material boiling between 63–64° at 18–19 mm., yield 77%.

Anal. Calcd. for $C_5H_{10}O_2$: C, 58.81; H, 9.87. Found: C, 58.45; H, 9.79.

Another run using 0.91 mole of sodium and 1.2 moles of allyl bromide wherein the ethylene glycol was separated from the β-hydroxyethyl allyl ether by ether–water partition, and the last of the hydroxy ether recovered by extracting the aqueous solution with ether, gave an 81% yield after the usual procedures of drying and distilling.

β-Bromoethyl Allyl Ether.—To 75.3 g. (0.278 mole) of phosphorus tribromide in a flask surrounded by an ice-bath was added slowly, with constant stirring, a mixture of 71 g. (0.695 mole) of β-hydroxyethyl allyl ether and 12.5 g. (0.156 mole) of dry pyridine. The mixture was stirred for one hour and then allowed to stand for an equal interval before distilling under reduced pressure. The distillate was washed twice with dilute sodium hydroxide, twice with dilute sulfuric acid, and once with water. After drying over anhydrous sodium sulfate, distilling and redistilling through a 60-cm. Vigreux column, a 40% yield of β-bromoethyl allyl ether was obtained. It boiled at 68.5–69° (36 mm.).

Anal. Calcd. for C_5H_9OBr: Br, 48.43. Found: Br, 48.19.

Using the Palomaa and Kenetti procedure,[13] which consists of the addition of the alcohol–pyridine mixture to cold phosphorus tribromide and allowing the reaction mixture to stand for a few hours, unmodified except that the crude bromide was distilled off under reduced pressure as soon as the addition was over, a 45% yield was obtained.

In another run, wherein the phosphorus tribromide was added to the mixture of β-hydroxyethyl allyl ether and pyridine at 0°, and the whole allowed to stand overnight, a 35% yield was realized.

Reaction between β-Bromoethyl Allyl Ether and Potassium Hydroxide.—Into a 125-cc. distilling flask was placed 42.5 g. of β-bromoethyl allyl ether, after which 43 g. of finely powdered potassium hydroxide was added. The mixture was heated slowly on an oil-bath to 110°, at which point volatile material began to distil. The bath temperature was raised slowly. When no more would come over (bath temperature was 174°), the heating was stopped. The distillate weighed 11.1 g. That this material was vinyl allyl ether was shown by the fact that practically all of it distilled at 65–66° (741 mm.). The refractive index, $n^{24}\text{D}$ 1.4101, was also in good agreement. The yield was 51%.

Upon taking up the residue in the flask with water, 12 cc. of impure bromoethyl allyl ether was recovered.

Ethyl Dimethylketal.—A mixture of 39 g. (0.26 mole) of ethyl orthoformate, 13 g. (0.23 mole) of dry acetone, 58 g. (1.3 moles) of absolute alcohol and 0.055 g. of *p*-toluenesulfonic acid was refluxed for ten minutes, neutralized with sodium ethoxide, cooled with running water and diluted with 400 cc. of distilled water. The upper layer which separated was washed three times with 50-cc. portions of distilled water and then allowed to dry over anhydrous potassium carbonate. After filtering, the material was distilled and the portion boiling between 113–115° was collected. The yield was 22.6 g. (75%).

Allyl Dimethylketal and Ethyl Allyl Dimethylketal.—To a mixture of 54 g. (0.41 mole) of ethyl dimethylketal and 160 g. of dry allyl alcohol was added 0.1 g. of *p*-toluenesulfonic acid. The whole was refluxed for ten minutes and then the color was discharged with sodium ethoxide. The alcohol mixture was distilled off slowly (up to a temperature of 97°), using a 60-cm. electrically heated Vigreux column with partial condensation head. The remainder was fractionated through this same column under reduced pressure. Refractionation gave 7 g. (12%) of ethyl allyl dimethylketal boiling at 43–45° at 26 mm., and 24 g. (38%) of allyl dimethylketal, boiling at 61° at 26 mm. (also 46–48° at 13–14 mm.).

Anal. of ethyl allyl dimethylketal. Calcd. for $C_8H_{16}O_2$: C, 66.62; H, 11.19. Found: C, 67.00; H, 11.23.

Anal. of allyl dimethylketal. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.31. Found: C, 69.18; H, 10.35.

α-Methylvinyl Allyl Ether.—To 25 g. of allyl dimethylketal was added 0.1 g. of *p*-toluenesulfonic acid in a 50-cc. flask topped with a short Vigreux column connected to a water condenser set for distillation. The material was heated to gentle refluxing on an oil-bath, whereupon 21 g. of a volatile distillate was collected during a period of five hours. The bath temperature changed from 145 to 200° during this time. The distillate was shaken with four times its volume of distilled water, and the separated upper layer washed twice more with equal volumes of distilled water, after which the weight was 12 g. After drying over anhydrous potassium carbonate, the material was filtered and distilled through a 60-cm. Vigreux column. Three and one-half grams of α-methylvinyl allyl ether was collected, boiling at 87.5–88° (745 mm.). A small amount (1.5 g.) of allylacetone was separated at 126–129°. The residue was mainly unreacted allyl dimethylketal.

The allylacetone was characterized by its semicarbazone, m. p. 102–103° (reported[14] as 100–102°). The ether was analyzed.

Anal. Calcd. for $C_6H_{10}O$: C, 73.41; H, 10.28. Found: C, 73.02; H, 10.03.

Decomposition of Ethyl Allyl Dimethylketal in the Presence of *p*-Toluenesulfonic Acid.—A mixture of 6.4 g. of ethyl allyl acetonal and 0.04 g. of *p*-toluenesulfonic acid was heated as in the previous experiment. Five grams of material was collected while the bath temperature was raised slowly from 120 to 180°. The distillate was shaken with 50 cc. of distilled water, and the resulting upper layer washed twice with 10-cc. portions of water before drying over anhydrous potassium carbonate. After filtering, the material was distilled in a 2-cc. modified Claisen distilling flask at atmospheric pressure.

Fraction	B. p., °C.	Wt., g.	$n^{20}\text{D}$
1	82–88	0.10	..
2	88–90	.53	1.4155
Residue	..	.24	..

This distillate was chiefly α-methylvinyl allyl ether.

α-Chloro-β-bromoethyl Allyl Ether.—To 43.7 g. of a mixture of bromoacetaldehyde and tribromoparaldehyde at 0° was added 20.6 g. of dry allyl alcohol. At this temperature, dry hydrogen chloride was introduced with constant stirring until a 17.5 g. increase in weight was noted. At the end of the reaction two colorless layers had formed. The lower one was placed over anhydrous calcium chloride and the excess hydrogen chloride was evaporated under reduced pressure. A light-brown color appeared after standing for two days. After filtering, the α-chloro-β-bromoethyl allyl ether weighed 44 g. (62% yield).

In another run crystals of tribromoparaldehyde settled out during the reaction. The yield in this case (59.3%) was based on the unrecovered aldehyde.

α-Phenyl-β-bromoethyl Allyl Ether.—Phenylmagnesium bromide was prepared in the usual way from 176 g. (1.12 moles) of bromobenzene, 27 g. of magnesium and 400

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[13] Palomaa and Kenetti, *Ber.*, **64**, 799 (1931).

[14] Von Braun and Stechele, *ibid.*, **33**, 1472 (1900).

cc. of dry ether. After cooling to 0°, a 1:1 dry ether solution of 134 g. of α-chloro-β-bromoethyl allyl ether was added with constant stirring. The material was added slowly enough so that the mixture remained cold. After the reaction was over, stirring at 0° was continued for twenty minutes before hydrolyzing with dilute hydrochloric acid. The ether layer was separated and dried over anhydrous calcium chloride.

After filtering, the ether was distilled off on the steam-bath, 3.5 g. of solid sodium hydroxide was added and the residue distilled under reduced pressure. Sixty-six grams (41% yield) of α-phenyl-β-bromoethyl allyl ether was obtained, distilling between 130–142° at 18–21 mm. Several refractionations were necessary in order to obtain a pure product, b. p. 129–130° (12 mm.). The major impurity was diphenyl.

Anal. Calcd. for $C_{11}H_{13}OBr$: Br, 33.16. Found: Br, 32.99. *Analysis* for unsaturation.[15] Subs., 0.2623; cc. of 0.5017 *N* $KBrO_3$–KBr soln. added, 6.43. Cc. of 0.1768 *N* $Na_2S_2O_3$ req. to back-titrate, 5.54. Double bonds per molecule, 1.03.

α-Phenylvinyl Allyl Ether.—To 18 g. of α-phenyl-β-bromoethyl allyl ether in a small distilling flask was added 4.5 g. of finely-powdered potassium hydroxide and the mixture allowed to stand for two hours. Heat was evolved during the addition and a red-brown color was developed. The system was placed under a pressure of 4 mm. and the bath was slowly heated up until gentle refluxing occurred. After one-half hour's refluxing, distillation was permitted to occur and 9 g. of material was collected. Since this gave a positive test for bromine in the sodium fusion test, it was treated further with 1.7 g. of finely powdered potassium hydroxide in a 12-cc. distilling flask. Under a pressure of 12 mm., the material was slowly heated up to refluxing, and maintained for one-half hour. Upon distillation, it was found that the entire distillate (3 g. or 25% yield) came over at 104–105° (12 mm.). A very small amount of water was collected also. The distillate was dried over anhydrous sodium sulfate and filtered therefrom. This unsaturated, colorless liquid gave no halogen test when fused with sodium.

Anal. Calcd. for $C_{11}H_{12}O$: C, 82.45; H, 7.56. Found: C, 82.01; H, 7.36.

Acid Hydrolysis of Vinyl Ethers

Vinyl Allyl Ether.—A few drops of vinyl allyl ether was dissolved in 5 cc. of 95% alcohol and two drops of concentrated hydrochloric acid was then added in order to hydrolyze the ether. After the addition of 5 cc. of a saturated solution of 2,4-dinitrophenylhydrazine in 95% alcohol, the mixture was boiled for one minute. Water was added to incipient cloudiness, and the hydrazone was permitted to crystallize. After two recrystallizations, the melting point of the orange crystals was 164–164.5°. A mixed melting point with authentic acetaldehyde 2,4-dinitrophenylhydrazone (m. p. 166°) showed the two materials to be identical (mixed m. p., 165–165.5°). A mixed melting point with the corresponding formaldehyde derivative (m. p. 165°) gave a thirty-degree depression.

α-Methylvinyl Allyl Ether.—This ether was treated in an identical manner. The 2,4-dinitrophenylhydrazone, after two crystallizations from alcohol, melted at 125°. The mixture m. p. with authentic acetone 2,4-dinitrophenylhydrazone (m. p. 125°) was 125°.

α-Phenylvinyl Allyl Ether.—A small amount of the ether was dissolved in dilute alcohol and semicarbazide hydrochloride was added. After gentle heating, the semicarbazone was permitted to form. The melting point, after one recrystallization from dilute alcohol, was 198–199°. A mixed melting point (199–200°) with authentic acetophenone semicarbazone (m. p. 200–201°) showed these two materials to be identical.

Pyrolysis of the Ethers

Vinyl Allyl Ether.—The method used here consisted in passing the vapors of the ether through a tube (16 × 0.7 cm.) which was heated to a constant temperature by the refluxing vapors of a proper bath material.

When naphthalene was used to provide a temperature of 215–218°, no rearrangement was observed. When 6.7 g. of vinyl allyl ether was passed through the tube during a period of twenty minutes, the 6.5 g. of recovered material proved to be unchanged ether.

When phenyl ether (b. p. 252–255°) was used, however, definite rearrangement was observed.

Run	Ether used, g.	Product	Time of run, min.
1	3.92	3.64	50
2	11.0	10.6	115

In these runs, 40–50% of a higher-boiling substance (b. p. 99–104°) was isolated from the recovered material, while the rest proved to be unreacted vinyl allyl ether. After several refractionations, 2.5 g. (approx. 50% of the combined fractions, b. p. 99–104°) came over constantly between 103–104° (749 mm.). This material had a pungent aldehyde-like odor and reacted immediately with Schiff's reagent. It was found to be much more soluble than vinyl allyl ether upon shaking with water. This fraction had the following constants: d^{20}_4 0.852; n^{20}_D 1.4191.

Anal. Calcd. for C_5H_8O: C, 71.38; H, 9.59. Found: C, 70.99, 71.08; H, 9.53.

The dimethone[16] derivative of allylacetaldehyde was prepared, and melted sharply at 98° after several recrystallizations from alcohol.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.79; H, 8.73. Found: C, 72.94; H, 8.62.

The 2,4-dinitrophenylhydrazone of allylacetaldehyde also was prepared. After three recrystallizations from alcohol, the melting point remained unchanged at 120°.

α-Methylvinyl Allyl Ether.—The same apparatus was used as in the case of vinyl allyl ether. The vapors of 3.6 g. of α-methylvinyl allyl ether were passed through the tube, which was heated to 255° by the refluxing vapors of phenyl ether, during the course of one hour. Three and three-tenths grams of material was recovered. On distillation, practically all of this distilled at 126–127° at 745 mm. Properties of allylacetone: n^{20}_D 1.4199; d^{20}_4 0.842; *MR* (found) 29.47, *MR* (calcd.) 29.45.

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(15) Davis, Crandall and Higbee, *Ind. Eng. Chem.*, *Anal. Ed.*, **3**, 108 (1931).

(16) Klein and Linser, *Mikrochemie*, Pregl Festschrift, 204 (1929) "Methone" is a trade name for dimethyldihydroresorcinol.

The presence of the CH_3CO- group was indicated by the good iodoform test obtained from a drop of this material. Preparation of the semicarbazone (m. p. 103°) and the 2,4-dinitrophenylhydrazone[17] (m. p. 108–108.5°) further confirmed its identity.

α-Phenylvinyl Allyl Ether.—When 1.31 g. of this ether was refluxed gently under atmospheric pressure for fifteen minutes, a red-brown color developed. After cooling, the system was distilled at 12–13 mm. The entire volatile portion (0.93 g.) came over between 105–116°. A small amount of a deep red-brown, viscous material remained as residue. The refractive index $n^{20}D$ of the distillate was 1.5417.

The semicarbazone was prepared in the usual manner and found to melt, after two recrystallizations, at 156–157°. The oxime was also recrystallized twice and had the melting point of 53°.[18] A mixed m. p. with a sample of authentic acetophenone oxime (m. p. 57–58°) showed definitely that these two materials were different. Simple mixing gave a sticky mass, which was completely melted at 45.5°. This distillate is, therefore, identified as γ-butenyl phenyl ketone.

Ozonolysis of Allylacetaldehyde.—One gram of allylacetaldehyde was dissolved in 100 cc. of dry carbon tetrachloride and an excess of a 5% ozone-in-oxygen stream passed into the solution at 0°. The resulting ozonide was hydrolyzed in the presence of the solvent with 70 cc. of water and the reaction completed by refluxing for one and one-half hours. At this point, the freshly-prepared and well-washed silver oxide from 15 g. of silver nitrate was added and the mixture was further refluxed for one hour. After the evaporation of the carbon tetrachloride by gentle heating on the steam-bath, the mixture was filtered.

Most of this filtrate was distilled, the distillate made up to 110 cc., and a determination of the Duclaux values made.

	Cc. alkali required
Original 10 cc.	2.90
First 10 cc. distilled	1.20
Second 10 cc. distilled	1.30
Third 10 cc. distilled	1.40

Duclaux values found: 4.14, 4.48, 4.83. The theoretical values for formic acid are: 3.95, 4.40 4.55. This distillate slowly decolorized potassium permanganate solution.

After the formic acid had been distilled off, the residue was treated with excess of hydrochloric acid to precipitate the remaining silver. After filtering, the filtrate was evaporated to dryness.

A small amount of this residue was dissolved in water and neutralized with dilute sodium hydroxide. The *p*-bromophenacyl ester of the acid was prepared in the usual manner and was recrystallized from an alcohol–acetone mixture; m. p. 209–210°. A mixed melting point with authentic *p*-bromophenacyl succinate (m. p. 213.5–214°) showed the identity of the two materials. The value was 212–212.5°.

Summary

A number of methods of preparing vinyl allyl ethers have been investigated.

These ethers were found to rearrange smoothly upon heating at temperatures of 175–255°. Only one product was found to any appreciable extent in each case, indicating a clean-cut reaction. It was shown that allylacetaldehyde, allylacetone, and ω-allylacetophenone were formed in this way, respectively, from vinyl allyl ether, α-methyl vinyl allyl ether, and α-phenylvinyl allyl ether. These three ethers are listed in the order of decreasing thermal stability.

The rearrangement of vinyl allyl ether to allylacetaldehyde is analogous to the rearrangement of phenyl allyl ether to *o*-allylphenol.

EVANSTON, ILLINOIS RECEIVED MAY 31, 1938

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[17] Allen, THIS JOURNAL, **52**, 2958 (1930), reports m. p. of 104°

[18] Helferich and Lecher, *Ber.*, **54**, 930 (1921), report the m. p. of the semicarbazone of γ-butenyl phenyl ketone as being 156–157°, and that of the oxime as 53–54°.

[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

The Polycondensation of Acrolein

BY EVERETT E. GILBERT[1] AND JOHN J. DONLEAVY

It has been shown[2] that in the presence of dilute aqueous alkalies, α-methylacrolein polycondenses by a Michael mechanism to yield hydroxy polyaldehydes. The purpose of this communication is to report a similar reaction for acrolein.

Several investigators have recorded the precipitation of a white solid upon the addition of alkalies to an aqueous solution of acrolein. McLeod[3] obtained a product softening at 83° and decomposing with evolution of gas at 94–95°. The substance was soluble in alcohol, but insoluble in water and in hydrocarbon type solvents. Upon heating, thermal depolymerization occurred with the formation of acrolein. Another observer[4] obtained a white powder softening at

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[1] This communication describes work done by Everett E. Gilbert in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry.

[2] Gilbert and Donleavy, THIS JOURNAL, **60**, 1737 (1938).

[3] McLeod, *Am. Chem. J.*, **37**, 34 (1907).

[4] Nef, *Ann.*, **335**, 220 (1904).

115° and decomposing at 128–130°. A third group[5] described the powder as being converted to a viscous mass upon heating to temperatures between 80–110°; the solubilities were the same as those recorded above. No attempt ever has been made[6] to characterize any of the acrolein polymers.

A series of samples of the solid was prepared under widely varying conditions. They gave an immediate precipitate with Tollens' reagent, a definite although delayed test with Schiff's reagent, and an immediate precipitate of manganese dioxide with neutral aqueous permanganate at room temperature. The samples did not possess sharp melting points; decomposition temperatures were noted as low as 80° and as high as 125°.

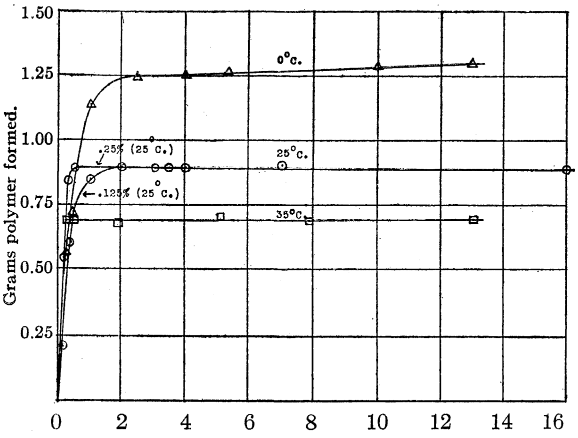
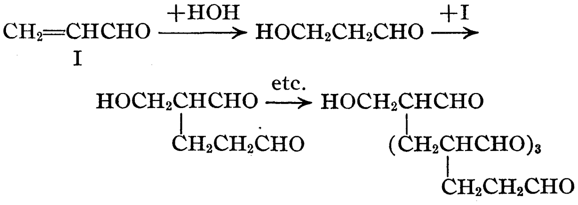


Fig. 1.

Analyses upon specimens variously prepared checked one another in being 4% lower in carbon than calculated for $(CH_2{=}CHCHO)_n$; the hydrogen was slightly higher than calculated. By analogy to the type of product similarly obtained from α-methylacrolein, it was concluded tentatively that the polyacrolein was a hydroxypolyaldehyde formed from five acrolein molecules and one water molecule. This was established by the preparation of a monoöxime (in the cold), and by the preparation of a tetra-2,4-dinitrophenylhydrazone (in the hot). A polyacrylic acid also was obtained by cautious oxidation with permanganate in the cold—followed by dehydration. Direct determinations of the molecular weight in freezing dioxane gave values which fell between one and two times the calculated molecular weight. Molecules possessing hydroxyl groups and such high densities of strongly polar aldehyde groups might be expected to associate.

Acrolein polycondenses by a Michael reaction in a manner similar to α-methylacrolein. The addition of water to acrolein yields hydracrylic aldehyde, the active methylene group of which condenses with acrolein by a Michael reaction producing a new active methylene group which again condenses by the Michael reaction with another acrolein molecule. These reactions are known to be catalyzed by alkalies; the reaction would continue until the formation of the pentamer. These steps are summarized in the equations



$$\underset{\text{I}}{CH_2{=}CHCHO} \xrightarrow{+HOH} HOCH_2CH_2CHO \xrightarrow{+\text{I}}$$

$$\underset{\textstyle CH_2CH_2CHO}{HOCH_2\underset{|}{C}HCHO} \xrightarrow{\text{etc.}} \underset{\underset{\textstyle CH_2CH_2CHO}{|}}{\underset{\textstyle (CH_2CHCHO)_3}{HOCH_2\underset{|}{C}HCHO}}$$

The above structure of the pentamer (containing acrolein units) would allow the formation of acrolein observed by McLeod[3] during thermal depolymerization.

A series of reaction velocity curves was obtained for the formation of the polymer under varying conditions to determine whether or not its mode of formation is consistent with the Michael mechanism advanced above. The values obtained are recorded in Table I; some of these are plotted in Fig. 1. The following conclusions were drawn from an examination of these

TABLE I

YIELD OF ACROLEIN POLYMER OBTAINED UNDER VARYING CONDITIONS

Percentages refer to strength of catalyst solution added.

Hrs. 0.125%	G. 25°	Hrs. 0.25%	G. 25°	Hrs. 1.0%	G. 25°
0.40	0.596	0.25	0.843	0.20	0.767
1.00	.850	.50	.890	.50	.857
2.00	.890	3.50	.891	3.00	.893
4.20	.862	4.00	.894	7.00	.913
17.25	.870	7.00	.906	16.00	.887
0.25%	0°	0.25%	35°	165 hrs.	25°
0.25	0.572	0.25	0.697	0.125%	0.210
.50	.721	.50	.703	.25%	.538
1.00	1.138	1.88	.671	1.0%	.839
2.50	1.250	5.12	.700		
4.00	1.258	7.82	.682		
5.33	1.275	13.00	.694		
10.00	1.285				
13.00	1.297				

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[5] C. Moureu and C. Dufraisse, *Chemistry & Industry*, **40**, 858A (1921).

[6] C. Ellis, "The Chemistry of Synthetic Resins," Reinhold Publishing Corporation, New York, N. Y., 1935, p. 502.

data: (1) the reaction is an equilibrium type, since the curves become straight and parallel to the x-axis; (2) the rapidity with which equilibrium is reached depends upon the concentration of the alkaline catalyst (at a given temperature), although the position of the equilibrium point depends upon the temperature alone; (3) the equilibrium point is shifted to the left by a rise in temperature. It has been shown[7] that these phenomena are characteristic of the Michael reaction. It has also been shown[8] that substituents tend to hinder the Michael reaction. Thus acrolein yields a pentamer by the Michael polycondensation, while α-methylacrolein yields principally a trimer.

Experimental

The acrolein was used as received from Eastman Kodak Co.; it contained about 0.1% hydroquinone.

In determining the points for the velocity curves, the following procedure was employed. Two cubic centimeters of acrolein was dissolved in 20 cc. of distilled water. The stopper of the flask was then wired down securely. It was attached to the rotator of an isothermal bath (constant to within 0.03°), and was then rotated for fifteen minutes to attain the desired temperature. It was unstoppered quickly and 1 cc. of aqueous sodium hydroxide of specified strength was added. The flask was restoppered immediately and rotated for the desired time, after which it was removed from the bath. One cubic centimeter of dilute sulfuric acid was added to stop the reaction. The white precipitate was filtered on weighed filter paper, washed thoroughly with distilled water, and dried *in vacuo* for fifteen hours over concentrated sulfuric acid to constant weight. The data reported in Table I were obtained in this way.

The polymer is a white fluffy powder which cannot be crystallized; it was found to be soluble in alcohols, ketones and in dioxane, but insoluble in hydrocarbons and in water. These observations are in accord with previous work.[3-5]

Included among the specimens subjected to analysis were the following: (1) samples made by the addition of aqueous catalyst of the following strengths: 0.25, 0.5, and 1.0%; (2) samples made with 0.25% catalyst at 11, 25 and 40°; (3) white samples which had been filtered immediately, and those allowed to become yellow from longer exposure to the alkaline reaction medium; (4) specimens which had been reprecipitated from acetone by the addition of benzene. Nine samples were analyzed; the value cited below is the average from which no single analysis varied more than ±0.25%.

Anal. Calcd. for $C_{15}H_{22}O_6$: C, 60.40; H, 7.38. Found: C, 60.48; H, 7.37. (Calcd. for $(CH_2{=}CHCHO)_n$: C, 64.28; H, 7.14.) One sample prepared with 0.125% alkali analyzed to the tetramer. Calcd. for $C_{12}H_{18}O_5$: C, 59.50; H, 7.42. Found: C, 59.62; H, 7.50. These values were unchanged after reprecipitation from acetone with benzene.

The method of Oxford[9] was used for determining the molecular weights. The dioxane was dried and distilled over sodium, and the method was checked at intervals against naphthalene. Calcd. for the pentamer: mol. wt., 298. Found: mol. wt., 370, 376, 388, 472, 443, 485, 440, 582, 580. The same values were obtained at different concentrations.

Preparation of the Tetra-2,4-dinitrophenylhydrazone of the Polymer.—The method employed was essentially that suggested by Shriner and Fuson.[10] One equivalent of dinitrophenylhydrazine was employed for each aldehyde group. A brick-red solid was obtained upon cooling the reaction mixture. The crude product was fractionally crystallized from 250 cc. of 95% ethyl alcohol. The first crop was dried *in vacuo* for twelve hours over concentrated sulfuric acid. It decomposed at about 120° upon heating.

Anal. Calcd. for $C_{39}H_{38}N_{16}O_{18}$: C, 46.1; H, 3.74; N, 22.0. Found: C, 46.2; H, 3.55; N (Dumas), 21.63.

Preparation of the Monoöxime of the Polymer.—Two grams (0.007 mole) of the polymer was dissolved in 30 cc. of methyl alcohol. Two and one-half grams of hydroxylamine hydrochloride (0.36 mole) dissolved in methanol was added, and 2.9 g. (0.36 mole) of finely powdered sodium acetate also. The flask was sealed tightly and shaken vigorously at room temperature for three hours. The solution was then filtered free of sodium chloride and evaporated in a vacuum desiccator. During the evaporation more salt separated which was filtered. The solution was taken to dryness, and the white residue was thoroughly triturated with four fresh portions of distilled water. It was then dried *in vacuo* over concentrated sulfuric acid. Upon heating the oxime softened at 68° (uncorr.).

Anal. Calcd. for $C_{15}H_{23}NO_6$: C, 57.5; H, 7.35; N, 4.47. Found: C, 57.3; H, 7.20; N (Kjeldahl), 4.45.

Oxidation of the Polymer to Polyacrylic Acid.—One and seven-tenths grams (0.006 mole) of polymer was suspended in 50 cc. of distilled water; the suspension was cooled in an ice-bath. A solution of 3.2 g. (0.02 mole) of potassium permanganate and 0.4 g. of sodium hydroxide (0.01 mole) in 200 cc. of water was then added dropwise to the cooled suspension. Thorough mixing was ensured by the use of a stirring motor. The precipitation of manganese dioxide commenced almost immediately. Stirring was continued for about fifteen minutes after the addition was completed. The manganese dioxide was filtered by suction and thoroughly washed with three 20-cc. portions of hot water. The filtrate (placed in a large crystallizing dish) was put under vacuum over concentrated sulfuric acid. The solution was acidified after evaporation to a small volume. Since no precipitate formed, the evaporation was continued to dryness; a light brown resin separated. This was extracted thoroughly with four 30-cc. portions of boiling acetone and the acetone solution then filtered. Upon the addition of benzene, white flocks separated which were filtered and dried *in vacuo*. A white powder was obtained, yield 0.4 g. Upon heating it did not show a definite melting point, but began to sinter at about 70°. It was insoluble in dioxane and in hydrocarbons.

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[7] Ingold, *J. Chem. Soc.*, **119**, 1976 (1921).

[8] Cooper, Ingold and Ingold, *ibid.*, **129**, 1869 (1926).

[9] Oxford, *Biochem. J.*, **28**, 1325 (1934).

[10] Shriner and Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1935, p. 148.

Anal. Calcd. for $(CH_2{=}CHCOOH)_x$: C, 50.0; H, 5.56. Found: C, 50.0; H, 5.39.

Summary

Acrolein polycondenses in the presence of dilute alkalies by a Michael mechanism to give a hydroxypentaldehyde. The rate of polymerization was measured under varying conditions.

New Haven, Conn. Received June 7, 1938

[Contribution from the Chemical Laboratory of the University of Washington]

The Condensation of *n*-Butyraldehyde with 2-Butanone. II[1]

By S. G. Powell and Donald A. Ballard

In a previous paper[2] it was shown that *n*-butyraldehyde reacts with 2-butanone under the influence of dilute potassium hydroxide solution to form a ketol which yields 3-methyl-3,2-heptenone (I) upon dehydration. Eccott and Linstead[3] carried out a similar series of reactions with *n*-butyraldehyde and acetone and obtained 3,2-heptenone (A). When, however, they treated a mixture of the aldehyde and acetone with a strong solution of sodium hydroxide they obtained as a direct product of the reaction a substance which they concluded was a geometrical isomer of (A). The present investigation was undertaken in an attempt to prepare in a similar manner the isomeric forms of 3-methyl-3,2-heptenone.

When *n*-butyraldehyde was added to a mixture of 2-butanone and a strong solution of sodium hydroxide we obtained a substance (II) which gave the analytical figures for $C_8H_{14}O$. The semicarbazone of (II) after recrystallization from dilute methanol melted constantly at 141–142°, whereas that of (I) melts at 168°. The semicarbazone of α-ethyl-α-hexenal, which results from the condensation of two molecules of *n*-butyraldehyde, melts at 152°.[4]

The substance (II) was almost completely soluble in a solution of sodium sulfite and sodium bicarbonate, showing it to be an α,β-unsaturated ketone or aldehyde.

Upon reduction with sodium and moist ether (II) gave 3-methyl-2-heptanol, although in small yield. This led to the belief that the substance was in fact the isomer of (I), which also yields 3-methyl-2-heptanol upon reduction. In order to determine the configuration of their two substances Eccott and Linstead prepared a 3,2-heptenone from an α-hexenoic acid of known configuration. Following the same procedure we prepared a 3-methyl-3,2-heptenone from α-methyl-α-hexenoyl chloride and methyl zinc iodide and found it to be identical with (I). On oxidation with sodium hypobromite, (I) gave this same α-methyl-α-hexenoic acid. However, the same acid was obtained when (II) was oxidized. At this point the semicarbazone of (II) was recrystallized carefully from dilute ethanol instead of methanol and the semicarbazone of α-ethyl-α-hexenal was isolated. It was also possible to isolate the 2,4-dinitrophenylhydrazone of α-ethyl-α-hexenal from the products of the reaction between (II) and 2,4-dinitrophenylhydrazine. A current of air was then passed through a sample of (II) for several hours to oxidize part of the aldehyde. From the residue, after washing with alkali, it was possible to prepare the semicarbazone of (I). The substance (II) was therefore merely a mixture of (I) and α-ethyl-α-hexenal.

As α-ethyl-α-hexenal might also exist in two modifications, it was prepared both by the action of alkali upon *n*-butyraldehyde and by the dehydration of *n*-butyraldol with iodine. Both products gave the same semicarbazone.

In view of the foregoing it seemed advisable to study further the reaction between *n*-butyraldehyde and acetone. By following the procedure of Eccott and Linstead we obtained the substance (A) which gave a semicarbazone melting at 152°, as reported by these authors. However, this was found to be identical with the semicarbazone of α-ethyl-α-hexenal. As a further check we treated (A) with 2,4-dinitrophenylhydrazine and isolated the 2,4-dinitrophenylhydrazone of α-ethyl-α-hexenal and also one that was identical with that obtained from the 3,2-heptenone produced by dehydrating the ketol.

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(1) This paper is an extract from a thesis presented by Donald A. Ballard in partial fulfilment of the requirements for the doctorate at the University of Washington.

(2) Powell, This Journal, **46**, 2514 (1924).

(3) Eccott and Linstead, *J. Chem. Soc.*, 911 (1930).

(4) Batalin and Slavina, *J. Gen. Chem.* (U. S. S. R.), **7**, 202 (1937).

Experimental

The Direct Condensation of 2-Butanone with *n*-Butyraldehyde.—One hundred and forty-four grams of *n*-butyraldehyde was added in a slow stream to a mixture of 144 g. of 2-butanone and 1000 cc. of a 2.5% sodium hydroxide solution. The reaction was allowed to proceed until the first vigorous reaction had subsided and then the mixture was shaken for fifty-six hours. The upper layer was separated, washed with water and distilled. The fraction of b. p. 72–74° (20 mm.), 117 g., was shaken for fifteen hours with a mixture of 234 g. of sodium sulfite heptahydrate, 78 g. of sodium bicarbonate and 660 cc. of water. The aqueous solution was made alkaline with 40 g. of sodium hydroxide and distilled with steam. The oily portion of the distillate was separated, dried with calcium chloride and distilled; b. p. 77–78° (25 mm.); yield 77 g.

Anal. Calcd. for $C_8H_{14}O$: C, 76.12; H, 11.11. Found: C, 76.13; H, 11.30.

The semicarbazone was prepared in the usual manner from 1 g. of semicarbazide hydrochloride, 1.5 g. of sodium acetate and 0.8 g. of the ketone. The crude product melted at 137–140° and after recrystallization from dilute methanol at 141–142°.

Anal. Calcd. for $C_9H_{17}ON_3$: N, 22.94. Found: N, 22.9, 23.0.

Twenty-two grams of the condensation product was hydrogenated partially by passage with hydrogen over nickel at 200°. The partially reduced product (17 g.) was mixed with 100 cc. of ether and 250 cc. of water and treated with 7 g. of sodium. The material was worked up in the usual manner, yielding 10 g. of product, b. p. 70–90° (20 mm.). This was oxidized with a solution of 10 g. of sodium dichromate and 14 g. of sulfuric acid in 75 cc. of water, keeping the temperature below 50°. After stirring for several hours the mixture was steam distilled. The oily portion of the distillate was separated, dried with calcium chloride and distilled, yielding, beside high boiling substances, 2.5 g. of material, b. p. 57–62 (20 mm.). The semicarbazone of this melted at 82–84° after recrystallization from dilute methanol, as did a mixture of it with the semicarbazone of 3-methyl-2-heptanone.

3-Methyl-3,2-heptenone.—A solution of 12 g. of α-methyl-α-hexenoyl chloride in 20 cc. of dry benzene was added to the methyl zinc iodide prepared from 25 g. of methyl iodide and the resulting ketone isolated in the usual manner. The crude ketone (10 g.) was shaken for five hours with a mixture of 10 g. of sodium sulfite heptahydrate, 8 g. of sodium bicarbonate, and 60 cc. of water.[5] The mixture was extracted with ether and the aqueous portion made alkaline with 4 g. of sodium hydroxide and distilled with steam. The resulting ketone yielded a semicarbazone melting at 166–168°, identical with that obtained from the 3-methyl-3,2-heptenone formed by dehydrating the ketol.[2]

The α-methyl-α-hexenoyl chloride was prepared by the action of phosphorus trichloride on α-methyl-α-hexenoic acid, which in turn was prepared by the method of Kon, Linstead and McLennan.[6,7] The 2,4-dinitrophenylhydrazone, orange crystals, m. p. 137°, was prepared by the method of Allen.[8]

Anal. Calcd. for $C_{14}H_{18}O_4N_4$: N, 18.3. Found: N, 18.4, 18.5.

Oxidation of 3-Methyl-3,2-heptenone.—A solution of 55 g. of sodium hydroxide in 470 cc. of water contained in a one-liter flask was cooled to 0° and 80 g. of bromine added with constant stirring, keeping the temperature below 10°. The solution was again cooled to 0°, 21 g. of 3-methyl-3,2-heptenone (obtained by dehydration of the ketol) added, and the mixture stirred for four hours. The bromoform and carbon tetrabromide were then distilled off with steam. The residue was cooled to 60°, 67 cc. of sulfuric acid added, the mixture distilled with steam, and the distillate extracted three times with ether. The combined extracts were dried with calcium chloride, the ether removed, and the residue distilled, yielding 5 g. of acid, b. p. 127–130° (20 mm.); neut. equiv. calcd. 128; found 129.5.

***p*-Toluidide.**—The acid chloride was prepared and dissolved in benzene. Two equivalents of *p*-toluidine was added and the mixture heated to boiling for a few minutes. The benzene layer was washed with water, dilute hydrochloric acid, dilute sodium hydroxide, and finally with water again. The benzene was evaporated off and the residue recrystallized from petroleum ether, m. p. 85–88°.

Anal. Calcd. for $C_{14}H_{14}ON$: N, 6.45. Found: N, 6.37, 6.26.

A sample of the *p*-toluidide prepared in the same manner from the acid obtained by the method of Kon, Linstead and McLennan was found to be identical.

Oxidation of the Direct Condensation Product.—This was oxidized in the same manner as the 3-methyl-3,2-heptenone, yielding an acid b. p. of 130–135° (25 mm.); neut. equiv. 130; m. p. of the *p*-toluidide, 85–88°.

α-Ethyl-α-hexenal.—A solution of 12 g. of sodium hydroxide in 65 cc. of water was placed in a flask fitted with a reflux condenser and mechanical stirrer, and 72 g. of *n*-butyraldehyde rapidly added. Stirring was continued for thirty minutes, the oil separated, dried with calcium chloride and distilled; b. p. 75–82° (24 mm.); yield 40 g. The semicarbazone melted at 152° after recrystallization from dilute methanol.

α-Ethyl-α-hexenal was also prepared by heating 15 g. of *n*-butyraldol (prepared by the method of Grignard and Vestermann[9]) with a few crystals of iodine; yield 11 g., b. p. 71–74° (30 mm.). The semicarbazone melted at 152°.

The 2,4-dinitrophenylhydrazone melted at 124–125°.

Anal. Calcd. for $C_{14}H_{18}O_4N_4$: N, 18.3. Found: N, 18.4, 18.2.

Isolation of the Components of the Direct Condensation Product.—A stream of air was drawn through 60 g. of the product for twelve hours. It was then shaken with dilute sodium hydroxide solution, dried with calcium chloride, and again treated with air for twelve hours. The treatment with sodium hydroxide was repeated and then air drawn through the residue for thirty-six hours. At the end of this time the material was again shaken with sodium hydroxide solution and the residual oil dried and distilled, yielding 22 g., b. p. 70–90° (20 mm.), and 7 g., b. p. 90–

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[5] Tiemann and Tigges, *Ber.*, **33**, 561 (1900).

[6] Kon, Linstead and McLennan, *J. Chem. Soc.*, 2453 (1932).

[7] The authors are indebted to Dr. T. R. Liston for the preparation of the necessary α-methyl-α-hexenoic acid and also for many valuable suggestions during the course of this investigation.

[8] Allen, THIS JOURNAL, **52**, 2956 (1930).

[9] Grignard and Vestermann, *Bull. soc. chim.*, **37**, 420 (1925).

140° (20 mm.). On redistillation the first fraction gave 10 g. of material of b. p. 70–75° (20 mm.). The crude semicarbazone of this fraction melted at 150–160°. After recrystallization it melted at 163–167° as did a mixture of it and the semicarbazone of 3-methyl-3,2-heptenone obtained by the dehydration of the ketol.

The sodium hydroxide extracts were combined and extracted with ether. The aqueous portion was acidified with dilute sulfuric acid and extracted with ether. The ether solution was dried, the ether removed, and the residue distilled. The acid boiled at 136–137° (20 mm.); neut. equiv., 145. The neutral equivalent of α-ethyl-α-hexenoic acid is 142.

The Direct Condensation of *n*-Butyraldehyde with Acetone.—This was carried out according to the directions of Eccott and Linstead.[3] The crude product was fractionated, yielding the following fractions: up to 90° (21 mm.), 62 g.; 90–130° (21 mm.), 17 g.; 130–180° (18 mm.), 43 g.; residue 30 g. The first fraction was carefully redistilled through a Podbielniak column, yielding 3 fractions.[10] The semicarbazones and 2,4-dinitrophenylhydrazones of each fraction were prepared and their melting points are given in Table I.

TABLE I

	B. p., °C. (19 mm.)	Wt., g.	M. p. (°C.) of crude semicarbazone	M. p. (°C.) of crude 2,4-dinitrophenylhydrazone
1	–65	3	110–120	95–100
2	65–69	29	123–133	99–110
3	69–71	11	143–148	120–122

By repeated crystallization of the crude derivative in each case, we were able to isolate a semicarbazone melting at 152°, identical with that of α-ethyl-α-hexenal. Fraction 3 was apparently almost entirely α-ethyl-α-hexenal. In order to identify the other component of fractions 1 and 2, the crude 2,4-dinitrophenylhydrazones were dissolved in alcohol, and the solution cooled, when crystals of the 2,4-dinitrophenylhydrazone of α-ethyl-α-hexenal separated. The mother liquor was evaporated to dryness and the residue dissolved in warm gasoline. When the solution was cooled a further crop of the 2,4-dinitrophenylhydrazone of α-ethyl-α-hexenal was obtained. The mother liquor was evaporated to dryness and the residue recrystallized from alcohol. This substance melted at 125–126° but was not identical with the 2,4-dinitrophenylhydrazone of α-ethyl-α-hexenal, m. p. 124–125°, as a mixture of the two melted at 100–110°.

A sample of 3,2-heptenone was prepared by dehydrating the ketol with oxalic acid, according to the method of Eccott and Linstead, and converted into the 2,4-dinitrophenylhydrazone. This substance melted at 125–126° and was identical with that obtained above.

Anal. Calcd. for $C_{13}H_{16}O_4N_3$: N, 19.2. Found: N, 18.9, 19.0.

Summary

1. An unsuccessful attempt was made to prepare *cis* and *trans* forms of 3-methyl-3,2-heptenone. An unsuccessful attempt was also made to prepare the *cis* and *trans* forms of 3,2-heptenone as described by Eccott and Linstead.

2. The 2,4-dinitrophenylhydrazones of α-ethyl-α-hexenal, 3,2-heptenone, and 3-methyl-3,2-heptenone were prepared.

3. The *p*-toluidide of α-methyl-α-hexenoic acid was prepared.

SEATTLE, WASH.

RECEIVED MAY 31, 1938

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[10] Podbielniak, *Ind. Eng. Chem., Anal. Ed.*, **3**, 179 (1931).

[CONTRIBUTIONS FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

Researches on Nitrogenous Glucosides. IV. Some New Attempts to Synthesize Pyrimidine Glucosides

BY TREAT B. JOHNSON AND WERNER BERGMANN

The authors desire to report in this paper new data resulting from some special experiments applied in their researches on nitrogenous glucosides, which do not find their proper place in other papers to be published on this subject. The first contribution of importance from this Laboratory was made in 1930 when Hilbert and Johnson[1] synthesized successfully 3-glucosidouracil by interaction of 2,6-dimethoxypyrimidine with tetraacetylbromoglucose. The resulting acetyl derivative gave the desired nucleoside on hydrolysis. Later Hilbert[2] applied a similar reaction using 2-methoxy-6-aminopyrimidine and tetraacetylbromoglucose in order to obtain the corresponding glucoside of cytosine, but without success. It is of interest to note here that E. Fischer also failed in his attempts to prepare glucosides of both uracil and cytosine by the action of tetraacetylbromoglucose on the silver salts of these two pyrimidines.[3] Recognizing the limitations of this method of approach to practical methods of synthesizing nitrogenous glucosides, we next turned our attention to the study of techniques based on the use of sugar isocyanates and corresponding ureas as starting points. The only

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[1] Hilbert and Johnson, THIS JOURNAL, **52**, 4489 (1930).

[2] Hilbert, *ibid.*, **56**, 190 (1934).

[3] E. Fischer, *Ber.*, **47**, 1377 (1914).

sugar isocyanate derivatives recorded in the literature previous to our work were tetraacetylglucose isocyanate $C_{14}H_{19}O_9NCO$ and the corresponding isothiocyanate $C_{14}H_{19}O_9NCS$ described by E. Fischer in 1914.[3] This work of Fischer has been repeated in this Laboratory by different workers and several attempts have been made to utilize such simple sugar constructions for the preparation of nitrogenous glucosides in the hydantoin and pyrimidine series. Haring and Johnson[4] prepared Fischer's glucose isothiocyanate and showed that it adds as expected to α-amino acids or their esters, giving hydantoic acid derivatives which can be condensed smoothly to hydantoins. They prepared the first known glucoside derivatives of 2-thiohydantoin and hydantoin. Johnson and Bergmann[5] reëxamined Fischer's work on the preparation of tetraacetylglucose isocyanate $C_{14}H_{19}O_9NCO$ and its urea derivative, but failed in their attempts to synthesize pyrimidine glucosides from these simple sugar combinations.

In the experimental part of this paper is recorded the history of some interesting derivatives which have resulted from other types of reactions applied by the authors for the synthesis of new nitrogenous glucoside derivatives.

Experimental Part

Extension of Fischer's Isocyanate Work to Other Sugars.—We have found that as a rule the isocyanates of sugars are difficult to obtain in a pure form.[5] In most cases examined only amorphous products have been obtained in our researches. That these amorphous products sometimes contain considerable amounts of the desired isocyanate derivative can be demonstrated easily by their conversion into the corresponding ureas by the action of strong ammonia solution. The yields, however, are generally too low for service in practical synthesis.

1-Arabinose-isocyanate ⟶ 1-Arabinose-urea.—Triacetobromoarabinose was refluxed in dry xylene with twice the theoretical amount of anhydrous silver cyanate for several hours. After filtration and dilution of the xylene with petroleum ether an oil separated which solidified to a resin-like substance and from which no crystalline material could be obtained. The crude reaction product finally was suspended in concentrated ammonia solution when it dissolved immediately. The acetyl groups of the glucoside were removed by this treatment, and by application of a method of purification described in our previous paper we succeeded in isolating a beautiful crystalline urea derivative of 1-arabinose melting at 192°. It showed an optical rotation of $\alpha^{25}\text{D}$ +51.9° (0.1197 g. in 3.0686 g. of water gave d + 2.02°). This substance proved to be identical with 1-arabinose urea which has been described previously by Helferich.[6]

Xylose-isocyanate ⟶ sym-Dixylose-urea.—Triacetobromoxylose was refluxed as usual with silver cyanate in xylene for several hours. The amorphous reaction product which was obtained after filtration and addition of petroleum ether was treated with concentrated aqueous ammonia in the usual way. From the reaction mixture we separated a substance which crystallized in fine needles. It showed no sharp melting point, turning brown at 230° and charring at 250°. It gave an optical rotation of $\alpha^{25}\text{D}$ −20.5° (0.112 g. in 3.07 g. water gave d − 748°). The substance was identified as *sym*-dixyloseurea previously described by Helferich.[6]

Anal. Calcd. for $C_{11}H_{20}O_9N_2$: C, 40.73; H, 6.22. Found: C, 40.91; H, 6.39.

Heptaacetyllactose-isothiocyanate, $C_{12}H_{14}O_3(OCOCH_3)_7$-NCS.—As a rule it has been the authors' experience that the isothiocyanate derivatives of sugars are easier to obtain in a pure crystalline condition than the corresponding isocyanates. Seven grams of heptaacetylbromolactose was refluxed with 5 g. of silver thiocyanate in xylene for ten minutes. After addition of petroleum ether to the filtered solution crystals of the isothiocyanate began to separate. After purification by crystallization from chloroform and petroleum ether the isothiocyanate was obtained in the form of large prismatic crystals. It melted at 169–170°.

Anal. Calcd. for $C_{27}H_{35}O_{17}NS$: C, 47.82; H, 5.20. Found: C, 47.89; H, 5.39.

Heptaacetyllactose-ethylthiourethan, $C_{29}H_{41}O_{18}NS$.—This was prepared by refluxing the above isothiocyanate derivative in absolute ethyl alcohol. It crystallizes from hot alcohol in the form of needles melting at 119°. Like many other thiourethans it contains water of crystallization.

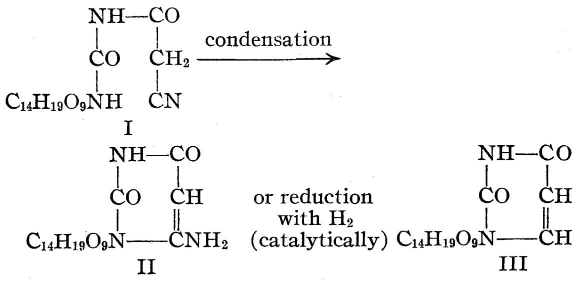
Anal. Calcd. for $C_{29}H_{41}O_{18}NS$: C, 46.94; H, 5.85. Found: C, 47.10; H, 5.81.

Heptaacetyllactosethioureido-ethyl acetate, $C_{31}H_{44}$-$O_{19}N_2S$.—One one-hundredth mole of the above isothiocyanate and 0.015 mole of ethyl glycine hydrochloride were refluxed in chloroform, containing a few drops of pyridine, for two hours. The excess of solvent was then expelled *in vacuo*, water added to the residue and the condensation product extracted with ether. After drying the ether solution, petroleum ether was added, when crystals of the reaction product separated. It deposited in the form of octahedra melting at 100°.

Anal. Calcd. for $C_{31}H_{44}O_{19}N_2S$: C, 47.68; H, 5.68. Found: C, 47.61; H, 5.73.

Attempts to Prepare Pyrimidine Glucosides in the Barbituric Acid Series.—The following proposed synthesis of a glucosido-uracil was studied:

A. Tetraacetylglucose-urea + cyanacetic acid



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(4) Haring and Johnson, THIS JOURNAL, **55**, 395 (1933).

(5) Johnson and Bergmann, *ibid.*, **54**, 2360 (1932).

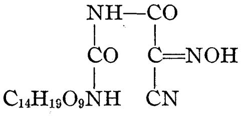
(6) Helferich, *Ber.*, **59**, 69 (1926).

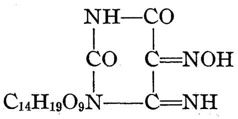
Four grams of tetraacetylglucose-urea, 1 g. of cyanoacetic acid and 2 cc. of acetic anhydride were heated at 100° for ten minutes. On adding water to the cooled solution a crystalline substance separated. After crystallizing several times from dilute alcohol it melted constant at 135°.

Anal. Calcd. for $C_{18}H_{23}O_{11}N_3$: C, 47.15; H, 5.27; N, 9.17. Found: C, 47.16; H, 5.24; N, 9.12.

Theoretically this substance could be either an acyclic or a cyclic compound (I or II). In order to determine its constitution molecular proportions of the compound and sodium nitrite were warmed in water for several minutes. The solution became yellow in color and on acidifying with acetic acid prismatic, plate-like crystals separated. After recrystallization from boiling water they melted at 179–180°. That we are dealing here with a nitroso derivative of the acyclic compound I as represented by formula IV is supported by the yellow color, and, furthermore, by the fact that cyanoacetic acid itself and sodium nitrite interact in a similar manner.

Anal. Calcd. for $C_{18}H_{22}O_{12}N_4$: C, 44.34; H, 4.75; N, 11.50. Found: C, 44.42; H, 4.74; N, 11.18.


IV


V

If the reaction product resulting from condensation with cyanoacetic acid is to be represented by the cyclic structure II, it should react with ammonia with removal of the acetyl groups and with formation of the stable cyclic glucoside. We found, however, that such treatment yielded smoothly glucose urea, leading to the conclusion that formula I and not II represents the correct constitution of the original condensation product.

Anal. Calcd. for glucose urea: C, 37.82; H, 6.35. For $C_{10}H_{15}O_7N_3$ (from II): C, 41.53; H, 5.22. Found: C, 37.93; H, 6.40; N, 12.36.

Under no conditions did we succeed in converting the ureide I into the pyrimidine II by the action of alkali.

We also attempted to effect ring closure of the ureide I by means of catalytic hydrogenation as previously applied successfully by Rupe,[7] and later by Johnson and Bergmann[8] for the preparation of uracil and thymine, respectively. We obtained no evidence of the formation of a uracil-glucoside derivative. An attempt finally was made to condense tetraacetylglucose-urea with malonic acid to obtain a barbituric acid glucoside derivative. Twelve grams of acetic anhydride, 10 g. of acetylglucose-urea and 2.7 g. of malonic acid were heated at 100° for thirty minutes. We obtained a deep orange colored solution. Dilution with water led to the precipitation of a crystalline substance from which we succeeded in separating a product that crystallized from methyl alcohol without coloration after treatment with norite. It melted at 206–207°. The results of analysis indicated that we were not dealing with a barbituric acid derivative, but with the acyclic compound *di-(tetraacetylglucose)-ureide of malonic acid*, $C_{14}H_{19}O_9NH\text{-}CONHCOCH_2CONHCONHC_{14}H_{19}O_9$.

Anal. Calcd. for $C_{33}H_{44}O_{22}N_4$: C, 46.68; H, 5.23; N, 6.60. Found: C, 46.51; H, 5.34; N, 6.86.

When this diureide was allowed to interact with alcoholic ammonia at ordinary temperature, glucose urea was formed.

Summary

1. Methods have been described for preparing 1-arabinose-urea, *sym*-dixylose-urea and heptaacetyllactose isothiocyanate and derivatives.

2. Condensation of cyanoacetic acid with tetraacetylglucose-urea leads to the formation of the ureide $C_{14}H_{19}O_9NHCONHCOCH_2CN$. Attempts to condense this to a pyrimidine construction were unsuccessful.

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[7] Rupe, *Helv. Chim. Acta*, **8**, 850 (1925).

[8] Johnson and Bergmann, THIS JOURNAL, **55**, 1733 (1933).

NEW HAVEN, CONN.

RECEIVED APRIL 4, 1938

[CONTRIBUTION FROM THE BUREAU OF CHEMISTRY AND SOILS, U. S. DEPARTMENT OF AGRICULTURE]

Fixation of Active Nitrogen by Organic Compounds

BY LOUIS B. HOWARD[1] AND GUIDO E. HILBERT

The most promising of various possible methods for directly introducing some form of elementary nitrogen into organic substances is the one utilizing active nitrogen[2] which consists essentially of atomic nitrogen. General experience has shown that molecular nitrogen is inert toward organic compounds and no catalyst has yet been discovered which will activate nitrogen to the extent that it will interact with organic materials. In this connection, it is noteworthy that practically all of many assumed reactions between nitrogen and organic molecules proceed with an increase in free energy.[3] In contrast to the ordinary form of nitrogen, atomic nitrogen, in view of its high reactivity, trivalent-like structure, $\left(\mathrm{N}\!\!<\right)$, and relatively long life, would be expected to interact

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[1] Now in the Bureau of Entomology and Plant Quarantine, Whittier, California.

[2] For a recent review see Sponer, "Molekülspektren und ihre anwendung auf chemische Probleme," II Text, Verlag von Julius Springer, Berlin, 1936, p. 458, and also Kneser, *Ergeb. exakt. Naturw.*, **8**, 229 (1929).

[3] We are grateful to Dr. R. Wiebe and Dr. R. T. Milner for having made many of these calculations.

with organic compounds. Practically the only work carried out in this direction has been done by Strutt, and by Willey and Rideal,[4] who examined superficially the behavior of a number of compounds toward active nitrogen produced by a condensed discharge. Relatively small amounts of materials[5] were worked with and apart from hydrogen cyanide the production of nitrogenous material of an organic nature[6] was not demonstrated.

In the investigation of the interaction of active nitrogen and organic materials, we were mainly interested in determining whether nitrogen can be fixed to yield a relatively complex product and, if so, what the nature of the product is, since this information is of value in elucidating the mechanism of the reaction. Diphenylacetylene was chosen as the organic partner in the reaction since the aromatic portion of the molecule was expected to confer properties to the nitrogenated material which would make it easy to handle, a matter of considerable importance as small quantities must of necessity be manipulated. Another apparent advantage in favor of diphenylacetylene is the vulnerability of the acetylenic linkage and this was expected *a priori* to be attacked to yield benzonitrile as follows

$$C_6H_5C{\equiv}CC_6H_5 + 2N\!\begin{smallmatrix}\diagup\\ -\\ \diagdown\end{smallmatrix} \text{ or } N_2^* \longrightarrow 2C_6H_5CN$$

In order to gain further information on the mechanism of the reaction the behavior of active nitrogen toward benzonitrile and toward tetrahydronaphthalene also was studied. The active nitrogen used in this investigation was produced by an uncondensed discharge except in two experiments where the nitrogen was activated by a condensed discharge.

Apparatus and Experimental Data

Apparatus.—After preliminary trials the apparatus shown in Fig. 1 was used in the final studies. It consists of three sections: (1) a purification train for removing, as far as possible, oxygen and water from the nitrogen, (2) a discharge tube for activating the nitrogen and (3) a reaction bulb with accessories for introducing the organic material and collecting the reaction products.

Purification of the nitrogen by the following method gave the best results. The nitrogen (Linde water-pumped) was conducted from the tank through tube A, 4 cm. in diameter and 50 cm. long, which was packed with pellets of potassium hydroxide, and then through B, which was heated electrically at 410°.[7] Tube B, 3 cm. in diameter and 100 cm. long, was packed with approximately 500 g. of copper wire, in pieces 0.16 mm. in diameter and 1 cm. long, which was repeatedly oxidized and reduced with air and hydrogen at about 410° to activate the surface. From this furnace the nitrogen was passed through trap C, cooled with liquid air and filled with copper turnings to turbulate the gas and increase the cold surface. The purified gas was then passed through two filed stopcocks into the activation chamber D. In a single run, nitrogen at flow rates up to 8 cc. per second and in volumes as great as 1000 liters could be handled conveniently. After completion of the experiment the copper in the tube B was readily regenerated by passing hydrogen gas through the three way stopcocks at either end.

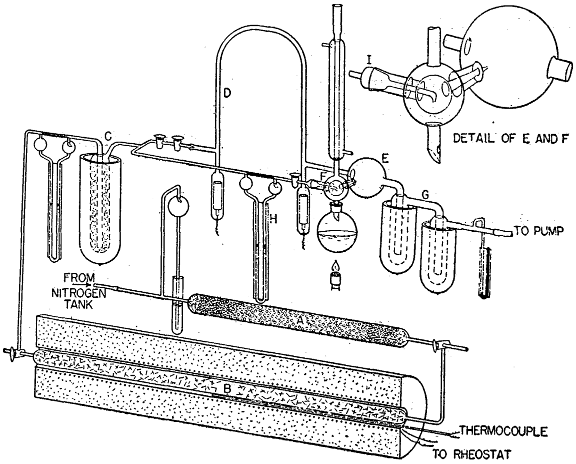

Fig. 1.—Apparatus for the fixation of active nitrogen by organic compounds.

The discharge tube D was fitted with hollow aluminum[8] electrodes, 2 cm. in diameter and 5 cm. long, mounted on tungsten leads. The path of the discharge between the electrodes was about 1 meter long and the current was produced by a General Electric sign transformer operating on 60 cycles and delivering a secondary current of 30 m. a. at 15,000 v.

From D the active nitrogen was conducted into E, where it mixed with the organic vapor which entered from the vaporizing bulb F. The two liquid air cooled traps G served to condense that portion of the reaction product which was not deposited on the walls of E. The unreacted nitrogen was eliminated from the apparatus by a Megovac pump. Bulb F (shown in detail in Fig. 1) consisted of a small jacketed chamber opening into E through a jet at right angles to the stream of excited nitrogen. The vapor

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[4] Strutt, *Proc. Roy. Soc.*, (London) **A85**, 219 (1911); **88**, 539 (1913); **91**, 303 (1915); and Willey and Rideal, *J. Chem. Soc.*, 669 (1927).

[5] Acetylene, benzene, naphthalene, pentane, heptane, methyl bromide, ethyl chloride and iodide, chloroform, bromoform, 1,1-dichloroethane and ethyl ether were investigated.

[6] In the reaction with benzene there was some indication that benzonitrile was formed. On the walls of the reaction chamber a brown-black solid was produced but no test for the presence of combined nitrogen was made.

[7] Under similar conditions, Stiehler, Chen and Clark, This Journal, **55**, 892 (1933), obtained nitrogen containing less than 2.4 × 10^{-6}% of oxygen.

[8] Tiede and Hey, *Ber.*, **66**, 85 (1933), tested several metals as electrode materials and found aluminum to give the highest concentration of active nitrogen.

pressure of the organic compound under study was controlled by refluxing a liquid with a suitable boiling point in the external heating system. Passage of the organic material into E was facilitated by a stream of purified nitrogen from C, the pressure of which was regulated by a filed stopcock and recorded by the flowmeter H. In order to recharge F, the glass tube between F and H was cut and the sealed in jet I removed.

Materials.—**Diphenylacetylene** (m. p. 60°) was prepared by the procedure of Schlenk and Bergmann.[9] After several recrystallizations from alcohol it was dried and stored over phosphorus pentoxide *in vacuo*. **Benzonitrile** from the Eastman Kodak Company was purified by triple extraction with dilute sodium hydroxide and dilute sulfuric acid. After drying over potassium carbonate, it was distilled and only the middle fraction collected; b. p. 191°. **Tetrahydronaphthalene** from the Eastman Kodak Company was purified by fractional distillation in which the middle of three fractions was collected: b. p. 208°.

Action of Active Nitrogen Produced by an Uncondensed Discharge on Diphenylacetylene

General Procedure for Carrying out the Reaction.—Diphenylacetylene in bulb F was heated to 100°, the discharge tube put in action, and the system adjusted with regard to pressure and flow rate of nitrogen (see Table II for the different pressures and flow rates used). When a strong lemon-yellow afterglow filled the reaction bulb E and the traps, the stopcock between H and I was opened slightly in order to facilitate the entrance of the organic material into E. Immediately thereafter a violet glow, suggestive of the cyanogen spectrum, filled the reaction bulb and the first liquid-air trap. As the amount of diphenylacetylene introduced was increased, the violet glow in the reaction bulb was quenched and only faintly visible at the point of entrance of the active nitrogen into E; an intense violet glow was, however, exhibited in the first trap. This condition remained constant even though the rate of introduction of the organic material was increased considerably. Generally the rate of flow of gas through F was so regulated that the violet glow in E was just quenched since it was desired to have an excess of diphenylacetylene in the reaction. Shortly after initiation of the experiment a yellowish-brown film was noticeable on E. Eventually E became wholly covered with a relatively thick layer of the brownish-black opaque product and considerable material was deposited in the two traps.

Isolation and Description of Reaction Products.—After all the sample had been introduced, the discharge was discontinued and the pressure brought up to atmospheric. The liquid air containers were removed from the traps and the system swept out for about four hours with purified nitrogen at a rate approximating 20 l. per hour. *Hydrogen cyanide* was collected in a solution of sodium hydroxide and determined by the Liebig method. The reaction bulb and traps were detached from the apparatus and had a distinct mixed odor of *benzonitrile*, *phenyl isocyanide* and hydrogen cyanide. Much of the *dark brown amorphous solid I*, which is the major product of the reaction, was removed by a combination of scraping and extraction with hexane.[10] Collection of the insoluble product on a filter was followed by thorough pulverization and repeated extraction with warm hexane to remove the last traces of the unreacted acetylene derivative. After drying *in vacuo* at 100° and weighing, it was submitted to elementary analysis. The solid material which could not conveniently be removed from E and G was dissolved in concentrated sulfuric acid and the nitrogen determined by the Kjeldahl method. An aliquot of the combined hexane extracts was likewise analyzed for nitrogen. In order to show the relative amounts of nitrogen obtaining in these fractions the representative results for experiment 3 (see Table II) are given in Table I.

TABLE I

NITROGEN DISTRIBUTION

Fraction	Nitrogen, mg.
Hydrogen cyanide	96
Recovered solid	250
Sulfuric acid solution	98
Hexane extracts	41

The sum of the amounts in the last three fractions is listed in Table II under the column "nitrogen fixed as solid." It is apparent that a relatively unimportant amount is extracted by hexane and this fraction was not further investigated.

The amount of benzonitrile formed in the reaction was so small that it could not be identified by chemical means. An alcoholic extract of some of the slightly pasty solid product formed in an experiment was distilled and the first fraction (one-third) diluted twenty-five times. The absorption bands of this solution were determined by using a quartz spectrograph and a hydrogen discharge tube as a source of light. Spectrographic results although suggestive that benzonitrile was present were not wholly satisfactory as the apparent presence of diphenylacetylene in the unknown tended to confuse the interpretation of the results.

The average of duplicate carbon, hydrogen and nitrogen analyses of (I) prepared under a variety of conditions is recorded in Table II. The percentages of nitrogen listed were determined by the Dumas method and were always from 0.2 to 1.0% higher than the values obtained by the micro Kjeldahl method in which the material was digested for twenty minutes as generally recommended. In a few cases, the percentage of oxygen present in the solid was determined by direct analysis,[11] in order to account for the fact that the sum of the carbon, hydrogen and nitrogen values did not total 100%. The value for oxygen obtained by direct analyses differed by 0.5 to 1.0% from the figure calculated by difference. We believe that the analyses for nitrogen by the Dumas method are low and responsible for this discrepancy. In this connection, it is of interest that certain high melting nitrogenous materials have been found by Milner and Sherman[12] to give low

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[9] Schlenk and Bergmann, *Ann.*, **463**, 76 (1928).

[10] Most of the diphenylacetylene did not react and is to be found in this solution.

[11] Dr. R. T. Milner kindly carried out these determinations by his unpublished modification and adaptation to the semi-micro scale of the method by ter Meulen, *Rec. trav. chim.*, **43**, 899 (1924); **53**, 118 (1934).

[12] Milner and Sherman, *Ind. Eng. Chem., Anal. Ed.*, **8**, 331 (1936).

nitrogen values when determined by the Dumas method. Re-analysis of specimens prepared in experiments 1, 3 and 6 after they had stood from eighteen months to two years in stoppered containers from which no effort to exclude air was made, indicated that the products had been altered. The new results (see analyses f in Table II) were uniformly lower in carbon and nitrogen and higher in oxygen while hydrogen fluctuated but little.

When heated (I) showed a little shrinkage at 300° but remained unmelted at 320°. Upon much stronger heating it decomposed without melting to give ammonia, a small quantity of colorless oil and a considerable residue of charred material. The oil had a foul, isonitrile-like odor and appeared to be insoluble in dilute hydrochloric acid; the acid extract gave a negative color test for aniline with sodium hypochlorite.

Solubility tests showed (I) to be very slightly soluble in alcohol, ether, hexane, benzene and xylene, partially soluble in nitrobenzene and acetonitrile and readily soluble in benzonitrile, from which it was precipitated by hexane. It dissolved fairly readily in concentrated hydrochloric or glacial acetic acid from which solution it was not precipitated either by chilling or dilution with much water but only by making alkaline. The precipitated product was flocculent and continued washing resulted in an increased tendency of the solid to remain suspended, thus exhibiting a behavior quite similar to the peptization of a colloid. Its elementary analysis differed but slightly from the original; in accordance with a sodium ash of 3% the value for nitrogen was 3% less.

Some qualitative information on the mode of attachment of nitrogen in the molecule was secured by the following experiments. Emich's test[13] for the $>\!N-\overset{|}{\underset{|}{C}}-N\!<$ grouping by fusion of (I) with calcium oxide and subsequent formation of the characteristic yellow silver salt of cyanamide was positive. That some of the nitrogen can be removed as ammonia was shown by the following experiment. Weighed samples of about 0.05 g. each were heated for different lengths of time in Kjeldahl flasks with 2 *N* sodium hydroxide and the liberated ammonia collected in standard acid. The amount of nitrogen given off as ammonia after one, three and four hours of digestion was 2.60, 3.37 and 3.83%, respectively, of the weight of the sample. An attempt to hydrolyze the solid by heating 0.2 g. with 25 cc. of concentrated hydrochloric acid in a sealed tube at 180° for three hours was unsuccessful. No ammonium chloride or other crystalline material could be isolated from the acid solution. The insoluble material apparently differed from the original only in being much less soluble in cold concentrated sulfuric acid. Treatment with hot glacial acetic acid and zinc dust affected (I) only slightly. A brown flocculent solid was recovered and melted at 215–235° (dec.). In appearance and solubility it resembled the original product.

Oxidation with nitric acid yielded crystalline material, whereas chromic oxide in acetic acid and potassium permanganate in acetone did not give tractable products. Two grams of (I) was treated with a solution of 50 cc. of concentrated nitric acid and 75 cc. of water. A reaction occurred immediately with evolution of oxides of nitrogen and after twenty minutes of refluxing the solid was largely dissolved, giving a dark orange colored solution. After heating for two hours, the reaction mixture was cooled and the liquid fraction decanted from the insoluble tarry material. The acid solution was made alkaline and then slightly acidified with hydrochloric acid. *A buff colored solid (II)* (0.32 g.) separated and was collected on a filter, washed with cold water and dried. It was practically insoluble in benzene, slightly soluble in ether and partially soluble in alcohol. Extraction with benzene in a Soxhlet apparatus for one day left a residue of 0.12 g. (*Anal.* Found: C, 58.7; H, 3.2; N, 9.7, 9.6; ash, 4.8.) Evaporation of the benzene extract left only an intractable tar. The weakly acidic filtrate from (II) was extracted repeatedly with ether, and the extracts combined, filtered and evaporated to dryness *in vacuo*. The solid residue was subjected to fractional sublimation under diminished pressure at 100°; from the sublimed material there was obtained 0.15 g. of recrystallized *benzoic acid;* m. p. 122°. Continued sublimation at 135° yielded 0.1 g. of a light yellow crystalline material; m. p. 175–185°. Crystallization from water gave a nearly colorless product; m. p. 215–220° in a closed capillary.

Anal. Calcd. for $(C_{10}H_7NO_5)_x$: C, 54.3; H, 3.2; N, 6.3; O, 36.2. Found: C, 54.8, 55.1; H, 3.4, 3.6; N, 6.5; O (by difference), 35.3, 34.8. *Neutral equivalent.* Sub., 3.27 mg.: 2.54 cc. of 0.01 *N* NaOH. Found: 129.

Increased purification of the nitrogen used in the nitrogenation affected the composition of the solid reaction product and influenced the behavior of the discharge. Nevertheless, the reaction appeared to proceed in the same manner and the properties of (I) were not changed appreciably although the percentage of oxygen was lowered markedly. As the oxygen content of the nitrogen was diminished the discharge persisted at higher pressures. For example, when tank nitrogen without purification was used a pressure greater than 10 mm. extinguished the discharge, whereas when rigorously purified nitrogen was used pressures up to 25 mm. were attainable before the discharge failed. For comparison, the data from one of the experiments (No. 1) performed by using nitrogen containing an appreciable amount of oxygen have been included in Table II. In this case the nitrogen was passed over heated copper gauze and then through a liquid air trap. In all other recorded work (Table II) nitrogen purified by the scheme outlined earlier was used.

Variation in Stray Discharge.—In order to demonstrate the unimportance of stray discharge, which unavoidably leaks from the discharge tube to the reaction bulb, a sheath of copper foil cooled by an air blast was wrapped about the tube joining D and E and grounded to a water line. Although this did not completely eliminate the stray discharge it did materially lessen the amount reaching E. This was applied in experiment 4 which otherwise differed in no way from 3. Inspection of Table II shows that the yield of fixed nitrogen did not fall off.

Action of Active Nitrogen Produced by an Uncondensed Discharge on Benzonitrile.—The general procedure was similar to that already described in the experiments on diphenylacetylene. In this case owing to its high vapor pressure at room temperature it was not necessary to heat the benzonitrile. When the stopcock at I was closed, an in-

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[13] Emich, *Monatsh.*, **10**, 321 (1889).

tense violet glow of excited cyanogen filled E. This was extinguished completely when the stopcock was opened slightly. Although some of the reaction product was deposited on the walls of E, the major portion, consisting essentially of a very dark brown solid partially dissolved in unchanged benzonitrile, collected in the traps. The hydrogen cyanide was swept out, collected and determined as in the diphenylacetylene experiments. The contents of the traps were filtered, and the solid thoroughly extracted with hexane. A current of nitrogen was continually swept over the product during these manipulations. The material was desiccated at 100° *in vacuo* for about three hours and immediately submitted to analysis (see expt. 7 in Table II). The filtrate from the solid was diluted with a large quantity of hexane and the flocculent material, which separated, reprecipitated from benzonitrile with hexane. It was dried and analyzed and appears to be identical with the first fraction. *Anal.* Found: C, 65.64; H, 3.73; N, 26.08. The hexane filtrates were combined and concentrated on the water-bath, giving an oil which by fractional distillation was found to consist almost wholly of unreacted benzonitrile; b. p. 190.5; n^{25}_{D} 1.5257.

The solid matter remaining in the traps was not taken up in concentrated sulfuric acid and determined for total nitrogen, since in this case such a value is not a measurement of the total nitrogen fixed. In one experiment, 9, the total yield of solid product was determined. The material that was easily separated was combined with the residue recovered from the acetonitrile, which was used to clean out E and G; weight 0.85 g.

Action of Active Nitrogen Produced by an Uncondensed Discharge on Tetrahydronaphthalene.—This run was carried out in exactly the same manner as that described for diphenylacetylene and in its general appearance differed only in that the cyanogen glow was much weaker and the trap contents at the end of the experiment were almost entirely liquid. After the hydrogen cyanide was swept out, the liquid in the traps was poured directly into hexane and the tar-like solid which precipitated triturated with hexane until a dark brown amorphous solid was obtained. It was collected on a filter in an atmosphere of nitrogen, dried *in vacuo* at 76° for one hour and immediately analyzed. The residues in the traps and from the hexane washings were dissolved in concentrated sulfuric acid and the nitrogen determined by the Kjeldahl method. The results are recorded in Table II.

Action of Active Nitrogen Produced by a Condensed Discharge on Diphenylacetylene.—Modification of the apparatus used in the previous experiments was effected by introducing three Leyden jars across the transformer and by connecting a spark gap in series with the discharge tube, the gap being quenched by a blast of air. Instead of being orange-yellow, the color of the discharge was more reddish-blue. Although unchanged with respect to color the after glow was markedly stronger. In Table II are tabulated results secured in two experiments, namely, 5 and 6. The formation of the solid on the walls of the reaction vessel appeared to take place more rapidly than in the corresponding experiments in which the uncondensed discharge was used. The properties and composition of the solid, however, were about the same.

Discussion

From the results shown in Table II it is concluded that active nitrogen reacts with diphenylacetylene, benzonitrile or tetrahydronaphthalene and initiates the formation of the organic nitrogenous material isolated. All other possible reactions which can account for the products seem to have been eliminated. For example, the early experiments in which the nitrogen used contained an appreciable amount of oxygen—one of these, 1, is recorded in Table II—gave products containing as much as 10% oxygen and were open to the criticism that nitrogen oxides instead of active nitrogen might have interacted with diphenylacetylene. That nitrogen oxides are not involved to any great extent in the later work is shown by experiments 2–4, where rigorously

TABLE II

EXPERIMENTAL DATA AND RESULTS

Expt.	Organic material	g.	Pressure in system, mm.	Duration of run, hours	Rate of nitrogen flow, g./hr	Total nitrogen used, g.	Nitrogen fixed as HCN, mg.	Nitrogen fixed as "solid," mg.	Analyses of solid product, % C		H		N		O Detd.	O Differ.
1	Diphenylacetylene	10	8–9	29	..	...[d]	139	255	71.2	69.8[f]	5.0	4.7	15.3	15.0		8.5
															9.3	10.5
2[a]	Diphenylacetylene	10	4	33	9	286[e]	12	57	71.9		4.5		18.1			5.5
3[a]	Diphenylacetylene	10	9	16	29	455[e]	96	389	76.9	75.2[f]	4.9	4.7	15.6	14.8		2.6
4[a,c]	Diphenylacetylene	10	9	15	29	442[e]	92	432	77.2		4.7		16.3		1.0	1.8
5[b]	Diphenylacetylene	5	9	14	29	403[e]	110	513	72.9		4.7		18.2			4.2
6[b]	Diphenylacetylene	5	9	8	29	228[e]	58	243	74.5	74.0[f]	4.3	4.6	15.4	15.0		5.8
7[a]	Benzonitrile	10	9	39	29	1109[e]	293[g]	...	64.7		3.9		25.5			5.9
8[a]	Benzonitrile	10	9	31	29	897[e]	292[g]	...	64.1		4.2		26.5			5.2
9[a]	Benzonitrile	5	9	17	29	498[e]	118[g]	238[g] (yield 0.85 g.)	64.0		4.2		28.0			3.8
10[a]	Tetralin	10	9	28	29	811[e]	175	400	74.1		6.5		16.7			2.7

[a] Uncondensed discharge. [b] Condensed discharge. [c] Stray discharge reduced considerably. [d] The nitrogen contained appreciably more oxygen than that used in the other experiments. [e] Purity of nitrogen was highest attained in this work. [f] Data obtained from reanalyses made eighteen to twenty-four months later. [g] This cannot be considered as representing only the nitrogen fixed in the reaction since the starting material contained 13.6% of nitrogen.

purified nitrogen was employed. The oxygen content of the products was lowered markedly (in 4 to 1%) without decreasing appreciably the amount of fixed nitrogen. Our experience indicates that it is a very difficult matter to prepare these nitrogenous products entirely free from oxygen, particularly for large scale experiments where the quantities of nitrogen required make impractical production of oxygen-free nitrogen from a chemical source. The contribution to the nitrogenous products by a reaction, between molecular nitrogen and the organic matter, induced by stray discharge is negligible. In no. 4 stray discharge was reduced considerably below that obtaining in no. 3 without affecting the yield of fixed nitrogen and in no. 2 the decrease in the pressure of the system diminished the yield of products, although in so far as stray discharge alone is concerned lowering the pressure in this range conduces to increased stray discharge.

Interaction of the aromatic compounds and active nitrogen yields essentially a polymerized nitrogenous solid and hydrogen cyanide. The yield of solid was greatly influenced by a change in the pressure of the system, thus increasing the pressure from 4 to 9 mm., increased the yield sevenfold. The ratio of nitrogen fixed by diphenylacetylene as hydrogen cyanide to nitrogen fixed as solid for the uncondensed discharge experiments 2–4 varies from 1:4 to 1:5. Experiments 5 and 6 in which a condensed discharge was employed also gave ratios varying from 1:4 to 1:5 and approximately the same yields of products. Averaging numerous determinations of carbon, hydrogen and nitrogen on specimens obtained under different conditions gives ratios of C:H:N that fluctuate from 4.4:3.3:1 (expt. 2) to 5.4:4.2:1 (expt. 7). Under the same conditions as obtained in the diphenylacetylene experiment, benzonitrile yields a solid similar in appearance and physical properties to the acetylene derivative but differing by containing 7% more nitrogen. In this case the yield of hydrogen cyanide is threefold greater. The action of active nitrogen on tetrahydronaphthalene was studied with the object of determining the mole ratio between the combined nitrogen and the original material in the reaction product and of determining the fate of the aliphatic hydrogen. The yield of hydrogen cyanide in this reaction is double that given by diphenylacetylene. Naphthalene is not formed and the solid product although physically similar has a much higher hydrogen content and an empirical formula close to $(C_{10}H_{10}N_2)_x$. It is to be noted that although the ratios of nitrogen to organic material in the reaction product obtained in the different experiments agree among themselves moderately well for a particular reactant, the ratio changes markedly from compound to compound. Thus, for every two molecules of the original aromatic compound,[14] the nitrogenated solid from the diphenylacetylene experiment contains about six atoms of nitrogen, that from the tetrahydronaphthalene experiment about four atoms of nitrogen and that from the benzonitrile experiment about three atoms of nitrogen. This change in the ratio is perhaps not surprising when it is considered that a decrease in this ratio was accompanied by an increase in the ratio of nitrogen fixed as hydrogen cyanide to nitrogen fixed as solid.

For comparative purposes, an exploratory experiment was performed to investigate the behavior of an aliphatic compound, isoprene, toward active nitrogen. A strikingly different result was secured. Practically no solid matter is formed and instead a nitrogenous low-boiling liquid in good yield and generating ammonia on hydrolysis is produced. In view of the apparent simplicity of this product, further studies with unsaturated aliphatic compounds, which are not being contemplated by us, would be expected to yield fruitful information.

The general mechanism of the reaction appears to involve a number of consecutive processes, (1) the interaction of atomic nitrogen and the aromatic compound to form an active intermediate, (2) stabilization of the intermediate to form the solid on the wall and (3) bombardment and further reaction of the solid with active nitrogen. In the collision between the organic molecule and active nitrogen it is not unlikely that a fragment is ejected. The structure of this fragment probably depends on the point of attack of the active nitrogen on the organic molecule and this view accounts, in part at least, for the formation of the simpler materials, hydrogen cyanide, excited cyanogen, (CN*), benzonitrile, etc. That a nitrogen-free, organic particle of relatively high molecular weight is not split off is suggested by the absence of this type of material in the products of the reaction. The most reasonable explanation

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[14] We are, of course, assuming that the empirical formula of the original organic material has not suffered any great change on reacting with active nitrogen to form the solid.

for the high nitrogen content of the solid is that a considerable quantity of nitrogen is introduced by the reaction of active nitrogen with the solid on the walls of the vessel. The similar results secured by the employment of either a condensed or uncondensed discharge for the activation of nitrogen are in accord with the present concept that active nitrogen consists principally of atomic nitrogen, which most probably is the form taking part in the above reaction.

Comparison of the results of this work with those obtained by Kroepelin and Vogel[15] in the study of the action of atomic hydrogen on oleic acid and paraffin oil reveals a striking similarity in the course of the two reactions. (1) In both cases the initial reaction involves combination with the active element and the probable simultaneous formation of free radicals. (2) The active intermediates formed are subsequently stabilized and yield, to a certain extent, brown polymerization products. (3) The introduction of oxygen into the products can be avoided only by using an atmosphere absolutely free from oxygen.

Acknowledgment.—We are indebted to Drs. Wulf, Jones and Melvin for numerous experimental suggestions, to Dr. Wulf for the aid received in discussions on the theoretical aspects of this work and to Mr. Testa for the difficult and clever job of glass blowing on the apparatus.

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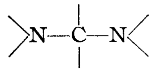
[15] Kroepelin and Vogel, *Ber.*, **68**, 684 (1935); see also v. Bogdandy, Polanyi and Veszi, *Z. angew. Chem.*, **46**, 15 (1933).

Summary

Nitrogen activated by a condensed or uncondensed discharge reacts with diphenylacetylene to form a brown nitrogenous high-melting solid, hydrogen cyanide, excited cyanogen (CN*) and probably traces of benzonitrile and an isonitrile. From its physical and chemical properties, the brown solid, which is the major product of the reaction, appears to be a complex material of high molecular weight. It contains about 16–18% nitrogen, is resistant to acid hydrolysis, liberates ammonia on alkaline hydrolysis, yields benzoic acid and an unidentified, crystalline acid possessing nitrogen on nitric acid oxidation and seems to contain  $>N-\overset{|}{\underset{|}{C}}-N<$ group. Tetrahydronaphthalene and benzonitrile also react with atomic nitrogen to form amorphous solids having physical properties similar to the product from the acetylene derivative. The ratios of fixed nitrogen to organic material in the solid products from the three compounds decrease in the order diphenylacetylene, tetrahydronaphthalene, benzonitrile. In accordance with this, the ratios of nitrogen fixed as hydrogen cyanide to nitrogen fixed as solid decrease in the reverse order. In contrast to the behavior of the aromatic compounds, isoprene with active nitrogen gives instead of a polymerized solid a low-boiling nitrogenous liquid. The results are discussed with reference to the general mechanism of the reaction.

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Condensations by Sodium. XIV. The Phthalic Acids and Some Factors Influencing Yields of Butyl- and Dimethylmalonic Acids

BY AVERY A. MORTON AND FRANKLIN FALLWELL, JR.

This paper describes the formation of all the phthalic acids in these reactions employing sodium and shows that they arise from two distinct sources. When phenylsodium, prepared by refluxing benzene with amylsodium, is carbonated, a third to a fifth of the total acids formed is a mixture of iso- and terephthalic acids, the remainder being benzoic acid. On the other hand preparing the same reagent, phenylsodium, in the presence of sodium benzoate, refluxing and treating the product with carbon dioxide gives the ortho isomer as the sole phthalic acid present. These results demonstrate clearly that there are two types of organosodium intermediates present. According to our common conventions one would be a *m*- or *p*-phenylenedisodium compound and the other sodium *o*-sodiobenzoate. The non-identity of their carbonation products provides a sharp distinction, the lack of which made tracking to the possible sources of butylmalonic acid[1] very difficult.

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[1] Morton, Fallwell and Palmer, THIS JOURNAL, **60**, 1426 (1938).

Phenylenedisodiums, sources of the iso- and terephthalic acids, do not come from dimetalation of benzene by amylidenedisodium, a conclusion reached after a series of experiments with increasing ratios of benzene to amylsodium failed to show formation of these acids at the expense of butylmalonic acid (Fig. 1). This careful study was necessary because a chance agreement[2] in the yields of butylmalonic acid and these phthalic acids before and after addition of 150 ml. of benzene as well as the non-formation of the latter in a low temperature exchange had suggested such a possibility. The complete curve shows these products quite unrelated to each other. An earlier experiment[1] already has indicated that disproportionation of phenylsodium in boiling benzene does not occur appreciably, thus eliminating this possible source of phenylenedisodium. The plotted results of the present work show a slight maximum at 55 ml. of benzene which falls off somewhat as the quantity of benzene is increased. The mechanism field is therefore narrowed and includes the possibility that benzene has been attacked simultaneously or successively by two molecules of amylsodium. In addition this study had revealed a pronounced minimum for the combined yields of caproic and benzoic acids which corresponds with a slight maximum in the yield of phthalic acids. A molal ratio for benzene to amylsodium of two to one was present at this point, an interesting circumstance which together with the peculiarity for the existence of a minimum in the total acids and the failure to get more than 15% of the benzene converted into phenylsodium even under the most favorable circumstances, promises to make an interesting field for further study.

Abnormal reactivity and orienting influences prevail in this series. The sodium carboxyl group, for example, acts in the same manner as do the dimethylamino and methoxyl[3] groups in directing an entering sodium atom to the ortho position. Dimethylaniline and anisole have labile hydrogen atoms in the ortho rather than in the para position. Isophthalic acid predominates by four to one over terephthalic acid, a result calling for *m*-phenylenedisodium as the chief product of the double metalation of benzene. Such results emphasize the novelty in the behavior of these organosodium reagents. One characteristic difference marks these reactions from those in which the ordinary rules of orientation have been derived. In general chemical changes here occur on solid surfaces rather than in homogeneous solutions, a circumstance suggesting that the normal orienting influences may be shelved in the presence of a powerful reagent which operates through an initial adsorption of the molecule. The unpredicted nature of our results may be judged in the light of an observation of Gilman and Kirby[4] that a mixture of benzene, diethylmercury and potassium acted normally, giving phthalic and terephthalic acids after carbonation.

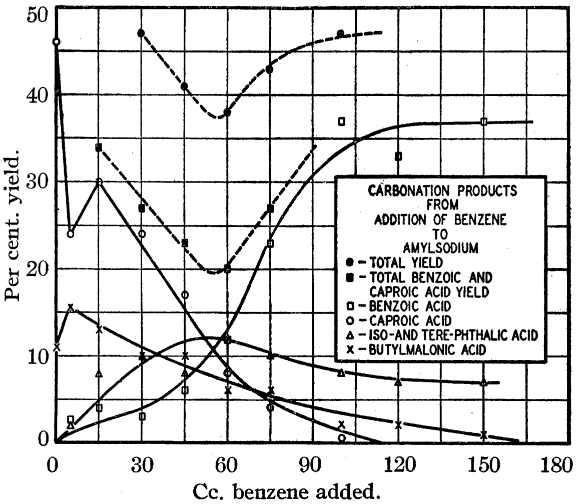

Fig. 1.

Another unusual feature in this work is the difference in the type of reaction which occurs on sodium benzoate when it is added before or after preparation of phenylsodium. The product in the former instance is largely phthalic acid and in the latter is chiefly triphenylcarbinol. Here also we believe the result is influenced by variations in the types of adsorption possible for we have observed that sodium benzoate is readily adsorbed on sodium, so much so in fact that it will completely block the reaction between sodium and amyl chloride if allowed to stand in contact with the metal for a few hours before addition of the chloride.

On the general principle that active nickel will labilize the hydrogen atom we attempted to improve the yield of phthalic acid by carrying out a reaction in the presence of this catalyst. A slight improvement only was realized. A similar experiment on sodium caproate, however, more than

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(2) Morton and Hechenbleikner, THIS JOURNAL, **58**, 2599 (1936).

(3) Morton and Hechenbleikner, *ibid.*, **58**, 2599 (1936); see also Niederl, Roth and Plentl, *ibid.*, **59**, 1901 (1937).

(4) Gilman and Kirby, *ibid.*, **58**, 2074 (1936).

doubled the yield of butylmalonic acid. Preparation of dimethylmalonic acid from sodium isobutyrate was not influenced by the use of nickel.

Experiments

Procedure.—The usual quantities consisting of 35 g. of fine sodium sand and 75 ml. of technical amyl chloride (Eastman Kodak Co.) were employed. The apparatus was the same as described in an earlier paper.[1] Unless otherwise noted the sand was activated prior to reaction by addition of about 5 ml. of *n*-amyl alcohol. This change in manipulation eliminated entirely a short induction period usually observed, changed the yields of caproic and butylmalonic acids to 35 g. (46%) and 5.5 g. (11%), respectively, and increased the ratio of mono- to dicarboxylic acid considerably. The usual amounts obtained without activated sand are around 30 and 16% for the two acids concerned. Two and one-half hours are required for addition of amyl chloride to the metal, one hour for stirring at 25–30° after addition, and one hour for carbonating at 35–40°. The solvent was petroleum ether except in those cases where benzene was used to provide phenylsodium as the organometallic reagent. Here also the use of activated sodium caused a small increase in the yield of benzoic acid.

Iso- and Terephthalic Acids.—Following the preparation of amylsodium as before described, 5, 15, 30, 45, 60, 75, 100, 120 and 150 ml. of thiophene-free benzene were added in separate experiments, the mixture in each case heated to 80° for two hours, and then cooled to below 40° for carbonation. Separation of the mixture of caproic and benzoic acids was accomplished first by petroleum ether and then by benzene extraction accompanied by distillation, that of the insoluble phthalic acids by filtration, and that of butylmalonic acids by extraction with ether. Corresponding yields for the amounts of benzene mentioned above are: for caproic acid, 17, 22, 17, 13, 6, 3, trace, 0, 0 g. (24, 30, 24, 17, 8, 4, trace, 0, 0%); for butylmalonic acid 7.7, 6.5, 5, 5, 3, 3, 1, 1, trace, g. (16, 13, 10, 10, 6, 6, 2, 2, trace, %); for benzoic acid, 2, 3, 2.5, 4.5, 9, 17, 28, 25, 28 g. (3, 4, 3, 6, 12, 23, 37, 33, 37, %); for phthalic acid, 1.2, 4, 5, 4, 6, 5, 4, 3.5, 3.5, g. (2, 8, 10, 8, 12, 10, 8, 7, 7%). For a graph of these results see Fig. 1. A single run in which 15 ml. of the benzene was present in the mixture before addition of amyl chloride produced 14 g. (19%) of caproic acid, 7.5 g. (15%) of butylmalonic acid, 3 g. (4%) of benzoic acid and 3 g. (6%) of the phthalic acid mixture.

Separation of the phthalic acid through the barium salts[5] is incomplete. On converting to the *p*-bromophenacyl[6] esters for identification, the insolubility of the tere- isomer in chloroform was noted. By one such separation the melting point of the crude iso- ester was 174–178° as compared with 179° for the pure material; that of the crude tere- isomer was 215–222° (pure compound is 225°). Products separated by means of the barium salts could be further purified by this method. The approximate composition was 80% iso- and 20% tere-.

Phthalic Acid.—Benzoic acid, 20 g., was added to 45 g. of sodium sand in benzene solution. Immediately after formation of sodium benzoate, 5 ml. of *n*-amyl alcohol was added and the mixture stirred for ten minutes. Amyl chloride, 15 ml., was next added to form the phenylsodium after the usual manner. The mixture was then heated for two hours at 80°. Upon cooling to about 30°, carbonating and decomposing, there was found 2.5 g. (6% referred to benzoic acid) of phthalic acid, decomposing at 160–180° followed by subliming as the anhydride in long white needles, m. p. 110–123 in the crude state (pure 128°). Neutralization equivalent of the crude product was 86 (pure 83). From the same reaction 1.5 g. (3%) of triphenylcarbinol was recovered. Repetition of the experiment using amylsodium instead of phenylsodium yielded 0.3 g. (1.0%) only of phthalic acid probably because the mixture could not be refluxed at so high a temperature.

Triphenylcarbinol.—Sodium benzoate was prepared in a separate container and then added to phenylsodium prepared in the customary manner in benzene as a solvent. After two hours of heating at 75°, carbonating and separating the products, 10.0 g. (24%) of triphenylcarbinol and 0.5 g. (1%) only of phthalic acid were obtained. Yields are calculated on the basis of the sodium benzoate added. Another method of introducing sodium benzoate after formation of phenylsodium was to pass carbon dioxide very slowly (two hours) into the organosodium reagent while the mixture was kept near 50°. Triphenylcarbinol, 7.5 g. (14%), calculated on the amyl chloride originally added was recovered. The amount of phthalic acid obtained was 0.8 g.

Catalytic Action of Nickel.—Raney nickel catalyst from 4 g. of the alloy was added in a benzene suspension to the mixture of sodium caproate and phenylsodium obtained by addition of 75 ml. of amyl chloride to sodium and sodium caproate (20 g. of the acid and 45 g. of metal) in benzene solution. After two hours of heating at 75° and subsequent carbonating, 10 g. (36% calculated on the caproic acid used) of butylmalonic acid, in addition to benzoic and recovered caproic acid, was obtained together with 0.8 g. of triphenylcarbinol. Use of double the amount of nickel (from 8 g. of the alloy) caused little change (9 g. or 33%) in the butylmalonic acid yield. The usual yield of this malonic acid in absence of nickel is 16.5%.

When sodium benzoate mixed with nickel was added to phenylsodium under the same conditions used for preparation of triphenylcarbinol above, the yield of ortho phthalic acid was 1 g. (2%). The yield of dimethylmalonic acid from sodium isobutyrate as described below was unaffected (28%) by addition of nickel.

Dimethylmalonic Acid.—A fine suspension of sodium isobutyrate, from isobutyric acid (20 g.) and sodium (10 g.) in benzene as a solvent, was added to phenylsodium prepared as before stated. After two hours of stirring at 75° the mixture was carbonated. Dimethylmalonic acid, identified by neutralization equivalent and decomposition point, was recovered along with a mixture of benzoic and unreacted isobutyric acid. The yield was 8.0 g. or 27% calculated on the basis of the isobutyric acid. Preparation of the sodium isobutyrate in a separate vessel was necessary in this case because its formation prior to addition of amyl chloride inhibited the latter reaction.

Summary

Iso- and terephthalic acids apparently are formed from phenylenedisodiums, which in turn

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(5) Smith, This Journal, **43**, 1920 (1921).

(6) Kelly and Kleff, *ibid.*, **54**, 4444 (1932).

arise from sodium exchange reactions between benzene and two amylsodium molecules.

Phthalic acid is formed in these processes as a result of sodium benzoate being present during addition of amyl chloride to sodium in benzene solution.

If sodium benzoate is added after formation of phenylsodium the yield of phthalic acid is suppressed and that of triphenylcarbinol is increased.

Nickel as a catalyst causes a considerable increase in yield of butylmalonic acid, a slight increase for phthalic acid and no change in the quantity of dimethylmalonic acid.

The sodium metal can be activated by addition of a small amount of amyl alcohol. The total yield of acids and the proportion of caproic acid is thereby increased.

CAMBRIDGE, MASS. RECEIVED JUNE 3, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF MOUNT HOLYOKE COLLEGE]

Bromo Ethers Derived from Hydantoins Having Terminal Ethylene Double Bonds in the C-5-Position

BY DOROTHY A. HAHN, MARGARET J. MCLEAN AND HELEN T. MURPHY[1]

The addition of bromine to each of two geometric isomers of ethyl N-3-methyl-C-5-benzalhydantoin-N-1-acetate, m. p. 50.5–51.5° and 121–122°, respectively, has been reported.[2] It was stated at that time that a molar quantity of bromine was decolorized as rapidly as added to a solution of either unsaturated hydantoin in carbon tetrachloride and that no evolution of hydrobromic acid took place until after the solution had been heated. In separating the product the carbon tetrachloride was replaced gradually by absolute alcohol and under these conditions a white crystalline compound, m. p. 113–113.5°, was precipitated which on analysis was found to contain one molecule of alcohol. The latter was obviously not present in the form of alcohol of crystallization since it could not be removed even by heating in a high vacuum. The formation of this compound was assumed tentatively to take place in the following way

$$\mathrm{C_2H_5OOCCH_2NCON(CH_3)COC{=}CHC_6H_5 \xrightarrow{Br_2} C_2H_5OOCCH_2NCON(CH_3)COCBrCHBrC_6H_5}$$

the latter compound then losing hydrobromic acid and adding ethanol to form

$$\mathrm{C_2H_5OOCCH_2NCON(CH_3)COC{=}CBrC_6H_5C_2H_5OH}$$

This interpretation of the reaction was based not only upon the results of analysis and the fact that dense fumes of hydrobromic acid had been evolved during the process of heating, but also upon references in the literature which established the formation of unsaturated monobromo derivatives following the addition of bromine to unsaturated hydantoins possessing analogous configurations.[3]

In repeating this experiment it was discovered that although both modifications of ethyl N-3-methyl-C-5-benzalhydantoin-N-1-acetate when treated in this way gave the same compound, m. p. 113–113.5°, a second and more soluble product, m. p. 92–94°, isomeric with the first was also formed in both cases. On the assumption that this represented a geometric modification of the higher melting compound, it was examined spectrographically since it was known that different types of unsaturated hydantoins could be identified readily, and that even isomers could be distinguished one from the other by means of their absorption curves.[4] The results of this investigation were very surprising since while the absorption curves of the two products indicated isomers, they also showed clearly that both belonged to the class of *saturated* and not unsaturated hydantoin derivatives.[5] This discovery led to a consideration of possible molecular configurations for compounds having the above composition that would account for the existence of isomeric saturated hydantoins. And since, due to the presence of two asymmetric carbon atoms, stereo

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[1] The preparation of N-1,N-3-dimethyl-C-5-benzalhydantoin and its derivatives together with the investigation of their respective absorption spectra must be credited to Miss Helen T. Murphy, an honor student at Mount Holyoke College. The spectrographic work was carried out under the direction of Dr. Hildegard Stücklen, Assistant Professor of Physical Chemistry, to whom grateful acknowledgment is due.

[2] Litzinger, THIS JOURNAL, **56**, 676 (1934).

[3] Wheeler, Hoffman and Johnson, *J. Biol. Chem.*, **10**, 154 (1911); Wheeler and Hoffman, *Am. Chem. J.*, **45**, 375–6 (1911); Johnson and Hoffman, *ibid.*, **47**, 20 (1912).

[4] Seikel, THIS JOURNAL, **59**, 436 (1937).

[5] (a) Hahn and Evans, *ibid.*, **50**, 809 (1928); (b) Hahn and Dyer, *ibid.*, **52**, 2505 (1930); Seikel, unpublished work.

modifications were to be expected[6] in the case of a molecule having the following arrangement of atoms

$$C_2H_5OOCCH_2NCON(CH_3)CO\underset{*}{C}(OC_2H_5)\underset{*}{C}HBrC_6H_5$$

the two isomers in question were finally assumed to represent, respectively, racemic modifications of this type.

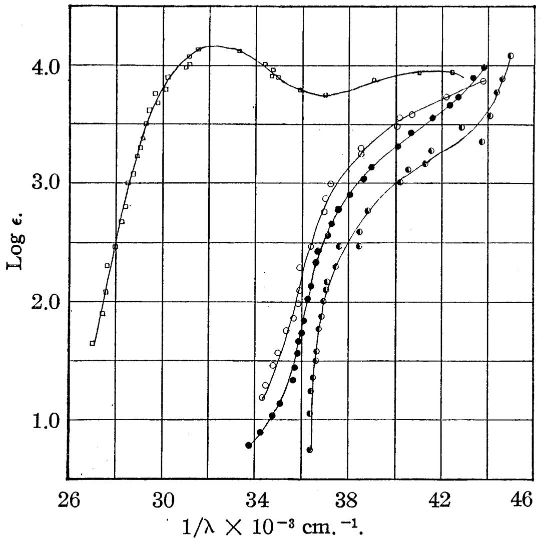

Fig. 1.—□-□-□ N-1,N-3-dimethyl-C-5-benzalhydantoin, $CH_3NCON(CH_3)COC{=}CHC_6H_5$,; N-1,N-3-dimethyl-C-5, 5-ethoxy-bromobenzylhydantoin, $CH_3NCON(CH_3)COC(OC_2H_5)CHBrC_6H_5$; o-o-o isomer, m. p. 141–143°; ●-●-● isomer, m. p. 119.5–121.5°; ◐-◐-◐ N-1,N-3-dimethyl-C-5-benzylhydantoin, $CH_3NCON(CH_3)COCHCH_2C_6H_5$.

Recently the behavior of N-1,N-3-dimethyl-C-5-benzalhydantoin, $CH_3NCON(CH_3)COC{=}CHC_6H_5$, has been investigated under conditions closely analogous to those which have just been described. Although only one of the two geometric isomers of this substance which are theoretically possible has as yet been isolated (p. 817),[5a] this reacts with bromine to form two isomeric compounds, m. p. 141–143° and 119.5–121.5°, which correspond in composition to the formula, $CH_3NCON(CH_3)CO\underset{*}{C}(OC_2H_5)\underset{*}{C}HBrC_6H_5$. These isomers again have been assumed to represent different racemic mixtures, respectively, since such an interpretation is in agreement with the results of analysis and also with the character of the absorption curves of the two compounds. The latter are not only closely analogous to those of the two isomeric ethoxybromo derivatives of ethyl N-3-methyl-C-5-benzalhydantoin-N-1-acetate[7] but both pairs of curves show a marked similarity to that of N-1,N-3-dimethyl-C-5-benzylhydantoin,[8] which can be prepared directly by reducing the corresponding unsaturated compound. On the other hand, they differ radically from the curve of N-1,N-3-dimethyl-C-5-benzalhydantoin.[9]

Due to the fact that the dibromo addition products, the formation of which precedes the formation of both of the above pairs of isomeric ethoxybromo derivatives, are extremely soluble and also very unstable compounds they have not as yet been isolated. It has been observed, however, that the corresponding addition products which are formed when C-5-benzalhydantoin and N-3-methyl-C-5-benzalhydantoin are treated, respectively, in carbon tetrachloride with molar quantities of bromine, are almost insoluble in neutral solvents. An attempt, therefore, is being made to prepare these compounds in pure condition, although they also are very unstable and are difficult to separate completely from the unacted upon unsaturated hydantoins from which they are obtained, since these too are relatively insoluble substances. Even at this stage of the investigation, however, it seems probable from a preliminary study of these products that the same general relationships can be shown to exist between unsaturated hydantoins of this type and their respective dibromo, alkoxybromo and oxybromo derivatives that have been reported recently to maintain in the case of 2,4-diketotetrahydropyrimidines and their corresponding derivatives.[10] This investigation is well under way and will be reported later in detail.

Experimental

Ethyl N-3-Methyl-C-5,5-ethoxy-bromobenzylhydantoin-N-1-acetate, $C_2H_5OOCCH_2NCON(CH_3)COC(OC_2H_5)CHBrC_6H_5$, exists in two isomeric modifications, m. p.

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[6] Hahn and Seikel, THIS JOURNAL, **58**, 647 (1936).

[7] The spectra of ethyl N-3-methyl-C-5-benzalhydantoin-N-1-acetate and its derivatives were examined several years ago by Dr. Margaret K. Seikel (unpublished work). Since the absorption curves of these compounds are almost identical with those of the corresponding derivatives of N-1,N-3-dimethyl-C-5-benzalhydantoin, it has seemed more confusing than helpful to try to represent both sets in the same figure.

[8] *Cf.* ref. 5a, p. 817. This same compound is also formed when each of the two isomeric ethoxybromo derivatives of N-1,N-3-dimethyl-C-5-benzalhydantoin is reduced under the action of hydrogen iodide and red phosphorus.

[9] Compare the four curves in the accompanying figure.

[10] Johnson and Sprague, THIS JOURNAL, **59**, 2436 (1937).

113–113.5° and 92–94°, both of which are formed when either of the two geometric isomers of ethyl N-3-methyl-C-5-benzalhydantoin-N-1-acetate is treated with bromine under conditions which have already been described.[2] The lower melting and more soluble product was not isolated from the reaction mixture, however, until later when oily residues deposited from filtrates from the isomer, m. p. 113–113.5°, were examined. It was finally obtained by a process of fractional crystallization and when pure separated from concentrated alcohol solutions in the form of well-defined colorless prisms, which suffered no loss in weight when heated at 70°.

Anal. Calcd. for $C_{15}H_{15}O_4N_2Br{\cdot}C_2H_5OH$: N, 6.78; Br, 19.35. Found: N, 6.96, 7.05; Br, 19.88, 20.05.

It is interesting to note that in repeating these experiments and using "seed" to induce crystallization, 10.0 g. of the unsaturated ester, m. p. 50.5–51.5°, gave 6.2 g., m. p. 110–112°, as a first precipitate and 3.1 g., m. p. 80–84°, on concentrating the filtrate; while 10.0 g. of the unsaturated ester, m. p. 121–122°, gave 3.3 g., m. p. 110–112°, as a first precipitate and 6.1 g., m. p. 80–84°, on concentrating the filtrate.

N-1,N-3-dimethyl-C-5,5-ethoxy-bromobenzylhydantoin, $CH_3\overline{NCON(CH_3)COC}(OC_2H_5)CHBrC_6H_5$, exists in two isomeric modifications, m. p. 141–143° and 119.5–121.5°, both of which were formed under the following conditions. Bromine,[11] dissolved in chloroform (3.8 g. in 38 cc.), was added rapidly at room temperatures to a colorless solution of N-1,N-3-dimethyl-C-5-benzalhydantoin (p. 817)[5a] in the same solvent (5.0 g. in 15 cc.) until a permanent color remained after shaking. No hydrobromic acid was evolved during this process, which occupied only a few minutes, but when the solution was heated dense fumes of the mineral acid were given off. After the solution had been concentrated to a volume of 25 cc., an equal quantity of absolute alcohol was added and the mixture evaporated rapidly over a steam-bath to 25 cc. This process was repeated 5 or 6 times or until the odor of chloroform was no longer noticeable. The boiling solution (50 cc.) was then set aside to crystallize. The first precipitate, when filtered, washed with absolute alcohol and dried, weighed 4.22 g., m. p. 137–139°. A second precipitate, which was obtained by concentrating the filtrate and wash alcohol to 20 cc., consisted of 2.6 g., m. p. 103–106°. Small additional amounts of both products were obtained from the filtrate from the second precipitate, the combined weights of all representing a yield of more than 90% of the theoretical as calculated on the basis of the above formula. So far as could be observed there was no reason for suspecting the presence of any other substances in the reaction mixture. The two products were purified by recrystallization from absolute alcohol, in which the second is much the more soluble. Both separated from their boiling solutions, on cooling, in the form of large transparent hexagonal prisms or plates, which showed no loss in weight on heating.

Anal. Calcd. for $C_{14}H_{17}O_3N_2Br$: C, 49.28; H, 5.02; Br, 23.42. Found: (m. p. 141–143°) C, 49.41, 49.60; H, 5.01, 4.96; Br, 23.97, 23.86; (m. p. 119.5–121.5) C, 49.76, 49.58; H, 5.01, 5.26; Br, 23.47, 23.52.

Both compounds when heated for one hour at 110° with hydrogen iodide and red phosphorus were transformed into N-1,N-3-dimethyl-C-5-benzylhydantoin,[8] which was identified by comparison with an analyzed specimen.

The absorption curves of these two isomers, together with curves of the unsaturated hydantoin (p. 817)[5a] from which they were obtained and the corresponding saturated hydantoin[8] which resulted from their reduction, are represented in the accompanying figure. The spectrographic measurements were made by the Henri method[12] using a Hilger E2 quartz spectrograph. Each compound was dissolved in absolute alcohol which had been freed from all traces of benzene by fractional distillation with a Fenske column (3.5 × 1.5 cm.). The source of light was a copper-silver spark and Eastman No. 40 photographic plates were used except for the region below 2400 Å., when "Ultraviolet Spectrographic" plates were used.

Summary

N-1,N-3-dimethyl-C-5-benzaldehydantoin, when treated in chloroform solution with a molar quantity of bromine, gives an addition product which loses hydrobromic acid on heating and when the chloroform is replaced by absolute alcohol, is subsequently transformed into an ethoxybromo derivative. The latter exists in two isomeric modifications, both of which yield N-1,N-3-dimethyl-C-5-benzylhydantoin when heated with hydrogen iodide and red phosphorus.

The absorption curves of the two isomers, on comparison with those of N-1,N-3-dimethyl-C-5-benzylhydantoin and other saturated hydantoins of the same general type, indicate that both represent saturated compounds. Moreover, these two curves closely resemble those of the two isomeric ethoxybromo derivatives of ethyl N-3-methyl-C-5-benzalhydantoin-N-1-acetate which were obtained from the latter by means of similar transformations.

SOUTH HADLEY, MASS. RECEIVED JUNE 10, 1938

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[11] The calculated molar quantity of bromine equals 3.69 g.

[12] Henri, "Études de Photochemie," Gauthier-Villars, Paris, 1919, p. 5; *cf.* E. P. Carr and G. F. Walter, *J. Chem. Phys.*, **4**, 756 (1936).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

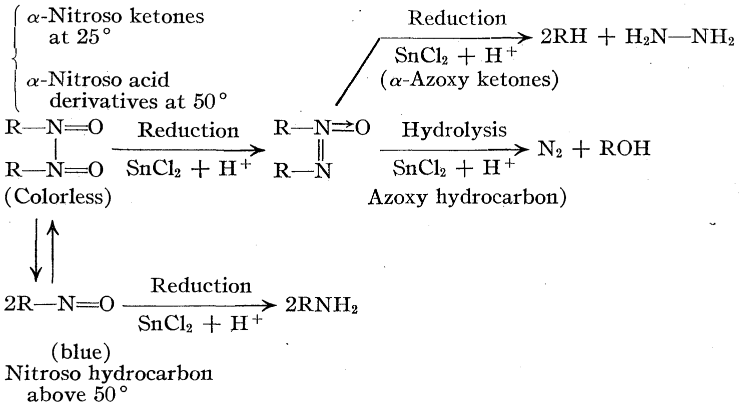
Aliphatic Azoxy Compounds. III. 2-Azoxy-2,5-dimethylhexane[1,2]

BY JOHN G. ASTON AND DAVID E. AILMAN

In order to study the reaction of the azoxy group in aliphatic organic compounds it was desirable to prepare an azoxy compound without any other functional groups. 2-Azoxy-2,5-dimethylhexane was chosen because of the availability of starting materials and lack of volatility with consequent ease of isolation of the product and intermediates.

It was soon found impossible to obtain this compound by reduction of the corresponding nitroso compound either at room temperature or at 57–60° with stannous chloride in acid solution. At room temperature the nitroso compound decomposed without reduction (see experimental section); at 57–60° a 58% yield of the corresponding amine was obtained. These results are important for above 55° the dissociation of the bis-nitroso compound is apparent. In the case of α-nitroso esters, where no such dissociation is evident at 55°,[1b,3] azoxy compounds may be obtained in good yields under similar conditions and no amine is produced. These facts indicate that the linkage in the bisnitroso compounds is through the nitrogens and that reduction to the amine proceeds through the monomolecular form since no amine has ever been found among the reduction products of aliphatic azoxy compounds.[1a]

The situation is made clear by the scheme



2-Azoxy-2,5-dimethylhexane eventually was prepared in 68–75% yield by condensing the corresponding nitroso compound with the corresponding hydroxylamine in the presence of solid potassium hydroxide at 50°. The use of concentrated sulfuric acid gave but 21% yield. Condensation of the corresponding nitro compound and amine in the presence of metallic sodium at reflux temperature gave a 10% yield. Both reactions are known in the aromatic series.[4]

Attempts to reduce this azoxy compound with stannous chloride and hydrochloric acid merely resulted in the hydrolysis of the compound to nitrogen, octenes, dimethylisoamylcarbinol and 2-chloro-2,5-dimethylhexane.

The accompanying mechanism seems plausible for this new type of decomposition as in the hypothetical intermediate II one sees a close analogy with the diazonium salts, the part enclosed by the dotted square being analogous to the $-\mathrm{N}^+\equiv\mathrm{N}$ of these salts.[5] While the hydrolysis occurs rapidly at reflux temperature in the presence of 6 *N* hydrochloric acid and stannous chloride, with 6 *N* hydrochloric acid alone (or with stannic chloride) the reaction is negligible.

The decomposition of the *bis*-nitroso compound by acid to yield nitrogen and nitrous oxide obviously can be formulated in a manner similar to the hydrolysis of the azoxy compound.

When treated with methylmagnesium iodide in diisoamyl ether at 100° for eighty minutes, less than 20% of addition was observed. This is hardly consistent with the open chain formula of the azoxy group since aromatic azoxy compounds seem to react as expected.[6] If the azoxy group in aliphatic compounds had the ring structure, the intermediate II postulated in the hydrolysis could be formed by ring cleavage.

It is hoped to report on the be-

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[1] The first two papers of this series are: (a) THIS JOURNAL, **54**, 1530 (1932); (b) *ibid.*, **56**, 1387 (1934).

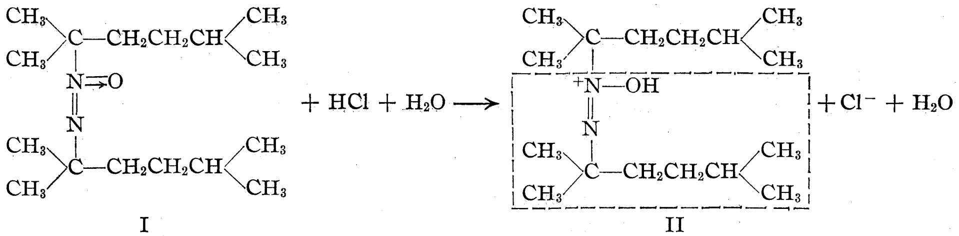
[2] Presented before the Organic Division of the American Chemical Society at Rochester, N. Y., September, 1937.

[3] Sidgwick, Taylor and Baker, "The Organic Chemistry of Nitrogen," Oxford University Press, 1937, p. 215.

[4] *Cf.* ref. 3, p. 427; Brand and Stohr, *Ber.*, **39**, 4065 (1906); Angeli and Marchetti, *Atti accad. Lincei*, [5] **15**, 480 (1906); *Brit. Chem. Abstracts*, i, 716 (1906).

[5] That the accompanying olefins are also a consequence of such a mechanism was kindly called to our attention by Dr. F. C. Whitmore (see Whitmore and Langlois, THIS JOURNAL, **54**, 3442 (1932).

[6] Cumming and Ferrier, *J. Roy. Tech. Coll. Glasgow*, **2**, 49 (1929); Bigelow, *Chem. Rev.*, **9**, 155 (1931).



I II

$$\longrightarrow \text{ROH} + \text{R—N=N—OH} + \text{HCl}$$

$$\text{III} \quad \text{R—N=N—OH} \longrightarrow \text{ROH} + N_2$$

where R = Me_2C-*i*-Am

havior of this compound with other reducing agents and the products of addition of organometallic compounds in the near future.

Experimental

Hydrolysis of 2-Nitroso-2,5-dimethylhexane.—Sixteen and four-tenths grams (0.115 mole, monomolecular basis) of nitroso compound was refluxed with 50 cc. of concentrated hydrochloric acid. The decomposition started explosively with the evolution of a large amount of nitrogen containing less than 2% of nitrous oxide. This gas sample, and all others in the work, was identified by distillation of the liquefied gas and vapor pressure measurements on the fractions. After refluxing for a half hour the oil was steam distilled. A tarry scum remained behind. The distillate gave, after drying with potassium carbonate, 0.85 g. (0.008 mole, 7% yield) of octenes, 6.0 g. (0.043 mole, 37% yield) of dimethylisoamylcarbinol and 2-chloro-2,5-dimethylhexane and 3.0 g. of high-boiling material, n^{20}_D 1.430. The octene fraction boiled at 106–120° (730 mm.), n^{20}_D 1.416, and gave positive reactions with bromine water and alkaline permanganate. From the carbinol-chloride fraction was obtained 4.6 g. of material boiling at 80–86° (100 mm.), n^{20}_D 1.4232–1.4240, which was nearly pure chloride.

Anal. Calcd. for $C_8H_{17}Cl$: Cl, 23.8; mol. wt., 148.6. Found: Cl (Stepanoff), 23.3, 23.9; mol. wt. (cryoscopic in benzene), 146.5, 147.3.

The pure chloride was obtained by passing gaseous hydrogen chloride into dimethylisoamylcarbinol keeping the mixture cool with tap water until constant weight was obtained. It boiled at 86° (100 mm.), n^{20}_D 1.4231.

The Action of Stannous Chloride and Concentrated Hydrochloric Acid on 2-Nitroso-2,5-dimethylhexane at 60°.—Six grams (0.042 mole) of 2-nitroso-2,5-dimethylhexane[7] was melted and added dropwise during twenty minutes to a rapidly stirred solution of 16 g. (0.071 mole) of crystalline stannous chloride dihydrate, in 50 cc. of concentrated hydrochloric acid held throughout the reaction at 57–60°. The blue color of the nitroso compound disappeared immediately with each addition; 90 cc. of 28% potassium hydroxide solution was added keeping the temperature below 45° to prevent loss of material by volatilization. Each addition of alkali precipitated basic tin salts which gradually redissolved. On neutralization and distillation of the solution 0.3 g. of octenes (0.0027 mole, 6.4% yield) and 0.54 g. (0.0039 mole, 9.2% yield) of a mixture of dimethylisoamylcarbinol and the corresponding chloride was obtained.

The solution was made strongly alkaline by the addition of 75 cc. more of 28% potassium hydroxide solution, and the amine was steam distilled. After drying with anhydrous potassium carbonate, distillation gave 3.17 g. (0.024 mole, 58% yield) of amine, b. p. 94° (150 mm.), 141.0° (733.6 mm.).[8]

Anal. Calcd. for $C_8H_{19}N$: C, 74.42; H, 14.73. Found: C, 73.63; H, 14.65.

The hydrochloride, after crystallization from alcohol, melted at 171°.

Anal. Calcd. for $C_8H_{20}NCl$: Cl, 21.5. Found: Cl (Volhard), 21.2.

A positive isonitrile test was obtained. The *p*-toluenesulfonamide[9] melted at 89.5–90°; mixed m. p. with an authentic sample showed no lowering.

The Action of Stannous Chloride and Concentrated Hydrochloric Acid on 2-Nitroso-2,5-dimethylhexane at Room Temperature.—A typical experiment is described; 8.5 g. (0.06 mole) of the solid *bis*-nitroso compound was added rapidly to a well-stirred solution of 8.3 g. (0.037 mole) of stannous chloride in 12.5 cc. of concentrated hydrochloric acid. The temperature, originally 27°, rose to 31° and fell slowly. The stirring was stopped as soon as the oily layer was colorless (not over ten minutes elapsed from the beginning of the addition). Nitrogen, containing a small amount of nitrous oxide, was evolved (the total gas was 5% of the nitrogen content of the sample).[10] Titration with permanganate showed that only 12% of the stannous ion had been oxidized. The mixture was diluted with 100 cc. of ice water and the oil was removed by solution in ether, washed with water, washed with sodium carbonate solution to remove acids, and dried with calcium chloride. Distillation gave 0.5 g. (0.0045 mole, 7.4% yield) of low-boiling material, n^{20}_D 1.419, (probably octenes); 2.5 g. (0.018 mole, 30% yield) of liquid boiling at 100–105° (150 mm.), n^{20}_D 1.422; and a residue amounting to 4.9 g. of a light yellow, very viscous oil, n^{20}_D 1.472, which contained tin and chlorine and which could not be distilled at 80° under the pressures of a mercury vapor pump.

The liquid, b. p. 100–105° (150 mm.), was evidently a

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[7] Piloty and Ruff, *Ber.*, **31**, 457 (1898).

[8] Konowalow, *ibid.*, **28**, 1852 (1895); *Chem. Zentr.*, **77**, II, 312 (1906).

[9] Hinsberg and Kessler, *Ber.*, **38**, 906 (1906).

[10] If at this point the mixture is nearly neutralized with sodium hydroxide solution and steam distilled, the products are: 8% yield of low-boiling material (probably octenes), 53% yield of a mixture of dimethylisoamylcarbinol and chloride, and 3–9% yield of 2-amino-2,5-dimethylhexane.

mixture of dimethylisoamylcarbinol and the corresponding chloride. It was converted to the pure chloride, b. p. 98° (150 mm.), $n^{20}D$ 1.4230, by gaseous hydrogen chloride.

Anal. Calcd. for $C_8H_{17}Cl$: Cl, 23.8; mol. wt., 148.6. Found: Cl (Stepanoff), 24.0; mol. wt. (cryoscopic in benzene), 150.

When the viscous oil was boiled with concentrated hydrochloric acid, a blue color was visible in the refluxing oil for a short time. Nitrogen was evolved, and the oily material had the odor of dimethylisoamylcarbinol.

Preparation and Properties of 2-Azoxy-2,5-dimethylhexane.—Four grams (0.0276 mole) of 2-β-hydroxylamino-2,5-dimethylhexane[11] and 3.6 g. (0.025 mole) of 2-nitroso-2,5-dimethylhexane and 1.0 g. of anhydrous potassium carbonate were heated together at 50° for nine hours without apparent reaction; 1.0 g. of solid potassium hydroxide was added to the mixture. After eighteen hours more at 50° the reaction mixture was yellow green in color, showing that a reaction of the blue nitroso compound had taken place. Water was added to dissolve the salts and the oil was taken up in ether and dried with sodium sulfate. Distillation gave 5.1 g. (0.019 mole, 75% yield) of the colorless azoxy compound, b. p. 111° (5 mm.), $n^{20}D$ 1.4434, d^{20}_4 0.8564.

Anal. Calcd. for $C_{16}H_{34}ON_2$: C, 71.04; H, 12.68; N, 10.36; mol. wt., 270.3. Found: C, 70.67; H, 12.63; N (Dumas), 10.75; mol. wt. (cryoscopic in benzene), 273, 270.

2-Azoxy-2,5-dimethylhexane was also prepared by a procedure similar in every way to the above except that anhydrous magnesium sulfate followed by concentrated sulfuric acid were substituted for the potassium carbonate and potassium hydroxide, respectively. The yield of azoxy compound was 21%. The addition of the sulfuric acid caused some charring and not more than 0.5 cc. of acid was added. No other products were identified.

The Reaction of 2-Amino- with 2-Nitro-2,5-dimethylhexane in the Presence of Metallic Sodium.—Seven-tenths gram (0.03 gram atom) of sodium in the form of freshly cut chips was added gradually to a refluxing solution of 5.0 g. (0.039 mole) of the amine and 6.2 g. (0.039 mole) of the nitro compound. The products were worked up as above and gave 1.0 g. (0.0037 mole, 9.5% yield) of impure azoxy compound, b. p. 100–125° (4 mm.), $n^{20}D$ 1.4415, which was not redistilled. Other products were not identified.

The reaction of 2-azoxy-2,5-dimethylhexane with methylmagnesium iodide in the apparatus of Kohler and Richtmyer[12] showed the absence of active hydrogen and gave less than 20% addition during 80 minutes at 100°.

The Action of Stannous Chloride and Dilute Hydrochloric Acid on 2-Azoxy-2,5-dimethylhexane.—Ten and three-tenths grams (0.038 mole) of azoxy compound was mixed with 25 g. (0.11 mole) of stannous chloride in 225 cc. of 6 *N* hydrochloric acid solution. The mixture was refluxed for four hours in an apparatus for collecting the evolved nitrogen (generally about 60% of the theoretical) over 50% potassium hydroxide solution, and then the oil layer was steam distilled. Titration showed that less than 5% of stannous ion had been oxidized. The oily product, neutralized with sodium carbonate, and dried with calcium chloride, gave on distillation: 3.3 g. (0.03 mole, 38% yield) of octenes b. p. 113–120° (730 mm.), $n^{20}D$ 1.416; 3.6 g. (0.026 mole, 33% yield) of a mixture of dimethylisoamylcarbinol and 2-chloro-2,5-dimethylhexane, b. p. 98–103° (150 mm.), $n^{20}D$ 1.4221; and 0.6 g. (0.0022 mole, 6% yield) of recovered azoxy compound.

Individual octenes were not identified. Positive reaction with bromine water and with alkaline permanganate demonstrated their olefinic character. The octenes were converted to dibromides by reaction with bromine vapor and expulsion of excess bromine with dry air. Calcd. for $C_8H_{16}Br_2$: mol. wt., 272. Found: (cryoscopic in benzene), 274. Attempts to distil this dibromide gave a colorless oil, b. p. 100–113° (30 mm.), $n^{20}D$ 1.478, which rapidly turned red-brown and gave low analyses for bromine and mol. wt.

The carbinol–chloride mixture was analyzed. Calcd. for 65 mol. % $C_8H_{17}Cl$, 35 mol. % $C_8H_{18}O$: C, 67.5; H, 12.26; Cl, 16.20. Found: C, 66.7; H, 12.27; Cl, 16.21. The mixture was then converted with gaseous hydrogen chloride to pure chloride, b. p. 98° (150 mm.), $n^{20}D$ 1.423. Calcd. for $C_8H_{17}Cl$: mol. wt., 148.6. Found: (cryoscopic in benzene), 150.

Attempts to hydrolyze 0.5-g. samples of the azoxy compound with 6 *N* hydrochloric acid alone, or with stannic chloride, resulted in only negligible amounts of gas being evolved on refluxing for several minutes. With stannous chloride, a sample gave up its nitrogen almost quantitatively on refluxing for a half hour without oxidation of the stannous ion. The nitrogen was pure as shown by vapor pressure measurements. Evidently stannous chloride is a specific catalyst for the hydrolysis.

In conclusion we wish to thank Dr. G. H. Messerly for help with the distillation of the small quantities of gases and their identification by vapor pressure measurements.

Summary

1. 2-Nitroso-2,5-dimethylhexane was reduced to 2-amino-2,5-dimethylhexane in 58% yield with stannous chloride and concentrated hydrochloric acid at 60°.

2. The action of stannous chloride and concentrated hydrochloric acid on 2-nitroso-2,5-dimethylhexane at room temperature did not give appreciable reduction but only decomposition. Nitrogen, nitrous oxide, octenes, dimethylisoamylcarbinol, 2-chloro-2,5-dimethylhexane, and very small amounts of 2-amino-2,5-dimethylhexane were among the decomposition products.

3. The hydrolysis of 2-nitroso-2,5-dimethylhexane by refluxing with concentrated hydrochloric acid produced nitrous oxide, nitrogen, octenes, dimethylisoamylcarbinol and 2-chloro-2,5-dimethylhexane.

4. 2-Azoxy-2,5-dimethylhexane was prepared in excellent yield by condensing the corresponding

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(11) Piloty and Steinbock, *Ber.*, **31**, 221 (1898).

(12) Kohler and Richtmyer, THIS JOURNAL, **52**, 3736 (1930).

β-hydroxylamine and nitroso compound in the presence of alkali.

5. 2-Azoxy-2,5-dimethylhexane was shown to be non-reactive with methylmagnesium iodide.

6. The hydrolysis of 2-azoxy-2,5-dimethylhexane with dilute hydrochloric acid catalyzed by stannous ion produced nitrogen, octenes and dimethylisoamylcarbinol.

STATE COLLEGE, PENNA. RECEIVED JUNE 9, 1938

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Aliphatic Azoxy Compounds. IV. The Preparation of Certain α-Azoxy Ketones. The Molecular Refractions and Parachors of Aliphatic Azoxy Compounds[1]

BY DAVID E. AILMAN

In order to study the molecular refractions and parachors of aliphatic azoxy compounds, additional liquid azoxy compounds are desirable. Ethyl 2-methyl-2-azoxy-propionate[2] and 2-azoxy-2,5-dimethylhexane[3] have been described elsewhere.

This paper describes the preparation and properties of ethyl α-azoxyisopropyl ketone and α-azoxyisopropyl isobutyl ketone of which only the former is a liquid whose molecular refraction and parachor have been compared with those of the compounds mentioned above.

Experimental

Ethyl α-Azoxyisopropyl Ketone.—Ten grams (0.039 mole, bimolecular basis) of bimolecular ethyl α-nitrosoisopropyl ketone[4] was reduced with 10.8 g. (0.048 mole) of crystalline stannous chloride $SnCl_2 \cdot 2H_2O$, in 15.8 cc. of concentrated hydrochloric acid,[5] keeping the temperature 30–36° for twenty minutes. A titration with permanganate showed that 0.040 mole of stannous ion had been oxidized. After nearly neutralizing the acid solution with sodium carbonate the liquid azoxy compound was removed by solution in ether, dried with potassium carbonate, and distilled, collecting 5.18 g. (0.021 mole; 55% yield), b. p. 126–126.5° (6 mm.), n^{20}_D 1.4587, d^{20}_4 1.0151.

Anal. Calcd. for $C_{12}H_{22}O_3N_2$: C, 59.45; H, 9.16; N, 11.57; mol. wt., 242.3. Found: C, 58.85; H, 9.09; N (Dumas), 11.72; mol. wt. (cryoscopic in benzene), 240, 241.

Reduction of Ethyl α-Azoxyisopropyl Ketone.—Eight grams (0.033 mole) of the azoxy compound on stirring with a solution of 31 g. (0.14 mole) of stannous chloride in 45 cc. of concentrated hydrochloric acid for seven hours at a maximum temperature of 65° (maintained for one hour), oxidized only 46% of the stannous ion (calculated for reduction to ketone and hydrazine[5]). (The excess stannous ion was determined by permanganate titration, which does not distinguish between stannous ion and hydrazine. This has been corrected for.) The isolation of 1.5 g. of a semicarbazone which melted a few degrees below the m. p. of ethyl isopropyl ketone semicarbazone (each recrystallization raised the m. p., but the amounts became too small to handle), together with the isolation of 0.5 g. of dibenzalazine (sharp m. p. and mixed m. p. with an authentic sample) showed that a reduction of the type observed with methyl α-azoxyisopropyl ketone[5] had occurred.

α-Azoxyisopropyl Isobutyl Ketone.—Eight grams (0.025 mole) of the *bis*-nitroso ketone[4] was reduced with 6.9 g. of stannous chloride in 13 cc. of concentrated hydrochloric acid. On chilling, after the reduction was complete, the oil crystallized. The product was recrystallized from lukewarm alcohol–water and then melted at 30–31°. The yield of purified product was 4.0 g. (0.013 mole, 52% yield).

Anal. Calcd. for $C_{16}H_{30}O_3N_2$: C, 64.39; H, 10.14; mol. wt., 298.2. Found: C, 63.97; H, 10.65; mol. wt. (cryoscopic in benzene), 310, 297, 300.

Molecular Refraction and Parachor

In Table I are given the properties of the liquid aliphatic azoxy compounds prepared to date. Densities were determined with a 2-cc. pycnometer. Surface tensions were measured with a DuNouy tensimeter which had been checked against water and alcohol.

TABLE I

No.	Compound	Mol. wt.	n^{20}_D	d^{20}_4	γ_{20}
1	2-Azoxy-2,5-dimethylhexane[3]	270.4	1.4434	0.8564	28.27
2	Ethyl α-azoxyisopropyl ketone	242.3	1.4587	1.0151	35.88
3	Ethyl 2-methyl-2-azoxypropionate[2]	274.3	1.4412	1.0562	33.56

In Table II are given in column 2 the observed molecular refractions; in column 3 the summation of Eisenlohr atomic refractivities,[6] exclusive of the azoxy grouping; and column 4 the refractivity

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[1] Presented in part before the Organic Division of the American Chemical Society at Rochester, N. Y., September, 1937. *Cf.* preceding paper.

[2] Aston and Parker, THIS JOURNAL, **56**, 1387 (1934).

[3] Aston and Ailman, *ibid.*, **60**, 1930 (1938).

[4] Aston and Mayberry, *ibid.*, **57**, 1888 (1935).

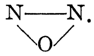
[5] *Cf.* Aston, Menard and Mayberry, *ibid.*, **54**, 1530 (1932).

[6] Eisenlohr, *Z. physik. Chem.*, **75**, 585 (1910); **79**, 129 (1912).

deduced for the atoms of the N_2O group. The index numbers (Col. 1) refer to the compounds identically numbered in Table I.

TABLE II

No.	M. R. exptl. (a)	Σ atomic ref. exclusive of N_2O group (b)	Ref. due to the atoms of the N_2O group (a) − (b)
1	83.772	76.088	7.684
2	65.217	57.638	7.579
3	68.602	60.924	7.678
		Mean	7.647 ± 0.045

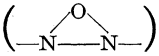
We may take the value of N_2 in aliphatic azo compounds as 6.32.[7] From other evidence it is known that the azoxy group in aromatic compounds has the open chain structure. The group refractivity should be obtained by adding the appropriate value for semipolar oxygen to the above value for N_2. Since the existing data do not yield a definite value, as a first try one adds the value for carbonyl oxygen, 2.211. The result is 8.531. A negative exaltation of about 0.9 unit is required to produce agreement with the measured value. Using the value for ether oxygen, 1.643, instead of that for carbonyl oxygen, gives a total of 7.96 units. This value, for no good reason, agrees well with our measured value of 7.65 when we consider that we have not taken into account the loss of the double bond of N=N in forming . It is interesting to note, however, that the molecular refraction of nitrous oxide is 7.58[8] and it has the open chain structure.

In order to calculate the value for aromatic compounds it seems reasonable to add the exaltations observed in aniline and nitrobenzene, 0.85 and 0.78 respectively, to the above value of 8.53, making a total for the azoxy group in aromatic compounds of 10.16. The observed value is 13.25 based on azoxybenzene.[7b] In other words a further positive exaltation of 3.1 units is necessary to produce agreement. Thus consideration of the results on a comparable basis uncovers a discrepancy of the order of 4 units between the experimental group refractivity in aliphatic compounds and in the unsubstituted aromatic compound if both had the same structure. Another method of comparison is to compare the difference of 1.33 between the above values for aliphatic azoxy and azo compounds with the difference of 0.61 between azoxy- and azobenzene.[9] The results obtained with meta substituted aromatic azo and azoxy compounds give a similar result but with ortho and para substituted compounds the difference is as much as two units lower (−1.4).[9] In the face of this big variation among aromatic compounds themselves, it might be said that the difference between azoxy and azo compounds in the aliphatic series is in accord with the difference in the aromatic series. The agreement however may be fortuitous. In view of this the value obtained for the molecular refraction of the azoxy group in aliphatic compounds is difficult to interpret.

In Table III (Col. 2) are given the parachors (*P*) deduced from the data of Table I. In column 3 of this table are given the parachors (P_1) calculated using Sugden constants[10] on the basis that the azoxy group has the structure $-N{=}\overset{|}{N}\longrightarrow O$ (*i. e.*, that the oxygen is semi-polar). The parachor value used for semi-polar oxygen was −1.6.

TABLE III

	P	P_1	P_2
2-Azoxy-2,5-dimethylhexane	729.2	724.8	719.9
Ethyl α-azoxy-isopropyl ketone	584.8	586.8	581.9
Ethyl 2-methyl-2-azoxy propionate	625.8	620.4	615.5

In column 4 are given the parachors (P_2) calculated on the basis that the azoxy group has its atoms arranged in a ring ().

The agreement is close between the experimental values and those calculated on the basis of the open chain structure.

Similar results have been obtained with aromatic azoxy compounds[10] (p. 119).

The difference between the measured values for aliphatic compounds and those calculated on the basis of a ring might be due to a different parachor value for the heterocyclic ring. This alternative is not particularly appealing but cannot be rejected.

One significant fact bearing on their constitution stands out from the chemical behavior of aliphatic azoxy compounds. It is that the azoxy group does not behave like that in aromatic compounds in which it has unquestionably the unsymmetrical open chain structure. The absence of color in all aliphatic azoxy compounds thus

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[7] (a) Barrick, Drake and Lochte, THIS JOURNAL, **58**, 160 (1936), have measured the molecular refractions of 2,2′-azo-bispropane, 2,2′-azobisbutane, and isopropyl-azo-*s*-butane; (b) Auwers and Heimke, *Ber.*, **61**, 1030 (1938), have studied the methyl and ethyl esters of azoisobutyric acid. From these five compounds we have calculated the mean value of N_2 in azo compounds to be 6.32 ± 0.05.

[8] Brühl, *Z. physik. Chem.*, **25**, 647 (1898).

[9] Auwers, *Ber.*, **61**, 1042 (1928).

[10] Sugden, "The Parachor and Valency," Alfred A. Knopf, New York, 1930, pp. 38 and 116.

far prepared differentiates them from the aromatic azoxy compounds. However, this may be due to absence of conjugation. As a ring structure for the azoxy group in aliphatic compounds is not inconsistent with the data on molecular refraction, one must admit of this possibility, although it requires the assumption of a special parachor value for this ring.

The author wishes to thank Professor J. G. Aston for suggesting this problem.

Summary

1. Ethyl α-azoxyisopropyl ketone and α-azoxyisopropyl isobutyl ketone were prepared by reduction of the corresponding *bis*-nitroso compounds with stannous chloride in concentrated hydrochloric acid.

2. The molecular refractions and parachors of three liquid aliphatic azoxy compounds have been determined and yield a constant value for the azoxy groups.

3. There is no evidence that the azoxy group in aliphatic azoxy compounds has the unsymmetrical open chain structure rather than that of a three-membered ring.

STATE COLLEGE, PENNA. RECEIVED JUNE 9, 1938

[CONTRIBUTION FROM THE DEPARTMENTS OF BIOCHEMISTRY, UNIVERSITY OF NORTH CAROLINA, AND THE CHICAGO MEDICAL SCHOOL]

Studies on Proteins in Liquid Ammonia. IV. On the Enzymatic Hydrolysis of Proteins Reduced by Metallic Sodium in Liquid Ammonia[1]

BY EVAN W. MCCHESNEY[2] AND RICHARD G. ROBERTS

Previous papers of this series[3] have shown that, of the reactions of proteins in liquid ammonia, perhaps the most interesting is that with metallic sodium. The proteins behave as acids, hydrogen gas is liberated, and sodium salts are formed. From these salts the sodium can be displaced by the addition of ammonium salts such as the chloride or sulfate. During the reaction with sodium reducible groups in the proteins, such as the —S—S— linkages in cystine, undergo reduction. This reaction has been demonstrated by du Vigneaud, Audrieth and Loring.[4]

Goddard and Michaelis[5] have shown that if keratins, such as wool, are treated with sodium thioglycolate in aqueous solution, they undergo reduction of the —S—S— linkages of the cystine residues, forming "kerateines" which are digestible by pepsin and trypsin, even if the resultant —SH groups are reoxidized during the course of the isolation of the kerateine. They postulate that the —S—S— groups act as "very firmly established cross links uniting the elementary fibers of polypeptide chains," and that reduction of the —S—S— groups destroys the fibrous pattern of the protein. Routh[6] has confirmed these observations and has extended them to show that powdered wool, produced by prolonged grinding of wool in a ball mill, is digested about half as fast as casein under comparable conditions.

It occurred to us that it would be of interest to determine whether proteins subjected to reduction by metallic sodium in liquid ammonia are altered with respect to their digestibility by enzymes, and to study proteins of several types, including silk fibroin. This protein is an albuminoid and has been shown[3a] to react rapidly with sodium in liquid ammonia to give a product soluble (as the free acid) in both ammonia and water. Its behavior should be of interest by comparison to wool, since the presence of cystine in the molecule has not been demonstrated.

In this work five substances have been studied: peptone, a substance previously digested by pepsin; egg albumin, a protein not readily digested by trypsin; casein, a protein readily digested by trypsin; wool, an albuminoid containing cystine; and silk fibroin, an albuminoid not containing cystine.[7]

Materials.—Commercial Witte's peptone, egg albumin (Merck impalpable powder), casein (Hammarsten), washed sheep's wool, and silk fibroin (prepared from silk noils supplied by the Cheney Bros. Silk Mills, South Man-

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[1] Presented at the Dallas meeting of the American Chemical Society, April 19, 1938.

[2] Present address: Winthrop Chemical Co., Rensselaer, N. Y.

[3] (a) McChesney and Miller, THIS JOURNAL, **53**, 3888 (1931); (b) Miller and Roberts, *ibid.*, **56**, 935 (1934); (c) Roberts and Miller, *ibid.*, **58**, 309 (1936).

[4] Du Vigneaud, Audrieth and Loring, *ibid.*, **52**, 4500 (1930).

[5] Goddard and Michaelis, *J. Biol. Chem.*, **106**, 605 (1934); **112**, 361 (1935).

[6] Routh, *J. Biol. Chem.*, **123**, Proc., civ (1938).

[7] Analysis by the Sullivan method showed that cystine is entirely lacking in silk fibroin.

chester, Conn.). The trypsin used was a commercial product (Digestive Ferments Co., Trypsin, 1:110).

Methods.—For the reduction experiments, 10 g. of the protein (dried for forty-eight hours at 80°) was suspended in about 200 cc. of liquid ammonia (dried over sodium) and 3 g. of metallic sodium was added. The reaction was allowed to proceed for two hours, then the equivalent amount of ammonium chloride (7 g., c. p. grade) was added. The ammonia was allowed to evaporate through a mercury seal, and the product was collected. It was then ground in a mortar, and dried in a desiccator over concentrated sulfuric acid until no odor of ammonia could be detected.

Half of the product was now dissolved, or suspended, in 100 cc. of water. A portion of 1 cc. was removed, and the amount of acid or alkali needed to bring the whole solution to a reaction just faintly acid to phenolphthalein was determined and added. Trypsin, 0.2 g., was added, and enough water to make a total volume of 200 cc. Amino nitrogen was immediately determined by the method of Van Slyke, after which toluene was added as a preservative, and the solution was incubated at 37°. Amino nitrogen was determined at intervals of one, three, seven, and fourteen days thereafter. Total nitrogen in solution was determined by the Kjeldahl method at the end of the fourteenth day.

The control experiments were of two types. In one type the native protein, 5 g., was brought into solution at *p*H 8, 2.5 g. of sodium chloride (c. p.) and 0.2 g. of trypsin were added, followed by enough water to make a total volume of 200 cc. The digestion and analyses were run as before. In the second type of control (referred to in the table as the "NH_3 control"), metallic sodium, 3 g., was dissolved in about 200 cc. of liquid ammonia and the exact equivalent of ammonium chloride (as judged by the disappearance of the blue color) was added immediately. Then the protein, 10 g., was added and the ammonia was allowed to evaporate. The product was powdered, dried over sulfuric acid, and analyzed as before.

Experimental Data.—The results are shown most conveniently in the form of tables.

TABLE OF RESULTS

	Amino nitrogen					
Days	Mg./cc.	% total sol. N	Mg./cc.	% total sol. N	Mg./cc.	% total sol. N
	Peptone		Reduced peptone		Casein	
0	0.63	18	0.71	21	0.34	9
1	1.32	37	1.38	39	1.54	40
3	1.54	43	1.42	41	1.70	44
7	1.63	46	1.42	41	1.84	48
14	1.63	46	1.52	43	1.86	49
Total N in soln. end digest, mg./cc.	3.53		3.44		3.83	
	Reduced casein		Reduced silk fibroin		NH_3 control, Silk fibroin	
0	0.10	11	0.50	13	0.08	7
1	.27	30	.84	22	.24	21
3	.28	30	.93	25	.25	22
7	.29	31	1.09[8]	29	.30	27
14	.35	38	1.00	27	.33	29
Total N in soln. end digest, mg./cc.	0.92		2.77		1.13	
	"Egg albumin"		NH_3 control, "Egg albumin"		Reduced "Egg albumin"	
0	0.07	3	0.10	4	0.31	11
1	.13	5	.32	13	.45	16
3	.20	7	.46	18	.55	19
7	.25	9	.73	28	.64	22
14	.32	11	1.05	41	.66	23
Total N in soln. end digest, mg./cc.	2.85		2.56		2.87	
			Reduced wool		NH_3 control, wool	
0			0.11	4	0.01	4
1			.58	22	.05	22
3			.71	27	.06	27
7			.86	32	.07	32
14			.92	35	.07	32
Total N in soln. end digest, mg./cc.			2.64		0.22	

Discussion of Results

It is apparent that reduction of small molecules of the order of polypeptides, as in peptone, does not affect their digestibility by trypsin appreciably. Any changes such as tautomerization which occur during the reaction with sodium, would be expected to be reversed when the sodium is neutralized and the product is dissolved in water. Furthermore, the treatment with sodium would not be expected to alter significantly the structure of the molecules, their solubility, or the degree of their dispersion. For casein the results are somewhat difficult to interpret. The protein becomes more insoluble in water (at *p*H 8) as a result of the treatment with sodium in liquid ammonia, or with liquid ammonia alone, and its digestibility is decreased markedly in spite of the fact that the amount of the enzyme is greater relative to the amount of protein in solution. This would seem to indicate that the treatment in some manner causes the molecule to become more compact: decreases the extent of dispersion.

Egg albumin seems to be partly denatured by treatment with liquid ammonia since it is not completely soluble in water after having been suspended in ammonia. However, the treatment seems to open up the molecule in some way, since the increase in digestibility is very striking. The increase in the digestibility of reduced albumin probably, therefore, can be attributed to the action of the ammonia, not the sodium. The reason for the difference between the behavior of the two albumins (one reduced, one not, both ammonia-treated) is not apparent.

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(8) Evidently analytical error.

The amount of digestion of native wool and silk fibroin by trypsin is of course practically negligible. Both ot these become digestible when treated with sodium in liquid ammonia, the results for wool being particularly striking. In the case of silk fibroin, it is evident that some dispersion occurs in both the reduced and the ammonia-control samples. The rate of digestion of the material actually in solution in the water is practically the same in both cases. The greater dispersion of the reduced material is probably due to some alteration in structure during the reaction with sodium. Sufficient information on the structure of silk fibroin is not available to make it possible to suggest what this alteration may be. However, if the molecular weight is as great as postulated by Bergmann and Niemann[9] (217,000), then it would seem as if some of the cross ties between the polypeptide chains must be ruptured. Since there are no —S—S— linkages, the rupturing would have to be (on the basis of present knowledge) by a reaction of the nature of ammonolysis.

The results with wool would be anticipated, perhaps, from the work of Goddard and Michaelis. Wool is only slightly dispersed in ammonia, and the product of the ammonia treatment is only slightly dispersed in water. However, that material which is dispersed digests about as rapidly as the reduced wool. The wool which is subjected to reduction is much more highly dispersed in water (not completely, however), probably due to reduction of the —S—S— linkages and consequent rupture of the cross ties between the polypeptide chains, hence digests rather rapidly.

It is worthy of note that in every case in which the protein was treated with sodium, the ratio of amino nitrogen to total nitrogen is increased (except in wool where the figures for the control are too small to be significant). This is strikingly demonstrated in the case of egg albumin where the native protein and the ammonia control each show about 4% of nitrogen in the amino form, while the reduced sample shows 11%. This would seem to indicate that some reaction of the nature of ammonolysis is occurring, with the rupture of some peptide bonds.

Acknowledgment.—We wish to thank Dr. W. D. Block of the University of Michigan for running the cystine analysis on silk fibroin.

Summary

The digestibility (by trypsin) of a number of proteins has been studied after treatment with sodium in liquid ammonia and compared with their behavior in the native state (or after treatment with liquid ammonia alone). Peptone is not affected by the treatment, and the digestibility of casein is decreased. The digestibilities of egg albumin, silk fibroin, and wool are increased by the treatment with sodium in liquid ammonia. Controls treated only with liquid ammonia appear to digest as rapidly as the reduced materials when one considers the smaller amount of the protein dispersed by the ammonia in *the cases of silk fibroin and wool.*

CHAPEL HILL, N. C. RECEIVED MAY 27, 1938

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[9] Bergmann and Niemann, *J. Biol. Chem.*, **122**, 581 (1938).

[Contribution from the Department of Chemistry, Stanford University]

Saponins and Sapogenins. VIII. Surface Films of Echinocystic Acid and Derivatives

By C. R. Noller

Previous work[1] has indicated that echinocystic acid is a pentacyclic triterpenoid of the formula $C_{29}H_{45}(OH)_2COOH$. Nothing definite is known concerning the position of the functional groups. Since the same trimethylnaphthol is obtained by selenium dehydrogenation of echinocystic acid as has been obtained from hederagenin and oleanolic acid, it seems likely that all have one hydroxyl group in the same position. Moreover, the non-reactivity of the carboxyl group and of the double bond of these compounds indicates a similar location of these groups.

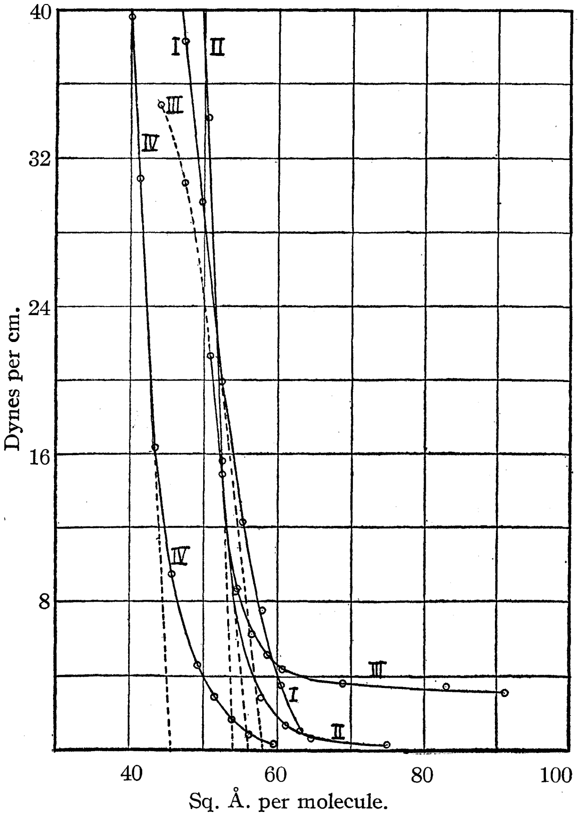
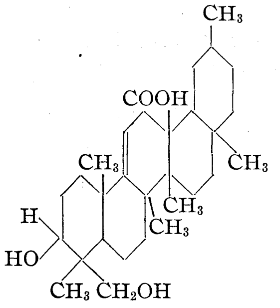


Fig. 1.—Pressure-area curves for surface films of: I, echinocystic acid; II, methyl echinocystate; III, echinocystic acid diacetate; IV, echinocystadienol.

In view of the extensive investigation of Askew[2] on surface films of a large number of triterpenoids, it was thought that similar measurements on echinocystic acid and its derivatives might give valuable information concerning its structure. Echinocystic acid gives a solid incompressible film occupying an area of about 58 sq. Å. per molecule (Curve I) as compared with an area of 54 sq. Å. for hederagenin. Methyl echinocystate (Curve II) and echinocystic acid diacetate (Curve III) give films very similar to that of echinocystic acid with areas of 56 and 54 sq. Å., respectively. All films show the phenomenon of contraction even at low pressures but it is much more pronounced with the methyl ester and the diacetate than with echinocystic acid.

Curve IV represents the data on films of echinocystadienol obtained by decarboxylating and dehydrating echinocystic acid. The area occupied is only 45 sq. Å. per molecule or about 20% less than that for the other three compounds. Examination of Askew's curves shows that hederabetulin, which is obtained by the decarboxylation of hederagenin,[3] occupies an area of about 46 sq. Å., in close agreement with that for decarboxylated and dehydrated echinocystic acid.



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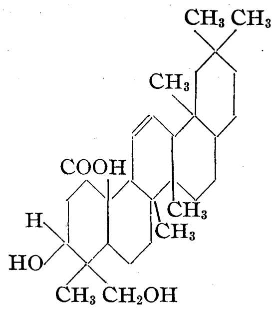

II

It is difficult to see how formula I proposed by Ruzicka[4] for hederagenin could account for this decrease in area. With the carboxyl group near the middle of the molecule the free acid should lie flat at low pressures and occupy a large area. Askew assumes that the molecules in the films of hederagenin have been forced to stand on end with

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[1] Bergsteinsson and Noller, This Journal, **56**, 1403 (1934); Noller, *ibid.*, **56**, 1582 (1934).

[2] Askew, *J. Chem. Soc.*, 1585 (1936).

[3] Winterstein and Meyer, *Z. physiol. Chem.*, **199**, 43 (1931); Winterstein and Stein, *ibid.*, **199**, 76 (1931). The formulas given by Askew for hederabetulin and dihydrohederabetulin diacetate are incorrect. Group B should be CH_2OH and CH_2OAc, respectively, while group C should be hydrogen in both cases.

[4] Ruzicka and Giacomello, *Helv. Chim. Acta*, **20**, 301 (1937).

the carboxyl group out of the water but if this were the case, hederabetulin and echinocystadienol should occupy the same area as hederagenin and echinocystic acid. If, however, the carboxyl group in these compounds occupies the position of that in formula II proposed by Kitasato,[5] one could assume that in the acids the molecules are tilted so that the carboxyl group also may touch the water but that in the decarboxylated compounds the molecules are permitted to stand on end and occupy a smaller area.

The chief difficulty with this explanation is the behavior of films of oleanolic acid which has a methyl group in place of the hydroxymethyl group. According to Askew's measurements this acid occupies an area of 48.5 sq. Å. However, Askew's dotted curve XIIIa, which presumably is for the initial film of oleanolic acid, approaches the curve for hederagenin indicating that the initial film, if it were stable, would occupy an area near that for hederagenin. It is conceivable that a second hydroxyl group nearer the B ring is necessary to help the carboxyl group to remain in the water.[6] The fact that oleanolic acid formed gaseous films on sodium hydroxide solutions does not appear to us to be significant since the methyl ester behaved likewise.

It seems to us that assigning the carboxyl group to the position indicated in formula II also provides a better explanation for the behavior of the methyl ester of hederagenin and echinocystic acid and of the diacetate of the latter. If formula I is correct, the free acids should lie flat and esterification should decrease the attraction of the carboxyl group for water and permit the molecules to stand on end and occupy a smaller area; or if it is assumed that the carboxyl group is out of the water in the case of the free acids, acetylation of the alcoholic hydroxyl groups should decrease their attraction for water and permit the molecule to lie flat and occupy a larger area. Actually esterification and acetylation have little effect on the areas occupied which is what one would expect if the groups are all close together near the end of the molecule.

The procedure used in making the measurements of surface pressure was identical with that previously described[7] except that the solvent consisted of 80 parts by volume of cyclohexane and 20 parts of isopropyl alcohol. The preparation of echinocystic acid and of its methyl ester and diacetate has been reported[1] and that of echinocystadienol will be described in a later publication.

Summary

Measurements of the area occupied by surface films of echinocystic acid and its derivatives indicate a close relationship in structure to hederagenin. It is postulated that the smaller areas occupied by hederabetulin and echinocystadienol have a bearing on the position of the carboxyl group in hederagenin and echinocystic acid and support the formula of Kitasato in which the carboxyl group is placed at the fusion of the A and B rings.

STANFORD UNIVERSITY, CALIF. RECEIVED MAY 24, 1938

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[5] Kitasato, *Acta Phytochim.* (Japan), **10**, 199 (1937).

[6] Unpublished work indicates that one of the hydroxyl groups of echinocystic acid is in a postion β to the carboxyl group. We have assumed that the fusion of the A and B rings is *trans* for both hederagenin and echinocystic acid and that the groups containing oxygen are *cis* with respect to each other.

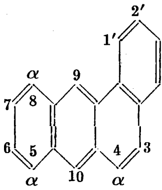
[7] Noller, THIS JOURNAL, **60**, 1629 (1938).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Synthesis of 4,9- and 4,10-Dimethyl-1,2-benzanthracenes[1]

BY LOUIS F. FIESER AND R. NORMAN JONES[2]

Of the ten known dimethylbenzanthracenes those which have shown the most interesting behavior in tests for carcinogenic activity carry substituents in either a meso- or an α-position of the anthracene nucleus. Such substitution is lacking in the 2′,6-, 2′,7-, 3′6-, 3′,7-, and 6,7-dimethyl derivatives,[3] and tests of the hydrocarbons by application to the skin of mice[4] have shown that the first four compounds are inactive and that the 6,7-dimethyl derivative is but weakly carcinogenic. On the other hand, the 5,6-dimethyl isomer[5] is a moderately rapidly acting carcinogen[4] comparable with 1,2,5,6-dibenzanthracene, the 5,9-isomer[6] and the 5,10-derivative[7] are about equal in potency to methylcholanthrene as sarcoma-producing agents, and the 9,10-dimethyl compound[8] is a highly active carcinogen.[9] 1′,10-Dimethyl-1,2-benzanthracene[10] has a substituent in the favorable meso position 10, but the presence of the 1′-methyl group seems to result in decreased activity, for the hydrocarbon has given no subcutaneous tumors in six months.[9] Although it is too early to formulate any but tentative conclusions, the results on record suggest that there is an interesting reinforcing effect of methyl groups in the *meso*- and α-positions. As a means of determining to what extent this effect may be general, it seemed desirable to add to the list of known dimethyl-1,2-benzanthracenes further compounds meeting the specifications indicated. The 4,9- and 4,10-dimethyl derivatives are of particular interest not only because of these considerations but because of the relationship of the former compound to 4,10-ace-1,2-benzanthracene,[11,12] which has been found to give tumors in rats[13] and in mice[14] (Shear[9]), in the latter case in remarkably small dosage.



The scheme of synthesis employed was selected for investigation partly because it offered the possibility of obtaining not only the aromatic hydrocarbons in question but their 1′,2′,3′,4′-tetrahydro derivatives. These seemed of interest in connection with studies in progress on other hydroaromatic derivatives of carcinogens,[15] and since the work was started Shear[9] has made the interesting observation that 1′,2′,3′,4′-tetrahydro-4,10-ace-1,2-benzanthracene[11] has marked carcinogenic activity, giving added significance to the corresponding tetrahydro-4,10-dimethyl compound.

The plan of synthesis is indicated in the chart and involves the introduction of a methyl group at the 4-position by the use of 6-methyltetralin (I) as a component in a phthalic anhydride synthesis. By applying to the intermediate keto acid II the synthetic operations introduced by Fieser and Newman[7] in one series (a) and those of Fieser and Hershberg[16] in another (b), it was possible to introduce methyl groups at positions 10 and 9, respectively. 6-Methyltetralin was synthesized by Krollpfeiffer and Schäfer[17] from toluene and succinic anhydride, and a hydrocarbon of similar boiling point was obtained by Schroeter[18] by the high-pressure hydrogenation of β-methylnaphthalene. As an indication of the structure of the hydrocarbon, Schroeter observed that the keto acid (II) resulting from the condensation of the substance with phthalic acid yielded a single anthraquinone on cyclization, whereas the corresponding acid from tetralin affords two isomers. The difference was attributed to the blocking action of the methyl group, and hence it was inferred that the substituent is contained

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[1] This investigation was conducted as part of a program of research receiving support from the National Cancer Institute.

[2] Commonwealth Fund Fellow.

[3] Cook, *J. Chem. Soc.*, 456 (1932).

[4] Cook, *Proc. Roy. Soc.* (London), **B111**, 485 (1932); Barry, *et al.*, *ibid.*, **B117**, 318 (1935).

[5] Cook and Haslewood, *J. Chem. Soc.*, 428 (1937).

[6] Newman, THIS JOURNAL, **59**, 1003 (1937).

[7] Fieser and Newman, *ibid.*, **58**, 2376 (1936).

[8] Bachmann and Chemerda, *ibid.*, **60**, 1023 (1938); Newman, *ibid.*, **60**, 1141 (1938).

[9] Shear, publication in press.

[10] Fieser and Seligman, THIS JOURNAL, **60**, 170 (1938).

[11] Fieser and Seligman, *ibid.*, **59**, 883 (1937).

[12] Dansi, *Gazz. chim. ital.*, **67**, 85 (1937).

[13] Morelli and Dansi, *Biochimica e terapia sper.*, **24**, 432 (1937).

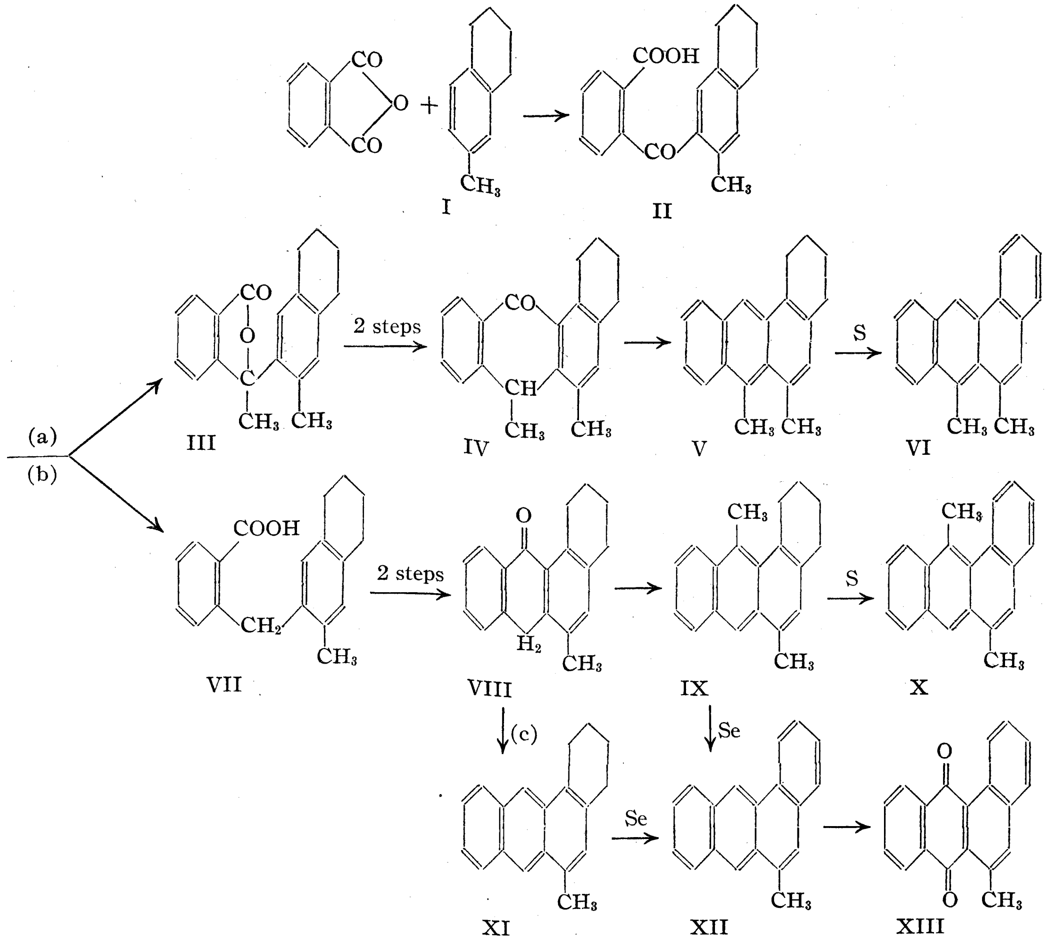
[14] Fieser and Campbell, THIS JOURNAL, **60**, 1142 (1937).

[15] Fieser and Hershberg, *ibid.*, **59**, 2502 (1937); **60**, 940 (1938).

[16] Fieser and Hershberg, *ibid.*, **59**, 1028 (1937).

[17] Krollpfeiffer and Schäfer, *Ber.*, **56**, 620 (1923).

[18] Schroeter, *ibid.*, **54**, 2242 (1921).



in the aromatic ring. In the present work this keto acid (II) was prepared from hydrocarbon obtained by hydrogenation and put through the steps of series (b) and (c) and thus converted into a product identical with a sample of the known 4-methyl-1,2,benzanthraquinone,[19] and the hydrocarbon XII and its picrate corresponded in properties with the descriptions given by Cook.[20] This evidence confirms the conclusion reached by Schroeter but does not distinguish between positions 7 and 8 as possible points of attachment of the phthalic acid residue in 6-methyltetralin. In order to settle the matter the keto acid was oxidized exhaustively with dilute nitric acid, and the sublimed product was found to be identical with pyromellitic anhydride. This proves that the structure II is correct and that 6-methyltetralin undergoes substitution at the 7-position. Since the yield of pure keto acid in the Friedel and Crafts reaction was low (42%) and the crude material contaminated with a considerable amount of other acidic products, it is possible that the material obtained by the hydrogenation of β-methylnaphthalene does not consist entirely of pure 6-methyltetralin but contains other hydro derivatives.

No difficulties were encountered in carrying the two series of syntheses to the stage of the isomeric dimethyltetrahydrobenzanthracenes, V and IX. The anthrone IV was obtained by cyclizing the reduction product of the lactone III with sulfuric acid and was isolated easily in a pure condition in the stable ketonic form. Acetylative cyclization[16] of the acid VII with zinc chloride catalyst gave an anthranyl acetate, and when this was cleaved with a Grignard reagent the enol liberated isomerized to the more stable keto form VIII in the process of recovery and purification. With respect to the relative stability of the keto and enol forms, 4-methyl- and 4,10-dimethyl-1′,2′,3′,4′-tetrahydro-1,2-benz-10-anthrone, like the unmethylated compound,[21] con-

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[19] Fieser and Peters, THIS JOURNAL, **54**, 3742 (1932).

[20] Cook, *J. Chem. Soc.*, 1592 (1933).

[21] Fieser and Hershberg, THIS JOURNAL, **59**, 2331 (1937).

form to the behavior noted for anthrone[21] rather than for 1,2-benz-10-anthrone.[16] In series (b) this was of advantage in facilitating the introduction of the 9-methyl group by a Grignard reaction.

The dehydrogenation of the tetrahydrides V and IX presented considerable difficulty, apparently because of the ready elimination of an alkyl group from a meso position of the 1,2-benzanthracene molecule. The dehydrogenation of the 4,9-dimethyl compound (IX) was tried first and when selenium was used the only reaction product which could be isolated in a satisfactory condition proved to be identical with the sample of 4-methyl-1,2-benzanthracene (XII) prepared from its tetrahydride with the use of selenium. It may be recalled that a similar loss of a *meso* (10)-isopropyl group has been noted in this Laboratory[16,21] in a dehydrogenation with selenium but that with sulfur the group was retained. It is also of interest that in a selenium dehydrogenation investigated by Cook[20] an isopropyl group was lost from the α-position 5. A methyl group in the α-position 4 seems to withstand treatment with selenium, at least in part, although the yield of the pure 4-methyl compound was never good. Since selenium was found unsatisfactory for the dehydrogenation of the dimethyl compounds, and as trial experiments with palladium charcoal seemed unpromising, sulfur eventually was employed. In each case the product was a hydrocarbon mixture, but on careful purification through the picrate or trinitrobenzene derivative it was possible to isolate an apparently homogeneous hydrocarbon having the composition required for a dimethyl-1,2-benzanthracene. The two hydrocarbons differ considerably in melting point and in the melting points of their derivatives and they are easily distinguishable, by analysis and properties, from the 4-methyl compound. Although the yields in the last step were quite low, the desired end was achieved and samples of 4,9- and 4,10-dimethyl-1,2-benzanthracene sufficient for tests of possible carcinogenic activity were obtained.

Experimental Part[22]

6-Methyltetralin (I).—Commercial β-methylnaphthalene was freed from sulfur by distillation from sodium at atmospheric pressure, and 100 g. of the purified hydrocarbon, mixed with 20 cc. of absolute alcohol, was hydrogenated in the presence of Raney nickel catalyst (5 cc. of the suspension) at an initial pressure of 1800 lb. (120 atm.) and a temperature of 130–135°. The reaction was stopped after the absorption of two moles of gas and the product was combined with that from a second batch and fractionated at atmospheric pressure through a 1-meter column. The chief fraction (96 g.) distilled at 222–226° (n^{20}D 1.5328), and a second fraction (44 g.) boiled at 226–227° (n^{20}D 1.5350); total yield, 68%.

***o*-(6-Methyl-7-tetraloyl)-benzoic Acid (II).**—Schroeter[18] prepared this acid in unspecified yield using benzene as the solvent. In our procedure a solution of 63 g. of 6-methyltetralin and 63 g. of phthalic anhydride in 500 cc. of tetrachloroethane was cooled to 0° and 120 g. of aluminum chloride was added with stirring in two and one-half hours while cooling in an ice-bath. After decomposition with ice and acid and removal of the solvent with steam, the solidified product in 800 cc. of 10% sodium carbonate solution was submitted to steam distillation, precipitated with acid, coagulated by boiling, collected and washed. The crude product (124 g., m. p. 135–140°) on crystallization from glacial acetic acid afforded 53 g. (42%) of colorless acid melting at 165–167°. A sample recrystallized to constant melting point from carbon tetrachloride formed small needles, m. p. 167.5–168° (Schroeter, 160°, uncorr.). It was evident that the crude reaction product contained considerable amounts of other acids. Schroeter isolated the acid II in the form of the ammonium salt and, while we found this a less satisfactory method of obtaining the acid in a pure condition than that adopted, use was made of partial purification through the ammonium salt to provide material suitable for reduction.

For proof of structure 1 g. of the keto acid was heated with 2 cc. of nitric acid (sp. gr. 1.42) and 4 cc. of water at 200–210° for one day; a fresh 2-cc. portion of concentrated acid was introduced and heating was continued for fifteen hours. After concentrating the solution, fuming acid precipitated a solid which was dried and sublimed at 250° and 15 mm. Recrystallized twice from dioxane and dried at 150° to remove solvent of crystallization, the product melted at 282–284° and gave no depression with a sample of authentic pyromellitic anhydride which had been freshly sublimed and crystallized and which melted at 283–285°.[23]

Series (b)

***o*-(6-Methyl-7-tetralylmethyl)-benzoic Acid (VII). (a) From Purified Keto Acid.**—The acid II (2 g., m. p. 164.5–165.5°) was heated with zinc dust (2 g.) and 2 *N* sodium hydroxide solution (50 cc.) for forty-eight hours on the steam-bath and after acidification the reaction product was extracted with ether, taken into soda solution, precipitated, and crystallized from methanol, giving 1.45 g. (76%) of long, white needles, m. p. 168.5–168.9°. After recrystallization the m. p. was 168.9–169.1°.

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.04; H, 7.19. Found: C, 81.48; H, 7.12.

(b) From the Crude Ammonium Salt.—The crude product (59 g.) of the Friedel and Crafts reaction from 32 g. of 6-methyltetralin was dissolved in 500 cc. of hot 1 *N* ammonia solution, and after clarification with Norite the

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[22] All melting points are corrected. Analyses by Mrs. Verna R. Keevil, Dr. C. Fitz, and the Arlington Laboratories.

[23] Observation of Dr. E. B. Hershberg; this value is believed to be more reliable than that reported previously by Fieser and Hershberg, THIS JOURNAL, **57**, 2196 (1935).

filtrate was treated with ammonium chloride and cooled to 0°. The ammonium salt of II separated in a crystalline condition and weighed 52 g. (the acid liberated from this material is impure). A mixture of this salt with 52 g. of zinc dust and 1 liter of 2 *N* sodium hydroxide solution was refluxed gently with mechanical stirring for twenty-four hours and the solution, filtered through sintered glass, was acidified with dilute hydrochloric acid. The crude precipitate (45 g.) on crystallization from methanol gave 22 g. of acid, m. p. 166.5–167.5°, and 4.5 g., m. p. 161.5–163.5°. The yield from 6-methyltetralin was 43%, as compared with an over-all yield of 32% via the purified acid.

1',2',3',4'-Tetrahydro-4-methyl-1,2-benzanthranyl-9-acetate.—The acid VII (3.5 g.) was refluxed for one and one-half hours with glacial acetic acid (21 cc.), acetic anhydride (14 cc.) and anhydrous zinc chloride (0.28 g.) and sufficient water was added carefully to the pale yellow solution to produce faint cloudiness. On cooling there separated 3.4 g. (89%) of long, pale yellow needles, m. p. 148–149°. Recrystallization from acetic acid raised the melting point to 150.5–151°.

Anal. Calcd. for $C_{21}H_{20}O_2$: C, 82.86; H, 6.62. Found: C, 82.40; H, 6.45.

1',2',3',4'-Tetrahydro-4-methyl-1,2-benz-9-anthrone (VIII).—The above acetate (6.5 g.) was refluxed for one hour in ether–benzene with the Grignard reagent from 11 g. of *n*-butyl bromide, and after hydrolysis the extracted product was crystallized from benzene–petroleum ether, giving colorless, non-fluorescent needles; yield, 5.54 g. (97%). Recrystallization raised the melting point slightly (0.5°) to 151.5–151.7°.

Anal. Calcd. for $C_{19}H_{18}O$: C, 86.98; H, 6.91. Found: C, 86.85; H, 6.81.

1',2',3',4'-Tetrahydro-4,9-dimethyl-1,2-benzanthracene (IX).—The anthrone VIII (3.75 g.) dissolved in benzene was added to the Grignard reagent formed by action of excess methyl chloride on 1 g. of magnesium. A deep red color developed and faded to yellow as the mixture was refluxed for one and one-half hours. After the addition of dilute acid to the cooled solution the organic layer (fluorescent) was washed and concentrated. The oily residue crystallized from methanol on seeding with a crystal previously obtained by the decomposition of the purified picrate (see below), giving 3.26 g. (88%) of small, pale yellow plates, m. p. 57–58°.

For the preparation of a pure sample, 2 g. of oily material in alcohol was treated with 2 g. of picric acid, yielding 2.5 g. of dark reddish-black needles of the **picrate**, m. p. 135.8–136.2° (1.65 g.).

Anal. Calcd. for $C_{20}H_{20}{\cdot}C_6H_3O_7N_3$: N, 8.59. Found: N, 8.83.

On decomposition of the picrate by chromatographic adsorption on activated alumina from benzene, the colorless, fluorescent filtrate on evaporation of the solvent and crystallization of the residue from methanol gave 0.65 g. of pale yellow plates of the hydrocarbon, m. p. 62.4–62.8°.

Anal. Calcd. for $C_{20}H_{20}$: C, 92.26; H, 7.74. Found: C, 92.55; H, 7.54.

Dehydrogenation of IX. (a) **With Sulfur: 4,9-Dimethyl-1,2-benzanthracene.**—A mixture of 500 mg. of the tetrahydride and 100 mg. of sulfur was heated slowly in a salt-bath in a stream of nitrogen. Evolution of hydrogen sulfide commenced at 180° and the mixture was maintained at 180–210° until liberation of this gas was complete (about four hours). The product was then distilled at 2 mm. pressure, yielding a ruby-red distillate which failed to crystallize from methyl or ethyl alcohol or to form a crystalline picrate. After passing a benzene solution of the oil through a tower of alumina there was obtained a light yellow oil which likewise failed to crystallize but which when dissolved in methanol with 300 mg. of trinitrobenzene yielded 135 mg. of long, bright red needles melting at 124.2–124.8°. The melting point of the complex remained unchanged on recrystallization, and by careful working of the mother liquors 195 mg. of satisfactory material was collected. This was adsorbed from benzene onto activated alumina, the trinitrobenzene being retained as a crimson zone at the top of the tower and the hydrocarbon forming a colorless zone having a blue fluorescence. After sectioning the tower this zone was eluted with benzene containing 5% methanol, and a solution of the pale yellow, oily residue in methanol slowly deposited small, faintly yellow needles, m. p. 73.3–74.3°; yield, 42 mg. (8.5%). Concentration of the mother liquors gave 13 mg., m. p. 69–71°. Recrystallization of the best material from methanol gave hydrocarbon melting at 75.1–75.5°. The picrate forms deep bronze colored needles, m. p. 116–116.4°, from methanol.

Anal. Calcd. for $C_{20}H_{16}$: C, 93.70; H, 6.30. Found: C, 93.68; H, 6.61.

(b) **With Selenium.**—The tetrahydride IX (800 mg.) was heated with 1.1 g. of selenium in a salt-bath at 300° for twenty-one hours, with the further addition of 1 g. of selenium in the course of the reaction. The product was extracted with boiling benzene and the solution was clarified by refluxing with metallic sodium and by two passages through activated alumina. Removal of the solvent and crystallization from methanol gave 350 mg. (44%) of 4-methyl-1,2-benzanthracene in the form of rosets of needles, m. p. 117.5–118.5°. Repeated crystallization from methanol raised the m. p. to 122.8–123.4°, and the sample gave no depression when mixed with the hydrocarbon prepared as described below. The picrate melts at 148–148.5°.

Series (c)

1',2',3',4'-Tetrahydro-4-methyl-1,2-benzanthracene (XI).—A mixture of 2 g. of the anthrone VIII, 10 cc. of toluene, 5 g. of zinc dust, and 100 cc. of 2 *N* sodium hydroxide was refluxed for forty-eight hours, with the further addition of 5 g. of zinc dust. The progress of the reduction was indicated by the development of blue fluorescence under ultraviolet light. The cooled reaction mixture was extracted repeatedly with benzene, and the solution was washed with acid and water and evaporated. The residue on crystallization from methanol afforded 1.1 g. (58%) of faintly yellow crystal clusters, m. p. 81.3–82.3°, and the mother liquors yielded 0.17 g. of material, m. p. 78–79°. Repeated crystallization from methanol–benzene gave faintly yellow clusters of needles, m. p. 82.3–82.9°. The picrate crystallized from methanol as deep reddish-brown needles, m. p. 158–158.2°.

Anal. Calcd. for $C_{19}H_{18}$: C, 92.63; H, 7.37. Found: C, 92.34; H, 7.61.

4-Methyl-1,2-benzanthracene.—Dehydrogenation of the tetrahydride XI (730 mg.) was accomplished by heating with selenium (2.1 g., added in portions) at 290–300° for twenty hours. The product, obtained by extraction with benzene and clarification with the use of sodium and an adsorption tower, was crystallized from methanol and gave 170 mg. (24%) of small, pale yellow needles, m. p. 119–120°. Repeated crystallization from alcohol–benzene gave material melting constantly at 124.1–124.6°.

Anal. Calcd. for $C_{19}H_{14}$: C, 94.18; H, 5.82. Found: C, 94.33; H, 5.61.

Cook[20] found the melting point 124.5–125.5° for the hydrocarbon and 149–150° for its picrate. The picrate prepared from the above sample formed brown-red needles, m. p. 148.5–149°; the trinitrobenzene derivative formed bright red needles, m. p. 163.5–164°. Oxidation of the hydrocarbon (29 mg.) with chromic anhydride in acetic acid at 60° gave, after crystallization from benzene–ligroin, 7 mg. of 4-methyl-1,2-benzanthraquinone, m. p. 167.5–168°, giving no depression when mixed with the sample prepared by Fieser and Peters.[19]

Series (a)

Lactone of 2-(α-Hydroxy-6,α-dimethyl-7-tetralylmethyl)-benzoic Acid (III).—A solution of 15 g. of *o*-(6-methyl-7-tetraloyl)-benzoic acid (II) in benzene was added to the Grignard solution from 4.8 g. of magnesium and excess methyl chloride in 100 cc. of ether. The solution became greenish-yellow and an oil deposited on the walls of the flask. After adding more benzene the mixture was refluxed for one and one-half hours, decomposed, and the product taken into benzene–ether. An amorphous white precipitate often separated at this point at the interface but eventually dissolved on vigorous shaking. In one experiment the solid was collected and found to be a magnesium complex which on being refluxed with methanol gives a flocculent precipitate and a solution containing the pure lactone. After washing the benzene–ether solution with sodium carbonate solution, removing the solvent, and crystallizing the product from methanol, there was obtained 7.85 g. (53%) of crystalline lactone, m. p. 112–113.5°. The recrystallized material formed granular prisms, m. p. 115–115.5°.

Anal. Calcd. for $C_{20}H_{20}O_2$: C, 82.16; H, 6.90. Found: C, 82.43; H, 6.96.

2-(6,α-Dimethyl-7-tetralylmethyl)-benzoic Acid.—The lactone III (8 g.) was refluxed for forty-two hours with amalgamated zinc (400 g.), toluene (150 cc.), glacial acetic acid (40 cc.), concentrated hydrochloric acid (160 cc.), and water (80 cc.), with three further additions of 50-cc. portions of acid. The product was extracted with benzene and the acidic portion taken into 10% sodium carbonate solution, precipitated, and dried in ether. Evaporation left a colorless oil which was obtained crystalline from methanol containing 10% of water; yield, 2.2 g., m. p. 165–165.5°. In a second reduction 5.5 g. of lactone gave 1.75 g. of the acid, and the combined neutral material from the two experiments on further reduction gave 0.9 g. of acid; total yield 13.5 g. (36%).

Recrystallized from aqueous methanol, the acid formed micro-needles, m. p. 165.5–166°; occasionally a second form was obtained melting at 147–148° and remelting after fusion at 165.5–166°.

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.63; H, 7.68.

1′,2′,3′,4′-Tetrahydro-4,10-dimethyl-1,2-benz-9-anthrone (IV).—The above acid (2.2 g.) was dissolved slowly in 50 cc. of concentrated sulfuric acid at room temperature and after one hour the red solution was poured onto ice and the precipitate extracted with ether. The ether solution, washed with water, soda and water, was dried and evaporated and the residue crystallized from methanol. This gave 1.6 g., m. p. 112–113°, and 0.18 g., m. p. 111–112°; yield, 86%. The recrystallized anthrone formed colorless blades, m. p. 112.8–113.4°.

Anal. Calcd. for $C_{20}H_{20}O$: C, 86.92; H, 7.30. Found: C, 87.41; H, 7.49.

1′,2′,3′,4′-Tetrahydro-4,10-dimethyl-1,2-benzanthracene (V).—For reduction, 3 g. of IV in 10 cc. of toluene was refluxed for thirty hours with 5 g. of zinc dust and 75 cc. of 2 *N* sodium hydroxide, with the further addition of 10 g. of zinc and 100 cc. of alkali. In contrast to the behavior noted in the reduction of the anthrone VIII, no fluorescence developed in the course of the reaction, probably because the intermediate dihydroanthranol persists in the alkaline medium and escapes dehydration. The reaction mixture was extracted thoroughly with benzene, and on washing the extract with dilute hydrochloric acid it acquired a fluorescence which became more pronounced on concentrating the washed solution. After removing the solvent the residual oil was distilled at 2 mm., yielding a yellow, fluorescent distillate which formed crystals, m. p. 77–80° from methanol (2.02 g.). As the melting point was not improved by recrystallization, the product was dissolved in alcohol with 3 g. of picric acid, yielding 2 g. of violet-black picrate, m. p. 145–146°. This was decomposed with sodium carbonate solution–benzene, giving 1.05 g. (37%) of microcrystalline hydrocarbon, m. p. 104–105°. Recrystallized from methanol, the substance formed pale yellow micro-needles, m. p. 105–105.5°. The purified picrate formed slender, violet-black needles, m. p. 146–147°.

Anal. Calcd. for $C_{20}H_{20}$: C, 92.26; H, 7.74. Found: C, 91.87; H, 8.01.

4,10-Dimethyl-1,2-benzanthracene.—For dehydrogenation 540 mg. of the tetrahydride V was heated with 120 mg. of sulfur for four hours at 190–215° in an atmosphere of nitrogen. The material collected after extraction with benzene and purification by chromatographic adsorption proved to be a mixture and the separation of a satisfactory product was a tedious process which need not be described in detail but which involved selective adsorption on alumina (some tetrahydride passed into the filtrate and was treated again with sulfur), elution with benzene–methanol, and fractionation both as the picrate and as the hydrocarbon. The best sample of picrate formed long black needles, m. p. 161.5–162°. After collecting in all 235 mg. of picrate melting at 161.3–161.9°, decomposition with sodium carbonate solution yielded 79 mg. of hydrocarbon, m. p. 108.5–111.5°, and further recrystallizations from methanol gave 17.5 mg. (3%) of opaque, pale yellow needles melting at 114–114.4° (softening at 113°).

Anal. Calcd. for $C_{20}H_{16}$: C, 93.70; H, 6.30. Found: C, 93.64; H, 6.61.

Summary

6-Methyltetralin, prepared by the catalytic hydrogenation of β-methylnaphthalene, is substituted in the 7-position in the Friedel and Crafts reaction with phthalic anhydride. The resulting keto acid has been used as the starting material for the synthesis of the 4-methyl and the 4,9- and 4,10-dimethyl derivatives of 1,2-benzanthracene, as well as their 1′,2′,3′,4′-tetrahydro derivatives, all of which are of interest in investigating the relationship between structure and carcinogenic activity. Although the syntheses were completed successfully, some difficulty was experienced in the dehydrogenations, apparently because of the ease of elimination of meso alkyl groups.

CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASS.
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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Separation of Sulfuric Acid from Nitric, Alkyl- and Arylsulfonic, and Alkylsulfuric Acids by Means of Liquid Ammonia

BY JOHN H. BILLMAN AND L. F. AUDRIETH

The ammonium salts of many oxy acids such as sulfuric, phosphoric, oxalic and arsenic are insoluble in liquid ammonia. Use has been made of the insolubility of some of these ammonium salts in liquid ammonia to effect the preparation of such nitrogen bases as hydrazine,[1] semicarbazide[2] and hydroxylamine[2] by ammonolysis of the respective sulfates, oxalates, phosphates and arsenates. The nitrogen bases are very soluble in liquid ammonia and are recovered in the anhydrous condition by evaporation of the solvent.

This marked insolubility of ammonium sulfate in liquid ammonia suggested that liquid ammonia might be used for the removal of excess sulfuric acid where the latter is employed either by itself or with other reagents. The experimental results reported in this paper demonstrate that it is possible (1) to separate quantitatively sulfuric and nitric acids by conversion into the ammonium salts and extraction of soluble ammonium nitrate with liquid ammonia; (2) to use liquid ammonia as a solvent for alkyl- and arylsulfonic acids, as well as alkylsulfuric acids; (3) to use liquid ammonia for the removal of excess sulfuric acid from compounds of the types listed under (2), especially where it is desired to produce directly the ammonium salts of the alkyl- and arylsulfonic acids and alkylsulfuric acids.

Experimental

It should be emphasized that no special apparatus is necessary in using liquid ammonia for the reactions outlined below. Filtration is carried out using ordinary Büchner funnels and filter flasks. It is a simple task to cool the funnel and flask quickly by running a small quantity of liquid ammonia through the filter. Filtration is simplified where sintered glass crucibles or filter funnels are used in place of filter paper. Naturally, good ventilation is not only desirable, but necessary.

Separation of Sulfuric Acid from Nitric Acid.—The separation and recovery of nitric and sulfuric acids in the spent acids after use in nitration reactions, by conversion into ammonium salts and extraction with liquid ammonia is practically quantitative. In a typical experiment a solution containing 20.8 g. of 96% sulfuric acid and an approximately equal quantity of concentrated nitric acid was neutralized with concentrated aqueous ammonia. The solution was evaporated and the solid residue treated with 200 cc. of liquid ammonia. The insoluble ammonium sulfate was removed by filtration, washed with liquid ammonia, heated at 60°[3] for several hours and weighed; yield, 26.8 g. of ammonium sulfate corresponding to a 99.3% recovery. No sulfate was found to be present in the ammonium nitrate recovered from the filtrate.

Solubility of Alkyl- and Arylsulfonic Acids and Alkylsulfuric Acids in Liquid Ammonia at −33°.—A representative number of compounds of this type were prepared and their solubility in liquid ammonia tested qualitatively. With the exception of laurylsulfuric acid, all compounds listed below are readily and easily soluble to the extent of at least 10 g. in 100 cc. of ammonia. Solution of these acids in liquid ammonia brings about their conversion into the ammonium salts. In a number of cases the products obtained upon evaporation of the liquid ammonia solution were recrystallized from absolute alcohol and analyzed for their nitrogen content. These compounds are listed in Table I.

In extending this study to other derivatives of these acids, it was found that the sodium salts of benzenesulfonic acid and *n*-butylsulfonic acid are very soluble in liquid ammonia, whereas the sodium salts of laurylsulfuric and benzylsulfonic acids are only slightly soluble.

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[1] Browne and Welsh, THIS JOURNAL, **33**, 1728 (1911).

[2] Audrieth, *ibid.*, **52**, 1250 (1930).

[3] Heating is necessary due to the fact that ammonium sulfate forms a number of ammonates which must be decomposed to obtain the anammonous salt.

TABLE I

Ammonium salts of acids	Mol. formula	Analysis, % N Calcd.	Found
Sulfanilic	$C_6H_{10}O_3N_2S \cdot {}^1/_2H_2O$	14.28	14.22
Benzenesulfonic	$C_6H_9O_3NS$	8.00	7.84
o-Aminobenzenesulfonic	$C_6H_{10}O_3N_2S \cdot {}^1/_2H_2O$	14.28	14.15
p-Toluenesulfonic	$C_6H_{11}O_3NS$	7.41	7.35
2-Aminotoluene-5-sulfonic	$C_7H_{12}O_3N_2S$	13.72	13.65
Naphthionic	$C_{10}H_{12}O_3N_2S$	11.66	11.36
d-Camphorsulfonic	$C_{10}H_{19}O_4NS$	5.62	5.54
o-Nitrobenzenesulfonic	$C_6H_8O_5N_2S$	12.67	12.49
m-Nitrobenzenesulfonic	$C_6H_8O_5N_2S$	12.67	12.78
p-Nitrobenzenesulfonic	$C_6H_8O_5N_2S$	12.67	12.77
β-Naphthalenesulfonic	$C_{10}H_{11}O_3NS$	6.22	6.07
Laurylsulfuric	$C_{12}H_{29}O_3NS$	4.94	5.07

Ammonium Ethyl Sulfate.—A mixture of 50 g. of sulfuric acid (96%) and 70 g. of ethanol was refluxed for two and one-half hours on the steam-bath. The reaction mixture was then saturated with gaseous ammonia and the excess of alcohol removed by evaporation. The solid residue was treated with 200 cc. of liquid ammonia, allowed to stand for one hour and the ammonia insoluble material removed by filtration, weight of ammonium sulfate recovered 32.2 g., corresponding to 23.9 g. of pure sulfuric acid. Evaporation of the filtrate yielded 28.6 g. of $C_2H_5OSO_3NH_4$, approximately 90% of the theoretical yield based upon the sulfuric acid which had reacted.

Ammonium Lauryl Sulfate.—Nineteen and two-tenths grams of lauryl alcohol in 40 cc. of ether was treated with 19 g. of concentrated sulfuric acid (96%) and allowed to stand at room temperature for forty-eight hours. After removal of the excess ether, the residual liquid was treated directly with gaseous ammonia, resulting in the formation of a solid mass. This mixture was digested for one hour with 400 cc. of liquid ammonia. Filtration and evaporation of the liquid ammonia solution yielded 10 g. of a white crystalline product possessing excellent detergent properties. This material was recrystallized from alcohol and washed with ether. Analysis showed this compound to be the ammonium salt of laurylsulfuric acid. The yield obtained corresponds to a 34% conversion of the alcohol into the ammonium salt. The ammonia-insoluble residue was found to contain unreacted alcohol, ammonium sulfate and some ammonium lauryl sulfate. Qualitative tests indicate that the solubility of ammonium lauryl sulfate is greater than 5 g. but less than 10 g. per 100 cc. of liquid ammonia at −33°. The solubility increases markedly, however, with rise in temperature.

Ammonium Sulfanilate.—Twenty-eight grams of aniline and 80 g. of concd. sulfuric acid were heated at 180–190° for five hours. The solid product was neutralized with aqueous ammonia and the resulting solution evaporated until the total volume of solid and liquid had been reduced to approximately 100 cc. The material was treated directly with 400 cc. of liquid ammonia, allowed to digest for one hour and filtered. Evaporation of the filtrate and subsequent drying of the product in a vacuum desiccator yielded 41.5 g. of the ammonium sulfanilate, $H_2NC_6H_4SO_3$-NH_4, corresponding to a 72% yield based on the aniline used. The product was sulfate free, indicating that removal of ammonium sulfate is possible even in the presence of considerable quantities of water.

Sodium and Ammonium Benzene Sulfonates.—Two 20-g. samples of benzene were converted into benzenesulfonic acid by treatment with 83.3 g. of fuming sulfuric acid (15% SO_3). One sample was neutralized in the cold with aqueous sodium hydroxide, the other with aqueous ammonia. The solutions were concentrated on a steam-bath to a sirupy consistency and each digested with 400 cc. of liquid ammonia. Removal of the ammonium sulfate and evaporation of the liquid ammonia filtrate gave in the first experiment 42.1 g. of sodium benzene sulfonate (91%) and in the other case 41.1 g. of the ammonium salt (91.5%). The above values are those obtained after the removal of diphenyl sulfone, which is soluble to a limited extent in liquid ammonia.

Summary

It has been demonstrated experimentally that liquid ammonia permits the quantitative removal of sulfuric acid as ammonium sulfate from mixtures containing nitric acid, alkyl- and arylsulfonic acids or alkylsulfuric acids.

URBANA, ILLINOIS RECEIVED JUNE 6, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Potassium Nitrilosulfonate

BY H. SISLER AND L. F. AUDRIETH

A study of the preparation and properties of potassium nitrilosulfonate was undertaken as one phase of an extended investigation of the chemistry of sulfamic acid and its derivatives. The nitrite–bisulfite reaction[1] has been suggested and used for the preparation of sulfamic acid. It is significant, however, that no information concerning the rate of hydrolysis and stability of the primary reaction product, the nitrilosulfonate, or of the intermediate imidodisulfonate, has been recorded. The present paper, therefore, concerns itself with a study of the preparation of potassium nitrilosulfonate and a characterization of its properties, specifically its hydrolysis under carefully controlled conditions. The potassium salts of imidodisulfonic and sulfamic acids were both prepared by hydrolysis of the nitrilosulfonate.

Experimental

Preparation of $N(SO_3K)_3 \cdot 2H_2O$.—The procedure of Claus and Koch[2] was modified as follows: A solution of 25 g. of potassium nitrite (0.294 mole) in 100 ml. of water is added slowly and with constant stirring to a hot solution of potassium bisulfite, prepared by saturating 75 g. (1.34 mole) of potassium hydroxide in 150 ml. of water with sulfur dioxide. Clouding of the solution takes place with formation of a mass of needle-like crystals. After standing for an hour in the mother liquor enough water (about 1500 ml.) is added in order to redissolve the precipitate on heating. The solution is then cooled to effect precipitation of the needle-like crystals which are separated by filtration, washed thoroughly with ice water, alcohol and ether and finally dried in a vacuum desiccator; yield of purified $N(SO_3K)_3 \cdot 2H_2O$, 74 g. (62% based on nitrite employed).

Anal. Calcd. for $N(SO_3K)_3 \cdot 2H_2O$: K, 28.8; S, 23.6. Found: K, 28.8, 28.7; S, 23.4, 23.8.

Care must be taken that the solution remains alkaline during recrystallization. If necessary, a few pellets of potassium hydroxide should be added. If the solution becomes acid the imidodisulfonate, rather than the nitrilosulfonate, will be obtained. It also is necessary that washing be thorough, otherwise some bisulfite may remain behind and bring about rapid decomposition of the nitrilosulfonate. Samples of the potassium salt, prepared as indicated above, have been kept in a vacuum desiccator for several weeks without decomposition.

Theoretically, one would expect a ratio of three moles of bisulfite to one of nitrite to give maximum yields. It is evident, however, from a series of comparable experiments carried out as described above, that excess bisulfite favors the formation of the nitrilosulfonate. With mole ratios of $KHSO_3:KNO_2$ between 6 to 4.5:1 yields of 64–62% were obtained. With smaller relative amounts of bisulfite the yield diminishes, becoming only 15% with a 1.50:1 ratio. Our results may be considered experimental confirmation of Raschig's[3] suggestion that the reaction is best represented by the equation

$$4KHSO_3 + KNO_2 \longrightarrow N(SO_3K)_3 + K_2SO_3 + 2H_2O$$

It is evident, furthermore, that at higher temperatures some nitrilosulfonate is always obtained whenever bisulfite and nitrite are brought together.

Properties of Potassium Nitrilosulfonate.—The compound is only slightly soluble in water and in liquid ammonia. A saturated aqueous solution gives no precipitate on the addition of solutions containing Mn^{++}, Mg^{++}, Ag^+, Cd^{++}, Co^{++}, Cu^{++}, and Fe^{++} ions, but, as stated in the literature,[2] gives a white flocculent precipitate with lead acetate. While no precipitate is formed immediately on the addition of Ba^{++}, the solution rapidly clouds on standing due to hydrolytic decomposition. Prior addition of acid to the solution causes immediate precipitation of barium sulfate. Contrary to reports in the literature,[4] a precipitate is obtained on the addition of barium hydroxide. This precipitate is momentarily dissolved by nitric acid, but a cloudiness appears almost immediately thereafter due to formation of sulfate ion by hydrolysis.

Hydrolysis of Potassium Nitrilosulfonate.—The study of the hydrolysis of potassium nitrilosulfonate was restricted to the range of dilute solutions due to the limited solubility of the compound. Duplicate experimental runs were carried out at 25, 40, 67 and 100°. In each case, a 1-g. sample (0.00246 mole) of potassium nitrilosulfonate dihydrate was dissolved in 400 ml. of water preheated to the temperature at which hydrolysis was to be studied. At regular time intervals 25-ml. portions of the solution were removed and titrated with standard sodium hydroxide solution using methylene blue–methyl red indicator. The course of the reaction thus could be followed readily by measuring the increase in the acidity of the solutions, as is evident from the following equations

$$N(SO_3)_3^{\equiv} + H_2O \longrightarrow HN(SO_3)_2^{=} + H^+ + SO_4^{=} \quad (1)$$

$$HN(SO_3)_2^{=} + H_2O \longrightarrow H_2NSO_3^- + H^+ + SO_4^{=} \quad (2)$$

$$N(SO_3)_3^{\equiv} + 2H_2O \longrightarrow H_2NSO_3^- + 2H^+ + 2SO_4^{=} \quad (3)$$

Complete hydrolysis, as represented by Equation 3, results in the formation of two moles of hydrogen ion per mole of nitrilosulfonate employed. The experimental results are represented graphically in Fig. 1 in which moles of hydrogen ion formed are plotted against time.

It is quite evident from Fig. 1 that hydrolysis with

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(1) Divers and Haga, *J. Chem. Soc.*, **69**, 1634 (1896).

(2) Claus and Koch, *Ann.*, **152**, 336 (1869).

(3) Raschig, "Schwefel- und Stickstoffstudien," Verlag Chemie, Berlin, 1924, p. 8.

(4) Mellor, "A Comprehensive Treatise on Inorganic and Theoretical Chemistry," Longmans, Green and Company, New York, N. Y., 1928, Vol. VIII, p. 668.

formation of one mole of hydrogen ion is quite rapid, even at 25°. This corresponds to the intermediate formation of the imidodisulfonate, as represented by Equation 1. The formation of the second mole of hydrogen ion is considerably slower, leading to the conclusion that the rate determining reaction in the complete hydrolysis of the nitrilosulfonate is that represented by Equation 2.

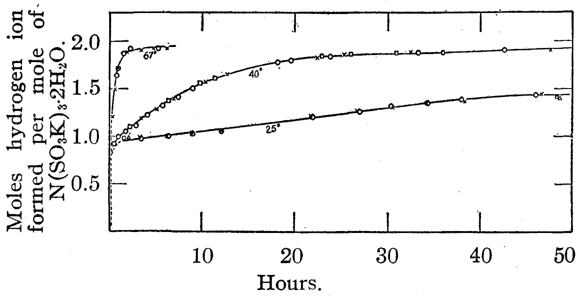

Fig. 1.—Hydrolysis of potassium nitrosulfonate.

In checking this assumption experimentally, it was found that neutral solutions of the intermediate product, potassium imidodisulfonate, did not become acid, that is, undergo hydrolysis, even over a period of eighteen hours at 67°. However, addition of an equimolar quantity of potassium acid sulfate, thus approximating the composition and concentration of the solution after the nitrilosulfonate had hydrolyzed in accordance with Equation 1, was found to bring about hydrolysis. In following the increase of acidity with time, results were obtained which checked satisfactorily with those plotted in Fig. 1.

It is significant that alkaline solutions of potassium nitrilosulfonate are resistant to hydrolysis, whereas neutral solutions undergo rapid decomposition. Solutions of the imidodisulfonate[5] seem to be quite stable, but in the presence of hydrogen ion undergo hydrolysis, thus leading to the conclusion that the reaction is acid catalyzed. Since the acid concentration approaches a constant value of two moles per mole of nitrilosulfonate hydrolyzed, it is apparent that the end-product, potassium sulfamate, H_2NSO_3K, is quite stable, even in presence of acid.

As is evident from Fig. 1 rise in temperature quite naturally increases rate of hydrolysis. Experiments carried out at 100°, using solutions of the same concentration, demonstrated that hydrolysis to the sulfamate is complete within one-half hour.

Potassium Imidodisulfonate.—In preparing this intermediate product the following procedure was adopted: 38 g. of $N(KSO_3)_3 \cdot 2H_2O$ was moistened with 16 ml. of 2% sulfuric acid and allowed to stand for twenty-four hours. The pasty mass was then filtered and the solid residue washed with 60 ml. of ice water. This product was recrystallized from a solution containing 10 ml. of concentrated aqueous ammonia in 60 ml. of water. The crystals obtained on cooling were washed with ice water, alcohol and ether and dried in a vacuum desiccator over sulfuric acid; yield, 12 g. (51%).

Anal. Calcd. for $HN(SO_3K)_2$: N, 5.53; K, 30.9. Found: N, 5.75; K, 30.4.

Potassium imidodisulfonate is much more soluble in water than the nitrilosulfonate. The addition of $BaCl_2$–HCl solution gives no immediate precipitate. Upon warming, or after standing for a short time, barium sulfate begins to form. This shows qualitatively that the imidodisulfonate is much more stable to hydrolysis than the nitrilosulfonate.

Preparation of Potassium Sulfamate by Hydrolysis of Potassium Nitrilosulfonate.—Sixty grams of potassium nitrilosulfonate (0.147 mole) was suspended in 300 ml. of water and boiled for seventy-five minutes. The solution was then neutralized with 20 g. of potassium carbonate (0.145 mole) and evaporated to dryness. The residue was placed in a Soxhlet apparatus and extracted with 80% ethanol for forty-six hours. Potassium sulfamate crystallized from the alcoholic extract on cooling; yield, 13.5 g. (67%).

Summary

1. Maximum yields of potassium nitrilosulfonate are obtained when the ratio of $KHSO_3$: KNO_2 is 4:1, or greater, and when the reaction is carried out at higher temperatures.

2. The hydrolysis of potassium nitrilosulfonate has been studied at 25, 40, 67 and 100°. The nitrilosulfonate is rapidly converted into the imidodisulfonate, which in turn hydrolyzes more slowly to give the sulfamate as the final product.

URBANA, ILLINOIS RECEIVED MAY 6, 1938

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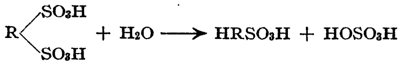
[5] It is of interest to point out the relationship between imidodisulfonic, pyrosulfuric, trithionic and hydroxylaminodisulfonic acids. In each of these compounds the SO_3H radicals are linked together by one of the following isosteric atoms or groups: O, S, NH, NOH. If these isosteres are represented by R the hydrolysis of any one of these four acids may be represented by the general equation:



$$R\begin{cases}SO_3H\\SO_3H\end{cases} + H_2O \longrightarrow HRSO_3H + HOSO_3H$$

[CONTRIBUTION NO. 136 FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF TEXAS]

Partial Molal Volumes of Lithium Chloride and of Sodium Nitrate in Liquid Monomethylamine

BY E. A. KELSO WITH W. A. FELSING

Introduction

The purpose of this investigation was to determine the densities and the partial and apparent molal volumes of salts at different temperatures in liquid monomethylamine. This investigation is one of a series[1] dealing with the thermodynamic properties of the methylamines and their solutions, with special reference to their use in the absorption type of refrigerating units.

It was found by Anderson[2] that the conductance of lithium chloride in liquid monomethylamine seemed to be abnormal over certain concentration ranges, possibly indicating compound formation. Bonnefoi[3] has shown the existence of compounds of the formula $LiCl{\cdot}CH_3NH_2$, $LiCl{\cdot}2CH_3NH_2$, $LiCl{\cdot}3CH_3NH_2$, and $LiCl{\cdot}4CH_3NH_2$. Since in the electrical conductivity of this salt in the liquid amine it was desirable to know how much of the solvent, in the more concentrated region, was tied up with the salt (*i. e.*, the ions), it was decided to determine the partial molal volumes of this salt (and of sodium nitrate) from density measurements.

Experimental

The experimental method consisted of determining at different temperatures the densities of methylamine solutions of these salts in a specially designed pycnometer, the volume of which was accurately known over a range of calibrations.

The Pycnometer.—The Pyrex pycnometer consisted of a bulb (approx. 9 cc.) sealed to a 1-mm. uniform bore capillary approximately 25 cm. long. To the other end of this capillary was sealed a no. 7 ground joint, to which was sealed a 6 cm. small diameter and small bore tube ending in another no. 7 ground joint. The pycnometer is shown in Fig. 1. The calibration was carried out by filling with mercury at 0°; the volume at any other temperature was calculated from the volume at 0° and the volume coefficient of expansion of Pyrex glass as calculated by Felsing and Thomas[1a] from the determinations of Buffington and Latimer.[4]

The Thermostat.—A Dewar flask 12 cm. in diameter and 20 cm. deep (inside measurements) served as a thermostat. A stirrer, heater, and cooling coil (supplied from a reservoir of cooling liquid by means of a circulating pump) together with a mercury-in-iron thermoregulator actuating a high-sensitivity relay system assured a temperature constancy of better than ±0.02° at any desired temperature. Thermometers calibrated by the U. S. Bureau of Standards were used throughout.

The Loading Apparatus.—The loading apparatus is shown in Fig. 1. The entire system was connected to a high-vacuum line.

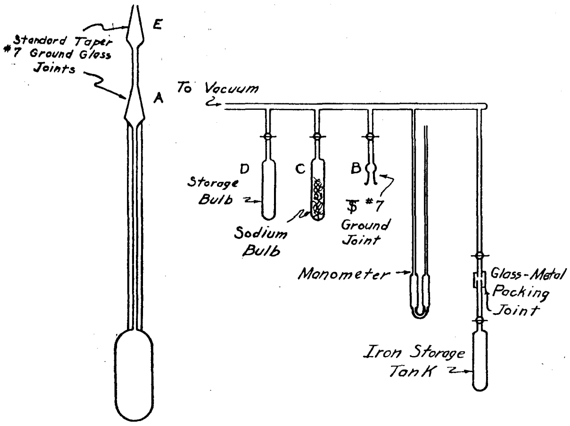


Fig. 1.—Density tube and methylamine loading apparatus.

Purification of Materials. (a) **The Solvent.**—The monomethylamine was prepared from Eastman C. P. hydrochloride. The salt as received was dried in an oven at 110° and over sulfuric acid in a desiccator. The *dry* salt was purified by the method of Bertheaume,[5] using purified and dry chloroform to remove the di- and trimethylamine hydrochlorides, and by the method of François,[6] using yellow mercuric oxide to remove any trace of ammonia. The gaseous amine was liberated by treatment of the purified hydrochloride with 50% potassium hydroxide, using the apparatus of Felsing and Wohlford.[1b] It was dried by passage over potassium hydroxide pellets followed by contact, as a liquid at 0°, with sodium wire. It was stored in a steel cylinder. (b) **The Salts.**—The lithium chloride was C. P. salt, recrystallized three times from conductivity water. It was dried at 110° in a stream of dry hydrogen chloride. The sodium nitrate was C. P. material recrystallized four times from conductivity water and was dried at 150°.

Method of Obtaining Data.—Solutions were prepared as follows. A definite volume of an aqueous stock solution of the salt was introduced into the bottom of the weighed pycnometer by means of a long thin capillary. The water

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[1] (a) Felsing and Thomas, *Ind. Eng. Chem.*, **21**, 1269 (1929); (b) Felsing and Wohlford, THIS JOURNAL, **54**, 1442 (1932); (c) Felsing and Jessen, *ibid.*, **55**, 4148 (1933); (d) Felsing and Buckley, *J. Phys. Chem.*, **37**, 779 (1933); (e) Felsing and Ashby, THIS JOURNAL, **56**, 2226 (1934); (f) Felsing and Phillips, *ibid.*, **58**, 1973 (1936).

[2] P. P. Anderson, Ph.D. Dissertation, The University of Texas, June, 1936.

[3] Bonnefoi, *Compt. rend.*, **127**, 516 (1898); *cf.* Gibbs, THIS JOURNAL, **28**, 1421 (1906).

[4] Buffington and Latimer, *ibid.*, **48**, 2305 (1926).

[5] Bertheaume, *Compt. rend.*, **150**, 1251 (1910).

[6] François, *ibid.*, **144**, 567 (1907).

was then removed by evacuation at slowly increasing temperatures, finishing at 100°. After admitting dry air, the pycnometer was weighed. The pycnometer was then connected to the loading system, the whole evacuated, and liquid methylamine condensed into the pycnometer by surrounding it with a dry ice–acetone mixture. The amount condensed was adjusted by experience to be sufficient to fill the pycnometer to the lower graduations of the capillary when at 0°. The small glass tube between the two ground joints was then sealed off, and the two portions weighed to ascertain the true weight of amine introduced. By means of the ground joint on the capillary, the pycnometer could be emptied back into the system without loss of amine.

Readings on the capillary were made after allowing at least one-half hour for temperature equilibrium to be attained. The weight of the liquid amine was corrected for the amount of gaseous amine above the liquid. The vapor was assumed ideal and the vapor pressure values were those of Felsing and Thomas.[1a]

All weights were corrected to vacuum.

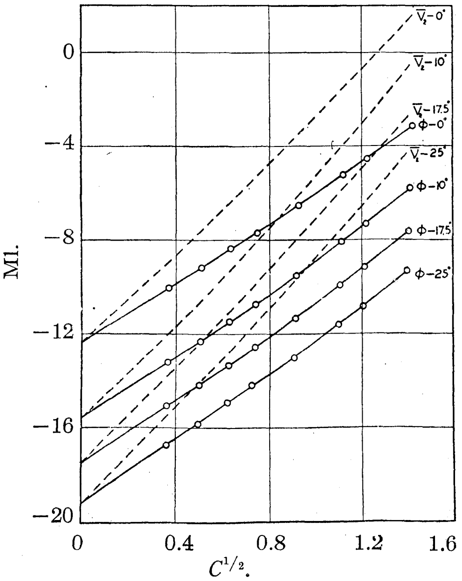

Fig. 2.—Partial and apparent molal volumes of lithium chloride in methylamine.

Experimental Data and Calculated Quantities

For lithium chloride, densities were determined at 0, 10, 17.5, and 25°; for sodium nitrate, at 0, 10, 18 and 25°. These densities are represented by the following relations, which reproduce the observed data to within ±0.01%.

Lithium Chloride *d* (g./ml.)

at 0° $= 0.68667 + 0.05088C - 0.00441C^{3/2}$
at 10° $= .67464 + .05289C - .00452C^{3/2}$
at 17.5° $= .66550 + .05413C - .00458C^{3/2}$
at 25° $= .65623 + .05511C - .00465C^{3/2}$

Sodium Nitrate, *d* (g./ml.)

at 0° $= 0.68667 + 0.07429C - 0.00495C^{3/2}$
at 10° $= .67464 + .07636C - .00559C^{3/2}$
at 18° $= 0.66490 + 0.07752C - 0.00569C^{3/2}$
at 25° $= .65623 + .07778C - .00520C^{3/2}$

The apparent molal volumes were calculated from the *observed* densities by the method of Gucker,[7] using the relation

$$\Phi = \frac{1000}{C} - \frac{1}{d_1}\left[\frac{1000d}{C} - M_2\right]$$

where C is the concentration of the solute in moles/liter of solution, d_1 the density of the solvent, d the density of the solution, and M_2 the molecular weight of the solute. These values are given by the following relations, which reproduce the calculated values to within ±0.1%.

Lithium Chloride

Φ at 0° $= -12.36 + 6.0469C^{1/2} + 0.27971C$
10° $= -15.59 + 6.1411C^{1/2} + .53926C$
17.5° $= -17.51 + 6.3741C^{1/2} + .42964C$
25° $= -19.21 + 6.6034C^{1/2} + .28775C$

Sodium Nitrate

Φ at 0° $= 17.45 + 3.2508C^{1/2} + 2.0660C$
10° $= 14.80 + 3.8672C^{1/2} + 2.3715C$
18° $= 13.42 + 4.2635C^{1/2} + 2.0986C$
25° $= 12.32 + 4.9056C^{1/2} + 1.6339C$

The partial molal volumes were then calculated by the expression given by Gucker[7]

$$\overline{V}_2 = \Phi + C^{1/2}\left[\frac{1000 - C\Phi}{2000 + C^{3/2}\partial\Phi/\partial C^{1/2}}\right]\frac{\partial\Phi}{\partial C^{1/2}}$$

The calculated values for $\overline{V}_2$ and for Φ are presented in Figs. 2 and 3. They represent an over-all accuracy of at least 0.1%.

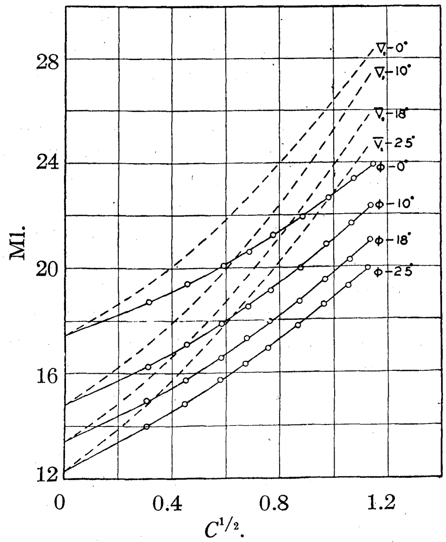

Fig. 3.—Apparent and partial molal volumes of sodium nitrate in methylamine.

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[7] Gucker, *J. Phys. Chem.*, **38**, 307 (1934).

Fitzgerald[8] cites some density data for lithium chloride and for sodium nitrate solutions in methylamine at 0°. However, a smooth curve cannot be drawn through his determined points; his values are mostly higher than those of this investigation and were only incidental to some conductivity and viscosity determinations.

The results for the apparent molal volumes of lithium chloride are very interesting when compared with the values obtained in other solvents.

APPARENT MOLAL VOLUME OF LiCl AT 25°

Solvent	Dielectric constant	Φ	Observer
Water	78	17.06	Geffcken[9]
Methyl alcohol	31.2	− 3.8	Vosburgh[10]
Ethyl alcohol	26.5	− 4.4	Vosburgh
Methylamine	<10.5	−19.21	K. & F.

As the dielectric constant decreases, the apparent molal volume also decreases. The value of <10.5 for the dielectric constant for methylamine was determined by Schlundt[11] on an impure sample. The correct value for pure methylamine is probably much lower than 10.5.

Negative values of the apparent and partial molal volumes have been obtained by other investigators for lithium and sodium hydroxides and for magnesium and copper sulfates in water. The negative values for lithium chloride obtained in this investigation seem to point definitely to a solvation of the lithium ions in the methylamine solution. Such solvation would explain, in part, the trends in electrical conductance observed by Anderson,[2] especially in the more concentrated region. The positive values for sodium nitrate would indicate a probable lack of extensive solvation.

Summary

1. The densities of solutions of lithium chloride and of sodium nitrate in liquid monomethylamine have been determined at different temperatures and have been recorded as functions of the concentration.

2. The apparent and partial molal volumes have been calculated and presented.

3. An approximate correlation between the apparent molal volume of lithium chloride and the dielectric constant of the solvent has been presented.

AUSTIN, TEXAS

RECEIVED JUNE 16, 1938

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[8] Fitzgerald, *J. Phys. Chem.*, **16**, 621 (1912).

[9] Geffcken, *Z. physik. Chem.*, **A155**, 1 (1931).

[10] Vosburgh, Connell and Butler, *J. Chem. Soc.*, 933 (1933).

[11] Schlundt, *J. Phys. Chem.*, **5**, 503 (1901).

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL CHEMISTRY, COLUMBIA UNIVERSITY]

The Synthesis of Dipeptides from α-Keto Acids[1]

BY DAVID SHEMIN AND ROBERT M. HERBST

The classical peptide syntheses of Emil Fischer, and the elegant methods of Bergmann have proved to be of great value both practically and theoretically. However, the possibility of synthesizing peptides from α-keto acids appeared attractive since biological materials other than amino acids could be utilized. The methods developed in this report are primarily of theoretical interest, although their further development in some specific instances may prove to be of practical value.

The conversion of α-keto acids into the corresponding amino acids has been accomplished in a variety of ways. The oximes of α-keto acids have been reduced to amino acids either with tin and hydrochloric acid,[2] or with sodium amalgam.[3] Knoop and Oesterlin[4] have succeeded in reducing α-keto acids to amino acids catalytically with hydrogen in the presence of ammonia. Herbst and Engel[5] have been able to convert α-keto acids into the corresponding amino acids by interaction with another α-amino acid, a reaction which has been accomplished recently in biological systems.[6,7] Of biochemical interest are the reduction of the oxime of pyruvic acid to *dl*-alanine by actively fermenting yeast,[8] the synthesis of alanine from pyruvic acid and ammonia by liver tissue slices,[9] and the formation of *l*-aspartic acid from oxalacetic acid and hydroxyl-

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[1] This report is from a dissertation submitted by David Shemin in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the Faculty of Pure Science, Columbia University.

[2] Gutknecht, *Ber.*, **13**, 1116 (1880).

[3] Gränacher, *Helv. Chim. Acta*, **5**, 610 (1922).

[4] Knoop and Oesterlin, *Z. physiol. Chem.*, **148**, 294 (1925); **170**, 186 (1927).

[5] Herbst and Engel, *J. Biol. Chem.*, **107**, 505 (1934); Herbst, THIS JOURNAL, **58**, 2239 (1936).

[6] Braunstein and Kritzmann, *Enzymologia*, **2**, 129 (1937).

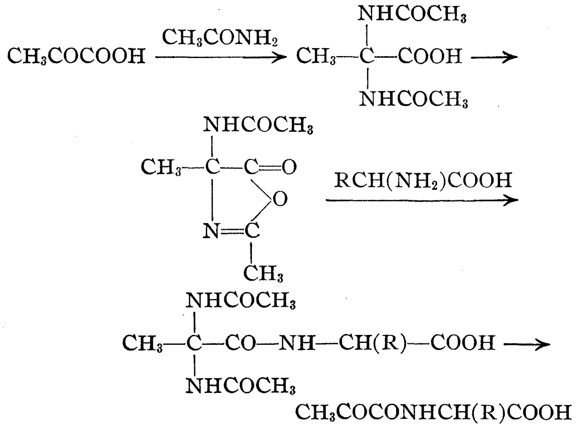
[7] Virtanen and Laine, *Nature*, **141**, 748 (1938).

[8] Maurer, *Biochem. Z.*, **189**, 216 (1927).

[9] Neber, *Z. physiol. Chem.*, **234**, 83 (1935).

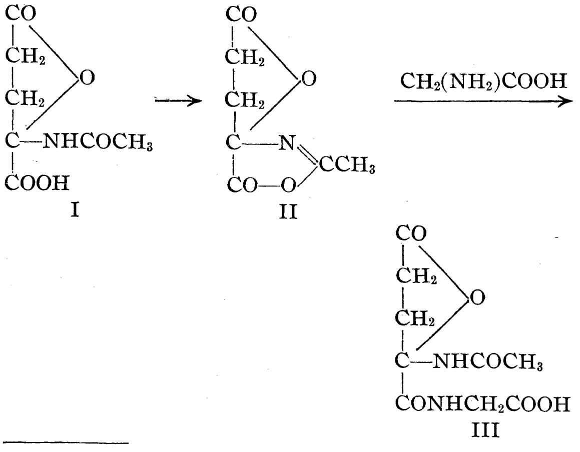
amine by the root nodules of leguminous plants.[10]

Bergmann and Grafe[11,12] have synthesized pyruvyl derivatives of α-amino acids by the following series of reactions



Two methods of converting the pyruvylamino acids into the corresponding dipeptides were tried, the second proving the more satisfactory: (a) catalytic reduction in the presence of ammonia, and (b) catalytic reduction of the oximes of the pyruvylamino acids. Preliminary experiments with the oximes of pyruvic and phenylpyruvic acids, under conditions similar to those employed for simple oximes by Hartung,[13] demonstrated its feasibility for the preparation of amino acids. By this procedure the reduction of the oximes of pyruvylglycine, pyruvylalanine and pyruvylphenylalanine was accomplished. In some cases it was found advantageous to work with the oxime esters.

Application of this synthesis to α-ketoglutaric acid was attempted. Condensation of this keto acid with acetamide led to the formation of the lactone of α-acetamino-α-hydroxyglutaric acid (I). This compound with acetic anhydride formed an azlactone (II) which was coupled with glycine to form the lactone of α-acetamino-α-hydroxyglutarylglycine (III).



The possibility of preparing glutamyl and glutaminyl peptides from the last named compound has not been explored.

Experimental

The melting points, yields and analyses of all compounds prepared are reported in Table I. With three exceptions the yields given are for the reaction leading directly to the product in question; for example, the yield of alanine is for the reduction of pyruvic acid oxime to alanine. The yields of pyruvylglycine oxime ethyl ester, pyruvylalanine ethyl ester and pyruvylphenylalanine oxime are over-all yields based on the amounts of the α,α-diacetaminopropionyl derivatives of glycine, alanine and phenylalanine used, since no intermediates were isolated.

Pyruvylamino Acids.—Pyruvylglycine and pyruvylphenylalanine were prepared as described by Bergmann and Grafe.[12] Pyruvylalanine was prepared by a similar procedure. The mixture obtained by the hydrolysis of α,α-diacetaminopropionylalanine was evaporated to dryness and extracted with dry acetone, from which pyruvylalanine, possessing the properties recorded by Bergmann and his collaborators,[14] was secured on concentration to a small volume and recrystallizing from acetone or ether–petroleum ether.

Ethyl Esters of Pyruvylamino Acids.—Solutions of the pyruvylamino acids, obtained by extracting the above residues with absolute ethyl alcohol instead of acetone, were saturated with hydrogen chloride and boiled under reflux for about half an hour. After the removal of the solvent as completely as possible under reduced pressure, pyruvylglycine ethyl ester was converted into the oxime without further purification; pyruvylalanine ethyl ester was purified by distillation in high vacuum.

Preparation of Oximes.—The oximes of keto acids and pyruvylamino acids were prepared in aqueous solution, those of the ethyl esters of pyruvylamino acids in 50% alcoholic solution by treatment with about one and a half equivalents of hydroxylamine hydrochloride and three equivalents of sodium acetate. The reactions were allowed to proceed for twelve to twenty-four hours at room temperature. The products either crystallized from the reaction mixture before or after acidification to Congo red or were isolated by extraction with ether. Purification was effected either by crystallization from hot water or from ether by addition of petroleum ether or by distillation in high vacuum.

Reduction of Oximes.—The oximes were reduced in alcoholic or aqueous alcoholic solution in the presence of Adams platinum oxide catalyst[15] with hydrogen under 2–3 atmospheres pressure. In some cases, especially with the

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(10) Virtanen and Laine, *Enzymologia*, **3**, 266 (1937).

(11) Bergmann and Grafe, *Z. physiol. Chem.*, **187**, 187 (1930).

(12) Bergmann and Grafe, *ibid.*, **187**, 196 (1930).

(13) Hartung, THIS JOURNAL, **50**, 3370 (1928).

(14) Bergmann, Miekeley and Kann, *Z. physiol. Chem.*, **146**, 247 (1925).

(15) Adams, Voorhees and Shriner, *Org. Syntheses*, **8**, 92 (1928).

TABLE I[a]

Compound	Empirical formula	M. p.,[b] °C.	Yield, %	Analyses, % Calculated C	H	N		Found C	H	N	
Alanine	$C_3H_7O_2N$	...	85	..	...	15.7	15.7[c]	..	...	15.6	15.9[c]
Phenylalanine	$C_9H_{11}O_2N$	...	81	65.5	6.8	8.5	8.5[c]	65.6	6.7	8.6	8.7[c]
Pyruvylglycine oxime	$C_5H_8O_4N_2$	202, dec.	78	37.5	5.0	...		37.8	4.9	...[d]	
Pyruvylglycine oxime ethyl ester	$C_7H_{12}O_4N_2$	127	50	44.7	6.4	14.9		44.6	6.3	14.3	
Alanylglycine	$C_5H_{10}O_3N_2$	...	70	..	...	19.2	9.6[c]	..	...	18.9	9.7[c]
Carbethoxyalanylglycine ethyl ester	$C_{10}H_{18}O_5N_2$	72.5–73.5[e]	16 [f]	48.8	7.4	11.4		48.9	7.5	11.4	
Carbethoxyalanylglycine	$C_8H_{14}O_5N_2$	120–121	52	44.0	6.5	12.8		43.9	6.6	12.7	
α,α-Diacetaminopropionylalanine	$C_{10}H_{17}O_5N_3$	175–176, dec.	85	46.3	6.6	16.2		46.3	6.7	16.1	
Pyruvylalanine	$C_6H_9O_4N$	143.5	73	45.3	5.7	8.8		45.2	5.8	8.8	
Pyruvylalanine oxime	$C_6H_{10}O_4N_2$	186	96	41.4	5.8	16.1		41.4	5.9	15.5	
Pyruvylalanine ethyl ester	$C_8H_{13}O_4N$	Liquid[g]	16.7	51.3	7.0	7.5		51.1	7.2	7.1	
Pyruvylalanine oxime ethyl ester	$C_8H_{14}O_4N_2$	Liquid[h]	86	47.5	7.0	13.9		46.5	7.0	13.3	
Alanylalanine	$C_6H_{12}O_3N_2$	...	76	..	...	17.5	8.8[c]	..	...	17.4	9.0[c]
Alanylalanine anhydride	$C_6H_{10}O_2N_2$	...	85	50.7	7.1	19.7		50.6	7.3	19.4	
Carbethoxyalanylalanine ethyl ester	$C_{11}H_{20}O_5N_2$	71–72	47	50.8	7.8	10.8		50.7	7.9	10.5	
Pyruvylphenylalanine oxime	$C_{12}H_{14}O_4N_2$	187–188, dec.	54	57.6	5.7	11.2		57.8	5.7	10.8	
Alanylcyclohexylalanine	$C_{12}H_{22}O_3N_2$	..	78	59.5	9.1	11.6	5.8[c]	59.2	8.9	11.3	5.7[c]
Benzoylcyclohexylalanine	$C_{16}H_{21}O_3N$	186–187	71	69.8	7.7	5.1		70.0	7.9	5.1	
Lactone of α-acetamino-α-hydroxyglutarylglycine	$C_9H_{12}O_6N_2$	210, dec.	18	44.3	5.0	11.5		43.9	5.0	11.4	

[a] The authors wish to thank Mr. William Saschek for the micro analyses reported in the table. [b] All melting points are corrected. [c] Amino nitrogen, determined according to Van Slyke. [d] Low values for the oximes were obtained by the micro Dumas technique. The micro Kjeldahl process was, of course, not directly applicable. [e] Fischer[16] reports the melting point of carbethoxyalanylglycine ethyl ester as 67.5° and that of carbethoxyalanylglycine as 122°, both corrected. [f] During the preparation of carbethoxyalanylglycine ethyl ester it is partially hydrolyzed to carbethoxyalanylglycine.[16] The combined yield of the two products, obtained in one experiment, amounted to 68%. [g] Distils at 95° bath temperature under 0.4 mm. pressure. [h] Distils at 160–170° bath temperature under 0.7–0.9 mm. pressure.

esters of the pyruvylamino acid oximes, it was found advantageous to carry on the reduction in solutions acidified with a small amount of hydrochloric acid.[13] Free amino acids and dipeptides were isolated from the reduction mixtures by evaporation to dryness after removal of chloride ions, and were purified by crystallization from water by the addition of alcohol. The dipeptide esters obtained by the reduction of the esters of the pyruvylamino acid oximes were isolated as carbethoxy derivatives following the technique of Fischer.[16,17] Phenylalanine was obtained without difficulty by reduction of the oxime of phenylpyruvic acid. However, when the oxime of pyruvylphenylalanine was reduced under the same conditions, alanylcyclohexylalanine was formed. From the latter, cyclohexylalanine was obtained by hydrolysis with dilute hydrochloric acid and isolated as the benzoyl derivative,[18] the identity of which was established by analysis and by mixed melting point determinations.

Lactone of α-Acetamino-α-hydroxyglutarylglycine, (III).—A suspension of 3 g. of α-acetamino-α-hydroxyglutaric lactone (I),[19] in 60 cc. of acetic anhydride was heated on a boiling water-bath until all the material had dissolved. About ten or fifteen minutes were required, during which time the solution became orange-yellow. After removal of the excess acetic anhydride *in vacuo*, the crude azlactone (II), a yellow viscous oil, was suspended in 30 cc. of acetone and treated immediately with a solution of 1.12 g. of glycine in 15 cc. of normal sodium hydroxide. The mixture, containing a trace of undissolved material, was shaken for thirty minutes, neutralized with 15 cc. of normal sulfuric acid, evaporated to dryness *in vacuo*, and extracted thoroughly with cold 95% alcohol. The alcoholic solution was evaporated to dryness; the residue was taken up in a small amount of water and decolorized with charcoal. The aqueous solution was then evaporated to dryness and the residue washed with cold alcohol. The insoluble portion, weighing 1.3 g., was recrystallized by suspension in hot alcohol and dropwise addition of water until solution took place. On cooling 0.7 g. of product separated from the solution.

On direct titration with 0.01 *N* sodium hydroxide, using phenolphthalein as the indicator, the substance immediately consumed somewhat more than one equivalent of alkali, and thereafter behaved like a lactone. The equivalent weight (calcd. 122; found 116, 128) was determined by back-titration with hydrochloric acid after treatment with a slight excess of alkali.

Summary

1. The possibility of synthesizing amino acids and dipeptides from α-keto acids has been demonstrated.

2. The oximes of pyruvic and phenylpyruvic acids were converted into the corresponding amino acids by catalytic reduction.

3. The pyruvyl derivatives of glycine, glycine ethyl ester, alanine, and alanine ethyl ester were converted into the corresponding dipeptides by catalytic reduction of their oximes. In the case of pyruvylphenylalanine oxime, reduction led to alanylcyclohexylalanine.

4. The azlactone of α-acetamino-α-hydroxy-

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(16) Fischer, *Ann.*, **340**, 123 (1905).

(17) Fischer, *Ber.*, **35**, 1095 (1902).

(18) Waser and Brauchli, *Helv. Chim. Acta.*, **6**, 199 (1923); *ibid.*, **7**, 740 (1924).

(19) The condensation of α-ketoglutaric acid with acetamide will be described in the succeeding paper.

glutaric lactone was condensed with glycine with the formation of the lactone of α-acetamino-α-hydroxyglutarylglycine.

NEW YORK, N. Y. RECEIVED JUNE 15, 1938

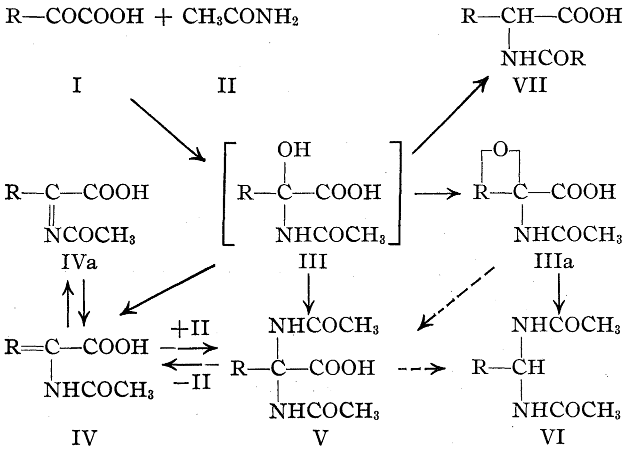
[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL CHEMISTRY, COLUMBIA UNIVERSITY]

The Condensation of α-Keto Acids and Acetamide[1]

BY DAVID SHEMIN AND ROBERT M. HERBST

In order to extend the dipeptide synthesis described in the preceding paper, it was necessary to prepare α,α-diacetamino derivatives from α-keto acids other than the pyruvic acid studied by Bergmann and Grafe.[2] The results obtained in the reaction of α-ketoglutaric acid with acetamide made desirable a more extensive study of this condensation, with a view to obtaining clearer insight into its mechanism.

The results obtained with the several α-keto acids studied are summarized in the following scheme



When α-ketoglutaric acid (I, R = $COOHCH_2CH_2$—) was condensed with acetamide (II) at 70°, the main product was the lactone of α-acetamino-α-hydroxyglutaric acid (IIIa, R = —$COCH_2CH_2$—). If the reaction was carried out at a higher temperature, or if IIIa was heated at a higher temperature with acetamide, a second product, γ,γ-diacetaminobutyric acid (VI, R = $COOHCH_2CH_2$—) was obtained. Whether V is an intermediate in this reaction, as indicated by the dotted arrows, or whether IIIa is decarboxylated, must remain an open question, but the opening of the lactone ring of IIIa by addition of acetamide appears to be a new reaction.

These results suggested that the formation of the diacetamino compounds proceeds in two steps, (a) addition of acetamide to the carbonyl group of the keto acid with the formation of an α-hydroxy-α-acetamino compound (III), and (b) replacement of the hydroxyl group of III by an acetamino group. This hypothesis seemed reasonable in view of the fact that benzaldehyde, on treatment with acetamide under suitable conditions, forms benzylidene-diacetamide.[3,4] However, it should be pointed out that in the preparation of α,α-diacetaminopropionic acid (V, R = CH_3—) from pyruvic acid and acetamide, a small amount of α-acetaminoacrylic acid (IV, R = CH_2=) is always formed.[2] If α-acetamino-α-hydroxypropionic acid (III, R = CH_3—) is formed as the first step in the reaction, loss of water from this intermediate readily explains the formation of α-acetaminoacrylic acid. In the case of α-ketoglutaric acid the intermediate (III) is stabilized by the formation of the lactone (IIIa). On the basis of the above hypothesis α-acetaminoacrylic acid would appear to be a by-product, but the possibility that it is an intermediate must be considered.

To test this point α-acetaminoacrylic acid (IV, R = CH_2=) was heated with acetamide. Surprisingly, almost quantitative conversion to α,α-diacetaminopropionic acid (V, R = CH_3—) resulted, so that α-acetaminoacrylic acid cannot be excluded as an intermediate. In this connection it should be recalled that α-aminoacrylic acid derivatives may be considered as tautomeric substances[2,5] capable of reacting in the forms IV or IVa. Acetamide may therefore add onto either the carbon–carbon double bond of IV or the car-

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[1] This report is from a dissertation submitted by David Shemin in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the Faculty of Pure Science, Columbia University.

(2) Bergmann and Grafe, *Z. physiol. Chem.*, **187**, 187 (1930).

(3) Bulow, *Ber.*, **26**, 1972 (1893).

(4) Chattaway and Swinton, *J. Chem. Soc.*, **101**, 1206 (1912).

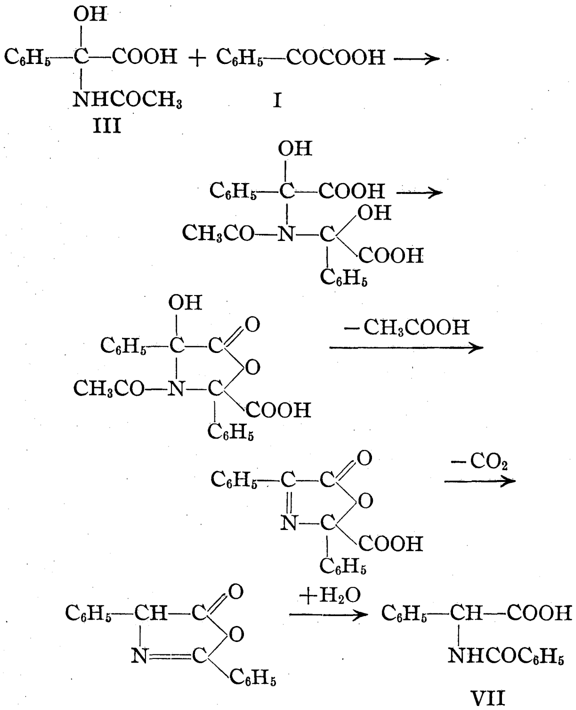
(5) Bergmann, Miekeley and Kann, *Z. physiol. Chem.*, **146**, 247 (1925).

bon–nitrogen double bond of IVa.[6] Our data permit no definite conclusion as to the mode of addition of acetamide to α-acetaminoacrylic acid. The only other examples tried, cinnamic acid and α-acetaminocinnamic acid, showed no tendency to react with acetamide. However, the side chain double bond of cinnamic acid is notoriously unreactive, and the presence of the benzene ring may elicit a similar condition in the case of acetaminocinnamic acid. This is supported by the observation that when phenylpyruvic acid was heated with acetamide, α-acetaminocinnamic acid was formed in excellent yield.

The condensation of benzoylformic acid with acetamide was also studied. In this case an intermediate of type IV cannot form, although IVa is still a possibility. Actually α,α-diacetaminophenylacetic acid (V, R = C_6H_5—) was formed in good yield, together with small amounts of α-benzoylaminophenylacetic acid (VII, R = C_6H_5—) and benzylidene diacetamide (VI, R = C_6H_5—). The latter probably resulted from the interaction of acetamide with benzaldehyde, formed by decarboxylation of benzoylformic acid. Attempts to decarboxylate α,α-diacetaminophenylacetic acid were unsuccessful.

The experimental results are best explained by the assumption that the first step in the reaction between α-keto acids and acetamide is the addition of acetamide to the carbonyl group of the keto acid with the formation of an α-acetamino-α-hydroxy derivative. The second step involves replacement of the hydroxyl group by another acetamino group either directly or through an unsaturated intermediate of the Schiff base type.

The formation of the α-benzoylaminophenylacetic acid resembles that of N-phenacetylphenylalanine from α-benzoylaminocinnamic acid or phenylpyruvic acid and aqueous ammonia,[7] and that of N-acetylalanine from ammonia and pyruvic acid.[8] Du Vigneaud and Irish[9] have recently demonstrated the significance of this reaction in the biological synthesis of amino acids. The following scheme is suggested to account for the conversion of III into VII (R = C_6H_5—).



Attempts to isolate the azlactone postulated in the above scheme were unsuccessful, and it was impossible to find evidence of a similar reaction in the case of any of the other α-keto acids studied.

Both the Erlenmeyer and the de Jong reactions can be explained by an analogous mechanism, ammonia being substituted for acetamide and water split out instead of acetic acid at the appropriate point. The formation of the amide of phenacetylphenylalanine in the Erlenmeyer reaction can be best explained by the assumption of an azlactone as a precursor, especially since Bergmann and collaborators[10] have shown that the azlactones of acylamino acids are converted into the respective amides by aqueous ammonia.

Experimental

α-Ketoglutaric Acid with Acetamide

α-Acetamino-α-hydroxyglutaric Lactone (IIIa, R = —$COCH_2CH_2$—).—α-Ketoglutaric acid (13.5 g.), prepared according to Neuberg and Ringer,[11] was treated with 6 g of acetamide at 70–75° under 10–15 mm. pressure for ten hours. The partially crystalline reaction mixture was extracted with four 50-cc. portions of hot ethyl acetate. The insoluble fraction (9.5 g.) was recrystallized from acetone–ether, from which it separated as colorless prisms which, on rapid heating, melted with decomposition at 196° (corr.). The substance was also soluble in water and alcohol, and crystallized from the latter on addition of ether. Opening of the lactone ring and esterification (see below) occur on prolonged boiling in alcoholic solution. The material was dried for analysis at 76° at 5 mm.

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[6] Dr. R. E. Steiger very kindly called our attention to the latter possibility.

[7] Erlenmeyer and Kunlin, *Ann.*, **307**, 146 (1899); Erlenmeyer, *ibid.*, **337**, 205 (1904).

[8] De Jong, *Rec. trav. chim.*, **19**, 259 (1900).

[9] Du Vigneaud and Irish, *J. Biol. Chem.*, **122**, 349 (1938).

[10] Bergmann, Stern and Witte, *Ann.*, **449**, 277 (1926).

[11] Neuberg and Ringer, *Biochem. Z.*, **71**, 226 (1915).

Anal. Calcd. for $C_7H_9O_5N$: C, 44.9; H, 4.9; N, 7.5. Found: C, 45.1; H, 4.7; N, 7.5.

On direct titration with standard alkali the substance behaved like a lactone. The equivalent weight determined by back-titration after dissolving in a slight excess of alkali was 88, calculated for $C_7H_9O_5N$, 93.5. No reaction took place with bromine in aqueous solution.

On hydrolysis with normal hydrochloric acid, a 95% yield of α-ketoglutaric acid was obtained, isolated as the 2,4-dinitrophenylhydrazone, m. p. 217° (corr.) with decomposition, and showing no depression when mixed with an authentic specimen.

Glutamic Acid Hydrochloride.—α-Acetamino-α-hydroxyglutaric lactone was boiled with absolute ethyl alcohol for three hours. The resultant unsaturated ester was hydrogenated in the presence of a platinum catalyst and hydrolyzed with normal hydrochloric acid, when glutamic acid hydrochloride was obtained.

Anal. Calcd. for $C_5H_9O_4N \cdot HCl$: N, 7.6; NH_2-N, 7.6. Found: N, 7.9; NH_2-N, 7.7.

γ,γ-Diacetaminobutyric Acid (VI, R = COOHCH$_2$-CH$_2$—).—A mixture of 18 g. of α-ketoglutaric acid and 15 g. of acetamide was heated at 110 ± 5° for eight to nine hours at 10–15 mm. pressure. The reaction mixture was then dissolved in 400 cc. of cold ethyl acetate. An oil separated which crystallized on standing in the refrigerator. The crystals were filtered off and washed with cold ethyl acetate and cold absolute alcohol. Recrystallization was effected by boiling a suspension of the material in hot absolute alcohol and adding water dropwise until solution was complete. On standing in the refrigerator the substance crystallized in the form of needles, m. p. 197° (corr.), in a yield of 3.5 g. The melting point was markedly depressed when the material was mixed with α-acetamino-α-hydroxyglutaric lactone.

Anal. Calcd. for $C_8H_{14}O_4N_2$: C, 47.5; H, 6.9; N, 13.9; equiv. wt., 202. Found: C, 47.6; H, 7.0; N, 13.6; equiv. wt., 203.

γ,γ-Diacetaminobutyric acid was also formed when the lactone of α-acetamino-α-hydroxyglutaric acid (1.87 g.) was heated with acetamide (1.8 g.) at 110°. By similar methods of isolation, 900 mg. was obtained, m. p. 197° (corr.), and showing no depression when mixed with the product described above.

Anal. Calcd. for $C_8H_{14}O_4N_2$: N, 13.9. Found: N, 13.7.

The constitution was determined by hydrolysis in aqueous acid solution to the semi-aldehyde of succinic acid, isolated as the *p*-nitrophenylhydrazone, m. p. 179.5° (corr.), in a yield of 55%. The melting point showed no depression when mixed with an authentic specimen.[12]

α-Acetaminoacrylic Acid with Acetamide

α,α-Diacetaminopropionic Acid (V, R = CH$_3$—).—α-Acetaminoacrylic acid was prepared from α,α-diacetaminopropionic acid according to Bergmann and Grafe.[2]

Anal. Calcd. for $C_5H_7O_3N$: N, 10.9. Found: N, 10.7.

α-Acetaminoacrylic acid (4.75 g.) was heated with acetamide (10 g.) at 110–115° under 10–15 mm. pressure for three hours. The fraction insoluble in ethyl acetate was recrystallized from hot 95% ethyl alcohol. The yield of pure α,α-diacetaminopropionic acid was 4.5 g., m. p. 189–190° (corr.) with decomposition. It did not take up bromine in aqueous solution.

Anal. Calcd. for $C_7H_{12}O_4N_2$: N, 14.9. Found: N, 14.9.

α-Acetaminocinnamic Acid with Acetamide

In an attempt to condense α-acetaminocinnamic acid with acetamide under comparable conditions, 94 per cent. of the α-acetaminocinnamic acid was recovered as such.

Phenylpyruvic Acid with Acetamide

α-Acetaminocinnamic Acid (IV, R = C$_6$H$_5$CH=).—A mixture of 12 g. of phenylpyruvic acid[13] and 12 g. of acetamide was heated for three hours at 110–115° under 10–15 mm. pressure. On recrystallization from boiling water with norite, the reaction mixture yielded 7.1 g. of pure α-acetaminocinnamic acid, m. p. 193° (corr.) with decomposition.

Benzoylformic Acid with Acetamide

α,α-Diacetaminophenylacetic Acid (V, R = C$_6$H$_5$—).—Benzoylformic acid (10 g.) was heated with acetamide (10 g.) for one hour at 110–115° under 10 mm. pressure. The initially clear melt solidified during the course of heating. Crude α,α-diacetaminophenylacetic acid (9.3 g.) remained after the reaction mixture was thoroughly extracted with ether (see below) and washed with cold alcohol. On recrystallization from 70–80% alcohol α,α-diacetaminophenylacetic acid separated in the form of microscopic crystals, containing one mole of water of crystallization, m. p. 201–202° (uncorr.) with foaming. The material was dried for analysis at 110° *in vacuo* over phosphorus pentoxide.

Anal. Calcd. for $C_{12}H_{14}O_4N_2 \cdot H_2O$: H_2O, 6.7. Found: H_2O, 6.5. Calcd. for $C_{12}H_{14}O_4N_2$: C, 57.6; H, 5.6; N, 11.2. Found: C, 57.4; H, 5.6; N, 11.2.

On boiling with normal hydrochloric acid, α,α-diacetaminophenylacetic acid yielded benzoylformic acid, identified as the 2,4-dinitrophenylhydrazone, m. p. 196° (uncorr.) with decomposition, and showing no depression when mixed with an authentic specimen.[14]

α-Benzoylaminophenylacetic Acid (VII, R = C$_6$H$_5$—).—The ether-soluble fraction of the above reaction product of benzoylformic acid and acetamide, on recrystallization from hot water, gave 220 mg. of α-benzoylaminophenylacetic acid, m. p. 175° (corr.) showing no depression when mixed with an authentic sample.[15]

Benzylidene Diacetamide (VI, R = C$_6$H$_5$—).—During the reaction of benzoylformic acid with acetamide variable amounts of benzylidene diacetamide were formed. This substance was separated from the diacetaminophenylacetic acid by its ready solubility in hot absolute alcohol, from which it crystallized in the form of long needles, m. p. 250° (uncorr.) with decomposition.

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[12] Dakin, *Biochem. J.*, **11**, 79 (1917).

[13] Phenylpyruvic acid can be prepared conveniently in yields of 90–96% of the theoretical by boiling α-acetaminocinnamic acid for three hours with 20 parts of normal hydrochloric acid.

[14] Corson, Sanborn, and Van Ess, THIS JOURNAL, **52**, 1623 (1930).

[15] Kossel, *Ber.*, **24**, 4145 (1891).

Anal. Calcd. for $C_{11}H_{14}O_2N_2$: N, 13.6. Found: N, 13.7.

When α,α-diacetaminophenylacetic acid was heated with acetamide under the above conditions for as long as five hours, no evidence of decarboxylation could be obtained, and only the starting material could be isolated from the reaction mixture.

Summary

1. The condensation of the following α-keto acids with acetamide has been studied: pyruvic, phenylpyruvic, α-ketoglutaric, and benzoylformic acids.

2. The condensation takes place in the following steps: (a) addition of acetamide to the carbonyl group of the keto acid with the formation of an α-acetamino-α-hydroxy acid, and (b) replacement of the hydroxyl group by a second acetamino group, either directly or by dehydration followed by addition of acetamide to the unsaturated intermediate.

3. Phenylpyruvic acid forms only α-acetaminocinnamic acid, and the latter does not add acetamide to its double bond under the experimental conditions chosen.

4. The opening of a lactone ring by addition of acetamide was observed with the lactone of α-acetamino-α-hydroxyglutaric acid.

5. In the condensation of benzoylformic acid with acetamide a secondary reaction analogous to the Erlenmeyer-de Jong reaction was observed. A mechanism is suggested to explain the formation of α-acylamino acids from α-keto acids by this reaction.

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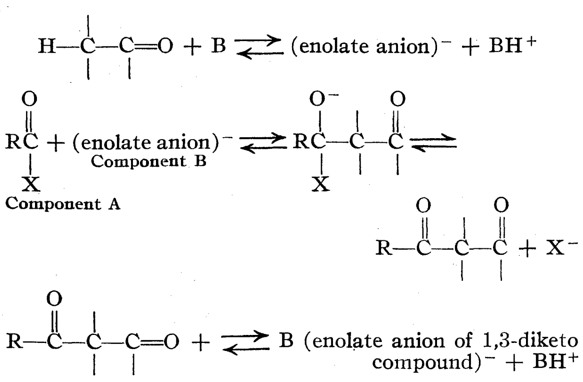
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF DUKE UNIVERSITY]

Condensations Brought about by Bases. III. The General Course of the Claisen Type of Condensation

BY CHARLES R. HAUSER

The equations proposed recently[1] for the Claisen condensation of ethyl esters may be generalized to include other carbon-carbon condensations in which a metallic enolate condenses with a compound of the general type RCOX, where X is an atom or group that is removed as an anion during the reaction. The general course for this type of condensation may be represented by the following ionic equations, in which B represents a base.



$$\mathrm{H{-}\underset{|}{\overset{|}{C}}{-}\underset{|}{C}{=}O} + \mathrm{B} \rightleftharpoons (\text{enolate anion})^- + \mathrm{BH}^+$$

$$\underset{\text{Component A}}{\mathrm{R\overset{\overset{O}{\|}}{\underset{\underset{X}{|}}{C}}}} + \underset{\text{Component B}}{(\text{enolate anion})^-} \rightleftharpoons \mathrm{R\overset{\overset{O^-}{|}}{\underset{\underset{X}{|}}{C}}{-}\overset{|}{\underset{|}{C}}{-}\overset{\overset{O}{\|}}{\underset{|}{C}}} \rightleftharpoons \mathrm{R{-}\overset{\overset{O}{\|}}{C}{-}\overset{|}{\underset{|}{C}}{-}\overset{\overset{O}{\|}}{\underset{|}{C}}} + \mathrm{X}^-$$

$$\mathrm{R{-}\overset{\overset{O}{\|}}{C}{-}\overset{|}{\underset{|}{C}}{-}\underset{|}{C}{=}O} + \rightleftharpoons \mathrm{B}\ (\text{enolate anion of 1,3-diketo compound})^- + \mathrm{BH}^+$$

The first equation represents an acid-base reaction in which a new acid and a new base (the enolate anion) are formed. The second equation represents a carbon-carbon condensation between the enolate anion, designated component B, and a compound of the type RCOX, which is designated component A.[2] This reaction gives an intermediate organic anion, which releases X as anion, forming the 1,3-diketo compound. The last equation represents another acid-base reaction in which the 1,3-diketo compound is converted into its enolate anion. This reaction can occur, of course, only if the 1,3-diketo compound contains an enolizable hydrogen, and if a sufficiently strong base is present.

A number of apparently diverse condensations, as, for example, the condensation of two molecules of an ethyl ester in the presence of a base, and the condensation of a molecule of acetoacetic ester (as enolate) with a molecule of an acid chloride are represented by these general equations. It is proposed that any reaction that is represented by the above equations be classified as a Claisen type of condensation.

While there is little doubt that the general mechanism of the Claisen type of condensation involves the formation of a metallic enolate as an active intermediate, the detailed mechanism by which this enolate condenses with a compound

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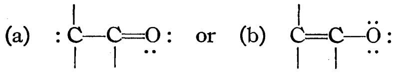
[1] (a) Hauser and Renfrow, THIS JOURNAL, **59**, 1823 (1937); (b) Renfrow and Hauser, *ibid.*, **60**, 463 (1938).

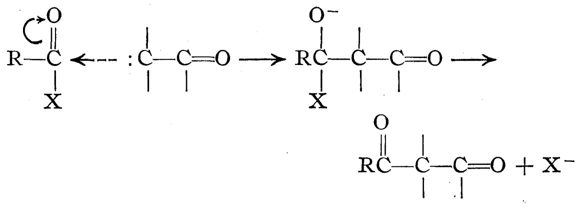
[2] In this connection see Arndt and Eistert, *Ber.*, **69**, 2383 (1936).

of the type RCOX is not entirely clear. Metallic enolates are capable of reacting as if their anions possessed either of the resonance forms

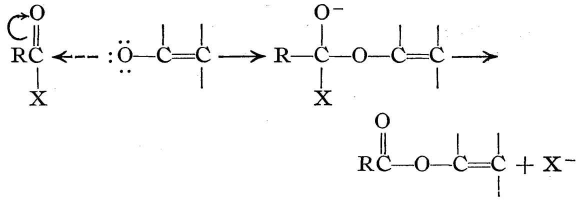


$$(a)\ :\overset{|}{\underset{|}{C}}-\underset{|}{C}=\ddot{O}:\quad \text{or}\quad (b)\ \overset{|}{\underset{|}{C}}=\underset{|}{C}-\ddot{O}:$$

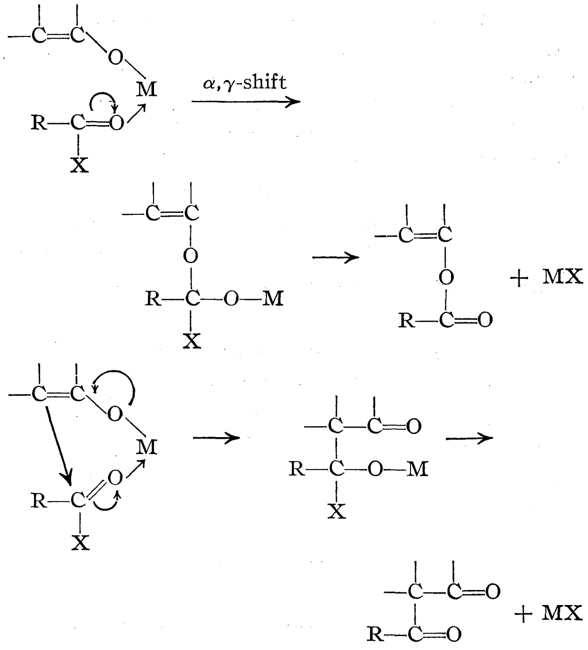
giving both carbon and oxygen derivatives. The carbon–carbon condensation represented by the above equations may be considered to involve an attack of resonance form (a) of the enolate anion on the potentially positive carbon atom of the carbonyl group in component A, thus



An oxygen–carbon condensation may be considered to involve a reaction of resonance form (b) of the enolate anion, thus



This simple representation, however, does not indicate the effect that component A may have on the course of the condensation as exhibited, for example, in the reactions of the sodium enolate of acetoacetic ester with certain acid chlorides; this enolate with acetyl or benzoyl chloride gives mainly the carbon derivative, but with chloroformic ester, mainly the oxygen derivative.[3] In the similar phenomena of oxygen- and carbon-alkylation of metallic enolates Johnson[4] assumes that a coördination complex is first formed: an α,γ-shift leads to oxygen ethers, and a cyclic mechanism leads to carbon alkylation. On the basis of these ideas the alternative courses of reaction of metallic enolates (especially those that would not be ionized appreciably) with compounds of the type RCOX might be represented as follows[5]



Whether or not further data will support these mechanisms remains to be determined. At the present time the ionic point of view of the Claisen condensation seems preferable. It is not only simpler but at least certain metallic enolates appear to be ionized; certain other enolates which may not be ionized appreciably, may be regarded as possessing potential ions. It is possible that a coördination complex between component A and the metallic enolate might lead to the transient formation of resonance structures (a) or (b). Regardless of the intimate mechanism, however, a carbon–carbon condensation between a metallic enolate and a compound of the type RCOX may be classified as a Claisen type of condensation.

The types[6] of component A of the condensation include esters, anhydrides,[7] acid chlorides,[7] and N-diphenylacetamide,[8] where X is OR, OOCR, Cl, and $(C_6H_5)_2N$, respectively. The types[6] of component B include the enolate anions of esters, aldehydes, ketones, N-diphenylacetamide,[8] and 1,3-diketo compounds.[9] Component B could also be the enolate anions of other types of compounds. A general formula for compounds whose anions might function as com-

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[3] See, for example, Hickinbottom, "Reactions of Organic Compounds," Longmans, Green and Company, New York, N. Y., 1936, p. 105, or Richter, "Organic Chemistry," Blakiston, Philadelphia, Pa., 1934, Vol. I, p. 474.

[4] See Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1938, p. 1651.

[5] The general formula $-\overset{|}{C}=\overset{|}{C}-O-M$ represents a metallic enolate. The enolic form of the enolate is shown because this, rather than the ketonic form, probably more nearly approximates the structure of the compound.

[6] It should be pointed out that not all of these types of components A and B have been condensed with each other.

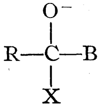
[7] See Hudson, Dick and Hauser, THIS JOURNAL, **60**, 1960 (1938).

[8] Chelintzev and Osetrova, *Ber.*, **69B**, 374 (1936).

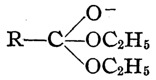
[9] The reaction of the enolate of a 1,3-diketo compound, such as acetoacetic ester, with an acid chloride (component A) will form a triketo compound of the type $RCOCH(COR)\underset{|}{C}O$.

ponent B is represented by the system $\text{H—}\overset{|}{\underset{|}{\text{C}}}\text{—}\underset{|}{\text{A}}\text{=X}$, where A is carbon or nitrogen and X oxygen or nitrogen. It should be pointed out also that the condensation of many basic anions or of Grignard reagents with a compound of the type RCOX may follow a course similar to that represented above, but it is probably best to classify as examples of the Claisen type of condensation only those reactions in which a carbon–carbon condensation occurs, and in which a metallic enolate or its anion serves as component B.

The types of base B that may be used to effect the Claisen condensation include the anions, $^-OC_2H_5$, $^-NH_2$, and $(C_6H_5)_3C^-$, and certain Grignard reagents.[10] The base that will effect a condensation between a particular set of components A and B is limited by several factors. In the first place, the base B, as well as the enolate anion, may condense with the carbonyl group of component A, giving the intermediate anion


$\text{R—}\overset{\text{O}^-}{\underset{\text{X}}{\text{C}}}\text{—B}$;

the latter on decomposition may form RCOB and X^-. This competing reaction should be expected especially when the equilibrium of the first equation above is on the left side (*i. e.*, when there is a high concentration of the base B), and when X of component A corresponds to a weaker base than B. In the common condensations of ethyl esters effected by sodium ethoxide the equilibrium of the first step is probably on the left side, but here the base B, which is ethoxide ion, is the same group as X of component A; consequently, any anion of the type


$$R\text{—}C\begin{cases}O^- \\ OC_2H_5 \\ OC_2H_5\end{cases}$$

that might be formed by reaction of ethoxide ion with component A, would on decomposition regenerate the original component A (ethyl ester) and original base B (ethoxide ion). On the other hand, if X of component A is chlorine, the ethoxide ion probably would convert most of the acid chloride into the corresponding ethyl ester and chloride ion. The very low yield of acetoacetic ester obtained from ethyl acetate in the presence of sodamide[11] is probably due to the predominance of a similar competing reaction between the amide ion $(NH_2)^-$ and the carbonyl group of the ester. In certain cases it is possible to minimize the competing reaction of the base B with component A by first converting the system $\text{H—}\overset{|}{\underset{|}{\text{C}}}\text{—}\underset{|}{\text{C}}\text{=O}$ into its enolate anion, and then allowing this anion to react with component A. Esters may be enolized by sodium triphenylmethyl,[12] and ketones by sodamide.[13] β-Keto esters, such as ethyl acetoacetate,[9] are commonly enolized by sodium ethoxide.

Other factors that limit the type of base B that may be used to effect a Claisen condensation are not well understood at the present time. One of the requirements appears to be that a weaker base must be formed than the one used to initiate the reaction. In all known condensations of ethyl esters by sodium ethoxide the β-keto ester that is formed is converted into its enolate; it should be noted that in this way only can a base (enolate anion) be formed that is weaker than the one (ethoxide ion) used to initiate the reaction. On the other hand, when sodium triphenylmethyl is used in condensations of ethyl esters it is not necessary[1b] for the β-keto ester that is formed to be converted into its enolate, because a weaker base, the ethoxide ion, is formed during the reaction. It should be pointed out, however, that condensation does not always occur even when it appears possible to form a weaker base.[14] Solubility relationships or perhaps other factors may play an important role in these condensations.

Summary

1. The general course of the Claisen type of condensation is outlined.

2. It is proposed that any reaction that involves the carbon–carbon condensation of a metallic enolate with a compound of the type RCOX, where X is an atom or group that is removed as an anion, be classified as a Claisen type of condensation.

3. Certain aspects of this type of condensation are discussed.

DURHAM, NORTH CAROLINA RECEIVED JUNE 11, 1938

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[10] Spielman and Schmidt, THIS JOURNAL, **59**, 2009 (1937).

[11] See Bergstrom and Fernelius, *Chem. Rev.*, **12**, 146 (1933).

[12] The anion of sodium triphenylmethyl is a base which readily enolizes the hydrogen on the α-carbon atom of an ester, but which appears to attack the carbonyl group of the ester only at a relatively slow rate. Apparently the latter reaction occurs only when it is not possible for an ester to be enolized. In this connection see Schlenk and Ochs, *Ber.*, **49**, 610 (1916).

[13] See Bergstrom and Fernelius, *Chem. Rev.*, **12**, 107 (1933).

[14] Roberts and McElvain [THIS JOURNAL, **59**, 2007 (1937)] have shown that ethyl isovalerate and ethyl *t*-butylacetate are not condensed by sodium ethoxide even though the β-keto esters that would be formed have hydrogen on the α-carbon atom.

[Contribution from the Chemistry Department of Duke University]

Condensations Brought about by Bases. IV. The Condensation of Ethyl Isobutyrate with Benzoyl Chloride, Benzoic Anhydride and Phenyl Benzoate as Examples of the Claisen Type of Condensation[1]

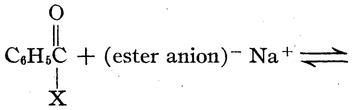
By B. E. Hudson, Jr., R. H. Dick and Charles R. Hauser

The general course of the Claisen type of condensation has been outlined in the third paper of this series.[2] It was pointed out that any reaction involving the condensation of a metallic enolate with a compound of the type RCOX, where X is an atom or group that is removed as an anion, may be classified as a Claisen type of condensation.

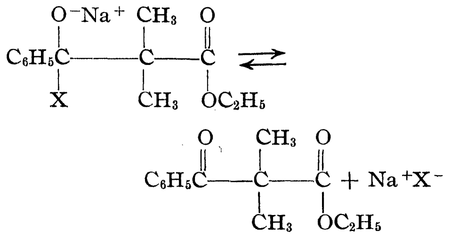
The purpose of this paper has been to investigate the possibility of condensing the simple esters, ethyl acetate, ethyl propionate and ethyl isobutyrate, with a series of compounds of the type C_6H_5COX, using sodium triphenylmethyl as the base. In order to minimize the competing reaction of sodium triphenylmethyl with RCOX, it seemed expedient first to convert the ester into its enolate by means of the sodium triphenylmethyl and then allow the enolate to condense with RCOX, but this procedure has been satisfactory only with ethyl isobutyrate.

Ethyl isobutyrate was added to an ether solution of sodium triphenylmethyl, and, after eight to ten minutes, benzoyl chloride,[3] benzoic anhydride, or phenyl benzoate was added. These reactions gave good yields (50–55%) of the carbon–carbon condensation product, ethyl benzoyldimethylacetate. No oxygen derivative was isolated. These carbon–carbon condensations, as well as the one between ethyl isobutyrate and ethyl benzoate,[4] are regarded as examples of the Claisen type of condensation. They may be represented by the following equations, where X of component A is chlorine, benzoate, phenoxide or ethoxide.

$$(CH_3)_2CHCOOC_2H_5 + (C_6H_5)_3C^-Na^+ \rightleftharpoons (\text{ester anion})^-\,Na^+ + (C_6H_5)_3CH$$



$$C_6H_5\underset{X}{\overset{\overset{O}{\|}}{C}} + (\text{ester anion})^-\,Na^+ \rightleftharpoons$$



$$C_6H_5\underset{X}{\overset{O^-Na^+}{C}}-\underset{CH_3}{\overset{CH_3}{C}}-\underset{OC_2H_5}{\overset{\overset{O}{\|}}{C}} \rightleftharpoons C_6H_5\overset{\overset{O}{\|}}{C}-\underset{CH_3}{\overset{CH_3}{C}}-\underset{OC_2H_5}{\overset{\overset{O}{\|}}{C}} + Na^+X^-$$

It should be pointed out that in order to obtain ethyl benzoyldimethylacetate when X is ethoxide it is necessary to acidify the reaction mixture within a short time,[5] because on standing in the presence of ethoxide ion (which is formed in the condensation), this β-keto ester is converted into ethyl benzoate and ethyl isobutyrylisobutyrate.[6]

The condensation of ethyl acetate or ethyl propionate with compounds of the type RCOX is difficult to control, first because these esters, in the presence of sodium triphenylmethyl, undergo self condensation very rapidly,[7] and, second, because the β-keto esters which result also are capable of condensing with many compounds of the type RCOX. When ethyl acetate or ethyl propionate is added to an ether solution of sodium triphenylmethyl the deep-red color of the latter changes quickly to a lighter color (orange or yellow) even at 0°; and at room temperature a good yield (43%) of ethyl acetoacetate[8] is obtained from ethyl acetate when the reaction is stopped by acidification within three minutes.[7]

It has not been possible to isolate a good yield of the primary condensation product from the reaction of ethyl acetate or propionate with a compound of the type RCOX. The addition of

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[1] This work was supported in part by a grant from the Duke University Research Council.

[2] Hauser, This Journal, **60**, 1957 (1938).

[3] This reaction serves as perhaps the best method for the preparation of ethyl benzoyldimethylacetate. Previously, it has been carried out on a small scale by Scheibler and Stein, *J. prakt. Chem.*, **139**, 105 (1934).

[4] Renfrow and Hauser, This Journal, **60**, 463 (1938).

[5] Ethyl benzoyldimethylacetate has been obtained from ethyl isobutyrate and ethyl benzoate by stopping the reaction after thirty minutes.[4] The yield of β-keto ester that could be isolated in this case, however, was only about one-third of that obtained from the condensation of ethyl isobutyrate with benzoyl chloride.

[6] Further details of this conversion will be published shortly.

[7] It should be pointed out that ethyl isobutyrate likewise undergoes self-condensation in the presence of sodium triphenylmethyl, but at a slower rate. See Hauser and Renfrow, This Journal, **59**, 1823 (1937).

[8] That the enolate of ethyl acetate is an intermediate in this condensation is indicated by the fact that when the ester is added to sodium triphenylmethyl, followed by the addition of iodine, ethyl iodoacetate is obtained (25% yield); Muller, Gawlick and Kreutzmann, *Ann.*, **515**, 109 (1934).

ethyl propionate to an ether solution of sodium triphenylmethyl at 0°, followed immediately by the addition of benzoyl chloride, gave only high boiling products, which were assumed to be benzoylated β-keto esters. The addition of a mixture of ethyl propionate and phenyl benzoate to sodium triphenylmethyl gave a very small yield of a product which apparently was the primary condensation product, ethyl benzoylmethylacetate, but in this case also a considerable amount of higher boiling material was obtained. Low yields of ethyl benzoylacetate[9] and ethyl benzoylmethylacetate (primary condensation products) have been obtained by adding mixtures of ethyl acetate and ethyl benzoate, and of ethyl propionate and ethyl benzoate, to solutions of sodium triphenylmethyl.

Experimental

Preparation of Sodium Triphenylmethyl.—For the condensations studied in this paper ether solutions of sodium triphenylmethyl were prepared by shaking together 63 g. of triphenylchloromethane, 2100 g. of 1% sodium amalgam and 1500 cc. of dry ether as described previously.[10] In some preparations 1500 g. of 1% sodium amalgam to 63 g. of triphenylchloromethane has been used. It is advisable to stop the shaking with the appearance of the deep-red color, and cool the reaction bottle with a wet towel; the shaking should then be continued for about thirty minutes longer. The ether solution of sodium triphenylmethyl may be analyzed as follows. A 50-cc. aliquot of the solution is run into 25 cc. of water in a separatory funnel. The water is drawn off and the ether solution extracted with three additional 25-cc. portions of water. The water is boiled to expel the ether, cooled and titrated with 0.2 *N* sulfuric acid using methyl red as indicator. It has been found that when a good grade of triphenylchloromethane is used the yield of sodium triphenylmethyl is almost quantitative.

Results with Ethyl Isobutyrate.—To the solution of sodium triphenylmethyl was added 25 cc. of ethyl isobutyrate, and the mixture shaken and allowed to stand at room temperature for eight to ten minutes. To the solution of enolate was added with shaking a solution of 21.5 cc. of a good grade of benzoyl chloride dissolved in 50 cc. of ether. The mixture became warm and a white precipitate of sodium chloride separated immediately. After standing at room temperature for several hours the mixture was distilled on a water-bath until the volume was reduced to 300–400 cc. A solution of 5 cc. of acetic acid in 300 cc. of water was added and the mixture shaken in a separatory funnel until two homogeneous layers were obtained. The aqueous layer was drawn off, the ether layer shaken with 10% sodium carbonate solution and dried over "Drierite." The ether solution was filtered from the Drierite and distilled on a water-bath until most of the ether was removed. The residue was cooled in a refrigerator and the precipitate of triphenylmethane filtered off and washed with several portions of ether. The filtrate after further removal of ether was distilled at 15 mm. and all material boiling up to 180° collected. The distillate was redistilled at 15 mm., collecting liquid boiling at 120–160°. A final distillation was carried out at 15 mm. and the fraction boiling at 146–148° taken as ethyl benzoyldimethylacetate.[3] The yield was 20.5–22.5 g. (50–55% of the theoretical amount). The isoxazolone prepared as described previously[4] melted at 69–70°.

Anal.[11] Calcd. for $C_{11}H_{11}O_2N$: N, 7.40. Found: N, 7.40, 7.54.

The condensations of ethyl isobutyrate with benzoic anhydride[12] and with phenyl benzoate were carried out in a similar manner. The yield of ethyl benzoyldimethylacetate obtained with benzoic anhydride was approximately the same as when benzoyl chloride was used; the yield obtained with phenyl benzoate was slightly less.

Results with Ethyl Acetate.—To the ether solution of sodium triphenylmethyl was added at room temperature 16 g. of ethyl acetate, and the solution shaken. The color changed in less than a minute from deep red to orange, and further addition of a little ethyl acetate produced no further color change. After standing for three minutes at room temperature 20 cc. of glacial acetic acid was added. The ether solution was washed with dilute sodium carbonate and dried with "Drierite." Most of the ether was distilled from a water-bath through a fractionating column. The remaining solution was cooled and the triphenylmethane which precipitated filtered off. On fractionation a little ethyl acetate was recovered, and 5 g. of ethyl acetoacetate (43% of the theoretical amount) boiling at 73–76° at 14 mm. was obtained.

A mixture of 17 g. of ethyl acetate and 29 g. of ethyl benzoate was added to the ether solution of sodium triphenylmethyl. After standing for several hours the products were isolated in the usual manner. Some ethyl benzoate was recovered and ethyl acetoacetate was obtained. A small fraction (2.9 g.) of ethyl benzoylacetate boiling at 164–168° at 15 mm. was obtained. This is the approximate boiling point reported in the literature.[13] The isoxazolone melted at 151–152° (corr.) which is in agreement with the melting point reported in the literature.[14]

Results with Ethyl Propionate.—Similar to ethyl acetate, ethyl propionate quickly changes the color of sodium triphenylmethyl.

Eighteen grams of ethyl propionate was added to a rapidly stirred ether solution of sodium triphenylmethyl at 0°, followed immediately by the addition of 25 g. of benzoyl chloride. No ethyl benzoylmethylacetate could be isolated. Mixed with triphenylmethane high boiling products were obtained which were assumed to be benzoylated products. These were not further investigated, since we were interested in the primary condensation products.

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[9] A better yield of ethyl benzoylacetate has been obtained from ethyl acetate and ethyl benzoate in the presence of sodium ethoxide; Claisen and Lowman, *Ber.*, **20**, 653 (1887).

[10] Hauser and Renfrow, THIS JOURNAL, **59**, 1825 (1937).

[11] Micro-Dumas by R. L. Peck.

[12] This experiment has been carried out by W. B. Renfrow, Jr.

[13] Claisen, *Ann.*, **291**, 71 (1896); see ref. 9.

[14] Moureu and Lazennec, *Compt. rend.*, **144**, 1281 (1907); Uhlenhuth, *Ann.*, **296**, 38 (1897).

A mixture of 17 g. of ethyl propionate and 35 g. of phenyl benzoate was added to the ether solution of sodium triphenylmethyl at room temperature. After standing overnight the products were isolated in the usual manner. Only a little ethyl propionate and phenyl benzoate were recovered. Similar to the experiment with benzoyl chloride, the triphenylmethane was contaminated with high boiling oils. A small fraction (1.5 g.) boiling at 153–156° at 11 mm. which was apparently ethyl benzoylmethyl acetate was isolated.

A mixture of 17 g. of ethyl propionate and 26 g. of ethyl benzoate was added to the ether solution of sodium triphenylmethyl at room temperature. After fifteen minutes the mixture was acidified with acetic acid, and the products isolated in the usual manner. Some ethyl benzoate was recovered, and ethyl propionylmethylacetate was obtained. Four grams of ethyl benzoylmethylacetate boiling at 154–156° at 11 mm. was isolated. Hope and Perkin[15] give 162–163° as the boiling point at 18 mm. The isoxazolone melted at 120.5–121.5° (corr.). Haller and Bauer[16] give 123–124° as the melting point of the isoxazolone after many recrystallizations.

Summary

1. The enolate of ethyl isobutyrate has been condensed with benzoyl chloride, benzoic anhydride, and phenyl benzoate to give good yields of ethyl benzoyldimethylacetate.

2. Ethyl acetate in the presence of sodium triphenylmethyl gives a good yield of ethyl acetoacetate within three minutes.

3. Ethyl acetate and ethyl propionate condense with ethyl benzoate in the presence of sodium triphenylmethyl but only low yields of ethyl benzoylacetate and of ethyl benzoylmethylacetate have been obtained.

4. These reactions are regarded as examples of the Claisen type of condensation.

DURHAM, NORTH CAROLINA RECEIVED JUNE 11, 1938

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[15] Hope and Perkin, *J. chem. Soc.*, **95**, 2045 (1909).

[16] Haller and Bauer, *Ann. chim.*, [10] **1**, 282 (1923).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

The Kinetics of the Hydrolysis of Ethyl Orthoformate in D_2O–H_2O Mixtures

BY FRANK BRESCIA AND VICTOR K. LA MER

Introduction

Recent work[1] on acid catalysis in heavy water has led to the general criterion that an increase in the rate in D_2O, over that in H_2O, is evidence that an equilibrium is maintained in the first stage of the reaction mechanism whereas a decrease in rate would indicate that the rate-determining step is a proton transfer in the first stage. In the case of a specific hydrogen-ion catalyzed reaction, the rate in H_2O–D_2O mixtures should be proportional to the relative concentration of D^+ and H^+, if these are the ionic species involved in the equilibrium. This was found to be the case for sucrose inversion,[2] which has been studied[3] over the range of H_2O–D_2O mixtures. We shall subject this hypothesis to further test by investigating the hydrolysis of ethyl orthoformate. This reaction,[4] which is specifically catalyzed by hydrogen ion, has been investigated carefully in H_2O for secondary salt[5] and solvent medium[6] effects. Recently, Hornel and Butler[7] have reported two measurements in a water of high deuterium content to determine the effect of deuterium substitution upon the dissociation constant of cacodylic acid.

Since the reaction is exceedingly sensitive to the concentration of hydrogen ions, acetic acid–sodium acetate buffers are well adapted for kinetic study. The thermodynamic and conductive properties of acetic acid have been studied carefully for the entire range of H_2O–D_2O mixtures.[8] The hydrolysis is accompanied by a relatively large volume change and therefore can be studied dilatometrically—a desirable characteristic when dilution must be avoided.

The velocity constant for a constant buffer ratio decreases steadily as the deuterium content of the solvent increases. This is contrary to the principle that the rate of a H^+ ion catalyzed reaction should increase. At the same time, however, the dissociation constant of acetic acid decreases 3.3-fold on passing from H_2O to D_2O so that it is possible that the rate when referred to the actual concentration of H^+ or D^+ ions increases.

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[1] Bonhoeffer, *Trans. Faraday Soc.*, **34**, 252 (1938); Wynne-Jones, *ibid.*, **34**, 245 (1938).

[2] La Mer, *Chem. Rev.*, **19**, 363 (1936); Hamill and La Mer, *J. Chem. Phys.*, **4**, 294 (1936).

[3] Moelwyn-Hughes and Bonhoeffer, *Naturwissenschaften*, **22**, 174 (1934); Gross, Suess and Steiner, *ibid.*, **22**, 662 (1934).

[4] Skrabal, *Z. Elektrochem.*, **33**, 322 (1927).

[5] Brönsted and Wynne-Jones, *Trans. Faraday Soc.*, **25**, 59 (1929).

[6] Harned and Samaras, THIS JOURNAL, **54**, 1 (1932).

[7] Hornel and Butler, *J. Chem. Soc.*, 1361 (1936).

[8] Korman and La Mer, THIS JOURNAL, **58**, 1396 (1936); Chittum and La Mer, *ibid.*, **59**, 2425 (1937).

Experimental Procedure

1. **The Apparatus.**—To carry out measurements on limited quantities of heavy water, it was necessary to construct a semi-micro dilatometer (Fig. 1), whose capacity (10 cc.) is about 1/20 of the customary macro apparatus, by reducing the area of the capillary proportionately. The radius of the capillary bore is 0.1277 mm.; its uniformity, determined with a comparator, shows an average deviation of 0.3% the largest single deviation being 0.6%; it is sensitive to a volume change of 0.001% since a change of 0.02 cm. can be read easily (with experience readings can be made to ± 0.01 cm.). The expansion produced by 10 cc. of 0.05 *M* ethyl orthoformate is about 4 cu. mm., which corresponds to a change in height of about 8 cm.

The difficulty of leaking stopcocks was overcome effectively by the use of spring collars and mercury seals. Leakage was tested for by raising the mercury column in the capillary above that in the reaction chamber. The column remained constant at any fixed height over a period of time, long compared to the time needed to complete a run. No difficulty due to sticking was experienced; nevertheless a buzzer was attached at the top of the capillary. A lubricant was unnecessary. The entire dilatometer was immersed in a thermostat at 25.050 ± 0.002°, determined with a B. of S. calibrated platinum resistance thermometer.

2. **Materials.**—Merck C. P. acetic anhydride was redistilled and the middle fraction, 138–139°, collected.

Kahlbaum analytical grade sodium acetate was recrystallized below 80°, dried and pulverized. It was dehydrated between 45–50° for twelve hours and dried completely at 110° for twenty-four hours.

Eastman ethyl orthoformate was shaken several times in a separatory funnel with an aqueous sodium carbonate solution to decompose ethyl formate and neutralize formic acid. The ethyl orthoformate layer was separated, dried over calcium chloride, filtered and distilled. The fraction of b. p. 145–145.5° was retained.

H_2O–D_2O Mixtures.—Waters of 95–99% deuterium content from Norsk Hydro were treated as follows: (a) atmospheric pressure distillation from alkaline permanganate, (b) atmospheric pressure distillation from acid dichromate, (c) slow vacuum distillation. The reaction products, ethyl formate and ethyl alcohol, cannot be removed by distillation. The following technique proved satisfactory for the recovery of the solvent: (a) refluxed for about twelve hours with acid dichromate and distilled at atmospheric pressure; (b) refluxed with alkaline permanganate below the boiling point for twenty-four hours; (c) slow vacuum distillation. The chromate test for alcohol gives a negative result. The densities of the waters were determined in a 10-ml. pycnometer.

3. **Procedure.**—In the early experiments, the buffered solutions were prepared directly in a weight buret which may be connected to the dilatometer by a mercury-sealed glass ground joint. When larger quantities of deuterium oxide became available, 30 cc. of a reactant solution was prepared in a flask. Five cc. of acetic acid was freshly prepared for each experiment by adding acetic anhydride to the water. Several drops were then added to sodium acetate dissolved in water of the same D content. Fifteen cc. of the prepared buffer solution was pipetted into the dilatometer. When temperature equilibrium was established, 0.125 cc. of ethyl orthoformate was added and the mixture stirred with a motor. Suction was applied to the mercury reservoir and the solution followed into the reaction chamber; stopcocks were closed, suction turned off and the buzzer turned on. Readings were taken every two minutes. The elapsed time from the addition of reactant to first readings was about five minutes. The remaining portion of the solution, used within two days to check the first run, was kept in a refrigerator.

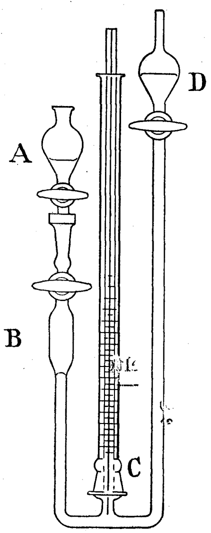

Fig. 1.—A, weight buret; B, reaction chamber; C, capillary; D, mercury reservoir. Approximately one-sixth actual size.

For a long period of time we were troubled with inability to obtain a constant end-point. The hydrolysis of ethyl orthoformate is complete within four hours, yet a very slow expansion of the solution continued over a period of two weeks. We first suspected hydrolysis of ethyl formate as a consecutive reaction. Investigation, however, established that this reaction produces no perceptible volume change. Dr. J. C. Hornel informs us that some previous investigators have corrected their end-point for drifts on the assumption that ethyl formate hydrolyzes slowly.

We observed that scrupulously cleaned apparatus yielded a satisfactory end-point but that on successive filling with duplicate solutions, the end-point reading continued to increase progressively with each refilling, until eventually refilling with water alone yielded a continuous slow expansion. We suspected bacterial decomposition. When the apparatus was sterilized with dilute nitric acid, washed with sterile water, and all buffer solutions preserved on ice, the difficulty entirely disappeared. With the technique described, we now achieve a final reading within six hours which remains constant to within ± 0.01 cm. for at least twenty-four hours.

The velocity constants were calculated by the usual first order formula

$$k = \frac{2.303}{t_2 - t_1} \log \frac{V_\infty - V_{t_1}}{V_\infty - V_{t_2}} \qquad (1)$$

where V_∞ and V_t are the dilatometer readings at time = ∞ and time = *t*; and also by Roeser's method of least squares for equal intervals.[9] The agreement between the two methods was always within 1%; the agreement between duplicate experiments was within 2%. A typical experiment is given in Table I, which shows the absence of drifts and freedom from sticking in the unusually narrow capillary.

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(9) Roeser, *Bur. Standards Bull.*, **16**, 363 (1920) (Scientific paper 388); Marlies and La Mer, THIS JOURNAL, **57**, 1812 (1935).

TABLE I

A TYPICAL EXPERIMENT

F_D = fraction of deuterium = $S(100)/0.1079$ = 25.91%. Molarity NaAc = 0.09732 mole/liter of solution. Molarity Ac_2O = 0.001010 mole/liter of solution.

	Run A				Run B	
t min.	V_t, cm.	t_1	t_2	k (eq. 1)	V_t, cm.	k (eq. 1)
0	8.84	0	14	0.0314	9.50	0.0314
2	9.40	2	16	.0317	10.10	.0314
4	9.95	4	18	.0320	10.64	.0312
6	10.47	6	20	.0318	11.18	.0314
8	10.95	8	22	.0320	11.67	.0313
10	11.40	10	24	.0320	12.11	.0315
12	11.85	12	26	.0317	12.56	.0315
14	12.23	0	24	.0316	12.98	.0313
16	12.62	0	26	.0316	13.36	.0313
18	12.99			Av. 0.0318	13.70	Av. 0.0314
20	13.31			a. d. 0.0002	14.06	a. d. 0.0001
22	13.63				14.37	
24	13.92				14.67	
26	14.20				14.96	
∞	18.40				19.30	

k by least square = 0.0317 = 0.0313

For comparison of the rate constants of different experiments, k is corrected to the rounded buffer ratio of 0.001000 M Ac_2O/0.1000 M NaAc.

$$\text{Thus } k_c = (0.0315)\,\frac{(0.09732)}{(0.001010)}\,\frac{(0.001)}{(0.1)} = 0.0304$$

The Specific Catalytic Coefficient of H_3O^+.—The specific catalytic coefficient $k_{H^+} = k/C_{H_3O^+}$. At a given ionic strength

$$C_{H_3O^+} = KC_{HAc}/C_{Ac^-}$$

$K = 2.87 \times 10^{-5}$ at $\mu = 0.1$ and 2.60×10^{-5} at $\mu = 0.05$, obtained by Harned and co-workers[10] in sodium chloride solutions, are used since the corresponding values for sodium acetate solutions are unknown.

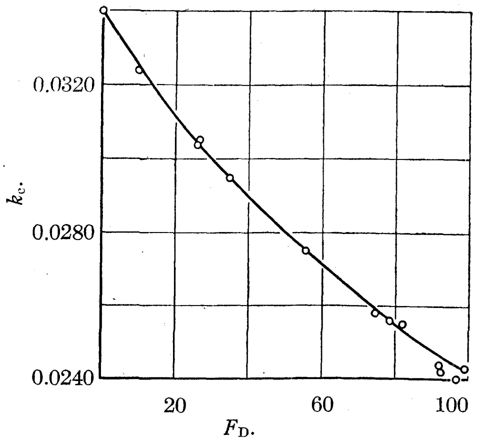

Fig. 2.

TABLE II

SPECIFIC CATALYTIC COEFFICENT OF H_3O^+

Molarity HAc	Molarity NaAc	Expts.	Av. k	$10^{-4}\,k_{H^+}$
0.0008918	0.08814	2	0.0171	6.02
.001422	.1434	1	.0185	6.03
.001312	.06573	2	.0311	5.81
.001989	.09941	2	.0336	5.85
.001926	.09616	2	.0341	5.98
.002255	.1128	2	.0348	5.92
.002444	.1214	1	.0358	5.95

Av. $k_{H^+} = 5.93 \times 10^4$; a. d. = 0.07

The average value $10^{-4}\,k_{H^+} = 5.93$ shown in Table II is in excellent agreement with the value of 6.0 reported by Harned and Samaras,[6] who employed a macro dilatometric method.

The experimental results for constant buffer ratio in mixtures of D_2O–H_2O are given in the first two columns of Table III, and are plotted against F_D in Fig. 2. The data exhibit the characteristic negative deviation from linearity.[11]

The specific catalytic coefficient of D_3O^+, k_{D^+}, is calculated from the value $k_C = 0.0242$ for $F_D = 100$, which is obtained by a short extrapolation from $F_D = 98$ in Fig. 2. C_{D^+} is obtained from

$$K_{DAc} = \frac{C_{D_3O^+}\cdot C_{Ac^-}}{C_{DAc}} = \frac{K_{HAc}}{3.3}$$

substituting 0.002 for C_{DAc}, 0.1 for C_{Ac^-}, and 2.87×10^{-5} for K_{HAc}. Hence, $k_{D^+} = 1.39 \times 10^5$ and the ratio of specific catalytic coefficients is

$$\frac{k_{D^+}}{k_{H^+}} = \frac{1.39 \times 10^5}{5.93 \times 10^4} = 2.35$$

This ratio is not in good agreement with the value 2.05 reported by Hornel and Butler.[7] Part of the discrepancy arises from the fact that these authors employed the value K_{HAc}/K_{DAc} 2.77 calculated from kinetic measurements. Our value 3.3 for the ratio of the dissociation constants is to be preferred since this value is obtained independently from e. m. f. and from conductance measurements.[8] Using 3.3, Hornel and Butler's k_{D^+}/k_{H^+} becomes 2.44, which is in better agreement.

Discussion

The concentration of protium and of deuterium ions in the mixtures of the oxides may be calculated from the kinetic data on the basis of the following considerations. The dissociation constants of acetic acid and of deuteroacetic acid are assumed to be independent of the deuterium content of the solvent water. This assumption is

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(10) Harned and Robinson, *ibid.*, **50**, 3157 (1928); Harned and Owen, *ibid.*, **52**, 5079 (1930).

(11) *Cf.* Refs. (2) and (4); La Mer and Greenspan, *Trans. Faraday Soc.*, **33**, 1266 (1937).

justified since the dielectric constants and the activity coefficients at constant ionic strength are practically independent of the D content of the solvent. That is

$$K_{HAc} = C_{H^+}C_{Ac^-}/C_{HAc} \qquad (2)$$

and is constant in any mixture of D_2O–H_2O at constant ionic strength. Similarly

$$K_{DAc} = C_{D^+}C_{Ac^-}/C_{DAc} \qquad (3)$$

in mixtures of D_2O–H_2O.

Twice the concentration of acetic anhydride equals the sum of the concentrations of acetic and deuteroacetic acids formed or

$$C_{HAc} + C_{DAc} = 2C_{Ac_2O} \qquad (4)$$

On the assumption that the velocity in D_2O–H_2O mixtures is proportional to C_{H^+} and C_{D^+}

$$k = k_{H^+}C_{H^+} + k_{D^+}C_{D^+} \qquad (5)$$

where k_{H^+} and k_{D^+} are the catalytic coefficients determined above and k, the measured rate constant in a water of deuterium content F_D.

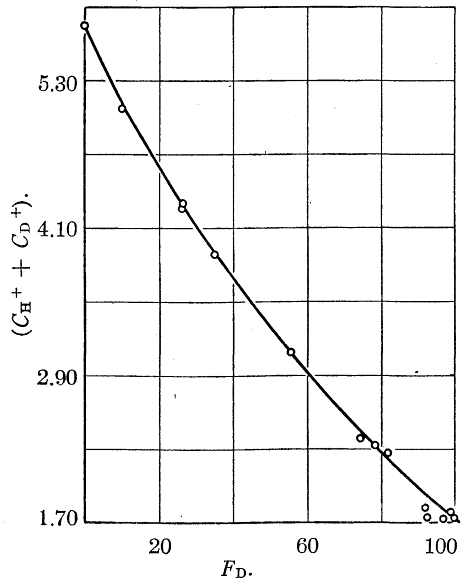

Fig. 3.

Dividing equation (2) by (3) and substituting C_{D^+} from (5), C_{DAc} from (4), and C_{HAc} from (2) gives

$$K = \frac{K_{HAc}}{K_{DAc}} = \frac{k_{D^+}}{k - k_{H^+}C_{H^+}}\left(\frac{2C_{Ac_2O}K_{HAc}}{C_{Ac^-}} - C_H^+\right) \qquad (6)$$

from which

$$C_{H^+} = \frac{k_{D_+}2C_{Ac_2O}K_{HAc}}{C_{Ac^-}(k_{D^+} - Kk_{H^+})} - \frac{Kk}{k_{D^+} - Kk_{H^+}} \qquad (7)$$

Hence, C_{H^+} can be calculated since all quantities on the right are known. k is the rate constant for buffer ratio 0.001 *M* Ac_2O/0.1 *M* NaAc denoted as k_c in Table III. Knowing the value of C_{H^+}, equation (5) yields C_{D^+}, and hence $(C_{H^+} + C_{D^+})$ and F_{D^+}, the fraction of deuterium ions. The sum $(C_{H^+} + C_{D^+})$ divided into k_c gives the specific catalytic coefficient, k_m, for each of the waters used, which is identical with k_{H^+} for H_2O and with k_{D^+} for D_2O.

A sample calculation of the typical experiment is given. Using equation (6)

$$3.3 = \frac{1.39 \times 10^5}{0.0304 - 5.93 \times 10^4\, C_{H^+}}\left(\frac{2(0.001)\,(2.87 \times 10^{-5})}{0.01} - C_{H^+}\right)$$

and solving, $C_{H^+} = 3.62 \times 10^{-7}$. Solving equation (5)

$$0.0304 = (5.93 \times 10^4)\,(3.62 \times 10^{-7}) + (1.39 \times 10^5)C_{D^+}$$

$$C_{D^+} = 6.40 \times 10^{-8}$$

$$C_{H^+} + C_{D^+} = 4.26 \times 10^{-7}$$

$$F_{D^+} = \frac{0.64}{4.26} \times 100 = 15.02 \text{ and}$$

$$k_m = \frac{0.0304}{4.26 \times 10^{-7}} = 7.13 \times 10^4$$

The results of similar calculations are summarized in columns (3) to (7) in Table III.

TABLE III

(1) F_D	(2) k_c from expt.	(3) $C_{H^+} \times 10^7$ calcd. from eq. (6)	(4) $C_{D^+} \times 10^7$ calcd. from eq. (5) and column (3)	(5) $(C_{H^+} + C_{D^+})$ 10^7 from columns (3) and (4)	(6) F_{D^+} from columns (4) and (5)	(7) $k_m \cdot 10^{-4} = \frac{k_c}{C_{H^+} + C_{D^+}}$
0	0.0340	5.74	0.0	5.74	0	5.93
9.86	.0324	4.79	0.288	5.08	5.68	6.39
25.91	.0304	3.62	.640	4.26	15.0	7.13
26.40	.0305	3.68	.624	4.30	14.5	7.09
35.15	.0295	3.10	.799	3.90	20.5	7.57
55.60	.0275	1.93	1.16	3.09	37.5	8.90
74.51	.0258	0.944	1.45	2.39	60.6	10.8
78.49	.0256	.827	1.49	2.32	64.3	11.0
81.89	.0255	.769	1.50	2.27	66.1	11.2
91.88	.0244	.129	1.70	1.83	93.0	13.3
92.51	.0242	.01	1.73	1.74	99.4	13.9
96.95	.0240	.00	1.73	1.73	100	13.9
98.81	.0243	.07	1.72	1.79	96.1	13.6
100	(.0242)	0	1.74	1.74	100	13.9

The results are plotted in Figs. 3 and 4.

Figure 3 shows that $(C_{H^+} + C_{D^+})$ plotted against F_D gives a sagging curve similar to Fig. 2. k_m plotted against F_{D^+} (Fig. 4) gives a straight line in agreement with the results of the hydrogen ion catalyzed sucrose hydrolysis. This, however, is not a proof since in calculating the C_{D^+} we use equation (5) which is based on the assumption that the rate is proportional to F_{D^+}. But we do have sufficient data to check this assumption by calculating the dissociation constant, $K_{H,D}$, for a weak acid in H_2O–D_2O mixtures and comparing with values determined by La Mer and Chittum from conductance data. $K_{H,D}$ is de-

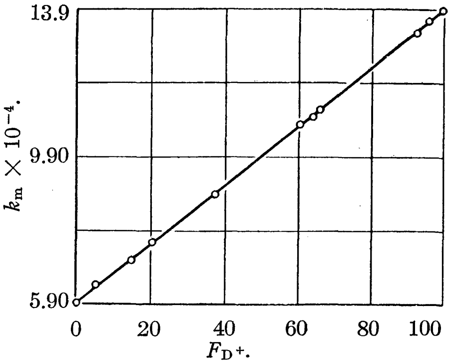

Fig. 4.

fined as $(C_{H^+} + C_{D^+})C_{Ac^-}/(C_{HAc} + C_{DAc})$. Substituting the values for $(C_{H^+} + C_{D^+})$, yields the results summarized in Table IV and plotted against F_D in Fig. 5. La Mer and Chittum's results[8] are represented by filled circles. Since the value 2.87×10^{-5} has been used for the dissociation constant of acetic acid for an ionic strength $\mu = 0.1$ and La Mer and Chittum report 1.84×10^{-5} for $\mu = 0$, we multiply their values by 1.56 for direct comparison. The kinetic results are in substantial agreement with those from conductance. This means that if we had not been able to calculate C_{H^+} and C_{D^+} from our kinetic data but were obliged to use the conductance data, the results would be substantially the same, *i. e.*, k_m plotted against F_{D^+} would yield a straight line, conforming to the basic assumption.

TABLE IV

F_D	10^5 $K_{H,D}$ Calcd. from kinetic data $\mu = 0.1$	10^5 $K_{H,D}$ La Mer and Chittum corr. to $\mu = 0.1$
0	2.87	(2.87)
9.86	2.54	
25.91	2.13	
26.40	2.15	
28.4		2.11
35.15	1.95	
48.4		1.70
55.60	1.55	
74.51	1.20	
77.1		1.16
78.49	1.16	
81.89	1.14	
91.88	0.92	
92.51	.87	
93		0.948
96.95	.87	
97		.897
98.81	.90	
100	.87	.87

The Rate-Determining Step.—The theory of intermediate complex formation offers two possibilities for the rate-determining step in an acid catalyzed reaction. The general scheme[12] may be represented as

$$\text{Substrate} + \text{HA} \underset{k_2}{\overset{k_1}{\rightleftarrows}} \text{A}^- + (\text{Substrate, H}^+) \xrightarrow{k_3} \text{Products}$$

Adopting the usual assumption that in the stationary state the probability of disappearance of the complex is unity, the velocity of the reaction may be written as

$$V = -\frac{dC_S}{dt} = kC_SC_{HA} = \frac{k_1k_3}{k_2 + k_3}\,C_SC_{HA}$$
$$\text{or } k = k_1k_3/(k_2 + k_3)$$

Previous researches and discussions[13] have led to the general conclusion that the rate-determining step in a specific hydrogen-ion catalyzed reaction is the rate of decomposition of the complex (k_3), which when multiplied by the equilibrium constant of the reaction: reactants $\rightleftarrows$ complex, yields the rate of the reaction. Then, for the ratio of the rates in D_2O and in H_2O

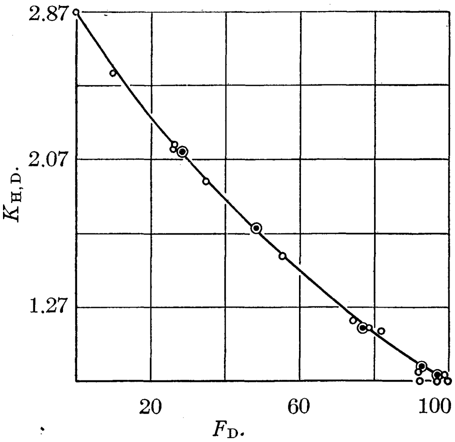

Fig. 5.—Results of La Mer and Chittum, ◉.

$$\frac{k_{D^+}}{k_{H^+}} = \frac{k_{3SD^+}\,K_{SD^+}}{k_{3SH^+}\,K_{SH^+}}$$

where K_{SD^+} and K_{SH^+} are the equilibrium constants involving the heavy and light complexes, respectively. From experiment, the ratio $k_{D^+}/k_{H^+} = 2.35$. If we assume the equilibrium in D_2O is shifted in favor of formation of SD^+ and if the rates of decomposition of SD^+ and SH^+ are

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(12) Skrabal, *Trans. Faraday Soc.*, **24**, 687 (1928).

(13) Pedersen, *J. Phys. Chem.*, **38**, 581 (1934); *Trans. Faraday Soc.*, **34**, 237 (1938); Wynne-Jones, *J. Chem. Phys.*, **2**, 381 (1934); *Trans. Faraday Soc.*, **34**, 245 (1938); Bonhoeffer and Reitz, *Z. physik. Chem.*, **A179**, 135 (1937); Bonhoeffer, *Trans. Faraday Soc.*, **34**, 252 (1938); Reitz, *Z. Elektrochem.*, **43**, 659 (1937); *Naturwissenschaften*, **24**, 814 (1936); Wilson, *J. Chem. Soc.*, 1550 (1936); Bell, *Proc. Roy. Soc.* (London), **A154**, 414 (1936); ref. 7.

assumed to be equal to kT/h on the basis of Eyring's theory,[14] then $K_{SD^+}/K_{SH^+} = 2.35$.

The increase in the rate on passing to the deutero catalyst is thus explained as the result of a shift in the equilibrium in favor of the heavy complex. We must, however, note that although Urey and Rittenberg[15] have calculated that the equilibrium constant for the reaction $H_2 + 2DCl = 2HCl + D_2$ is shifted in favor of DCl, the reverse was found for $H_2 + 2DI = 2HI + D_2$. The position of the equilibrium $CH_3COCH_3 + HDO = CH_3COCH_2D + H_2O$ was measured by Halford, Anderson and Bates[16] and they found that the equilibrium constant is about two in favor of formation of heavy acetone.

Conclusions

1. The kinetics of the hydrogen-ion catalyzed hydrolysis of ethyl orthoformate in acetic acid–sodium acetate buffers of constant ratio has been investigated over the entire range of H_2O–D_2O mixtures.

2. The specific catalytic constant for D_3O^+ ion is 2.35 times greater than for H_3O^+.

3. A semi-micro dilatometer was constructed for the kinetic measurements which yields results in excellent agreement with the macro results of Harned and Samaras in H_2O.

4. An equation, from which the concentration of hydrogen and deuterium ions can be calculated, is derived.

5. The rate constant for constant acid/salt ratio decreases with increasing D content and shows a negative deviation from linearity. The sum $(C_{H^+} + C_{D^+})$ follows a similar curve. The specific rate constant or catalytic coefficient increases with increasing D content, and is linear with respect to the fraction of deuterium ions.

6. The calculated dissociation constants of a weak acid in H_2O–D_2O mixtures, defined as $(C_{H^+} + C_{D^+})C_{A^-}$/Total undiss. acid, are in substantial agreement with values obtained from the conductance method.

7. The greater catalytic effect of D^+ ion is explained as a shift in the equilibrium $S + H^+ \rightleftarrows SH^+$ in favor of the deutero complex in agreement with Bonhoeffer's treatment.

NEW YORK, N. Y. RECEIVED MARCH 22, 1938

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[14] Eyring, *J. Chem. Phys.*, **3**, 107 (1935).

[15] Urey and Rittenberg, *ibid.*, **1**, 137 (1933).

[16] Halford, Anderson and Bates, THIS JOURNAL, **56**, 491 (1934); *ibid.*, **57**, 1663 (1935); see also Wirtz, *Z. physik. Chem.*, **B34**, 121 (1936); *Z. Elektrochem.*, **43**, 662 (1937).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

The Temperature Coefficients of the Base Catalyzed Decomposition of Nitramide in Deuterium Oxide

BY SILVESTER LIOTTA AND VICTOR K. LA MER

The basic decomposition of nitramide ($H_2N_2O_2$) to nitrous oxide and water is catalyzed by the presence of any molecule, for example, water or the anions of weak acids, which possesses the property of associating a proton; *i. e.*, by basic molecules in the Brönsted formulation. The molar catalytic constant, k, is related to the dissociation constant, K_A, of the acid, conjugate to the catalyst base, by the well-known empirical formula $G = kK_A^{\alpha}$. For carboxylic anions in water, $\alpha = 0.83$, indicating a high sensitivity of the substrate to changes in K_A. Since deuterium substitution always reduces the value of K_A by a factor of 2 to 4, depending upon the strength and type of the acid, it becomes of interest to investigate the effect of deuterium substitution upon the rate of anion catalysis by determining the effect upon the constant G and the sensitivity index α.

It is also one of the purposes of this investigation to study in how far the rate depressing action of deuterium substitution arises from a displacement of the energy of activation and of the entropy of activation.

When proto nitramide is dissolved in D_2O at least one and presumably both protons are exchanged instantaneously for deutons, producing deutero-nitramide as the effective substrate.[1] In their investigation of the effect of deuterium substitution upon the *solvent catalysis*, La Mer and Greenspan[2] found that the substitution of deuterium for protium in the solvent produced a 5.21-fold decrease in rate.

There are two possible mechanisms. The first, suggested by Brönsted and supported by Peder-

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[1] Unpublished measurements of Hochberg in this Laboratory. See La Mer, *Trans. Faraday Soc.*, **34**, 263 (1938).

[2] La Mer and Greenspan, *ibid.*, **33**, 1266 (1937).

sen and by Marlies and La Mer, postulates that the rate-determining step is the rate of transfer of the proton from the substrate to the catalyst base. The slower rate in D_2O on this mechanism would be ascribed to the slower rate of donation and of acceptance of deutons as compared to protons.

The second, based upon the transition state theory of kinetics, would ascribe the difference in rate on passing from the proto to the deutero systems to a shift in the equilibrium between reactants and critical complex with the additional possibility of a differential rate of decomposition of the proto and deutero complexes.

If one employs anions like acetate, benzoate and salicylate rather than the solvent as the effective catalyst base, the problem becomes somewhat simplified since the hydrogens attached to carbon do not exchange and the base remains unchanged regardless of the D content of the solvent. For a more detailed treatment of the general problem of isotopic exchange and the effects of deuterium substitution for hydrogen upon the properties of conductance, e. m. f. and acid-base catalysis the reader is referred to current reviews and symposia.[3]

The difficulty of obtaining sufficiently large quantities of water with high deuterium content when this investigation was initiated (1935) led to the development of a gas evolution apparatus[4] applicable to a precision study on a semi-micro scale. The apparatus, which requires only 10 cc. of solution, yields results which are even more precise than those obtained with the macro-types employing 60–100 cc. of solution.

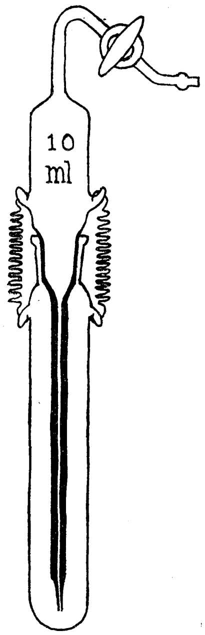

Fig. 1.—Special weight pipet.

Preparation of Materials

Nitramide was prepared by the improved method of Marlies and La Mer.[5]

Heavy water was initially purified by distillation at atmospheric pressure from alkaline permanganate, from acid chromate and finally vacuum distilled in an all-glass Pyrex still with a receiver cooled with solid carbon dioxide–alcohol mixture. The water was recovered by vacuum distillation after neutralization of excess acid with solid sodium hydroxide. After each cycle of use, neutralization and distillation, the deuterium content diminished by only 0.2%.

Sodium acetate was recrystallized from distilled water, and dried *in vacuo* over calcium chloride at 40° for three days. Complete dehydration was achieved in two days at 115° following a gradual elevation of temperature to prevent fusion of the hydrate. The purity of the reagents was established by kinetic comparisons with the values of $k_{\text{Ac}-}$ and $k_{\text{H}_2\text{O}}$ obtained in H_2O by previous investigators.

Acetic acid was prepared by adding acetic anhydride directly to the H_2O–D_2O solvent. The anhydride was triply distilled in a Pyrex Vigreux fractionating column, retaining as the final fraction the distillate boiling at 139.0 ± 0.1°.

Sodium benzoate and sodium salicylate were recrystallized twice from distilled water; **benzoic acid** twice from alcohol; **salicylic acid** twice from chloroform. All salts were dried in a vacuum desiccator.

The solutions were made up just before use by weighing acid, salt and solvent in the same container. Acetic anhydride and sodium acetate were added with a special weight pipet (Fig. 1). The latter was added in the form of a concentrated solution of known composition.

Apparatus and Experimental Procedure

The semi-micro apparatus contains a number of specific improvements which have been described in detail elsewhere. Four such instruments were immersed in a thermostat maintained within ± 0.004° at 15°, ± 0.002° at 25° and ± 0.003° at 35°, and checked against a B. S. standardized platinum resistance thermometer.

Since the decomposition yields only a few milligrams of H_2O and N_2O as the sole products, the composition of the solution is changed only by a small calculable decrease in D content and should, therefore, be available for successive runs without removal from the apparatus or variation in the concentration of the catalyst. This procedure was highly satisfactory in the previous work where hydrochloric acid solutions were involved but failed in the case of the sodium acetate solutions.

The conflicting reports in the literature on isotopic exchange with acetate ion naturally suggested that we were observing the effects of slow exchange of H by D on the carbons of the acetate ion. Specially designed experiments, however, established that no exchange takes place at 25° over two weeks' time since the densities of the recovered waters in these experiments remained constant to within five parts in 100,000.[6] The disturbance was finally traced to the instability of dilute sodium acetate–acetic acid buffers,[7] very likely through bacterial decomposition. This conclusion was confirmed by measuring the change in conductance with time, of a representative solution of 0.01 *M* sodium acetate and 0.04 *M* acetic acid with the following results

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(3) Symposium on proton transfers, *Trans. Faraday Soc.*, **34**, 229–265 (1938); Symposium on Deuterium, *Z. Elektrochem.*, **44** (Jan., 1938), Papers by Reitz p. 72 and Schwarzenbach p. 46; La Mer, *Chem. Rev.*, **19**, 363 (1936); Wynne-Jones, *ibid.*, **17**, 115 (1935).

(4) Greenspan, La Mer and Liotta, THIS JOURNAL, **59**, 1606 (1937).

(5) Marlies and La Mer, *ibid.*, **57**, 2008 (1935).

(6) Liotta and La Mer, *ibid.*, **59**, 946 (1937); Ives, *J. Chem. Soc.*, 81 (1938).

(7) MacInnes and Shedlovsky, *ibid.*, **54**, 1431 (1932); Chase, *ibid.*, **55**, 3072 (1933).

Time, days	0	1	2	3	5
Resistance, ohms	683	681	679	678	675

When the buffer solutions were prepared and used immediately thereafter, reproducible results were always obtained, which procedure was accordingly adopted.

Methods of Calculation

The anion catalyzed decomposition follows accurately the first order law in heavy water mixtures. Since the final pressure is proportional to the initial concentration (C_0) and the instantaneous concentration (C_1) is proportional to the difference between the final and instantaneous pressures

$$k^* = (1/t) \ln (p_\infty - p_0)/p_\infty - p) \qquad (1)$$

$$\text{or } \log (p_\infty - p) = \text{const.} - kt \qquad (2)$$

where $k = 0.4343\, k^*$.

The units of time and concentration are minutes and moles per liter, respectively. The graphical determination of k from $\log (p_\infty - p)$ *versus* t plots is too cumbersome and not sufficiently precise to warrant its use. An especially simple analytical method based on the principles of least squares, if the observations are separated by equal time intervals, suggested by Roeser,[8] has been found satisfactory by Marlies and La Mer.[9] This method gave the best agreement between independent experiments.

Unless the reaction requires an exceedingly long time for completion, p_∞ should be the most accurate measurement of the series since the readings can be repeated. Practically, however, the possibility of leaks in the apparatus or of side reactions like the decomposition of the buffer, require the use of the Guggenheim method[10] when the end-point cannot be determined more precisely than the running values of p. We found this method to be better for the exceedingly slow spontaneous decomposition at 15°.

The molar catalytic constant k is obtained from the relation $k = (k_{\text{obsd.}} - k_0)/C$, where k_0 is the velocity of the spontaneous decomposition due to the solvent and C is the concentration of the catalyst in moles per liter. When 0.01 M hydrochloric acid is used, $k_{\text{obsd.}}$ yields k_0 directly. The hydrochloric acid serves to eliminate the presence of hydroxyl ion and since at that concentration the acid catalysis is negligible, the rate is entirely due to the basic properties of the solvent. In this work we were obliged to use water of D content = 91.5% rather than 100% D_2O so that the respective catalytic constants are made up of two factors, the major part due to the 91.5% D_2O and a small part to the 8.5% H_2O.

Experimental Results

The values obtained for $k_{\text{obsd.}}$ and k are given in Table I. Variation in anion and acid concentration produced no variation in molar catalytic constant k. The values of the temperature coefficients for 15–25°, the energies of activation E and the frequency factor B in the integrated form of the Arrhenius equation

$$\log k = B - \frac{E}{2.3RT} \qquad (3)$$

are given in Table II. The values for H_2O were obtained by Baughan and Bell,[11] who use a least square treatment over a range of temperature. In Table III are listed the values of k at 15 and 25° as well as their ratios in the two solvents.

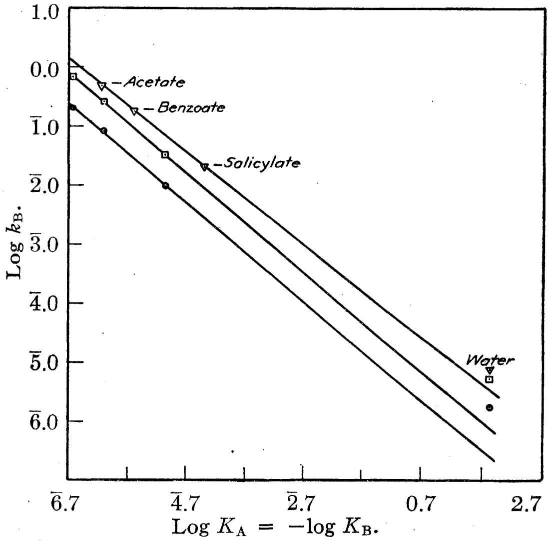

Fig. 2.—The relation between the logarithms of the velocity constants (ordinates) and dissociation constants (abscissas): ▽, H_2O at 15°; □, D_2O at 25°; ○, D_2O at 15°.

Discussion

Rate and Equilibrium Constants.—Brönsted's equation for generalized base catalysis

$$\log k_B = \log G - \alpha \log K_A \qquad (4)$$

is tested at F_D = 91.5% in Fig. 2 by plotting $\log k_B$ against $\log K_A$. The three anion bases chosen extend over a range of 1.4 units in $\log k$ and 1.6 units in $\log K_A$. Since the acidic dissociation constants in D_2O at 15° were not all

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[8] Roeser, *Bur. Standards Bull.*, **16**, 363 (1920) (Sci. paper 388).

[9] Marlies and La Mer, THIS JOURNAL, **57**, 1812 (1935).

[10] Guggenheim, *Phil. Mag.*, [7] **2**, 538 (1926).

[11] Baughan and Bell, *Proc. Roy. Soc.* (London), **158**, 464 (1937).

TABLE I

SUMMARY OF THE KINETIC DATA

Temp., °C.	Salt	%D = $\left(\frac{\Delta S}{0.1079} \times 100\right)$	C_{acid}	C_{anion}	$k_{\text{obsd.}} \times 10^5$	k	Mean k	k corr. to 15, 25 or 35°
15.066	Acetate	91.56	0.0392	0.1754	400	0.2030	0.2060	0.2042
			.0392	.1754	405	.2056		
			.0392	.01278	305.5	.2096		
15.077	Benzoate	91.28	.00734	.01247	125.4	.0845	.0823	.0816
			.00734	.01247	122.1	.0821		
			.00338	.00946	95.46	.0825		
			.00338	.00946	93.15	.0803		
15.078	Salicylate	91.10	.00816	.01855	29.40	.00955	.00963	.00954
			.00816	.01855	29.70	.00969		
			.00544	.01927	30.93	.00991		
			.00544	.01927	29.79	.00938		
15.077	Spontaneous	91.28	.01 HCl		9.23		100×10^{-6}	99×10^{-6}
					10.78			
24.893	Acetate	91.66	.0392	.004206	362.0	.722	0.719	0.728
			.0392	.004206	362.4	.723		
			.0392	.004816	408.2	.718		
			.0392	.004816	404.9	.712		
24.884	Benzoate	90.92	.00317	.00903	288.3	.262	.261	.264
			.00317	.00903	287.5	.261		
			.00493	.01432	440.8	.262		
			.00493	.01432	435.6	.259		
24.881	Salicylate	90.92	.00430	.01953	98.36	.0322	.0323	.0328
			.00422	.01839	95.03	.0326		
			.00422	.01839	94.30	.0322		
24.89	Spontaneous	91.5	Interpolated[2]		30.04		300×10^{-6}	304×10^{-6}
34.966	Spontaneous	90.84	0.01 HCl		94.35		949×10^{-6}	953×10^{-6}
					94.82			
					95.24			
					95.27			

TABLE II

	H₂O				D₂O (91.5%)			
Catalyst	$k_{25°}/k_{15°}$	B	E	$\log k^{25°}_{\text{H}_2\text{O}}$	$k^{25°}/k_{15°}$	B	E	$\log k^{25°}_{\text{D}_2\text{O}}$
Acetate	3.01	14.25	19,180	$\bar{0}.1703$	3.57	15.80	21,726	$\bar{1}.862$
Benzoate	2.91	13.89	19,260	$\bar{1}.740$	3.24	14.15	20,082	$\bar{1}.422$
Salicylate	3.18	13.56	20,080	$\bar{2}.823$	3.44	14.00	21,101	$\bar{2}.516$
Spontaneous	3.20	12.28	20,680	3.088	3.07 3.13 (25–35°)	11.16 (15–35°)	19,974 (15–35°)	$\bar{4}.483$

TABLE III

D₂O refers to 91.5% D content

Catalyst	$k^{15°}_{\text{H}_2\text{O}}$ (11)	$k^{15°}_{\text{D}_2\text{O}}$	$k^{25°}_{\text{H}_2\text{O}}$ (11)	$k^{25°}_{\text{D}_2\text{O}}$	$k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$ (15°)	$k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$ (25°)
Acetate	0.492	0.204	1.480	0.728	2.416	2.04
Benzoate	.183	.0816	0.550	.264	2.25	2.09
Salicylate	.0209	.00954	.0665	.0328	2.20	2.03
Spontaneous	383×10^{-6}	99×10^{-6}	1225×10^{-6}	$304. \times 10^{-6}$	3.86	4.02[a]

[a] Using Greenspan's more precise value for $k_0^{25°} = 1266 \times 10^{-6}$, then $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} = 4.12$.

available, the use of values of K_{A} measured at 25° may account for the minor discrepancies from linearity on the 15° curve.

In heavy water as well as in light water, the point representing the catalytic properties of the solvent acting as a base lies above the continuation of the line obtained with the anion bases. This is consistent with Pedersen's theory[12] that for bases of the same strength the catalytic effect increases in the series $B^- < B^0 < B^+$ provided the substrate is uncharged. The difference may also arise from the fact that H_2O is a base of a different chemical type from the carboxylic anions.

Since the Brönsted relation holds equally well for a mixed deuterium water as for pure H_2O, a plot of $\log k_{D_2O}$ *versus* $\log k_{H_2O}$ should yield a straight line, provided $\log K_{D_2O}$ *versus* $\log K_{H_2O}$ exhibits the same linear relationship. That this conclusion is valid may be demonstrated as follows.

Figure 3 shows that the $\log k_{D_2O}$ points adhere closely to the linear equation

$$\log k_{D_2O} = x \log k_{H_2O} + C \qquad (5)$$

at both temperatures.

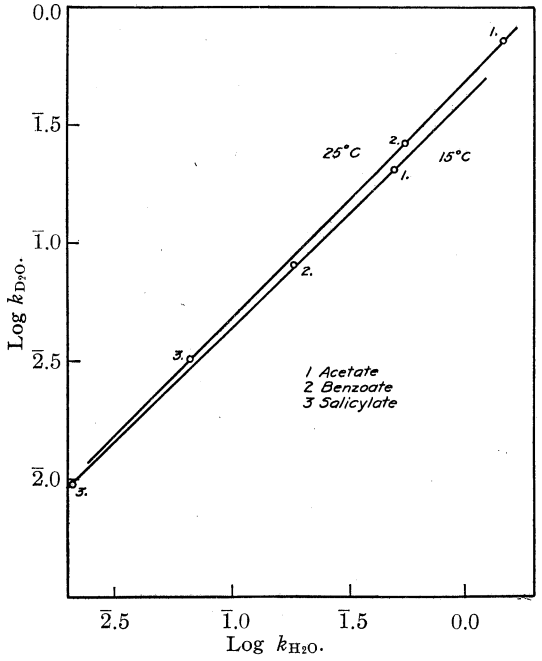

Fig. 3.—The logarithmic relation between the velocity constants in water and deuterium oxide at 15 and 25°: 1, acetate; 2, benzoate; 3, salicylate.

For light and heavy waters, respectively

$$\log k_{D_2O} = \log G_{D_2O} - \alpha' \log K_{D_2O} \qquad (6)$$

$$\log k_{H_2O} = \log G_{H_2O} - \alpha'' \log K_{H_2O} \qquad (7)$$

combining (5), (6) and (7) yields

$$\log K_{D_2O} = \frac{x\alpha''}{\alpha'} \log K_{H_2O} - \frac{x \log G_{H_2O} - \log G_{D_2O} + C}{\alpha'} \qquad (8a)$$

which is of the form

$$\log K_{D_2O} = y \log K_{H_2O} + C_0 \qquad (8b)$$

Substituting the kinetic data in equation (5): $x = 0.967$; $C = 9.611–10$ (Fig. 3); $\log G_{H_2O} = 5.792–10$; $\log G_{D_2O} = 4.998–10$; $\alpha' = 0.832$; $\alpha'' = 0.83$ (Table IV); yields $y = 0.965$ and $C_0 = -0.60$.

A plot of $\log K_{H_2O}$ *versus* $\log K_{D_2O}$ obtained from e. m. f.[13] data yields a straight line of slope $y = 0.972$ which is within 1% of the predictions, and $C_0 = -0.30$. The disagreement of 0.30 unit between the observed and calculated values of C_0 may arise from the uncertainty in executing the graphical solution, and in the accumulation of errors originally present in the constants obtained from equations (5), (6) and (7).

The studies of Brönsted and co-workers[14] on the decomposition of nitramide in *m*-cresol and H_2O furnish further data for testing this relation. Equation (4) holds in both solvents. The plot of the dissociation constants, $\log K_{\text{cresol}}$ *versus* $\log K_{H_2O}$ yield a linear relation with unit slope. In the case of velocities (Fig. 4) when the log k_{cresol} values of Brönsted, Nicholson and Del-

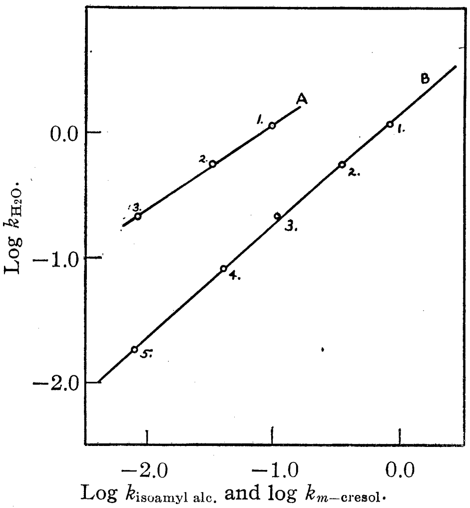

Fig. 4.—The logarithmic relation between the velocity constants in different solvents: A, H_2O *vs.* isoamyl alcohol; B, H_2O *vs.* *m*-cresol, 1, *p*-toluidine; 2, aniline; 3, *p*-chloroaniline; 4, *m*-chloroaniline; 5, *o*-chloroaniline.

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[12] Pedersen, *J. Phys. Chem.*, **38**, 581 (1934).

[13] Schwarzenbach, Epprecht and Erlenmeyer, *Helv. Chim. Acta*, **69**, 1292 (1936). Some of these data will require revision in the light of researches in progress in this Laboratory since the measurements involve galvanic cells with junction potentials. See Rule and La Mer, THIS JOURNAL, **60**, 1974 (1938).

[14] (a) Brönsted, Nicholson and Delbanco, *Z. physik. Chem.*, **169**, 379 (1934); (b) Brönsted, Delbanco and Tovberg-Jensen, *ibid.*, **169**, 361 (1934); (c) Brönsted and Duus, *ibid.*, **117**, 299 (1925); (d) Brönsted and Vance, *ibid.*, **A163**, 240 (1933).

banco are plotted against the log k_{H_2O} values of Brönsted and Duus, a straight line of slope $x = 1.11$ is also obtained. Since $\alpha_{H_2O} = 0.75$ and $\alpha_{m\text{-cresol}} = 0.84$, the calculated value for y in the equation corresponding to (8b) is $y = 0.99$, in excellent accord with the value of unity reported in reference (14b). A linear relation also obtains for the data of Brönsted and Vance[14d] using isoamyl alcohol as solvent (line A of Fig. 4).

Although several authors have shown that the logs of the dissociation constants in different solvents are related linearly when the solvents are as diverse as water, concentrated sulfuric acid and benzene,[15] no one appears to have called attention to the linear relationship between the logs of the velocity constants of a reaction obeying the Brönsted relation in two solvents.

The Arrhenius and Brönsted Equations.—Table IV summarizes the values of α and G in the Brönsted eq. (4). The decreases in rate arising either from a decrease in temperature or substitution of deuterium in the substrate and solvent are reflected almost exclusively in G and not in α. G may be interpreted as the rate for a hypothetical acid–base system K_A = unity. It appears that temperature and deuterium substitution operate primarily upon the fundamental kinetic properties of the substrate in the case of anion catalysis rather than upon the acid-base properties of the catalytic system.

TABLE IV

COMPARISON OF THE VALUES OF α AND G FROM THE BRÖNSTED EQUATION IN 91.5% D_2O WITH THOSE IN H_2O

Temperature, °C.		15	25
Present authors (D_2O)	α	0.832	0.845
	G	9.95×10^{-6}	2.94×10^{-5}
Baughan and Bell[11] (H_2O)	α	0.794	0.758
	G	8.44×10^{-5}	3.69×10^{-4}
Brönsted and Pedersen[16] (H_2O)	α	0.83	
	G	6.2×10^{-5}	

Baughan and Bell[11] report α equal to 0.76 at 25, 35 and 45°, but consider that the 4% increase to 0.79 at 15° is a real effect. Our data in D_2O do not support this view. Where comparisons can be made our data are in better agreement with those of Brönsted and Pedersen[16] than with those of Baughan and Bell.

In equation (3), $B = \log \frac{kT}{h} + \frac{\Delta S^*}{2.3R}$ where ΔS^* is Eyring's[17] entropy of activation which includes the contributions of all degrees of freedom (translational and internal) and kT/h is a pure frequency (ν) equal to $10^{14.6}$ (min.$^{-1}$) at 25°. In the collisional form of the statistical theory of kinetics,[18] kT/h is replaced by $Z°$, the collision frequency, which is equal to approximately $10^{12.2}$ (min.$^{-1}$) at 25°. In the notation of the English school, $B = \log A = \log PZ$; hence $\log P = S_{\text{act.}}/2.3R$. Here the entropy of activation, $S_{\text{act.}}$, as defined by La Mer,[18] does not contain the entropy contributions of the two translational degrees of freedom involved in the collision process. These contributions are contained in $Z°$.

Before the concept of entropy of activation was stressed[18] it was generally assumed that a catalyst effected an increase in rate solely by lowering the potential barrier (energy of activation). In Table V, we have decomposed $\Delta \log k = \Delta F^*/2.3RT$, where ΔF^* is the free energy of activation,

TABLE V

Catalyst referred to the "spontaneous" decomposition (H_2O) (11)	$\Delta \log k_{25}$	$\Delta \log A = \Delta B$	$-\Delta E/2.3RT$
Trimethylacetate	3.274	1.59	1.67
Acetate	3.082	1.97	1.10
Benzoate	2.652	1.61	1.04
Formate	2.318	1.33	0.96
Salicylate	1.735	1.28	.44
Monochloroacetate	1.579	1.01	.54
o-Nitrobenzoate	1.135	2.30	−1.20
Dichloroacetate	0.290	2.45	−2.19
Catalyst referred to the "spontaneous" decomposition (D_2O)			
Acetate	3.379	4.64	−1.28
Benzoate	2.939	2.99	−0.08
Salicylate	2.033	2.84	−0.83
Data in H_2O referred to D_2O for same catalyst			
Acetate	0.308	−1.55	1.85
Benzoate	.318	−0.26	0.59
Salicylate	.307	−0.44	.75
Spontaneous	.605	+1.12	− .52

R. P. Bell informs us (July 7, 1938) that the values in Baughan and Bell's Table IV[11] should be corrected to read

Monochloroacetic $A = 1.19 \times 10^{-13}$; $E = 19{,}640$
Dichloroacetic $A = 2.35 \times 10^{-14}$; $E = 23{,}160$

This produces a corresponding change in our Table V to read

	$\Delta \log k$	ΔB	$-\Delta E/2.3RT$
Monochloroacetate	1.574	0.80	0.77
Dichloroacetate	0.285	2.09	−1.81

These changes do not affect our conclusions.

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(15) Hammett and Deyrup, THIS JOURNAL, **54**, 2721 (1932); La Mer and Downes, *ibid.*, **55**, 1840 (1933); Hammett, *Chem. Rev.*, **13**, 61 (1933); La Mer, *ibid.*, **13**, 47 (1933).

(16) Brönsted and Pedersen, *Z. physik. Chem.*, **108**, 185 (1924).

(17) Eyring, *J. Chem. Phys.*, **3**, 107 (1935); Wynne-Jones and Eyring, *ibid.*, **3**, 494 (1935).

(18) La Mer, *ibid.*, **1**, 289 (1933).

into its component entropy and energy factors B and $E/2.3RT$, respectively. The data show that $\Delta \log k$, representing the catalytic effects of the anions referred to the solvent decomposition as a standard, is dominated more by an increase in the entropy of activation $\Delta B = \Delta S^*/2.3R$, than by a decrease in the energy of activation. This is particularly true of our data in 91.5% D. The only exception in H_2O is Baughan and Bell's result for trimethylacetate ion.

In their studies on the mutarotation of glucose, Hamill and La Mer[19] found that the increased catalysis of H^+ over that of the solvent decomposition, $\Delta \log k = 1.47$, was due to an increase in B of 3.48 units which was more than sufficient to overshadow the rate depressing effect of an increase of 1.95 units in $E/2.3RT$. Recently, Smith and Smith[20] report that the energy of activation of this reaction varies but very little with a series of catalysts. The marked changes in rate are due almost exclusively to a variation in $\log P$, *i. e.*, in the entropy of activation. From their data, B varies approximately as the square root of the acid dissociation constant K, a relation which Smith[21] had suggested previously for the acid–base catalyzed acetone–iodine reaction. The greater importance of entropy of activation is *not* confined to proton transfers but is illustrated also in the primary salt catalysis of ionic reactions. The Debye–Hückel limiting law requires that B increase with the square root of the ionic strength three times as rapidly as $E/2.3RT$.[22]

When the same anion catalyst operates in H_2O and in D_2O, we find (Table V) an almost constant difference in the free energy of activation ($\Delta RT \log k$), irrespective of the anion. The entropy and energy factors, however, appear to be specific to the anion, with the latter exercising a more predominant effect than the former.

Although equation (4) is a well-established empirical relation, which is obeyed closely in the nitramide decomposition and acetone–iodine reactions, no satisfactory theoretical derivation has been forthcoming. Brönsted[23] offered what he termed "a plausible (but) not absolutely cogent" development. Horiuti and Polanyi[24] "derive" equation (4) by assuming for a series of homologous reactions that

$$\log K = \Delta H/RT + \text{const.} \qquad (9)$$

$$\log k = E/RT + \text{const.} \qquad (10)$$

Equation (9) is an approximation which is not valid for the dissociation of weak acids over a range of temperature and does not hold for different acids since a change in the free energy of ionization between two acids is not generally followed by a corresponding change in the heat of ionization.[25] Horiuti and Polanyi's assumption that $\log k$ varies from catalyst to catalyst solely from changes in activation energy E is certainly not permissible in the light of the data discussed above. Any derivation which yields the Brönsted relation without consideration of entropy factors achieves the result by some fortunate cancellation which is not clear from the premises and the development.

Summary

1. Precision measurements of the anion catalysis of the decomposition of nitramide have been extended to waters of 91.5% deuterium content at 15 and 25°.

2. The velocity of anion catalysis is decreased approximately 2.3 fold at 15° and 2.0 fold at 25° for the bases, acetate, benzoate and salicylate ions on passing from H_2O to 91.5% D_2O.

3. The Brönsted equation $G = kK_A^\alpha$ relating velocity and dissociation constants holds accurately in D_2O. The exponent α characterizing the sensitivity of the substrate to basic catalysis is not perceptibly affected by temperature or by isotopic substitution. Most of the rate depressing effect of deuterium substitution is reflected in the constant G since K_A is also reduced.

4. Although the difference in the free energy of activation between proto and deutero forms is practically constant for these anion catalysts at 25°, the corresponding entropy and energy differences do not remain constant.

5. For a given solvent (H_2O) or (D_2O) the entropy factor is predominant in determining the rate for a series of anions, whereas for the same anion catalyst the energy of activation is the more important factor in deuterium substitution.

6. The spontaneous water reaction is of a different mechanism from the anion catalyzed process as judged by the influence of temperature and deuterium substitution.

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(19) Hamill and La Mer, *J. Chem. Phys.*, **4**, 395 (1935).

(20) Smith and Smith, *J. Chem. Soc.*, 1413 (1937).

(21) G. F. Smith, *ibid.*, 1744 (1934).

(22) La Mer and Kamner, THIS JOURNAL, **57**, 2662, 2668 (1935).

(23) Brönsted, *Chem. Rev.*, **5**, 231 (1928), pp. 318–321.

(24) Horiuti and Polanyi, *Acta Physicochimica, U. S. S. R.*, **2**, 505 (1935), pp. 516–520; Evans and Polanyi, *Trans. Faraday Soc.*, **34**, 23 (1938); see Guggenheim and Weiss' criticism, pp. 69–70 and the reply, p. 81.

(25) Hammett, *Trans. Faraday Soc.*, **34**, 73 (1938); *J. Chem. Phys.* **4**, 613 (1936).

7. The interdependence of the rates of a base catalyzed reaction and the dissociation constants of the catalysts on passing to new media is discussed in the light of the Brönsted equation. Attention is called to a linear relation between the logarithms of the rate constants in the two media.

New York, N. Y. Received March 31, 1938

[Contribution from the Department of Chemistry, Columbia University]

Dissociation Constants of Deutero Acids by E. m. f. Measurements

By C. K. Rule and Victor K. La Mer

Although the dissociation constants of weak acids are decreased by a factor of two- to four-fold on passing from H_2O to D_2O, there is disagreement regarding the underlying theory. One school holds that the ratio of the dissociation constants of the proto and deutero forms of an acid is a function of the strength of the acid; the second that the ratio is constant for acids of a given type; a third,[1] that the ratio is uniformly three regardless of type.

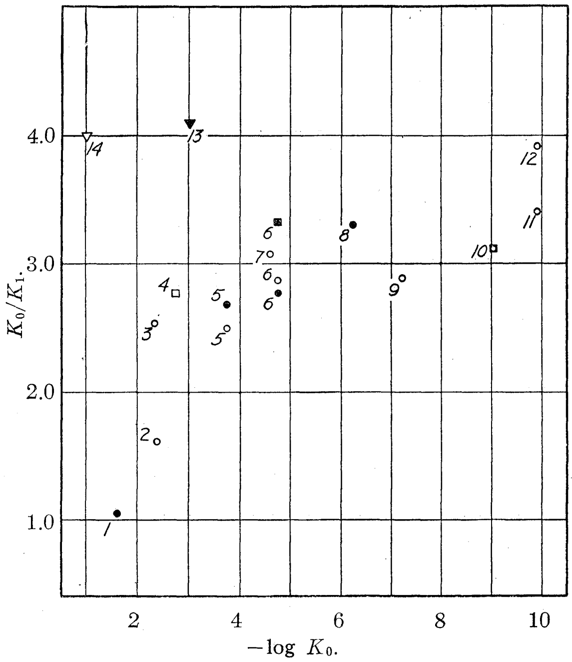

Fig. 1.—Dissociation constant ratios. Acids and references: 1 oxalic,[1a] 2 phosphoric (first),[3] 3 glycine,[3] 4 chloroacetic,[2] 5 formic,[1a,3] 6 acetic,[1a,4,23] 7 aniline hydrochloride,[3] 8 cacodylic,[1a] 9 phosphoric (second),[3] 10 ammonium chloride,[2] 11 glycine hydrochloride,[3] 12 trimethylamine hydrochloride,[3] 13 salicylic,[4] 14 picric.[1b] Methods of measurements: ● catalytic, ○ potentiometric with transference, □ conductimetric, ▽ distribution coefficient, ▼ potentiometric (approximate), ▣ conductimetric and potentiometric without transference.

Lewis and Schutz[2] predicted that the ratio will depend on the strength of the acid—being larger the weaker the acid. They assumed that the potential field is unchanged by the substitution of a deuteron for a proton. Then the deutero acid will have a lower zero point energy and will be less dissociated, the difference increasing with decreasing strength of the acid. They mention that the difference in the extent of dissociation of the proto and deutero acids will depend also on the difference between their entropies of dissociation.

On the other hand, Schwarzenbach[3] concludes from measurements on cells with liquid–liquid junctions that the ratio is a function of the type of the acid, being smaller for carboxylic acids than for amine hydrochlorides.

A critical consideration of the data in the literature shows that there is little accurate work upon which to base a decision between these conflicting theories. These data are shown in Fig. 1. The ratios of the dissociation constants of the proto to those of the deutero acids are plotted against the logarithm of the dissociation constants of the proto acids. The differences of 15 and 20% between the ratios reported by different investigators for acetic acid are an indication of the inaccuracy of the data.

When accurate measurements are required, the uncertainty introduced by the presence of liquid–liquid junctions between H_2O and D_2O should be avoided in potentiometric studies. Korman and La Mer[4] have demonstrated the suitability of the quinhydrone electrode for measurements in H_2O–D_2O mixtures. We have accordingly reinvestigated their cells

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(1) (a) Hornel and Butler, *J. Chem. Soc.*, 1361 (1936); (b) Gross and Wischin, *Trans. Faraday Soc.*, **32**, 879 (1936); (c) Drucker, *Trans. Faraday Soc.*, **33**, 660 (1937).

(2) Lewis and Schutz, This Journal, **56**, 1913 (1934). See also Halpern, *J. Chem. Phys.*, **3**, 456 (1935).

(3) Schwarzenbach, *Z. Elektrochem.*, **44**, 46 (1938).

(4) Korman and La Mer, This Journal, **58**, 1396 (1936).

$$\text{Ag–AgCl} \mid \text{HCl–DCl}\ (H_2O–D_2O)\ QQH_2–QQD_2 \mid \text{Pt} \quad \text{I}$$
$$\text{Ag–AgCl} \mid \text{HA–DA}(m_1),\ \text{MA}(m_2),\ \text{MCl}(m_3)\ (H_2O–D_2O)\ QQH_2–QQD_2 \mid \text{Pt} \quad \text{II}$$

at 25° and have extended the measurements to other acids and temperatures. QQH_2 and QQD_2 represent proto and deutero quinhydrone; HA and DA, the proto and deutero forms of a weak acid; MA, an alkali metal salt of the acid; MCl, an alkali metal chloride.

Since the cells are without liquid–liquid junctions, the cell processes are unambiguous

$$\text{I} \quad Q(H_2O–D_2O) + 2(H^+ + D^+) + 2Cl^-\ (H_2O–D_2O) + 2Ag(s) \rightleftarrows (QH_2–QD_2)\ (H_2O–D_2O) + 2AgCl(s)$$

$$\text{II} \quad Q(H_2O–D_2O) + 2(HA + DA)\ (m_1 \text{ in } H_2O–D_2O) + 2MCl(m_3 \text{ in } H_2O–D_2O) + 2Ag(s) \rightleftarrows 2AgCl(s) + (QH_2–QD_2)(H_2O–D_2O) + 2MA(m_2 \text{ in } H_2O–D_2O)$$

Apparatus and Experimental Procedure

Accurate measurements with the silver–silver chloride electrode require the exclusion of oxygen and liberal washing with the cell solution.[5] A semi-micro cell, Fig. 2, was devised which avoided waste of solution, exposure to air, or contact of the solution with any surfaces except Pyrex which had been steamed. The relatively higher ratio of glass and electrode surfaces to the volume of solution in the micro as compared to the macro technique demands special care in cleaning apparatus and eliminating contact with foreign gases.

Solutions were made up in a 50-cc. flask fitted with a ground glass cap, stopcock and a small ground glass joint. The solvent was run directly from the pycnometer into the flask; solids were added contained in micro weighing bottles; liquid solutes were added from weight burets. The flask containing the solution was attached to the vacuum and nitrogen gas lines and air was removed from the solution by repeated evacuation and shaking followed by the admission of nitrogen. Account was taken of the loss of water by evaporation.

The cell with electrodes in place was connected to the vacuum line. The flask containing the solution was connected directly to the cell through a ground glass joint. Having evacuated the cell, small amounts of solution were admitted to wash the silver–silver chloride electrodes. The wash solution was kept in contact with the electrodes for some ten minutes, was drawn off into a trap, and the washing was either repeated or the entire cell filled. No difference was observed between the potentials of cells in which the electrodes were rinsed twice and those in which they were rinsed only once. Each solution of 16 cc. sufficed to fill two cells, allowing for rinsing.

A Leeds and Northrup type K-II potentiometer was used with two Bureau of Standards Weston cells. The thermostats were maintained at 5, 25 and 45 ± 0.02° as determined by a B. of S. platinum resistance thermometer. No hysteresis was observed when the cells were transferred back and forth from one thermostat to another. Distillation of solvent was prevented by filling the cells completely. The potentials of the duplicate silver–silver chloride electrodes against the duplicate quinhydrone electrodes were recorded every ten minutes. Equilibrium was assumed when the potentials remained constant within 0.1 millivolt for an hour. No drift of potential was observed in the use of the quinhydrone electrode at 45° except when the cell contained a buffered solution of dihydrogen phosphate.

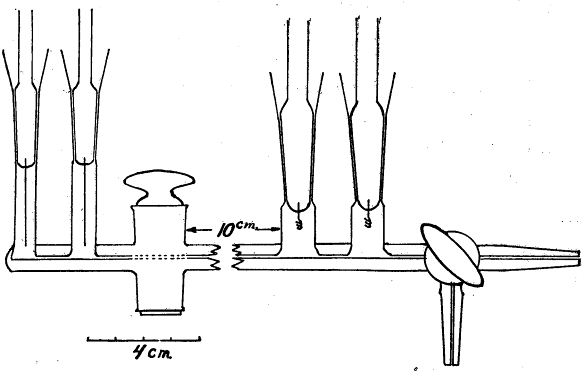

Fig. 2.

Purification of Materials.—Three preparations of quinhydrone were used—one made by the method of Biilman and Lund.[6] The others were Eastman, one of which was purified by recrystallization from conductivity water in an atmosphere of carbon dioxide. All gave the same potentials. Silver–silver chloride electrodes were made as described by Rule and La Mer,[7] the silver chlorate having been prepared from silver carbonate and chloric acid free from other halogens, and twice recrystallized.

Bureau of Standards benzoic acid was used. Sodium benzoate was recrystallized from alcohol and was neutral to phenolphthalein. Potassium dihydrogen phosphate was recrystallized three times and dried at 110°. Its loss of weight on ignition was 13.16% (theory 13.23%). When titrated against sodium hydroxide using phenolphthalein indicator, its molecular weight was found to be within 0.3% of the theoretical. $Na_2HPO_4 \cdot 2H_2O$ was a sample of special purity prepared for work with enzymes. It was exposed to the atmosphere until it had reached constant weight. Loss on ignition was 25.29% (theory 25.30%). Analysis for phosphate, by precipitation as $MgNH_4PO_46H_2O$ and weighing as $Mg_2P_2O_7$, showed 53.29% (theory 53.36%).

Sodium chloride was recrystallized by La Mer and Kamner.[8] Potassium chloride was recrystallized once. They were dried at 110°.

$H_2O–D_2O$ mixtures were recovered from previous experiments. The quinhydrone was oxidized by alkaline potassium permanganate in a flask kept at 80° for thirty-six hours or until permanganate was no longer reduced. The water was distilled *in vacuo* and redistilled *in vacuo* from an alkaline solution. Its density and conductivity were determined in a combined pycnometer and conductivity cell whose volume was 16 cc. The water was forced through a glass tube directly from the pycnometer into the flask in which the solution was made up. Water having a specific conductivity greater than 2.10^{-6} ohm^{-1} was not used.

Constant boiling hydrochloric acid was prepared according to Bonner and Titus.[9]

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(5) Güntelberg, *Z. physik. Chem.*, **123**, 199 (1926).

(6) Biilman and Lund, *Ann. chim.*, [9] **16**, 321 (1921).

(7) Rule and La Mer, THIS JOURNAL, **58**, 2339 (1936).

(8) La Mer and Kamner, *ibid.*, **57**, 2662 (1935).

(9) Bonner and Titus, *ibid.*, **52**, 633 (1930).

Nitrogen gas was freed from oxygen by passage through a tower containing copper spirals bathed with a solution of ammonium hydroxide saturated with ammonium chloride.[10] Ammonia and water were removed subsequently by means of two absorption towers filled with sulfuric acid solutions, followed by two traps cooled to −78°.

Methods of Calculation

The ratio of the dissociation constants of hydroquinone in H_2O and D_2O can be calculated from the difference of the electromotive forces of cell I when H_2O is replaced by D_2O.[11] Silver and silver chloride are solids whose activities are unity by definition whether the electrode be immersed in H_2O or in D_2O.[12]

Hence, the standard electromotive force of cell I is

$$E_0^0 = \frac{RT}{2F} \ln \frac{(QH_2)_0}{(Q)_0(HCl)_0} \tag{1}$$

when the solvent is H_2O, and is

$$E_1^0 = \frac{RT}{2F} \ln \frac{(QD_2)_1}{(Q)_1(DCl)_1} \tag{2}$$

when the solvent is D_2O.[14]

Subtracting E_0^0 from E_1^0

$$E_1^0 - E_0^0 = \frac{RT}{2F} \ln \frac{(QD_2)_1(Q)_0(HCl)_0^2}{(QH_2)_0(Q)_1(DCl)_1^2} \tag{3}$$

Introducing K_0 and K_1, the geometric mean of the first and second dissociation constants of hydroquinone and hydroquinone-d_2, respectively

$$E_1^0 - E_0^0 = \frac{RT}{2F} \ln \frac{(Q)_0(Cl^-)_0^2(Q^=)_1K_0^2}{(Q_1)(Cl^-)_1^2(Q^=)_0K_1^2} \tag{4}$$

The relative free energies of chloride ions and of quinone ions in H_2O and in D_2O not being known, we must assume that the factor $(Q)_0(Cl^-)_0^2(Q^=)_1/(Q)_1(Cl^-)_1^2(Q^=)_0$ is unity. Eq. (4) becomes

$$E_1^0 - E_0^0 = \frac{RT}{F} \ln \frac{K_0}{K_1} \tag{5}$$

Using this equation, the ratios of the dissociation constants of hydroquinone and hydroquinone-d_2 can be calculated from the difference of the standard electromotive forces of cell I when the solvent is D_2O and when it is H_2O.

On the other hand, the equilibrium constant, K_2, of the exchange reaction $QH_2 + 2DCl \rightleftarrows QD_2 + 2HCl$ can be calculated on the assumption that quinone has the same activity in D_2O as in H_2O. Equation (3) then reduces to

$$E_1^0 - E_0^0 = \frac{RT}{2F} \ln \frac{(QD_2)_1(HCl)_0^2}{(QH_2)_0(DCl)_1^2} = \frac{RT}{2F} \ln K_2 \tag{6}$$

The dissociation constants of other acids in H_2O–D_2O mixtures can be determined from the e. m. f. of cell II following the methods of Harned and co-workers[15] and Korman and La Mer,[4] who first applied the method to deutero acids. The e. m. f. of cell II for an H_2O–D_2O mixture in which the mole fraction of deuterium is *n*, is[16]

$$E_n = E_n^0 - \frac{RT}{2F} \ln \frac{(QH_2 + QD_2)_n}{(Q)_n(H^+ + D^+)_n^2(Cl^-)_n^2} \tag{7}$$

For low ionic strengths where the salt effect of the quinhydrone electrode is negligible $(QH_2 + QD_2)_n = (Q)_n$ and

$$E_n = E_n^0 - \frac{RT}{F} \ln \frac{1}{(H^+ + D^+)_n(Cl^-)_n} \tag{8}$$

In this equation E_n is the e. m. f. of cell II and E_n^0 is the standard e. m. f. of cell I when the fraction of deuterium in the solvent is the same for both cells. Defining the dissociation constant of an acid in an H_2O–D_2O mixture as[17]

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(10) Van Brunt, THIS JOURNAL, **36**, 1448 (1914).

(11) La Mer and Korman, *ibid.*, **57**, 1511 (1935).

(12) Drucker[1] has attempted to show, by measuring the cells

$Ag–AgCl\ |^1\ DCl(D_2O)\ |^2\ KCl(satd., H_2O)\ |^3\ KCl(H_2O)\ |\ HgCl–Hg$ A

$Ag–AgCl\ |^4\ HCl(H_2O)\ |^5\ KCl(satd., H_2O)\ |^6\ KCl(H_2O)\ |\ HgCl–Hg$ B

that the difference in the e. m. f. arises from the difference in the solubilities of silver chloride in H_2O and in D_2O. Brodsky[13] and Schwarzenbach[3] hold similar views.

This cannot be correct. It is well recognized that the silver–silver chloride electrode operates by virtue of the fact that the activities of silver and silver chloride in solution are independent of the solvent since they are in equilibrium with a solid phase of fixed activity. The magnitude of the solubility, so long as it does not change the ionic strength appreciably, cannot influence the electromotive force.

The difference of e. m. f. between cells A and B arises in fact from the liquid–liquid junction potentials 2 and 5.

(13) Brodsky, *Trans. Faraday Soc.*, **33**, 1180 (1937).

(14) In this paper symbols in parentheses represent activities. The symbol E^0 represents the standard electromotive force of cell I. The subscript 0 is used when the solvent is H_2O; and the subscript *n* when the solvent is an H_2O–D_2O mixture in which the mole fraction of deuterium is *n*.

(15) Harned and Owen, THIS JOURNAL, **52**, 5079 (1930); Harned and Ehlers, *ibid.*, **54**, 1350 (1932); **55**, 652 (1933).

(16) $(H^+ + D^+)$ in these equations means the sum of the activities of all the hydrogen and deuterium ions whether hydrated or not.

(17) That it is permissible thermodynamically to write the sums $(QH_2 + QD_2)_n$ and $(H^+ + D^+)_n$ in defining cell processes and dissociation constants in H_2O–D_2O mixtures can be shown as follows. When the quinhydrone electrode is used in an H_2O–D_2O mixture there will be two oxidation–reduction systems; one is composed of quinone and hydroquinone

$$E_a = E_a^0 - \frac{RT}{2F} \ln \frac{(QH_2)_n}{(Q)_n(H^+)_n^2}$$

and the other of quinone and hydroquinone-d_2

$$E_b = E_b^0 - \frac{RT}{2F} \ln \frac{(QD_2)_n}{(Q)_n(D^+)_n^2}$$

At equilibrium the potentials of the two systems are equal. Introducing into equation (7) the fraction, α, of hydroquinone-d_2 and the fraction, β, of deuterium ion and omitting the chloride ion we obtain either

$$E_n = E_n^0 - \frac{RT}{2F} \ln \frac{(QH_2 + QD_2)_n(1 - \alpha)}{(Q)(H^+ + D^+)_n^2(1 - \beta^2)}$$

or

$$E_n = E_n^0 - \frac{RT}{2F} \ln \frac{(QH_2 + QD_2)_n\,(\alpha)}{(Q)(H^+ + D^+)_n^2\,(\beta)^2}$$

Hence the normal potential of the quinhydrone electrode as defined

$$K_n = \frac{(\mathrm{H}^+ + \mathrm{D}^+)(\mathrm{A}^-)}{(\mathrm{HA} + \mathrm{DA})}$$

we substitute for $(\mathrm{H}^+ + \mathrm{D}^+)$ in equation (8)

$$E_n = E_n^0 = \frac{RT}{F} \ln \frac{(\mathrm{A}^-)_n}{(\mathrm{HA} + \mathrm{DA})(\mathrm{Cl}^-)_n K_n}$$

simplifying

$$\log K_n = \frac{E_n - E_n^0}{2.3RT/F} - \log \frac{(\mathrm{HA} + \mathrm{DA})_n(\mathrm{Cl}^-)_n}{(\mathrm{A}^-)_n}$$

Introducing the activity coefficients and the molal concentrations m_1, m_2 and m_3 of the acid, of its ion and of the chloride ion, respectively

$$\log K_n = \frac{E_n - E_n^0}{2.3RT/F} - \log \frac{m_1 m_3}{m_2} - \log \frac{f_1 f_3}{f_2} \quad (9)$$

In the case of acids whose anions have unit charge, the last term is the ratio of the activity coefficients of two univalent ions and, being sensibly unity, can be neglected. The error introduced will be particularly small when the ratio of the dissociation constants in H_2O and in D_2O is considered.

In the case of the dissociation of dihydrogen phosphate, the anion formed is a divalent ion and the last term in equation (9) becomes appreciable, requiring extrapolation of the data to infinite dilution. We set

$$\log f_1 f_3/f_2 = 2A\sqrt{\mu} + B\mu$$

where A is the theoretical constant of the Debye–Hückel limiting law and B is an empirical constant. Replacing the last term in equation (9) by these functions and transferring the term B to the left-hand side

$$\log K_n + B\mu = \frac{E_n - E_n^0}{2.3RT/F} - 2A\sqrt{\mu} - \log \frac{m_1 m_3}{m_2} \quad (10)$$

The data of Nims[18] on this system indicate that a plot of the right-hand side of equation (10) against the ionic strength, μ, gives a straight line at least to an ionic strength of 0.17. The intercept at zero ionic strength gives the logarithm of the thermodynamic ionization constant.

Experimental Results

In Table I are the observed potentials E_n^m for cell I, and the normal potentials, E_n^0.

TABLE I

ELECTROMOTIVE FORCE OF CELL I

Each recorded potential is the mean of measurements with two cells filled with the same solution. Each cell contained duplicate quinhydrone and duplicate silver–silver chloride electrodes.

$n = \frac{\Delta S}{0.1079}$	Moles of HCl per liter of solvent	25°		45°	
		E_n^m	E_n^0	E_n^m	E_n^0
0	0.03049	0.2897	0.4772	0.2756	0.4759
0	.02097	.2714	.4770	.2564	.4760
0	.011225	.2408	.4769	.2237	.4758
0.048	.02765	.2865	.4787	.2725	.4778
.048	.02482	.2809	.4783	.2665	.4774
.056	.02096	.2732	.4788	.2582	.4778
.056	.02034	.2714	.4785	.2562	.4774
.096	.01644	.2627	.4802	.2470	.4793
.096	.02094	.2744	.4801	.2594	.4791
.252	.02463	.2874	.4852	.2728	.4841
.252	.02169	.2810	.4850	.2660	.4839
.511	.02149	.2900	.4944		
.547	.01958	.2865	.4955		
.764	.01807	.2910	.5039	.2755	.5028
.775	.01869	.2937	.5052	.2782	.5038
.987	.02797	.3214	.5130		
		5°			
.252	.02169	.2988	.4879		
.511	.02149	.3080	.4976		

Unpublished data of Noonan and La Mer employing the cell Pt D_2/ DCl / AgCl–Ag indicate that the interionic activity coefficients of HCl and DCl do not differ appreciably. The molal potential of cell I was therefore calculated from the observed potentials, E_n^m, by subtracting the e. m. f. of the cell

$$\mathrm{H_2/HCl}\ (m=1)\mathrm{/AgCl\text{–}Ag\text{–}AgCl/HCl}\ (m)\mathrm{/H_2}$$

The e. m. f. of this cell was calculated from the data of Harned and Ehlers.[19]

The differences of the molal potentials for cell I when the solvent is an H_2O–D_2O mixture and when it is H_2O are plotted in Fig. 3 against the mole fraction, n, of deuterium in the solvent. A number of measurements were made in the neighborhood of 5% D_2O, where evidence for a minimum had been reported previously.[4] No minimum was found, the differences being an almost linear function of the fraction of deuterium in the solvent. The least squares equation of the curve, obtained from the data at 25°, is

$$E_n = E_0 + 0.02975n + 0.00985n^2 - 0.00301n^3 \quad (11)$$

The same equation fits the data equally well at 45 and at 5°, though additional data are desirable at the latter temperature. The temperature coefficient of the e. m. f. is consequently the same in H_2O, in D_2O and in their mixtures at

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by equation (7) differs from the normal potential E_a^0 only by the factor

$$\frac{RT}{2F} \ln \frac{(1-\alpha)}{(1-\beta)^2}$$

and from the potential E_b^0 by the factor

$$\frac{RT}{2F} \ln \frac{\alpha^2}{\beta}$$

These factors are constants for an H_2O–D_2O mixture containing a fixed fraction of deuterium.

(18) Nims, THIS JOURNAL, **55**, 1946 (1933).

(19) Harned and Ehlers, *ibid.*, **55**, 2179 (1933).

temperatures between 5 and 45°. The average deviation of the data from equation (11) is 0.2 mv.

Using equations (5) and (6), the exchange constant, K_2, and the ratios of the dissociation constants of hydroquinone and hydroquinone-d_2 were calculated and are shown in Table II.

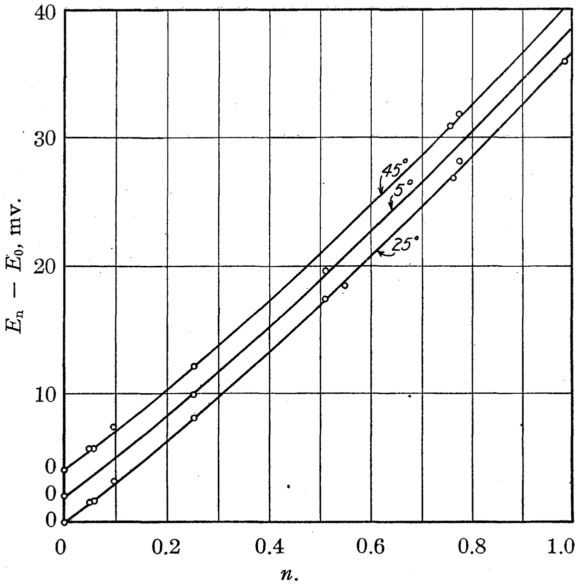

Fig. 3.—The molal potential of cell I as a function of the mole fraction of deuterium in the solvent. The curves for 5 and 45° have been displaced upward by 4 and 8 millivolts, respectively.

Table II

Temp., °C.	5	25	45
K_2	19.1	15.6	13.0
K_0/K_1	4.61	4.16	3.80

Since the temperature coefficient of the electromotive force is zero, the difference between the free energies of dissociation of hydroquinone and of hydroquinone-d_2 is the same as the difference in the heats of dissociation. The difference in the entropies is zero within 0.4 entropy unit.

In Table III are the data on the composition of the benzoic acid buffer solutions used in cell II, the e. m. f. data and the dissociation constants calculated from equation (9). The ratios K_n/K_0 are plotted in Fig. 4 against the mole fraction of deuterium in the solvent. K_n is the dissociation constant in an H_2O–D_2O mixture and K_0 is the dissociation constant in H_2O. The short extrapolation to D_2O was made using the equation

$$\frac{K_n}{K_0} = \frac{\left((H_2O) + M(HDO) + N(D_2O) + \frac{\sqrt{(D_2O)^3}}{\sqrt{(H_2O)^3}}\frac{1}{\sqrt{L}}\right)\sqrt{(H_2O)}\sqrt{L}}{\left(\sqrt{(H_2O)}\sqrt{L} + \frac{K_0}{K_1} - (D_2O)\right)\left((H_2O) + (HDO) + (D_2O)\right)} \qquad (12)$$

This is analogous to the equation employed by Gross, Steiner and Suess[20] and Orr and Butler.[21]

The significance of the constants L, M and N is shown by the equations

$$\sqrt{L} = \frac{(H_3O^+)}{(D_3O^+)}\frac{\sqrt{[D_2O]^3}}{\sqrt{[H_2O]^3}}$$

$$\frac{1}{M} = \frac{(H_3O^+)}{(H_2DO^+)}\frac{[HDO]}{[H_2O]}$$

$$\frac{1}{N} = \frac{(H_3O^+)}{(HD_2O^+)}\frac{[D_2O]}{[H_2O]}$$

In these equations, symbols in brackets represent moles per liter and symbols in parentheses represent activities.

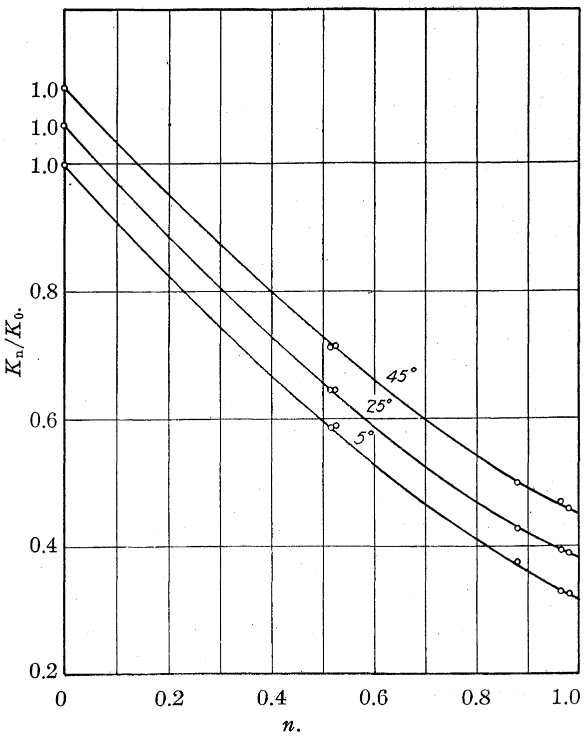

Fig. 4.—Dissociation constant ratios for benzoic acid as a function of the mole fraction of deuterium in the solvent. The curves for 25 and 45° have been displaced upward by 0.06 and 0.12 unit, respectively.

L can be calculated from the equation[3]

$$\log L = \frac{2F\Delta E}{2.3RT} + \log K_3$$

K_3 is the equilibrium constant of the reaction $D_2 + H_2O \rightleftarrows H_2 + D_2O$, calculated from the data of Farkas and Farkas for the equilibrium

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(20) Gross, Steiner and Suess, *Trans. Faraday Soc.*, **32**, 883 (1936).

(21) Orr and Butler, *J. Chem. Soc.*, 330 (1937).

TABLE III

COMPOSITION OF SOLUTIONS, E. M. F. DATA AND DISSOCIATION CONSTANTS FOR BENZOIC ACIDS

Figures in parentheses show the number of cells from which the e. m. f. data were obtained. The average of the data is recorded as E_n.

	Grams solute per liter solvent			25°			45°			5°		
$n = \frac{\Delta S}{0.1079}$	Benzoic acid	Sodium benzoate	NaCl	E^0_n	E_n	$K_n\ 10^5$	E^0_n	E_n	$K_n\ 10^5$	E^0_n	E_n	$K_n\ 10^5$
0.9787	0.04375	0.03771	0.04530	0.5128	0.1585	1.99 (2)	0.5116	0.1339	2.00 (1)	0.5158	0.1832	1.83 (1)
.9651	.02518	.02247	.07109	.5122	.1753	2.03 (2)	.5111	.1522	2.07 (1)	.5152	.1987	1.85 (1)
.8799	.02891	.04166	.1040	.5087	.1546	2.23 (3)	.5077	.1302	2.24 (4)	.5117	.1805	2.13 (3)
.5242	.01434	.02447	.07087	.4949	.1555	3.55 (1)	.4938	.1315₅	3.53 (1)	.4979	.1798	3.33 (1)
.5145	.01801	.01854	.05938	.4945	.1635	3.56 (1)	.4934	.1400	3.52 (1)	.4975	.1871	3.32 (1)
0	.02382	.02026	.03242	.4770	.1493	6.16 (1)	.4759	.1254	5.95 (1)	.4800	.1733	5.94 (1)
0	.01782	.02351	.05937	.4770	.1540	6.15 (1)	.4759	.1307₅	6.01 (1)	.4800	.1773	5.72 (1)
0	.04117	.04565	.01184	.4770	.1602	6.02 (3)	.4759	.1372	5.88 (2)	.4800	.1833	5.65 (2)
Weighted average for H_2O						6.09			5.93			5.68

$H_2O + HD \rightleftarrows HDO + H_2$, of Urey and Rittenberg for the equilibrium $H_2 + D_2 \rightleftarrows 2HD$, and of Topley and Eyring for the equilibrium $H_2O + D_2O \rightleftarrows 2HDO$[22]. ΔE is the difference between the e. m. f. of the cell $H_2 \mid HCl \mid AgClAg$ when the solvent is D_2O and when it is H_2O. We are indebted to Mr. Evan C. Noonan for permission to use his data for ΔE before publication. The constants ΔE, K_3, and L are given in Table IV.

TABLE IV

CONSTANTS FOR EQUATION (12)

Temp., ° C.	5	25	45
ΔE	0.0041	0.0042	0.0049
K_3	11.6	8.70	6.45
L	16.3	12.04	9.21
M	0.97	1.04	1.12
N	1.03	1.15	1.28

The constants M and N were obtained by fitting equation (12) to the data for the dissociation constant ratios for hydroquinone in H_2O–D_2O mixtures calculated by means of equations (5) and (11) (see Fig. 5). The constants M and N are given in Table IV and at 25° agree closely with the values 1.05 and 1.10 obtained by Orr and Butler.[21]

The ratios K_0/K_1 for benzoic acid, obtained by the extrapolation in Fig. 4, together with the differences of heats, entropies, and free energies of dissociation are shown in Table V.

TABLE V

DIFFERENCE OF MOLAL HEATS, FREE ENERGIES, AND ENTROPIES OF DISSOCIATION FOR BENZOIC ACID

°C.	K_0/K_1	$R \ln K_0/K_1$	H_1-H_0 cal.	F_1-F_0 cal.	S_1-S_0 cal./deg.
5	3.16	2.29	−9	636	−2.3
25	3.13	2.27	175	676	−1.7
45	3.04	2.21	379	703	−1.0

Subscript 1 refers to benzoic acid-*d;* subscript 0 to protobenzoic acid.

At 25° the heat of dissociation of benzoic acid-*d* is 175 cal. greater than that of protobenzoic acid and the entropy of dissociation is −1.7 calories per degree less.

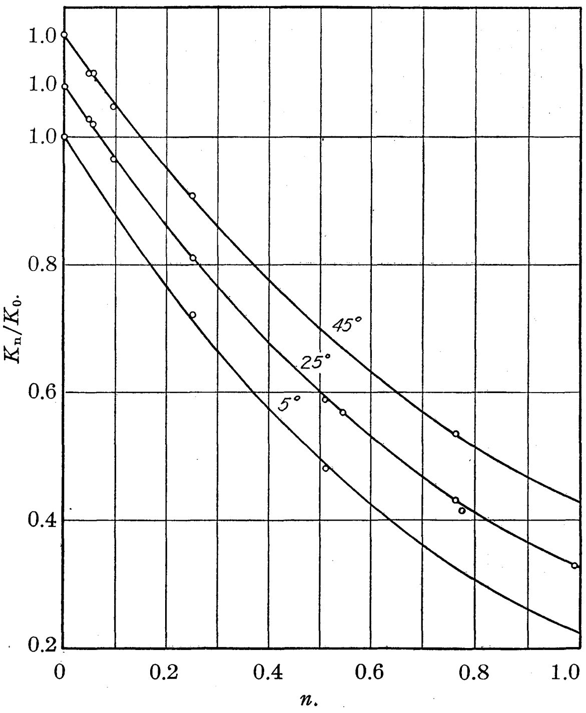

Fig. 5.—Dissociation constant ratios for hydroquinone as a function of the mole fraction of deuterium in the solvent. The curves for 25 and 45° have been displaced upward by 0.08 and 0.16 unit, respectively.

The composition of the phosphate buffer solutions used in cell II in the determination of the dissociation constant of $H_2PO_4^-$ at 25° and the e. m. f. data are given in Table VI. In Fig. 6 the dissociation constant data were extrapolated to infinite dilution employing equation (10). The extrapolated values are given in Table VII.

Equation (12) was employed in making the extrapolation to pure D_2O. The ratio K_0/K_1 is 3.62.

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[22] Farkas and Farkas, *Trans. Faraday Soc.*, **30**, 1071 (1934); Urey and Rittenberg, *J. Chem. Phys.*, **1**, 137 (1933); Topley and Eyring, *ibid.*, **2**, 217 (1934).

TABLE VI

COMPOSITION OF PHOSPHATE BUFFER SOLUTIONS AND E. M. F. DATA

Each recorded potential is the mean of measurements with two cells filled with the same solution. The figure in parentheses in column (4) represents moles of NaCl instead of KCl.

$n = \frac{\Delta S}{0.1079}$	Moles of solute per liter KH_2PO_4	Na_2HPO_4 $2H_2O$	KCl	μ	E^0_n	E_n	$-(\log K + B\mu)$
0	0.03671	0.01686	(0.03877)	0.1261	0.4770	0.0035	7.290
0	.01096	.01038	.01994	.06204	.4770	− .0357	7.242
0	.01051	.005967	.02145	.04987	.4770	− .0216	7.232
0	.001964	.001390	.004561	.01069	.4770	− .0697	7.155
0	.002908	.001304	.004749	.01157	.4770	− .0585	7.186
0	.008896	.003196	.008688	.02718	.4770	− .0345	7.199
0.9089	.01403	.01065	.01339	.05937	.5099	− .0365	7.734
.9069	.002699	.01755	.03192	.1116	.5099	− .0070	7.773
.9042	.02026	.01488	.01701	.08196	.5098	− .0280	7.751
.9854	.01897	.01524	.02045	.08521	.5137	− .0253	7.807

TABLE VII

DISSOCIATION CONSTANT RATIOS FOR $H_2PO_4^-$, 25°

n	$\log K_n$	$K_n\ 10^8$	K_n/K_0	K_0/K_1
0.000	$\bar{8}.810$	6.46	1	1
.9063	$\bar{8}.309$	2.04	0.316	
.9854	$\bar{8}.255$	1.80	0.279	
(1.000)	$\bar{8}.250$	1.78	0.276	3.62

Discussion

In Fig. 7 the ratios K_0/K_1 for benzoic acid, hydroquinone, and $H_2PO_4^-$ are plotted against log K_0. The length of the lines in the figure shows the estimated probable error of the dissociation constant ratio. In view of the fact that the dissociation constants of the proto and of the deutero acids were determined by exactly the same method, any constant errors of the method tend to cancel when their ratios are considered. The average deviation of the ratio should therefore be a fair measure of the probable error.

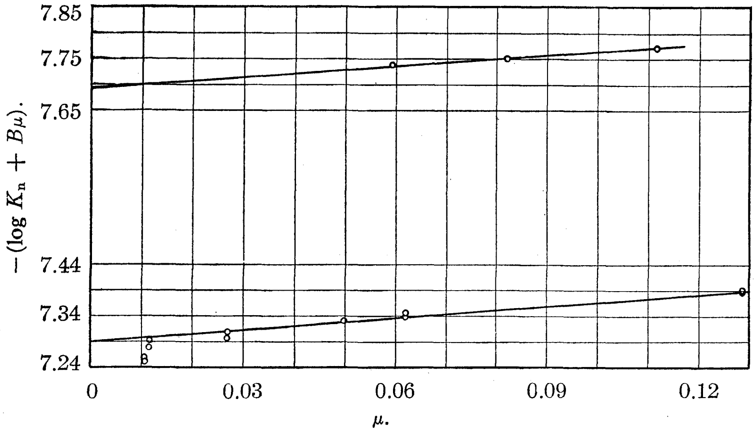

Fig. 6.—The secondary dissociation of phosphoric acid in H_2O–D_2O mixtures at 25° as a function of ionic strength. The lower curve refers to data obtained with H_2O. The upper curve refers to data obtained with 90.6% D_2O.

For benzoic acid, the average deviation of the data from the curve in Fig. 4 is 1%. For $H_2PO_4^-$, the necessity of extrapolating first to infinite dilution and afterward to pure D_2O increases the uncertainty of the result and 2% is a better estimate. For hydroquinone the assumptions underlying equation (5) introduce an error which cannot be estimated. On the basis of the average deviation of the e. m. f. data (0.2 mv.), the average deviation for the ratio K_0/K_1 is 1.6%.

The ratios for acetic acid (from the closely agreeing conductance and e. m. f. data of La Mer and Chittum[23] and of Korman and La Mer[4]) and for chloroacetic acid (from the conductance data of Lewis and Schutz[2]) are also plotted in Fig. 7. The data for acetic acid fit a curve similar to that for benzoic acid with an average deviation of about 1%. The precision of the data for chloroacetic acid cannot be estimated, for Lewis and Schutz do not report the exact fraction of deuterium in their H_2O–D_2O mixture. The dissociation constant for chloroacetic acid-*d*, is being redetermined in this Laboratory by Mr. James Yates.

The curve in Fig. 7 passes through or very near all the points and is consistent with an extrapolated ratio equal to unity at log K_0 = 1.75, or K_0 = 55, the dissociation constant of H_3O^+. The ratio decreases as the strength of the acid increases; for acids approaching the strength of H_3O^+, the dissociation constants may be the same in H_2O and in D_2O.

It should be noted that of all the data in the literature on the dissociation constants of deutero

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[23] La Mer and Chittum, THIS JOURNAL, **58**, 1642 (1936).

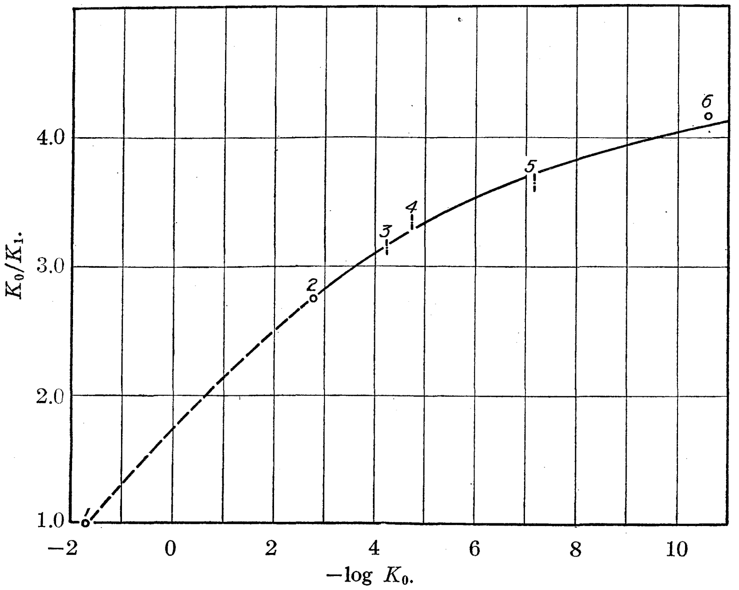

Fig. 7.—Ratios of dissociation constants for proto and deutero acids from conductimetric and potentiometric measurements.

	Acid	K_0	K_0/K_1	Reference
(1)	H_3O^+	55.5	(1)	
(2)	Chloroacetic	$1.72_5 \times 10^{-3}$	2.74	2
(3)	Benzoic	6.09×10^{-5}	3.13	This paper
(4)	Acetic	1.84×10^{-5}	3.33	23, 4
(5)	$H_2PO_4^-$	6.46×10^{-8}	3.62	This paper
(6)	Hydroquinone[a]	2.66×10^{-11}	4.16	This paper

[a] K_0 is the geometric mean of the first and second dissociation constants.[24]

acids, these are the only ones which have been obtained by modern conductimetric methods or by potentiometric methods employing cells without liquid–liquid junctions between H_2O and D_2O. We have pointed out the difficulty of interpreting the cell reactions and therefore the dissociation constant data obtained from cells with liquid junctions.

Summary

The cell Pt | QQH_2–QQD_2 HCl–DCl(H_2O–D_2O) | AgCl–Ag was reinvestigated at 25° and the measurements were extended to 5 and 45°. No minimum was found at 5% deuterium, the e. m. f. being an almost linear function of the deuterium content of the solvent. The temperature coefficient of the e. m. f. is the same in H_2O and in D_2O. The cell

$$\mathrm{Pt}\left|\ \mathrm{QQH_2\text{–}QQD_2}\ \begin{matrix}\text{Benzoic acid}\\ \text{Sodium benzoate } (\mathrm{H_2O\text{–}D_2O})\\ \text{Sodium chloride}\end{matrix}\ \right|\ \mathrm{AgCl\text{–}Ag}$$

was studied at 5, 25 and 45°. The heat of dissociation for benzoic acid d_1 is 175 calories greater than for protobenzoic acid at 25°. The difference in the entropies of dissociation is 1.7 calories per degree. The cell

$$\mathrm{Pt}\left|\ \mathrm{QQH_2\text{–}QQD_2}\ \begin{matrix}\mathrm{KH_2PO_4}\\ \mathrm{Na_2HPO_42H_2O}\ (\mathrm{H_2O\text{–}D_2O})\\ \mathrm{KCl}\end{matrix}\ \right|\ \mathrm{AgCl\text{–}Ag}$$

was studied at 25°.

The ratio of the dissociation constants for the deutero acid referred to, the proto acid for hydroquinone, $H_2PO_4^-$ and benzoic acid are compared with the ratios for acetic and chloroacetic acids as determined by other investigators using both thermodynamic and conductivity methods. The ratios decrease as the strength of the acid increases and may become unity for acids as strong as H_3O^+.

NEW YORK, N. Y. RECEIVED APRIL 25, 1938

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(24) Sheppard, *Trans. Am. Electrochem. Soc.*, **39**, 429 (1921).

[Contribution from the Laboratorium voor Physische Scheikunde der Universiteit te Leuven (Louvain)]

The Catalytic Interaction of Hydrogen and Deuterium with Ethylene and Deutero-ethylenes on Copper

By G. Joris,[1] H. S. Taylor[2] and J. C. Jungers[3]

Numerous efforts have been made to elucidate the detailed mechanism of the catalytic hydrogenation of ethylene by studies of the kinetics of interaction of ethylene with hydrogen and deuterium.[4] The possibility of a more penetrating analysis of the problem presented itself to us in the preparation of ethylene-d_4 and various deuterium-substituted ethylenes, permitting therefore catalytic studies in which the effect of the substitution of the unsaturated partner in the hydrogenation process could be tested independently with both hydrogen and deuterium as the addition agents.

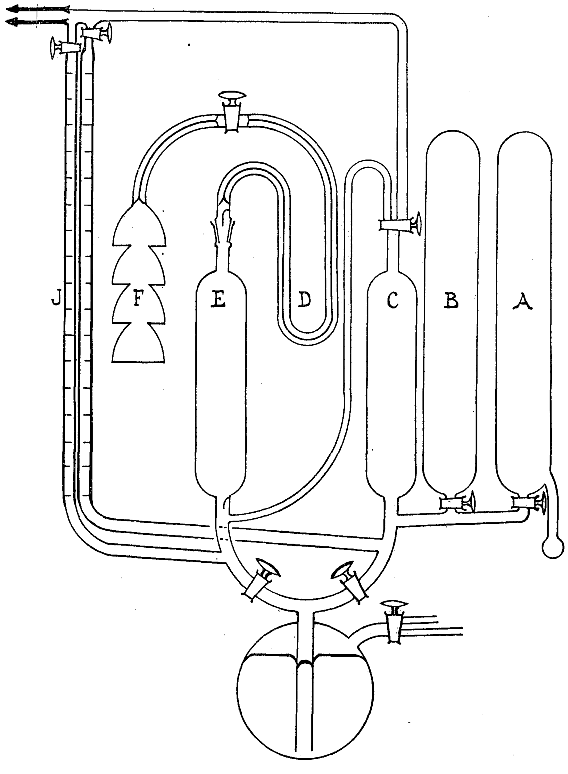

Fig. 1.

Experimental Details

Gases. Ethylene was obtained by the interaction of ethyl alcohol and sulfuric acid. The gas was freed from ether and acid fumes in the usual way and purified by liquefaction and fractionation. It was stored in a reservoir in the reaction system (Fig. 1) in which the process of condensation and removal of volatile impurities could be repeated at intervals if necessary.

Ethylene-d_4 was obtained by the action of zinc on ethylene dibromide-d_4 prepared by interaction of acetylene-d_2 and deuterium bromide. The acetylene-d_2 was prepared by interaction of 99.6% deuterium oxide with a high grade calcium carbide, freed from water by heating at 500° for several hours. The deuterium bromide was prepared by the hydrolysis of resublimed phosphorus pentabromide with 99.6% deuterium oxide. The ethylene-d_4 was purified by vacuum distillation and the middle fraction (6 liters) was admitted to a reaction reservoir, A, the walls of which had been covered with molten sodium to eliminate traces of bromine compounds which might have survived the purification process. Raman spectra observations of this product indicate that it is 90–95% C_2D_4 or better than 97.5% deuterium content of the hydrogen of the hydrocarbon.

Ethylene-d_2 was obtained by catalytic exchange between ethylene and deuterium oxide on an active nickel catalyst at 150° during several days. The central fraction of 6 liters from the purification process showed, by Raman spectra, that its D-content was slightly greater than 50%, and that it was composed predominantly of symmetrical *cis-* and *trans*-$C_2H_2D_2$, with much smaller amounts of the unsymmetrical $CH_2{=}CD_2$ and C_2H_3D and C_2HD_3.

The hydrogen and deuterium were obtained by electrolysis of appropriate solutions of NaOH and NaOD. The gases were purified over hot copper, dried over phosphorus pentoxide and liquid air and stored in receptacles of Type B. Some hydrogen used was further purified by adsorption on and desorption from charcoal.

Catalysts.—The copper catalyst employed was prepared by dehydration and reduction of a co-precipitated mixture of magnesium hydroxide–copper hydroxide in the molecular ratio 4:1 whose catalytic characteristics have been described already by Taylor and Joris.[5] In many of the experiments only 0.5 g. of catalyst, corresponding to 0.11 g. copper, was employed. In some of the last experiments 4 g. of the catalyst was used.

Apparatus.—The reaction vessel F (85-cc. volume) shown in Fig. 1 was of a shape which permitted the distribution of the catalyst on the horizontal areas of the several "stories," thus providing greater accessibility of catalyst to gas mixture. Gas mixtures were prepared in E, from the storage reservoirs, A and B, via the vessel C. The gases were introduced into the reaction vessel by raising the

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[1] Aspirant du Fonds National de Recherche Scientifique, Belgium.

[2] Francqui Professor, 1937, University of Louvain, Belgium.

[3] Docent, University of Louvain, Belgium.

[4] (a) Farkas, Farkas and Rideal, *Proc. Roy. Soc.* (London), **A146**, 630 (1934); (b) Klar, *Z. physik. Chem.*, **B27**, 317 (1934); *Z. Elektrochem.*, **43**, 379 (1937); (c) Pease and Wheeler, This Journal, **57**, 1149 (1935); (d) Farkas and Farkas, *Trans. Faraday Soc.*, **33**, 678, 827 (1937); This Journal, **60**, 22 (1938).

[5] Taylor and Joris, *Bull. soc. chim. Belg.*, **46**, 241 (1937).

mercury level in E, the gases passing through the trap D cooled in solid carbon dioxide–acetone mixtures to minimize access of mercury vapor to the catalyst system. During reaction, the mercury level was maintained at the glass point near the entrance to the capillary tubing, pressures, at constant volume, being read on the manometers J, through which, also, the apparatus could be evacuated. Between experiments, the catalyst was evacuated to a pressure of 10^{-4} mm. at the temperature of the succeeding experiment if above that of the preceding.

Procedure.—Experiments have been performed at −20, 0, 20 and 40°. The gas ratios studied were 1:1, 2:1 and 1:2, the unit pressure being 5 cm. for each component, 10 cm. for the constituent in excess in the non-stoichiometric mixtures.

Experimental Results

With the smaller amount of catalyst first used a small drift was noted in catalyst activity. The data have been presented graphically in Figs. 2–6, in small groups covering a particular variable to be investigated and in a sequence such that any variation due to the observed fatigue of the catalyst would be minimized in its effect on the conclusions to be drawn.

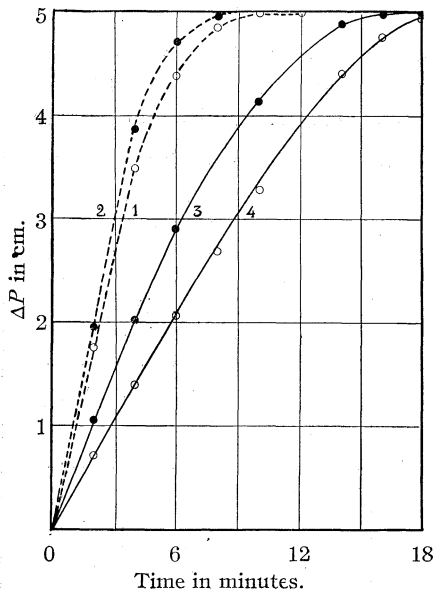

Fig. 2.—Experiments at 40° (5 cm., 5 cm.): 1, $C_2H_4 + H_2$ (40° 3); 2, $C_2D_4 + H_2$ (40° 2); 3, $C_2D_4 + D_2$ (40° 2); 4, $C_2H_4 + H_2$ (40° 3).

Note on Figs. 2–8.—Dotted lines indicate hydrogenation; full lines indicate deuterization. Circles indicate C_2H_4; dots indicate C_2D_4.

In Fig. 2 are presented the data on stoichiometric mixtures of the four gases taken in pairs in the order shown, reacting at 40°. These experiments show unquestionably (a) that ethylene-d_4 hydrogenates more rapidly than ethylene and (b) that the rate of reaction of both with deuterium is approximately one-half that with hydrogen. This latter result confirms that of Pease and Wheeler[4c] on a different but active copper catalyst.

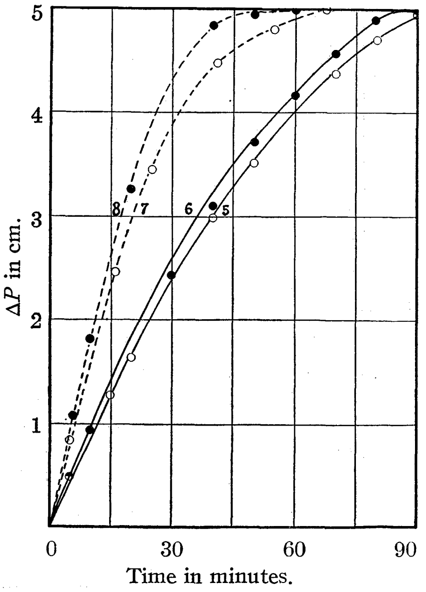

Fig. 3.—Experiments at 20°: 5, $C_2H_4 + D_2$; 6, $C_2D_4 + D_2$; 7, $C_2H_4 + H_2$; 8, $C_2D_4 + H_2$.

The data of Fig. 3 confirm both these conclusions for stoichiometric pairs of gases at 20°. The data with hydrogen are comparable with those at 40°. With deuterium the spread between the two ethylenes is less than at 40° but this is probably largely experimental error and, even in this case, ethylene-d_4 is still a faster reactant than ethylene.

Experiments 11–14 at 40° in Fig. 4 once more confirm these results and supply data on varying rate with varying concentration. The reaction is faster than that of the stoichiometric mixture in presence of excess deuterium and markedly slower with excess of the ethylenes. In the latter cases, also, the change in rate with time is much greater than with the stoichiometric mixtures. This is also shown by the data of Experiments 15–17 in Fig. 5, the rates of 16 and 17 again pointing to a reaction with deuterium somewhat less than half that with hydrogen.

The data of Experiments 20–23 at 40° presented in Fig. 6 show that the 50% D-substituted ethylene reacts at a rate intermediate to that of ethyl-

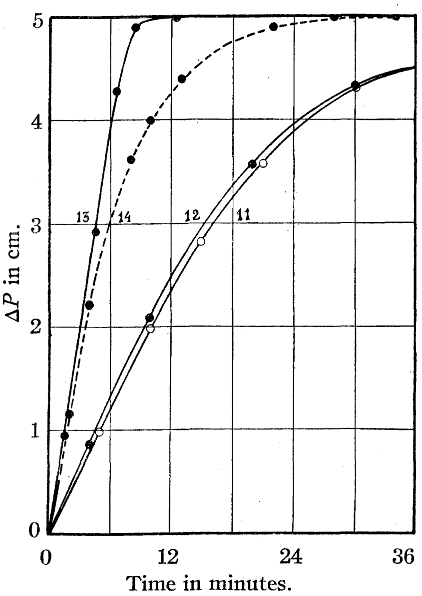

Fig. 4.—Experiments at 40°: 11, $2C_2H_4 + D_2$ (10 cm. C_2H_4 + 5 cm. D_2); 12, $2C_2D_4 + D_2$ (10 cm. C_2D_4 + 5 cm. D_2); 13, $C_2D_4 + 2D_2$ (5 cm. C_2D_4 + 10 cm. D_2); 14, $2C_2D_4 + H_2$ (10 cm. C_2D_4 + 5 cm. H_2).

ene and ethylene-d_4. A comparison of Experiments 20 and 23 gives an indication of the degree of reproducibility attainable in separated runs. At 0° the same influence of extent of deuterium substitution on the velocity is found.

To test the effect of catalyst deterioration on the results obtained, a new series of experiments was carried out with 4 g. of the copper oxide–magnesium oxide mixture as source of catalyst mass. In Fig. 7 are presented the data of the first experiments, Nos. 1, 2 and 3 on the new catalyst at 20° with stoichiometric mixtures of hydrogen and C_2H_4, $C_2(HD)_2$ and C_2D_4, respectively. It

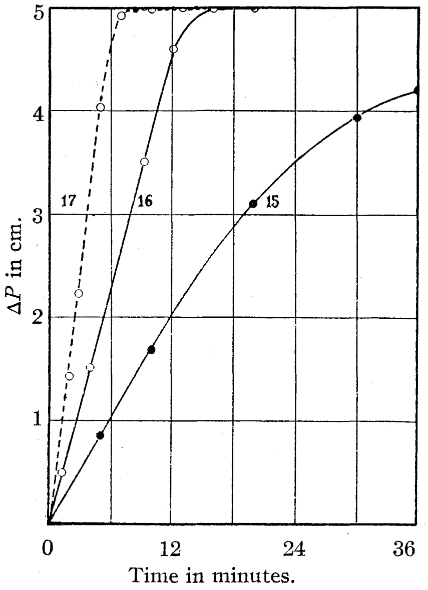

Fig. 5.—Experiments at 40°: 15, 10 cm. $C_2D_4 + D_2$; 16, 5 cm. $C_2H_4 + 2D_2$; 17, 5 cm. $C_2H_4 + 2H_2$.

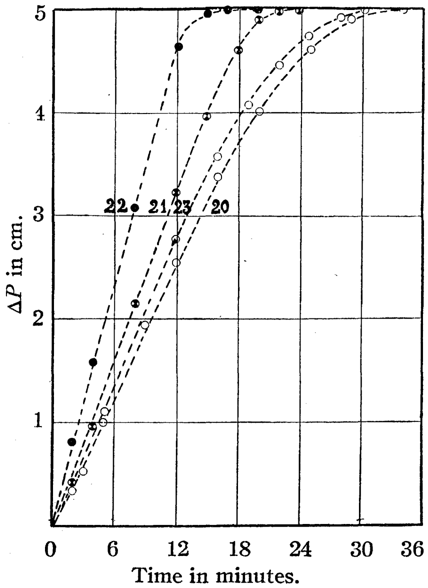

Fig. 6.—Experiments at 40°: 20, $C_2H_4 + H_2$; 21, $C_2(DH)_2 + H_2$; 22, $C_2D_4 + H_2$; 23, $C_2H_4 + H_2$.

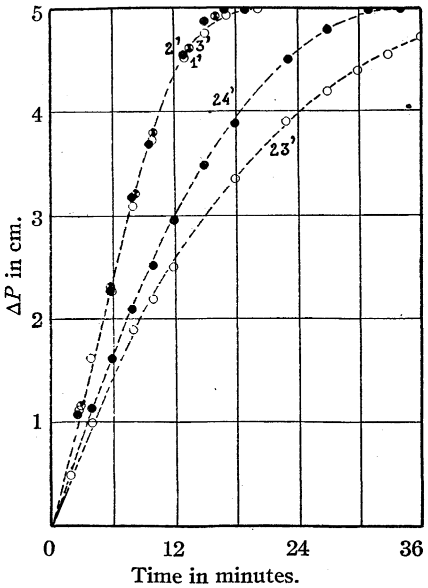

Fig. 7.—At 20°, influence of deterioration P, 5 cm.: 1′, $C_2H_4 + H_2$; 2′, $C_2(HD)_2 + H_2$; 3′, $C_2D_4 + H_2$; 23′, $C_2H_4 + H_2$; 24′, $C_2D_4 + H_2$.

will be noted that, initially, within the experimental error, all three ethylenes show the same rate of reaction. During the succeeding twenty experiments the activity of the catalyst showed a slow but progressive deterioration, which was accompanied by a progressive increase in the differences of hydrogenation rate between C_2H_4 and C_2D_4, as shown by Experiments 23 and 24 on the same diagram. With ethylene the half life has increased from six to twelve minutes, while that of ethylene-d_4 has changed from six to nine and one-half minutes. Since Experiment 24 with C_2D_4 succeeds Experiment 23 with C_2H_4 and still shows a faster reaction rate although catalyst activity is slowly decreasing, it is evident that the differences in rates observed with the deteriorating catalyst are a function of the two gases and not wholly to be ascribed to the deterioration process.

This is true also of the data presented in Fig. 8 for the effect of temperature in the range -20 to $+40°$ with the stoichiometric mixtures of C_2H_4 and C_2D_4 with hydrogen. The sequence of temperatures studied was -20, $+20$, 0 and 40°. In every case C_2D_4 was studied after C_2H_4 and except at $-20°$ is, in every case, the faster process. At 0, 20 and 40° the times for one-quarter reaction are, respectively, $T_{1/4}$ = 24, 20, 5.3, 4.6, 1.5 and 1.4 minutes. These data correspond to apparent activation energies of hydrogenation $E_{\text{obsd.}}(C_2H_4) = 11.8$ kcal. and $E_{\text{obsd.}}(C_2D_4) = 11.3$ kcal. In this temperature range, therefore, the differences between C_2H_4 and C_2D_4 decrease with increasing temperature. The differences are real but their trend with temperature may well be within the error of experiment. Since, in this temperature range, the influence of varying gas ratios (Fig. 4) points to a unimolecular reaction with respect to hydrogen, inhibited by ethylene, the observed activation energy $E_{\text{obsd.}}$ is related to the true activation energy E_t by the equations

$$E_{\text{obsd.}(C_2H_4)} = E_{t(C_2H_4)} - \lambda_{H_2} + \lambda_{C_2H_4}$$
$$E_{\text{obsd.}(C_2D_4)} = E_{t(C_2D_4)} - \lambda_{H_2} + \lambda_{C_2D_4}$$

where the λ's refer to the respective heats of adsorption. The small difference in observed activation energies (0.5 kcal.) is divided in some indeterminate manner between the true activation energies and the heats of adsorption of the two ethylenes. Since, in general, one would expect $\lambda_{C_2D_4}$ to be somewhat larger than $\lambda_{C_2H_4}$, it would follow that the true activation energy for the reaction between C_2H_4 and hydrogen would be somewhat more than 0.5 kcal. greater than the true activation energy in the hydrogenation of C_2D_4. As might be expected from this reasoning the rate of hydrogenation of C_2D_4 is actually greater than that of C_2H_4 and the intermediate case, $C_2H_2D_2$, is intermediate between these two extremes. Why the true activation energy should be greater for ethylene than for ethylene-d_4 is not apparent.

We can avoid these difficulties of detailed mechanism by stating the observed facts, quite generally, in terms of the concept of the activated complex. At a given ratio of hydrogen to any of the ethylenes, the rate indicates that the concentration of the activated complex $(C_2H_xD_{6-x})^*$ on the surface is greater, the greater the D-concentration of the complex.

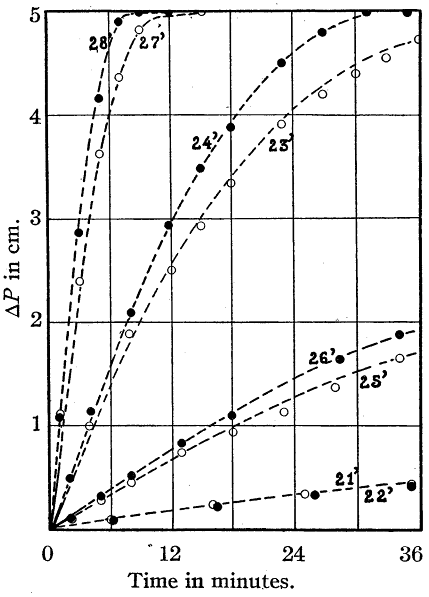

Fig. 8.—Influence of temperature on $H_2 + C_2H_4$ and C_2D_4 (5 cm.): 21' and 22' at $-20°$; 25' and 26' at 0°; 23' and 24' at 20°; 27' and 28' at 40°.

This same factor must also be operative in the reactions which involve the comparative rates of reaction between ethylene or ethylene-d_4 and hydrogen or deuterium. With either unsaturated hydrocarbon the velocity of reaction with deuterium is only one-half that with hydrogen. On surfaces largely covered with the unsaturated hydrocarbon, collision rates of hydrogen and deuterium with the free surface would introduce a factor of 1.4 in favor of the hydrogen reaction. What we have termed the concentration of activated complex would, as we have seen, favor more rapid reaction of deuterium by an amount of the order of 10%. It is therefore evident that a definite part of the difference in rates of reaction with hydrogen and with deuterium, approximately one-third of the total difference in rate, is to be ascribed to factors associated with zero-point energy differences of the hydrogen and deuterium, in their interactions with catalyst and substrate. In actual amount these are small, an energy difference of $\Delta E = 250$ cal. being sufficient, together with the collision factor and the concentration of complex, to account for the two-fold difference in velocity observed.

These considerations cannot be decisive in the experiments at −20° (Nos. 21 and 22) where the slow and approximately equal rates with C_2H_4 and C_2D_4 point to the availability of empty spaces for hydrogen adsorption as the rate-determining process.

Since the slow deterioration of the catalyst with time occurs progressively with any of the three ethylenes prepared by three different methods, we cannot ascribe it to impurities in the gases employed. Rather must it be ascribed to progressive irreversible reactions of the ethylenes themselves on the active catalysts which we have employed, leading to carbonaceous deposits on the most active centers, the deposits being retained during the evacuation procedures intervening between experiments. Such deterioration has been well established previously with nickel catalysts, but has not generally been noted hitherto with copper catalysts. The catalysts here used are, as we have already established,[5] very much superior in activity to copper catalysts hitherto studied. It is evident, from the data, that the rate-determining factors change with changes in the active centers studied, the differences between the rates of hydrogenation of C_2H_4, $C_2(HD)_2$ and C_2D_4 being negligible on the most active centers, and definite but relatively small on centers of lesser activity. This again illustrates the observation frequently made that the kinetics of a given heterogeneous surface reaction can vary widely with variation in the surface activity.[6]

Acknowledgment.—We wish to express our indebtedness to Professor Marc de Hemptinne who so kindly placed at our disposal the supplies that we have used of deuterium and of the various deutero-ethylenes.

Summary

1. The rates of addition of hydrogen and of deuterium to ethylene, ethylene-d_2 and ethylene-d_4 on active copper catalysts have been studied in the temperature range −20 to +40°.

2. The addition of deuterium occurs at a rate approximately one-half that of hydrogen on the several ethylenes.

3. Initially, on catalysts of high activity, no differences are observed in the rates of hydrogenation of the several ethylenes.

4. A slow deterioration of the catalyst, ascribed to irreversible reactions of ethylene leading probably to carbonaceous depositions, progressively occurs.

5. With decreasing activity due to this poisoning, small differences in the rates of hydrogenation of the ethylenes are observed, the more highly deuterized ethylenes reacting more rapidly.

6. Collision rates of hydrogen and deuterium with the surface are inadequate to account for the relative rates of addition observed. Zero-point energy differences are also involved.

7. The apparent activation energies of these reactions average 11.5 kcal. in the temperature range studied.

LOUVAIN, BELGIUM RECEIVED JUNE 6, 1938

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[6] See, especially, Pease, THIS JOURNAL, **45**, 1196 (1923), for varying kinetic behavior of the reaction $H_2 + C_2H_4$ on copper catalysts of varying activity.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE STATE COLLEGE OF WASHINGTON]

The System Ammonium Selenate–Magnesium Selenate–Water at 30°[1]

BY RALPH W. LAWRENCE AND G. BROOKS KING

Relatively few ternary systems of the type selenate–selenate–water have been investigated. Meyer and Aulich[2] studied the following systems at 25°: Na_2SeO_4–$MgSeO_4$–H_2O; K_2SeO_4–$MgSeO_4$–H_2O; K_2SeO_4–$CaSeO_4$–H_2O; Na_2SeO_4–$CaSeO_4$–H_2O; and K_2SeO_4–Na_2SeO_4–H_2O. It was of interest to study further salt pairs of this type and to compare these with the corresponding sulfate systems. The purpose of the present investigation was to study solubility relationships in the system $(NH_4)_2SeO_4$–$MgSeO_4$–H_2O. Although the double salt $(NH_4)_2SeO_4 \cdot MgSeO_4 \cdot 6H_2O$ has been reported, solubility data in this system appear to be entirely lacking.

Experimental

Materials and Apparatus.—The preparations of selenic acid and ammonium selenate have been described previously.[3] Magnesium selenate was prepared by dissolving magnesium carbonate in selenic acid and recrystallizing the salt.

An electrically controlled thermostat was employed, allowing the temperature to be maintained at 30 ± 0.05°.

Methods of Analyses.—The ammonium selenate was determined by distilling the ammonia from an alkaline solution into standard acid and the excess acid determined by titration with sodium hydroxide. The magnesium selenate was determined by precipitation of the magnesium as magnesium ammonium phosphate and subsequent ignition to the pyrophosphate. Both determinations were checked by using samples of known magnesium and ammonium content. Water was determined by difference. The results of duplicate determinations varied no more than three parts in one thousand.

Solubility Determinations.—Various mixtures of ammonium selenate, magnesium selenate hexahydrate, and water were weighed out approximately and placed in 6-inch (15 cm.) Pyrex test-tubes. Each of these tubes was closed by a cork through the center of which passed a glass stirrer, surmounted by a small air turbine. None of the samples were dissolved by heating because of the danger of hydrolysis of ammonium selenate.

The tube contents were stirred continuously for at least twelve hours before samples were taken for analysis. In order to ensure equilibrium, samples of the solutions were removed at intervals and analyzed. Analysis showed that in all cases equilibrium conditions were reached in less than twelve hours. Samples were removed from the solution by means of a small pipet equipped with a cotton filter, the pipet being pre-heated to slightly above the temperature of the thermostat. The solutions were weighed in glass-stoppered bottles. The tube and its content of wet residue was stoppered, the outside of the tube dried, and the tube and wet residue weighed. The residue was then transferred to a 100-ml. volumetric flask. Aliquot portions were taken for analysis.

The solubility of magnesium selenate was determined by removing samples at intervals of four hours until concordant results were obtained. A similar procedure was followed for ammonium selenate. Solubility determinations of samples of pure magnesium selenate made up at different times by different individuals gave concordant results. The same is true for ammonium selenate.

Results

The compositions of solutions and residues are given in Table I and are shown graphically in Fig. 1. Solid phases were determined by the method of Schreinemakers.[4]

TABLE I

THE SYSTEM $(NH_4)_2SeO_4$–$MgSeO_4$–H_2O AT 30°

Solution $(NH_4)_2SeO_4$ wt. %	Solution $MgSeO_4$ wt. %	Residue $(NH_4)_2SeO_4$ wt. %	Residue $MgSeO_4$ wt. %	Solid phase
	36.60			M[a]
1.25	36.66	0.43	54.40	M
2.24	36.74	8.45	49.79	M + D
2.29	36.76	12.61	40.00	M + D
2.25	36.78	5.16	48.05	M + D
Av. 2.26	36.76			M + D
2.53	36.08	17.52	36.35	D
5.03	27.60	28.33	34.00	D
9.73	17.48	27.92	29.23	D
16.60	8.95	33.37	29.90	D
20.24	5.63	33.28	27.03	D
26.20	3.24	35.63	28.05	D
33.60	1.55	37.57	27.46	D
36.40	1.17			D
40.50	0.70	39.60	26.90	D
52.26	.22	45.24	20.77	D
55.13	.18	82.31	3.53	D + A
55.17	.22	75.07	9.11	D + A
55.15	.22	70.30	7.34	D + A
Av. 55.15	.21			D + A
54.16				A

[a] M = $MgSeO_4 \cdot 6H_2O$. D = $(NH_4)_2SeO_4 \cdot MgSeO_4 \cdot 6H_2O$. A = $(NH_4)_2SeO_4$

At 30° three solid phases: $MgSeO_4 \cdot 6H_2O$, $MgSeO_4 \cdot (NH_4)_2SeO_4 \cdot 6H_2O$, and $(NH_4)_2SeO_4$ exist. The double salt exists over almost the entire range

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[1] Part of a thesis presented by R. W. Lawrence in partial fulfilment of the requirements for the degree of Master of Science at the State College of Washington.

[2] Meyer and Aulich, *Z. anorg. allgem. Chem.*, **172**, 321 (1928).

[3] Gilbertson and King, THIS JOURNAL, **58**, 180 (1936); King, *J. Phys. Chem.*, **41**, 797 (1937).

[4] Schreinemakers, *Z. physik. Chem.*, **11**, 75 (1893).

of concentrations. The solubility curve for $(NH_4)_2SeO_4$ was not experimentally realizable.

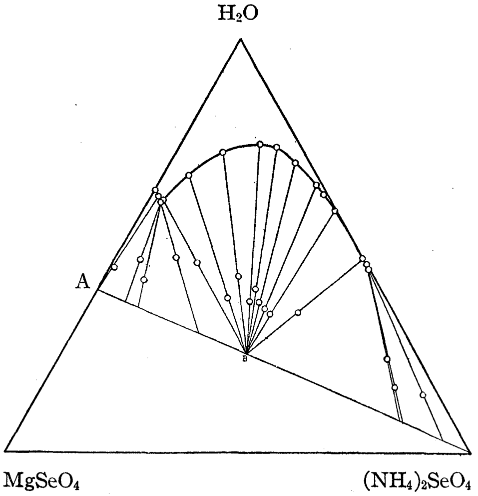

Fig. 1.—The isotherm at 30°: A represents $MgSeO_4 \cdot 6H_2O$; B represents $MgSeO_4 \cdot (NH_4)_2SeO_4 \cdot 6H_2O$.

Weston[5] investigated the corresponding sulfate system and found that the solubility curves of both $MgSO_4 \cdot 7H_2O$ and $(NH_4)_2SO_4$ could not be realized. The selenate and sulfate systems are analogous in nearly every respect.

It should be noted that the solubilities given here for both magnesium selenate and for ammonium selenate do not agree with previous determinations.[2,6] For the former, Meyer and Aulich give 31.2 wt. per cent. and for the latter, Tutton gives 57.9 wt. per cent. Tutton does not state his method for determining the solubility.

Approximate solubility determinations at 60° have been made. It was found that the same phases are present at that temperature as at 30°, the solubility of each phase increasing with increased temperature.

Acknowledgment.—Hydrogen peroxide used in the preparation of selenate salts was furnished by E. I. du Pont de Nemours and Company. This kindness is gratefully acknowledged.

Summary

1. The solubility relations in the system ammonium selenate–magnesium selenate–water have been determined at 30°.

2. The system is analogous to the corresponding sulfate system.

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[5] Weston, *J. Chem. Soc.*, **121**, 1223 (1922).

[6] A. E. H. Tutton, *ibid.*, **89**, 1071 (1906).

PULLMAN, WASHINGTON RECEIVED MARCH 21, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF KANSAS STATE COLLEGE, NO. 240]

Maleic Acid Production—Vapor Phase Oxidation of Five-Carbon Olefinic Acids[1]

BY W. L. FAITH AND M. F. YANTZI

It has been shown that maleic acid may be produced by the catalytic oxidation of crotonic acid, or the corresponding aldehyde.[2,3] The purpose of the present work was to study the catalytic vapor phase oxidation of several five-carbon olefinic acids under similar conditions. The major objective of the study was to determine whether the chief product of such oxidation would be maleic acid or a five-carbon unsaturated dicarboxylic acid.

Three acids were chosen for the work: 2-pentenoic acid, $CH_3CH_2CH{=}CHCOOH$; 3-pentenoic acid, $CH_3CH{=}CHCH_2COOH$; tiglic acid, $CH_3CH{=}C(CH_3)COOH$.

It was felt that the results of the study might aid research on the catalytic vapor phase oxidation of olefin hydrocarbons.

Preparation of the Acids.—The 2-pentenoic acid was prepared by the method of Boxer and Linstead.[4] The acid boiled at 103–111° under 19 mm. pressure.

The 3-pentenoic acid was prepared by the method of Linstead, Noble and Boorman.[5] This acid boiled at 90–92° under 10 mm. pressure.

Tiglic acid was prepared by the method of Michael and Ross.[6] The crystals melted at 64°.

Method and Apparatus.—The apparatus used for the oxidation of the 2- and 3-pentenoic acids was essentially the same as that previously described.[3] In the oxidation of the tiglic acid, a preheater for the primary air was added to prevent deposition of tiglic acid crystals in the tube leading from the vaporizer to the catalyst chamber.

The bath surrounding the vaporizer was maintained at

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[1] The experimental work reported here is a part of Project No. 137 of the Kansas State College Engineering Experiment Station.

[2] Otto Drossbach, U. S. Patent 1,880,991 (Oct. 4, 1932).

[3] W. L. Faith and A. M. Schaible, THIS JOURNAL, **60**, 52 (1938).

[4] S. E. Boxer and R. P. Linstead, *J. Chem. Soc.*, 740–751 (1931).

[5] R. P. Linstead, E. G. Noble and E. J. Boorman, *ibid.*, 557–561 (1933).

[6] A. Michael and J. Ross, THIS JOURNAL, **55**, 3684 (1933).

a constant temperature of 71.1° for the runs on the 2- and 3-pentenoic acids, and raised to 80.3° for those on tiglic acid. The catalyst, vanadium pentoxide deposited on a carrier of aluminum balls, also was prepared as before.

Analytical Methods

In most runs, 1 to 2 cc. of acid to be oxidized was introduced at a constant rate for a period of two hours.

Carbon dioxide was determined by passing a known portion of the exhaust gases through a gas-scrubbing bottle containing barium hydroxide solution for a period of twenty minutes during the run. The barium carbonate thus obtained was filtered, redissolved in hydrochloric acid and determined as barium sulfate in the usual manner.

The only acid product which formed in any quantity was maleic acid, and it was determined as the barium maleate monohydrate, using the same procedure as that described previously.[3] Check analyses on known mixtures of 2-pentenoic acid and maleic acid were accurate within 2%.

The purity of the barium maleate monohydrate was proved by the quantitative conversion to barium sulfate in the usual manner.

Anal. Calcd. for $C_4H_2O_4Ba \cdot H_2O$: Ba, 50.98. Found: Ba, 50.85, 50.86.

Further proof that the solid product was maleic acid (or anhydride) was shown by its conversion to fumaric acid under the influence of light in the presence of bromine.

In the case of known mixtures of 3-pentenoic acid and maleic acid, check analyses were accurate within 1.5%. Again the purity was proved by conversion to barium sulfate.

Anal. Calcd. for $C_4H_2O_4Ba \cdot H_2O$: Ba, 50.98. Found: Ba, 50.80, 50.81.

The acid was also converted to fumaric acid as above.

Check analyses on mixtures of maleic acid and tiglic acid were accurate within 2%, but since no maleic acid was found in the oxidation products of tiglic acid, a purity test was not made.

Aldehyde was determined by the neutral sodium sulfite method.[7] Maleic acid was found to offer no interference under the conditions of this test.

Discussion and Results.—Typical results obtained by oxidation of the three acids are shown in Table I. The 2- and 3-pentenoic acids showed little difference in their oxidation characteristics. Maximum maleic acid conversions were obtained at 450° with both acids. In all cases more carbon dioxide was produced than could be accounted for by the reaction

$$CH_3CH_2CH{=}CHCOOH + 3O_2 \longrightarrow HOOCCH{=}CHCOOH + CO_2 + 2H_2O$$

With both acids, maleic acid conversions increased with increasing molar air–acid ratios. No maleic acid was found in the products of tiglic acid oxidation.

A mixture of aldehydes was found in the products of all runs. No single aldehyde was identified. Tests for malonic, acetic, oxalic, glutaconic and citraconic acids were negative. It should be noted that conversions to carbon dioxide in excess of that accompanying maleic acid formation varied considerably. Apparently total oxidation increases with the age of the catalyst, although no difference could be detected in maleic acid conversions.

TABLE I

RESULTS OF OXIDATION OF FIVE-CARBON OLEFINIC ACIDS

Catalyst temp., °C.	Molar air–acid ratio	Conversion to maleic acid and CO_2, %	Complete conv. to CO_2, %	"Other acid"[a] conv., %	Aldehyde conv. mole, %
		A. 2-Pentenoic acid			
300	1580	26.3	8.4	24.8	
350	1580	35.6	13.5	5.7	
400	1580	38.8	18.3	3.8	
450	1580	33.8	17.2	1.9	
500	1580	29.6	15.0	1.9	
450	1180	27.9	34.1		
450	1580	32.8	26.0	5.1	
450	1940	34.1	26.0	1.5	
450	3040	34.8	28.6	1.5	
		B. 3-Pentenoic acid			
300	1060	25.4	6.7	12.0	18.8
350	1060	38.2	7.7	4.7	15.3
400	1060	42.5	11.8	2.1	12.9
450	1060	35.4	13.2	0.0	11.8
500	1060	30.9	17.0	0.0	11.2
		C. Tiglic acid			
270	840	0.0		85.6	1.0
350	840	.0	16.4	72.6	10.0
400	840	.0	28.6	58.6	25.0
450	840	.0	35.5	38.6	33.0

[a] Calculated in each case as the original acid.

Acknowledgment.—The authors wish to acknowledge the able assistance of H. F. Freeman who prepared the acids used in this investigation.

Summary

The catalytic vapor phase oxidation of 3 five-carbon olefinic acids was studied using a vanadium pentoxide catalyst.

2-Pentenoic acid was oxidized to maleic acid; a maximum conversion of 38.8% was obtained. 3-Pentenoic acid yielded maleic acid with a maximum conversion of 42.5%. Tiglic acid yielded only carbon dioxide and unidentified acids and aldehydes.

MANHATTAN, KANSAS RECEIVED APRIL 18, 1938

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(7) P. C. R. Kingscott and K. S. G. Knight, "Methods of Quantitative Organic Analysis," Longmans, Green and Co., New York, N. Y., 1914, p. 245.

[CONTRIBUTION FROM THE LABORATORY OF BIOLOGICAL CHEMISTRY, WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

The Two-Step Oxidation–Reduction of Lapachol, Lomatiol and Related Compounds

BY EDGAR S. HILL

A number of quinones, both naturally occurring and synthetic, have been found to oxidize and reduce in alkaline solution in two steps, with the formation of an intermediate compound, or semiquinone. Among these are the anthraquinonesulfonates,[1] β-naphthoquinone,[2] phenanthrenequinonesulfonate,[3] and phthiocol.[4] Phthiocol is a substituted hydroxynaphthoquinone and related to it by structure are a large number of hydroxynaphthoquinone derivatives, which, depending on the experimental conditions, form reversible oxidation–reduction systems. Some of these hydroxynaphthoquinones occur in a wide variety of plant materials, making their study of more than theoretical interest.

The author has been able to study successfully a number of these compounds by potentiometric methods and has found that their behavior in alkaline solution is similar to that of the quinones mentioned above. The compounds studied were lapachol, lomatiol, hydrolomatiol, hydroxyhydrolapachol, iso-β-lapachol, α-lapachone, β-lapachone, chlorohydrolapachol, bromo-β-lapachone, juglone and lawsone. The first five of these were found to be sufficiently stable in strongly alkaline solution to permit a thorough potentiometric study, and the remainder, although too unstable in alkaline solutions for similar study, were believed to oxidize and reduce in a similar way, on the strength of their structural relationship and on colorimetric experiments.

Fieser[5] has reported the normal potentials of lapachol, iso-β-lapachol, chlorohydrolapachol, hydroxyhydrolapachol, lomatiol, α-lapachone and β-lapachone, working only in 50% alcohol, 0.1 *N* in hydrochloric acid and 0.2 *N* in lithium chloride, using titanous chloride as reducing agent. No titrations were made in alkaline solution. Ball[6] has reported the normal potentials of several of these compounds for *p*H values ranging from 1.1 to 12.6, but obtained his values by the method of mixtures. Ball, working independently, recently has found[7] by titration methods that lapachol, in alkaline solutions, exhibits two-step oxidation and reduction, similar to phthiocol. The normal potentials of juglone have been reported by Conant and Fieser,[8] working again in alcoholic acid solution, and those of both juglone and lawsone by Friedheim,[9] working over a considerably wider *p*H range, who found that rapid decomposition in alkaline solution prevented the obtaining of titration curves reliable enough for analysis. Fieser and Fieser[10] were able to titrate lawsone (2-hydroxy-1,4-naphthoquinone) satisfactorily over the range *p*H 0.33–12.92.

Solutions of the quinones were titrated reductively over a *p*H range from 7.1 to 14.3. The technique of potentiometric titration was the usual one and the concentration of the oxidants used was 0.0005 *M* throughout. All potentials were measured at 30° and have been corrected to the hydrogen standard, and those values obtained in sodium hydroxide solutions have been corrected for liquid junction potentials. The buffers used are tabulated with the potential values.

The compounds successfully titrated were lomatiol, hydrolomatiol, lapachol, hydroxyhydrolapachol and iso-β-lapachol. Since there is little difference in the normal potentials of the various systems (the maximum difference between any two being only 4 to 6 mv.), only one compound, lomatiol, will be discussed in detail and the others but briefly.

Lomatiol is 2-(δ-hydroxy-β-isopentenyl)-3-hydroxy-1,4-naphthoquinone and occurs in the seeds of the Australian plants, *Lomatia ilicifolia* and *Lomatia longifolia*. The coloring matter is the same in both species and was first isolated by Rennie[11] and its constitution, synthesis, relation to and conversion into the other hydroxynaphthoquinone derivatives studied by Hooker.[12] Solutions of lomatiol were titrated reductively over a

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(1) E. S. Hill and P. A. Shaffer, *Proc. Am. Soc. Biol. Chem.*, **8**, li (1936); [*J. Biol. Chem.*, **114** (1936)].

(2) L. Michaelis, THIS JOURNAL, **58**, 873 (1936).

(3) L. Michaelis and M. P. Schubert, *J. Biol. Chem.*, **119**, 133 (1937).

(4) E. S. Hill, *Proc. Soc. Exptl. Biol. Med.*, **35**, 363 (1936).

(5) L. F. Fieser, THIS JOURNAL, **50**, 349 (1928).

(6) E. G. Ball, *J. Biol. Chem.*, **114**, 649 (1936).

(7) E. G. Ball, THIS JOURNAL, **59**, 2071 (1937).

(8) J. B. Conant and L. F. Fieser, *ibid.*, **46**, 1858 (1924).

(9) E. A. H. Friedheim, *Biochem. J.*, **28**, 180 (1934).

(10) L. F. Fieser and M. Fieser, THIS JOURNAL, **56**, 1565 (1934).

(11) E. H. Rennie, *J. Chem. Soc.*, **67**, 784 (1895).

(12) S. C. Hooker, THIS JOURNAL, **58**, 1181 (1936).

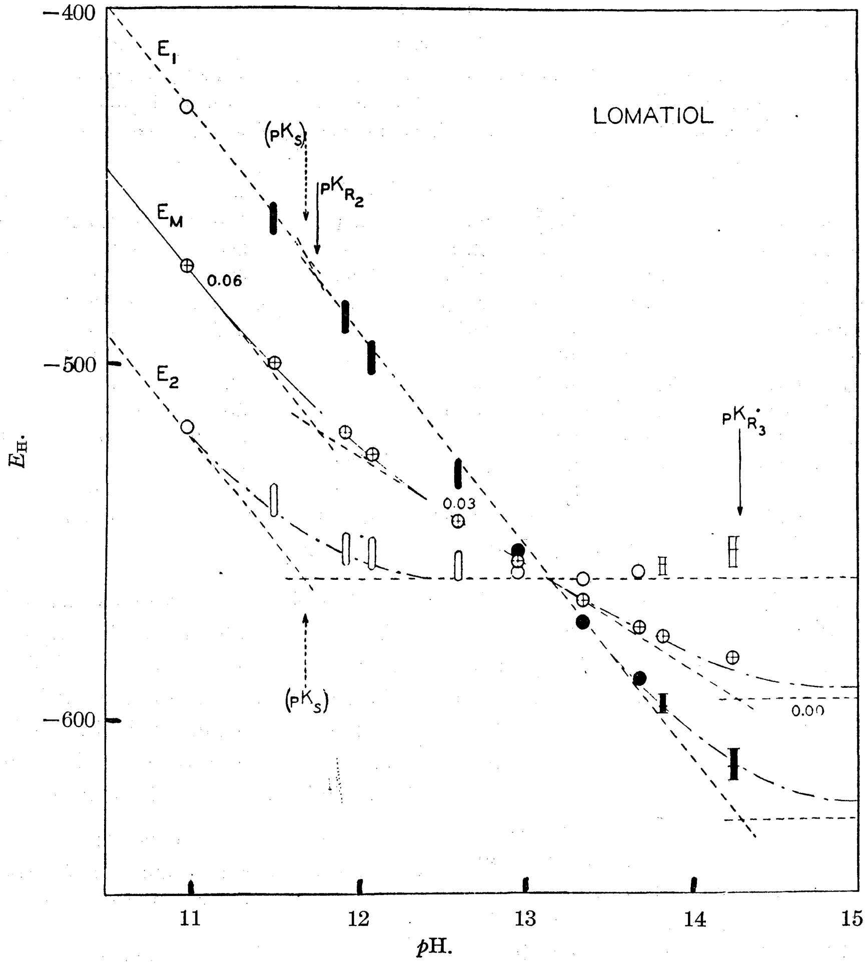

Fig. 1.—The three normal potentials, referred to the normal hydrogen electrode at 30°, of lomatiol, plotted against *p*H: E_m, normal potential of the system fully oxidized–fully reduced form; E_1, that of the system semiquinone form–fully reduced form; E_2, that of the system totally oxidized form–semiquinone form.

*p*H range from 7.1 to 14.3, and it was found from an analysis of the titration curves that the separation of the two steps begins a little above *p*H 9.0 and is more distinct in more alkaline regions.

A summation of the data for lomatiol is shown graphically in Fig. 1, giving the normal potentials plotted against *p*H. The separation never becomes so great as to produce a jump of the potential at 50% of the whole titration. The slopes of the titration curves varied all the way from 14.5 mv. at the lower limit to 36 mv. at about *p*H 14.24(3 *M* sodium hydroxide). Table I shows the variations in the slopes (E_i) and the attending variations in the formation constant, *K*, of the semiquinone and in the maximum ratio, *M*, of semiquinone to total material. The two steps always overlap so much that, at the most, about 61% of the total material in the form of the semiquinone is in equilibrium with the other forms. The curve (Fig. 1) shows a second dissociation constant of the reductant at about *p*H 11.74, which is in agreement with the findings of Ball,[6] and possibly a third in the neighborhood of *p*H 14.3, although titration data at this *p*H (3 *M* sodium hydroxide) are not too reliable on account of badly drifting potentials and the high liquid junction potentials involved. The separation of the two component systems is small and the precise location of the dissociation constant of the semiquinone is a bit uncertain. It is very close to the second dissociation constant of the reductant, possibly in the neighborhood of *p*H 11.68–11.7. The points on the E_1 and E_2 curves in this region are drawn elliptically to show possible variations; slight variations in the *S* value in this region will cause rather large varia-

TABLE I

LOMATIOL

Temperature: 30°. $E_m(E_0')$ represents the mean normal potential; E_1, E_2, normal potential of the lower and of the higher step; E_i, index potential; S, ½(100% axis − 0% axis) for a tangent drawn to all curves at 50% reduction, according to Elema[13]; K, semiquinone formation constant; M, maximum ratio of semiquinone to total material. Concentration of quinone: 0.0005 M.

*p*H	Buffer	$E_m(E_0')$, mv.	E_i, mv.	S	$E_2 - E_1$, mv.	E_1, mv.	E_2, mv.	K	M
7.1	Phosphate	−191.2	14.5	28	−104	−139.2	−243.2	0	0
9.87	Carbonate	−409	14.5	28.5	− 90	−364	−454	0.031	0.08
10.97	Phosphate	−473	14.5	28.5	− 90	−428	−518	.031	.08
11.49	Phosphate	−500.2	15.5	29.25	− 76	−462.2	−538.2	.055	.105
11.92	Phosphate	−520	16	29.75	− 66	−487	−553	.08	.124
12.08	Phosphate	−525.2	16.5	31	− 52	−499.2	−551.2	.17	.17
12.6	0.1 M NaOH	−545	18.5	35	− 20	−535	−555	.59	.277
12.96	0.2 M NaOH	−555.5	19.5	37.5	− 5	−553	−558	.83	.31
13.34	0.5 M NaOH	−566.9	22.5	42	+ 10	−571.9	−561.9	1.45	.39
13.68	1.0 M NaOH	−574	26.5	50	+ 32	−590	−558	3.4	.46
13.82	2.0 M NaOH	−577	32	55	+ 42	−598	−556	5.02	.54
14.24	3.0 M NaOH	−583	36	68.5	+62–66	−614–616	−552–550	10.0	.61

$K = (76.63S - 2)^2$, (13) $E_2 - E_1 = 0.06 \log K$, (14) $M = \sqrt{K}/(\sqrt{K} + 2)$. (3)

tions in the value of $E_2 - E_1$. The largest value for K was found to be 10. The fact that the titration curves were smooth, with no jump in the middle, is in keeping with the mathematical interpretations of Michaelis and Schubert,[3] which allow for no lateral points of inflection unless K is greater than 16.

The color changes are worthy of comment. In all lomatiol solutions above *p*H 8.0, the fully oxidized form is cherry-red. Between *p*H 10.0 and 12.6, the intermediate color is brownish-orange with a bluish tinge appearing as the *p*H increases. Above *p*H 13.0 the semiquinone color is brownish-violet and almost pure purple at *p*H 14.24. The completely reduced form is pale yellow below *p*H 13.0 and greenish-yellow above this point.

Parallel investigations on hydrolomatiol, lapachol, hydroxyhydrolapachol, and iso-β-lapachol resulted in potential values almost identical with those of lomatiol, and with only minor variations in the amount of semiquinone formation (Table II). All of these compounds have been described by Paternò, Hooker, Fieser, *et al.* Hydrolomatiol[12] is prepared by the hydrogenation of lomatiol. Lapachol[15–17] is 2-(γ,γ-dimethylallyl)-3-hydroxy-1,4-naphthoquinone and is found in the grain of a number of South American woods. Hydroxyhydrolapachol[15,16] can be prepared by the action of potassium hydroxide on β-lapachone. Iso-β-lapachol[18,5] is isomeric with lapachol, and differs only in color from the other compounds of this series. Solid iso-β-lapachol is brick-red, while the other compounds mentioned are yellow. In alkaline solution, it is intensely purple, the intermediate reduction stage is brownish-red and the completely reduced form is greenish-yellow.

TABLE II

COMPARISON OF THE VALUES OF K, THE SEMIQUINONE FORMATION CONSTANT

*p*H	Lomatiol	Hydrolomatiol	Lapachol	Hydroxyhydrolapachol	Iso-β-lapachol
7.1	0	..	..	..	..
9.87	0.08	..	..	..	..
10.2	..	..	0.034	..	..
10.4	..	..	..	..	0.11
10.97	.08	..	..	..	..
11.18	..	0.09	.05	0.05	.15
11.49	.10	..	..	..	..
11.75	..	..	.11	..	.19
11.92	.12	..	..	..	..
12.08	.17	.16	.14	.12	.25
12.6	.27	.24	.26	.21	.26
12.96	.31	.28	.29	.28	.29
13.34	.39	.38	.35	.34	.37
13.68	.46	.47	.46	.46	.46
13.82	.54	.55	.55	.55	.56
14.24	.61	.61	.61	.61	..

All of these compounds gave stable potentials during titration in all of the alkaline buffers except the strong sodium hydroxide solutions. Here, the quinones undergo decomposition and irreversible changes, causing drifting potentials. It is due to this instability that the values for E_2 in the range of *p*H 13.6–14.24 deviate from the

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(13) B. Elema, *Rec. trav. chim.*, **54**, 76 (1935).

(14) L. Michaelis, *J. Biol. Chem.*, **96**, 703 (1932).

(15) E. Paternò, *Gazz. chim. ital.*, **12**, 337 (1882).

(16) S. C. Hooker, *J. Chem. Soc.*, **61**, 611 (1892).

(17) L. F. Fieser, THIS JOURNAL, **49**, 857 (1927).

(18) S. C. Hooker, *J. Chem. Soc.*, **69**, 1355 (1896).

base line (Fig. 1). Table II shows a comparison of the maximum ratios of semiquinone to total material for all of the quinones. The E_1 and E_2 curves all intersect the E_0' curves in the neighborhood of pH 13.1–13.2. The values of pKr_2 agree closely with those of Ball,[6] and the values of E_0' vary but slightly. The E_0':pH curve for these compounds is about 10–12 mv. more positive than that of phthiocol. These quinones are extremely insoluble in acid solution, but titrations in alcoholic acid buffers failed to show any step formation in this region.

α-Lapachone, β-lapachone, chlorohydrolapachol and bromo-β-lapachone were not titratable in alkaline solution due to their rapid decomposition. α-Lapachone, first obtained by Games Paternò[15] by the action of nitric acid on lapachol, and later described by Hooker,[16] decomposes rapidly in alkali. The same is true of β-lapachone,[15,16] its ortho isomer. Both of these compounds are insoluble in alkalies in the cold, but are dissolved gradually by a boiling 1% solution of sodium hydroxide, and in so doing undergo change. Bromo-β-lapachone[15,16] can be obtained by treating lapachol with hydrogen bromide gas in chloroform solution, and is also extremely insoluble. The bromine of bromo-β-lapachone is easily displaced from the molecule by alkalies and the substance reverts to β-lapachone, making it useless for titration. Chlorohydrolapachol[16] is a product of the direct addition of hydrogen chloride to lapachol. In contact with dilute alkalies, chlorohydrolapachol is converted into a mixture of lapachol, hydroxyhydrolapachol, α-lapachone and β-lapachone, the latter two of which crystallize out, all of these complications making it impossible to study the compound potentiometrically. The similarity in structure of these compounds with the ones successfully titrated, coupled with the fact that slow reduction in test-tube experiments gives rise to similar intermediate color changes, seem to indicate that they too possess the ability to form semiquinones.

For the opportunity to study potentiometrically these compounds of the lapachol group, the author is greatly indebted to Dr. Louis F. Fieser, who kindly placed at his disposal pure samples of these materials left by the late Dr. Samuel C. Hooker, whose exhaustive study of hydroxynaphthoquinone chemistry is unique in the literature of organic chemical research.

The potentials of the naturally occurring hydroxynaphthoquinones, juglone and lawsone, were reinvestigated. Lawsone is 2-hydroxy-1,4-naphthoquinone and occurs in the leaves of the henna plant (*Lawsonia inermis*) and juglone, the coloring matter contained in the husks of walnuts, is 5-hydroxy-1,4-naphthoquinone. Friedheim[9] reported an irregularity in the slopes of titration curves obtained with these substances at pH 7 and above, and suggested that this irregularity pointed toward semiquinone formation. This possibility was not pursued, due to the instability of the pigments in alkaline media. On reinvestigating these compounds, the author also found it impossible to obtain reliable titration curves with juglone and lawsone at pH greater than 7.0 due apparently to the decomposition of these compounds in alkaline buffers. In the case of lawsone, which was extracted from henna leaves by the method of Tommasi,[19] the fault probably lay in the purity of the material used, since Fieser and Fieser,[10] working with a completely pure substance, were able to titrate this compound successfully in buffers as alkaline as pH 12.92. It is the intention of the author to reinvestigate the potentials of lawsone, using a thoroughly pure synthetic sample. The juglone used was prepared synthetically by oxidation of 1,5-dihydroxynaphthalene with chromic–sulfuric acid mixture, according to Bernthsen and Semper.[20] Test-tube experiments seemed to show intermediate colors when these quinones were oxidized and reduced, and, since they are so similar in structure to phthiocol, lomatiol, *et al.*, it might be suggested, pending further work, that these pigments be included among anionic semiquinone formers. On comparing juglone with lawsone and the aforementioned hydroxynaphthoquinones, one might draw the conclusion that substitution of the benzene ring containing the quinone oxygens has considerable to do with potentiometric stability.

Conclusion

Semiquinone formation by lomatiol, lapachol, and other hydroxynaphthoquinones has been investigated. The two-step character of the oxidation–reduction becomes evident at about pH 9.5 and becomes more distinct as the solution becomes more alkaline. The ratio of semiquinone to total material reaches a maximum of 0.61 at pH 14.24. It corresponds to an index potential of 36 mv. and a formation constant of 10. The

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(19) G. Tommasi, *Gazz. chim. ital.*, **50**, 263 (1920).

(20) A. Bernthsen and A. Semper, *Ber.*, **20**, 938 (1887).

data presented add both to the knowledge of naturally occurring pigments, and of substances with a quinoid structure as a group.

ST. LOUIS, MISSOURI RECEIVED JUNE 9, 1938

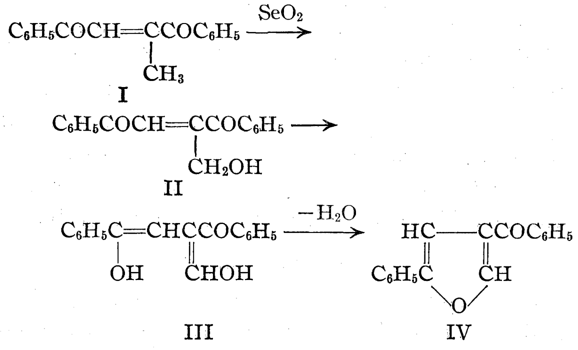
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

2-Phenyl-4-benzoylfuran

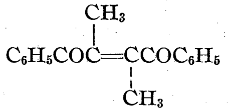
BY REYNOLD C. FUSON, C. L. FLEMING AND ROBERT JOHNSON

Very few β-keto furans are known and of these none has an unsubstituted α-position. 2-Phenyl-4-benzoylfuran (IV) is, therefore, unique. In the study of the application of the principle of vinylogy to ketones we chanced to prepare this furan and noted that its properties reflected its unusual structure. This observation led us to examine these properties in some detail.

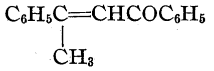
The furan was made by treating 1,2-dibenzoyl-1-propene (I) with selenium dioxide. Since the diketone is a vinylog of acetophenone it was expected that the methyl group would be attacked. Evidently this group is oxidized and the furan is formed by rearrangement and subsequent loss of water. Of especial interest in this connection is the observation that only one-half mole of selenium dioxide is required to convert one mole of the diketone (I) to the furan (IV). This corresponds to the amount of oxidation necessary to form the hydroxy compound (II). The latter could rearrange to the dienol (III) by a 1,5- or a double 1,3-shift. The dienol would be expected to lose water to form the furan.



This mechanism suggests that the method might be general for ketones of the type $RCOC{=}C{-}CH_3$. To test this idea we subjected 2,3-dibenzoyl-2-butene (V), dypnone (VI) and crotonophenone (VII) to a similar treatment. Only dypnone yielded a furan; the other two ketones were recovered unchanged even after long treatment with the oxidizing agent. This indicates that this method of preparing furans is highly specific. It should be mentioned that 2,4-diphenylfuran (VIII), the product obtained from dypnone, had been prepared in low yields by the oxidation of dypnone with nitrobenzene.[1]


$C_6H_5COC(CH_3){=}C(CH_3)COC_6H_5$

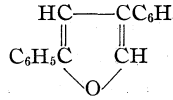
V


$C_6H_5C(CH_3){=}CHCOC_6H_5$

VI

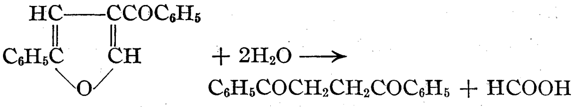
$C_6H_5COCH{=}CHCH_3$

VII

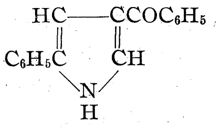


VIII

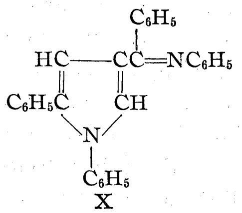
The most striking property of 2-phenyl-4-benzoylfuran is the ease with which it reacts with alkalies, ammonia or aniline. This appears less extraordinary if we consider that the compound is vinylogous with benzoic esters and might, therefore, be expected to be sensitive to hydrolytic and ammonolytic agents. Aqueous alkalies hydrolyze it rapidly to 1,2-dibenzoylethane and formic acid



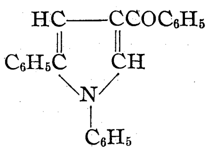
Ammonia and aniline convert the furan, respectively, into the pyrrole (IX) and the anil (X) of the expected phenylpyrrole.



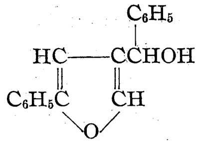
IX



X



XI



XII

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[1] Engler and Dengler, *Ber.*, **26**, 1446 (1893); *cf.* Delacre, *Bull. soc. roy. Belg.*, [3] **26**, 534 (1893).

Hydrolysis transforms the latter into the N-phenylpyrrole (XI) and aniline. It is of interest to note that the benzoylpyrrole (IX) does not show the sensitiveness to alkalies that characterizes the benzoylfuran (IV).

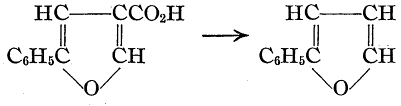
The furan was remarkably stable to acids. Long treatment with hot alcoholic hydrochloric acid partially transformed it into a high-melting derivative which appeared to be trimolecular. Its structure was not investigated further.

The behavior of the benzoylfuran under alkaline and acidic conditions is in distinct contrast with the usual reactions of the furan nucleus. In general this nucleus is characterized by stability to alkalies and extreme sensitiveness to acids, whereas the converse is true of the present furan. However, this is in harmony with the view already mentioned that β-keto furans are vinylogs of esters.

A number of reactions were carried out which affected only the carbonyl group. Oximes were prepared of the benzoylfuran (IV), the pyrrole (IX) and the N-phenylpyrrole (XI). Reduction of the furan gave a carbinol (XII) which was characterized by the formation of a benzoate and a *p*-nitrobenzoate. Attempts to effect differential oxidation were unavailing. Sodium chlorate in the presence of vanadium pentoxide gave only benzoic acid. Ozonolysis led to a similar result.

Confirmation of the structure of the benzoylfuran (IV) was obtained by degrading it to 2-phenylfuran (XIV). The furan formed an oxime which underwent the Beckmann rearrangement to give the corresponding anilide. The latter was hydrolyzed to 2-phenyl-4-furoic acid (XIII) which in turn was converted to 2-phenylfuran (XIV) by heating.

IV ⟶ oxime ⟶ anilide ⟶



XIII XIV

In contrast to the benzoylfuran (IV) the furoic acid (XIII) was very resistant to the attack of reagents. The ring was not attacked by alkalies or ammonia and decarboxylation could be effected only with difficulty.

Experimental

1,2-Dibenzoyl-1-propene (I).—This compound was prepared from mesaconyl chloride and benzene by a modification of the method described by Lutz and Taylor.[2] The following is a typical procedure. Twenty-five grams of mesaconyl chloride, prepared by the method of Meyer,[3] was added, with stirring, to an ice-cold suspension of 45 g. of aluminum chloride in 150 cc. of benzene. Fifteen minutes was required for the addition of the acid chloride. Stirring was continued for fifteen minutes after completion of the addition; the mixture was cooled in an ice-bath during the entire reaction period.

The reaction mixture was then hydrolyzed and worked up in the usual way. The solution was concentrated and cooled; a yellow solid separated and was collected on a filter. Two crystallizations from alcohol gave 32.0 g. of 1,2-dibenzoyl-1-propene; m. p. 52.0–52.5°. The yield was 85% of the theoretical amount. It was found necessary to work up the reaction mixture as rapidly as possible after hydrolysis. If this was not done the product was contaminated with a green oil which greatly retarded the separation of a crystalline product.

2-Phenyl-4-benzoylfuran (IV).—The oxidation was carried out in the usual way, using 60 cc. of dioxane, 2 cc. of water, 5.6 g. (0.05 mole) of selenium dioxide and 25.0 g. (0.10 mole) of the diketone. After eight hours the selenium was collected on a filter and washed with hot dioxane. The filtrate was poured into water; the brown solid which separated was collected on a filter and air dried. After crystallization from ether there was obtained 15.5 g. of 2-phenyl-4-benzoylfuran; the yield was 63% of the theoretical amount.

Anal. Calcd. for $C_{17}H_{12}O_2$: C, 82.24; H, 4.87; mol. wt., 248. Found: C, 82.69, 82.31; H, 4.96, 5.15; mol. wt., 249, 254.

The furan is sparingly soluble in ether, from which it separates as colorless needles which melt at 113.7–114.0°. It is moderately soluble in alcohol and glacial acetic acid. It reduces a potassium permanganate solution readily and decolorizes a carbon tetrachloride solution of bromine with the evolution of hydrogen bromide.

Dypnone.—This ketone was made by the method of Calloway and Green.[4] The oxidation of 22.3 g. (0.10 mole) of dypnone with 5.6 g. (0.05 mole) of selenium dioxide was carried out in the usual way. No crystalline material could be isolated from the tarry product and so it was distilled *in vacuo*. The 2,4-diphenylfuran (VIII) distilled at about 200° under 3 mm. pressure and solidified in the side-arm. After two crystallizations from alcohol there was obtained 2.3 g. of colorless plates; m. p. 110.7–111.0°. A solution of the pyran in concentrated sulfuric acid exhibited an intense violet fluorescence; this was reported also by Engler and Dengler.[1] The furan changed on standing, in the solid state or in solution, to an insoluble colorless powder which did not melt below 250°; this change was also noted by Delacre.[1]

Crotonophenone and 2,3-Dibenzoyl-2-butene.—Each of these compounds was recovered unchanged after long treatment with selenium dioxide.

Reactions of 2-Phenyl-4-benzoylfuran

Cleavage with Alkali.—A solution of 2.5 g. of the furan, 75 cc. of alcohol and 30 cc. of a 10% sodium hydroxide solution was heated under reflux for forty-five minutes. The resulting mixture was steam distilled; no product

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(2) Lutz and Taylor, THIS JOURNAL, **55**, 1177 (1933).

(3) Meyer, *Monatsh.*, **22**, 423 (1901).

(4) Calloway and Green, THIS JOURNAL, **59**, 810 (1937).

other than alcohol was found in the distillate. The residue was acidified with phosphoric acid and again steam-distilled; the clear distillate was acidic.

This distillate was neutralized with sodium hydroxide and evaporated to dryness. An aqueous solution of this salt reduced a solution of potassium permanganate immediately. A portion of the dry salt was heated with *p*-bromoaniline; after crystallization from dilute alcohol the product melted at 115.8–116.8°. A mixture of the product with an authentic specimen of *p*-bromoformanilide also melted at 115.8–116.8°.

The solid residue which remained in the flask after the steam distillation was collected on a filter and recrystallized from alcohol. There was thus obtained 0.7 g. of colorless needles; m. p. 145.2–146.2°. A mixture of this product with an authentic specimen of 1,2-dibenzoylethane also melted at 145.2–146.2°.

The same products were formed when the furan was treated with potassium carbonate under similar conditions.

Reaction with Hydrochloric Acid.—A solution of 1.0 g. of the furan, 20 cc. of concentrated hydrochloric acid and 50 cc. of alcohol was heated under reflux for eighty hours. The solution was diluted with water and cooled; a solid product separated. This material was collected on a filter and purified by recrystallization from alcohol. A portion of the product was insoluble in boiling alcohol and was removed. The solid which separated when the filtrate was cooled was isolated by filtration; there was obtained in this way 0.5 g. of unchanged starting material.

The insoluble product separated above was purified by several recrystallizations from aqueous acetone; it becomes brown at 211.5° and melts with decomposition at 214.8–215.8°.

Anal. Calcd. for $C_{51}H_{34}O_5$: C, 84.28; H, 4.72; mol. wt., 727. Found: C, 84.24, 84.10; H, 4.73, 4.65; mol. wt. (Rast), 686.

The compound separates from dilute acetone as colorless fluffy needles. It is insoluble in dilute acids and bases and forms a green solution in concentrated sulfuric acid. It does not contain chlorine.

The same product was formed by treating the furan with a methyl alcoholic solution of dry hydrogen chloride.

Reaction with Ammonium Hydroxide.—A mixture of 1.0 g. of the furan, 5 cc. of concentrated ammonium hydroxide and 10 cc. of alcohol was heated at 130–140° for eighteen hours. The reaction was carried out in a stainless steel bomb. A solid product was isolated from the reaction mixture by filtration and washed with water. This material was then extracted several times with boiling alcohol; the extract was discarded. After two crystallizations of the residue from dilute acetone there was obtained 0.5 g. of 2-phenyl-4-benzoylpyrrole (IX) in fine yellow needles which melted at 213.7–215.5°.

Anal. Calcd. for $C_{17}H_{13}ON$: C, 82.57; H, 5.30; N, 5.66; mol. wt., 247. Found: C, 82.73; H, 5.51; N, 5.42, 5.59; mol. wt. (Rast), 256.

The pyrrole is sparingly soluble in alcohol and readily soluble in ether and benzene. It is insoluble in dilute acids and bases; it forms an orange solution in concentrated sulfuric acid. It reduces a potassium permanganate solution readily and decolorizes a bromine solution with the evolution of hydrogen bromide. It was recovered unchanged after treatment with sodium hydroxide under conditions similar to those used in the cleavage of the parent furan. It forms an **oxime** which separates from dilute alcohol as fine, faintly pink needles which soften at 171° and melt with decomposition at 188.5–191.5°.

Anal. Calcd. for $C_{17}H_{14}ON_2$: N, 10.68. Found: N, 10.89.

Reaction with Aniline.—A solution of 5.0 g. of the furan in 50 cc. of dry aniline was heated under reflux for seventy-two hours. The solution was then cooled and concentrated under a pressure of 3 mm.; absolute alcohol was added to the residue. The solid product which separated was collected on a filter, washed with absolute alcohol and recrystallized from a mixture of dry benzene and petroleum ether (b. p. 60–90°). There was thus obtained 2.3 g. of a solid in the form of clumps of colorless needles. After further crystallization the anil (X) melted at 230.5–231.0°.

Anal. Calcd. for $C_{29}H_{22}N_2$: C, 87.40; H, 5.57; N, 7.03. Found: C, 87.59; H, 5.61; N, 7.08.

The anil is readily soluble in benzene and moderately so in absolute alcohol. In contact with concentrated sulfuric acid it turns yellow but does not dissolve.

The hydrolysis of the anil was carried out by adding 20 cc. of dilute hydrochloric acid to a suspension of 1.5 g. of the anil in 75 cc. of alcohol. A yellow color appeared instantly and the mixture became slightly warm. The reaction mixture was allowed to stand at room temperature for forty-eight hours and then was diluted with water. The solid product was isolated by filtration, dried and recrystallized from ethyl acetate. There was obtained in this way 0.8 g. of 1,2-diphenyl-4-benzoylpyrrole (XI) which melted at 240.0–241.0°. Further crystallization did not alter the melting point.

Anal. Calcd. for $C_{23}H_{17}ON$: C, 85.42; H, 5.30; N, 4.33. Found: C, 85.68, 85.87; H, 5.58, 5.37; N, 4.53.

The pyrrole (XI) separates from ethyl acetate or from a benzene–petroleum ether (b. p. 60–90°) mixture as colorless silky needles. It is practically insoluble in alcohol, sparingly soluble in acetone, ether or ethyl acetate and moderately soluble in benzene. It forms a straw-yellow solution in concentrated sulfuric acid. The **oxime** of the pyrrole was prepared in the usual way; it separates from dilute alcohol as colorless needles which melt at 215.5–218.5°.

Anal. Calcd. for $C_{23}H_{18}ON_2$: N, 8.28. Found: N, 8.13.

Reduction to the Carbinol.—A solution of the furan in ethyl acetate was treated with hydrogen in the presence of a nickel catalyst.[5] The solid residue obtained by evaporating the solution to dryness was crystallized from alcohol. The **carbinol** was thus obtained as colorless needles which melted at 128.1–129.1°.

Anal. Calcd. for $C_{17}H_{14}O_2$: C, 81.57; H, 5.64. Found: C, 81.82; H, 5.62.

The carbinol is readily soluble in ethyl acetate and in ether. It forms a wine-colored solution in concentrated sulfuric acid.

The benzoate, prepared in pyridine solution, separates from alcohol as colorless needles which melt at 123.1–124.1°.

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(5) Covert and Adkins, THIS JOURNAL, **54**, 4116 (1932).

Anal. Calcd. for $C_{24}H_{18}O_3$: C, 81.32; H, 5.12. Found: C, 81.11; H, 5.15.

The **p-nitrobenzoate** separates from alcohol as rosets of colorless needles which melt at 109.5–109.8°.

Anal. Calcd. for $C_{24}H_{17}O_5N$: N, 3.51. Found: N, 3.49.

Conversion to 2-Phenylfuran.—The oxime of 2-phenyl-4-benzoylfuran was prepared in absolute alcohol solution in the presence of pyridine. It is readily soluble in the common organic solvents and separates from dilute alcohol as colorless needles which melt at 149.0–149.4°.

Anal. Calcd. for $C_{17}H_{13}O_2N$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.70; H, 5.13; N, 5.46, 5.40.

The Beckmann rearrangement was carried out by adding phosphorus pentachloride to a solution of the oxime in absolute ether. After crystallization from alcohol with the aid of Norite the **anilide** of 2-phenyl-4-furoic acid was obtained as colorless plates which melted at 192.0–193.0°.

Anal. Calcd. for $C_{17}H_{13}O_2N$: N, 5.32. Found: N, 5.44.

The anilide was hydrolyzed with alcoholic potassium hydroxide; it was necessary to heat the solution under reflux for twenty-four hours to cause complete reaction. The aniline was separated by steam distillation and identified as 1-phenylazo-2-naphthol, m. p. 128–129°. The residue was treated with Norite and acidified. Crystallization from alcohol produced colorless needles of **2-phenyl-4-furoic acid** which melted at 208.0–209.0°.

Anal. Calcd. for $C_{11}H_8O_3$: C, 70.25; H, 4.25; neut. equiv., 188. Found: C, 70.20; H, 4.49; neut. equiv., 191, 190.

The acid is readily soluble in acetone, moderately soluble in alcohol, sparingly soluble in benzene, xylene, ether and chloroform. It forms a yellow solution in concentrated sulfuric acid.

The acid was not converted to the corresponding pyrrole when treated with ammonium hydroxide in a bomb at 180°. Decarboxylation did not occur when it was subjected to the following treatments:

1. A mixture of the acid and copper bronze was heated to 250°.
2. A mixture of the acid and copper bronze in quinoline was heated at 225° in a stream of nitrogen.
3. A mixture of the acid and copper bronze in benzylmethylaniline was heated at 280° for one hour.
4. A mixture of the sodium salt of the acid and soda-lime was heated for two hours at 375° under a pressure of 10 mm.

The reaction was finally carried out by heating the acid overnight at 275° in a high-pressure bomb. The **2-phenylfuran** obtained in this way had the following properties: b. p. 107–108° (18 mm.); $n^{20}{}_D$ 1.5968; $d^{20}{}_4$ 1.083. These data are in agreement with those found for a sample prepared by the method described by Kondo and Suzuki.[6]

Summary

1,2-Dibenzoyl-1-propene is transformed into 2-phenyl-4-benzoylfuran by treatment with selenium dioxide. The furan is readily hydrolyzed by aqueous alkalies to give 1,2-dibenzoylethane and formic acid. Ammonia and aniline react to give the corresponding pyrroles. By a series of reactions the benzoylfuran was degraded to the known 2-phenylfuran.

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[6] Kondo and Suzuki, *J. Pharm. Soc. Japan*, No. **544**, 501 (1927): *C. A.*, **21**, 3362 (1927).

URBANA, ILLINOIS RECEIVED MAY 31, 1938

NOTES

The Structure of Cholesteryl Chloride

BY ERNST BERGMANN

In work with cholesteryl chloride, as carried out in various laboratories and also in this Institute, certain conflicting evidence has accumulated with regard to its usual formula (I). The main point is the following one: while the two epimeric cholestyl chlorides react with sodium acetate under Walden inversion,[1] cholesteryl chloride has been found in our laboratory to give the same cholesteryl acetate which is obtained by direct acetylation of cholesterol.[2] Recently, Marker and co-workers[3] have reported that 7-oxocholesteryl chloride, the constitution of which follows from the characteristic absorption band at 270 mμ of α,β-unsaturated ketones[4] behaves "normally" toward sodium acetate, giving an acetate under configurational inversion. Besides that, Marker and his co-workers have pointed out that cholesteryl chloride reacts under much less drastic conditions than the other chlorides mentioned.[5]

Reactions of halogenides with acetate ions are

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[1] Marker and co-workers, THIS JOURNAL, **57**, 1755, 2358 (1935).

[2] That cholesterol and cholesteryl chloride have identical configuration, has been discussed in *Helv. Chim. Acta*, **20**, 590 (1937).

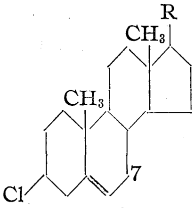
[3] Marker and co-workers, THIS JOURNAL, **59**, 619 (1937).

[4] Unpublished results from our laboratory (Miss F. Goldschmidt); compare for 7-oxocholesteryl acetate, Eckhardt, *Ber.*, **71**, 461 (1938).

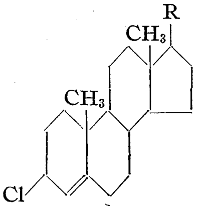
[5] Compare Mauthner, *Chem. Central.*, **80**, II, 1537 (1909).

now generally accepted to occur with Walden inversion,[2,6] with one exception, if the halogenide belongs to the allyl derivatives. In this case the possibility of allylic rearrangement prevents any prediction of the steric course taken by a substitution reaction. Therefore, the above difficulty would be overcome if cholesteryl chloride were able to react in the form (II),[7] deriving from *allo*-cholesterol.[8] The reaction of form (II) with sodium acetate would be accompanied by a shift of the double bond.[9] In the case of 7-oxocholesteryl chloride the conjugation with the carbonyl group would stabilize the C=C— double bond in the "classical" 5,6-position.

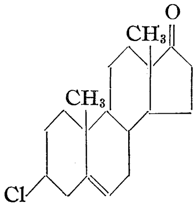
It is interesting to note that similar conditions have been observed by Linstead and Rydon[10] in the case of buten-(1)-ol-(4), which is converted by a mixture of sulfuric and hydrobromic acids partly into 4-bromobutene-(1), and partly into 4-bromobutene-(2). On the basis of Juvala's[11] results, the high substitution velocity, too, of cholesteryl chloride would be understood more easily.



I



II



III

Analogous considerations apply to the case of chloroandrostenone (III), which in contrast with the corresponding saturated chloroandrosterone is able to react with sodium benzoate without configurational inversion. This behavior may again be due to the possibility of III reacting in an allylic form.

Finally, it may be mentioned that this possibility is not necessarily limited to (I) and (III), but may apply to corresponding derivatives of other strong acids as, *e. g.*, toluenesulfonic acid.[12]

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[6] *Cf.* also Cowdrey, Hughes, Ingold, Masterman and Scott, *J. Chem. Soc.*, 1252 (1937). Fieser, in "The Chemistry of Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, 1937, p. 392, has not yet taken these facts into account.

[7] The allylic nature of certain reactions of cholesteryl chloride has been discussed by Wagner-Jauregg and Werner [*Z. physiol. Chem.*, **213**, 119 (1932)] on the basis of the old allylic formula for cholesterol.

[8] The preparation of the chloride corresponding with *allo*-cholesterol is prevented by the easy dehydration of this substance: Schoenheimer and Evans, THIS JOURNAL, **58**, 182 (1936); *J. Biol. Chem.*, **114**, 567 (1936).

[9] The ability of cholesteryl chloride to react as (I) will account for the hydrogenative formation of a cholestane and not a coprostane derivative.

[10] Linstead and Rydon, *J. Chem. Soc.*, 1995 (1934).

[11] Juvala, *Ber.*, **63**, 1989 (1930).

[12] Compare Stoll, *Z. physiol. Chem.*, **246**, 6 (1937).

THE DANIEL SIEFF RESEARCH INSTITUTE
REHOVOTH, PALESTINE
RECEIVED MARCH 4, 1938

Racemization During Esterification by Diazomethane

BY ERNST BERGMANN AND YAÏR SPRINZAK

In the course of experiments on Walden inversion, we had to prepare optically active methyl bromosuccinate. While esterification with methyl alcohol in the presence of concentrated sulfuric acid[1] gave satisfactory results, a series of experiments carried out with diazomethane gave invariably a racemic ester.

(–)-Bromosuccinic acid (1.5 g., rotation in acetone: c 3.000; l 9.9 cm.; α_D $-2.18°$, hence $[\alpha]_D$ $-72.7°$), finely pulverized, was added at zero temperature to a solution of diazomethane, prepared from ethyl nitrosomethylcarbamate (5 g.) and 25% methyl-alcoholic potash solution (7 cc.) in ether (30 cc.). The acid disappeared quickly; after thirty minutes of standing, the yellow solution was evaporated and the remaining racemic methyl bromosuccinate distilled *in vacuo;* b. p. 87° (2.5 mm.); yield 1.4 g. (Calcd. for $C_6H_9O_4Br$: Br, 35.5. Found: Br, 35.4).

As check experiments, a sample of the same (–)-bromosuccinic acid was kept for thirty minutes with a mixture of ether and methyl alcohol (6:1) and the optically active methyl ester in contact with diazomethane solution, prepared as above, for two hours. In both cases, no changes in optical rotation were observed.

Therefore we are inclined to assume that the racemization is connected in some way with the esterification mechanism. An analogous observation has been made incidentally by Stoermer and Starck[2] in the case of the optically active acid

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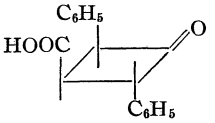
[1] Holmberg, *Ber.*, **59**, 125 (1926).

[2] Stoermer and Starck, *ibid.*, **70**, 479 (1937).



which is racemized too in the course of esterification by diazomethane.

Furthermore, the observation reported by Schlenk and Bergmann[3] may be recalled, that fluorene-9-carboxylic acid behaves—at least to a certain extent—abnormally toward diazomethane, giving dimethyl dibiphenylenesuccinate.

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[3] Schlenk and Bergmann, *Ann.*, **463**, 194 (1928).

THE DANIEL SIEFF RESEARCH INSTITUTE
REHOVOTH, PALESTINE
RECEIVED MARCH 4, 1938

Remark on the Mechanism of the Fittig Reaction

BY O. BLUM-BERGMANN

(1) Bachmann and Clarke[1] have shown, some years ago, that the by-products formed in the biphenyl synthesis from boiling chlorobenzene and sodium metal indicate the intermediary formation of free phenyl radicals. Analogous results are obtained at room temperature, working in benzene solution.

To bromobenzene (50 g.), dissolved in benzene (50 g.) in a Schlenk tube,[2] sodium slices (10 g.) were added in nitrogen atmosphere, reaction starting quickly and causing a marked rise in temperature. When this first reaction ceased, the mass was shaken for two days, diluted with benzene (100 cc.) and separated by decantation from the excess sodium metal. Water was added, the benzene solution washed several times with water, dried and evaporated *in vacuo* and the residue fractionated at 13–15 mm. (a) B. p. 123–129°. This fraction crystallized completely; it consisted of pure biphenyl; m. p. 69–71°; yield 6.8 g. (b) B. p. 165–200°. The yellowish oil solidified almost quantitatively, on trituration with methyl alcohol; yield 2.1 g. From methyl alcohol, stout prisms, m. p. 56–57°, which according to their physical properties and the analysis proved to be *o*-phenyl-biphenyl, described before by Bachmann and Clarke.[1] (Calcd. for $C_{18}H_{14}$: C, 93.9; H, 6.1; mol. wt., 230. Found: C, 93.5; H, 6.0; mol. wt. (camphor), 241, 236.) (c) B. p. 200–250°, yellowish oil, which crystallized on trituration with light petroleum (b. p. 80–100°) (yield 0.26 g.) and was purified from the same solvent. Long needles of triphenylene; m. p. and mixed m. p. with an authentic sample, 195° (Calcd. for $C_{18}H_{12}$: C, 94.7; H, 5.3; mol. wt., 228. Found: C, 94.6; H, 5.3; mol. wt. (camphor), 257, 255).

(2) Theoretically free phenyl radicals may occur either in the formation from sodium and bromobenzene of phenylsodium[3] or in the interaction between the latter compound and a second bromobenzene molecule or in both processes. Horn and Polanyi[4] showed that, on interaction with dilute sodium vapor, bromobenzene forms biphenyl, undoubtedly via phenyl radicals. On the surface of metallic sodium, on the other hand, it will be expected that a second sodium atom will always be near enough for phenylsodium formation when the first metal atom has removed the halogen from the C-Hal bond,[5] although, obviously, temporary radical formation cannot be excluded. Therefore it is more likely that the reaction of the alkylsodium compound with bromobenzene involves the intermediary production of the radicals. In favor of this, the observation may be reported that phenylsodium, on interaction with bromobenzene, gives triphenylene $(C_6H_4)_3$ too, indicating formation of phenyl radicals and their disproportionation into benzene and phenylene radicals C_6H_4.[6]

Diphenylmercury (6 g.) was shaken in benzene solution with sodium slices (10 g.) for two days;[7] the phenylsodium containing mass was then separated by decantation from the excess metal, and bromobenzene (7 cc.) (twice the theoretical amount) added. The mixture was kept at 70° for forty-eight hours and poured out into water. Treatment as above gave (besides some bromobenzene) (a) biphenyl, b. p. 120–160° (22 mm.), m. p. 65°, yield 1.45 g.; (b) triphenylene, b. p. 200–220° (13 mm.) after trituration of the crude product (1 g.) with light petroleum and recystallization from the same solvent, m. p. 194–195.5°.

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[1] Bachmann and Clarke, THIS JOURNAL, **49**, 2089 (1927). *Cf.* J. v. Braun and Kurtz, *Ber.*, **70**, 1224 (1937); Oldham and Ubbelohde, *J. Chem. Soc.*, 201 (1938).

[2] Compare Houben-Weyl, "Die Methoden der organischen Chemie," Vol. IV, Georg Thieme Leipzig, 1924, p. 959.

[3] Schlubach and Goes, *Ber.*, **55**, 2889 (1922).

[4] Horn and Polanyi, *Z. physik. Chem.*, **25B**, 151 (1934).

[5] Ziegler and Schaefer, *Ann.*, **479**, 150 (1930).

[6] In the famous experiments of Wieland, Popper and Seefried [*Ber.*, **55**, 1816 (1922)] on the dissociation of benzene-azotriphenylmethane, the occurrence of benzene instead of free phenyl may also be due to incidental formation of triphenylene which so far has not been isolated from the reaction mixture.

[7] Compare Schlenk and Holtz, *ibid.*, **50**, 268 (1917).

THE DANIEL SIEFF RESEARCH INSTITUTE
REHOVOTH, PALESTINE
RECEIVED MARCH 4, 1938

Hydrogenation of Ethylene and Partially Deuterized Ethylene on Catalytic Metal Surfaces

BY G. G. JORIS AND J. C. JUNGERS

The hydrogenation on catalytic copper of ethylene, ethylene-d_4 and partially deuterized ethylene (50%D) has been measured and found to be faster for the heavy compound.[1] To gain further information on this reaction and establish that this was not due to accidental circumstances, the hydrogenation of ethylene and partially deuterized ethylene was carried out on nickel, cobalt and platinum surfaces. The rates measured for mixtures of 5 cm. of ethylene and 7.5 cm. of hydrogen are given in the table and show

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[1] G. G. Joris, H. S. Taylor and J. C. Jungers, THIS JOURNAL 1982 (1938).

quite definitely that in all cases studied the reaction is faster for the heavy compound.

TIMES OF ONE-HALF REACTION (IN MIN.)

Catalyst	Temp., °C.	$C_2H_2D_2$	C_2H_4
Nickel	+64	13	28
Platinum	−21	12	18
Cobalt	0	2.8	3.5

The columns give the nature of the catalyst, the temperature of the experiment, the time of half reaction for the heavy and light compound.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF LOUVAIN
LOUVAIN, BELGIUM

RECEIVED JULY 21, 1938

Some Phenacyl and *p*-Substituted Phenacyl Esters

BY R. V. LUNDQUIST

Some phenacyl and *p*-substituted phenacyl esters of organic acids have been prepared for the identification of those acids. They were prepared by the method of Judefind and Reid.[1]

Heptylic Acid.—The phenacyl ester was a liquid.

Dichloroacetic Acid.—The phenacyl ester was a liquid; the *p*-bromophenacyl ester, observed m. p. 98.2 to 99.3°; the *p*-chlorophenacyl ester, observed m. p. 93.0 to 93.8°.

α-Bromo-*n*-butyric Acid.—The phenacyl ester was a liquid; the *p*-phenylphenacyl ester, observed m. p. 103.5 to 104.0°.

Acetylsalicylic Acid.—The phenacyl ester, observed m. p. 105.0 to 105.5°.

The esters were obtained in excellent yield and the solid esters were purified easily to a constant melting point.

(1) Judefind and Reid, THIS JOURNAL, **42**, 1043 (1920).

CONTRIBUTION FROM THE
CHEMISTRY LABORATORY
UNIVERSITY OF IDAHO
MOSCOW, IDAHO

RECEIVED MAY 25, 1938

Acid Dissociation Constants in Dioxane–Water Mixtures. A Correction of the Dissociation Constant of Benzoic Acid

BY CECIL C. LYNCH AND VICTOR K. LA MER

Professor Martin Kilpatrick and Dr. L. John Minnick of the University of Pennsylvania kindly called our attention to the fact that the dissociation constants of benzoic acid as given in the "International Critical Tables," Vol. VI, p. 279, are in error by a factor of ten and that this had led to an unnecessary restriction of statement in our paper of the above title.[1] When the most recent value for 25°[2] is plotted in our Fig. 8 instead of the erroneous "I. C. T." value (6.15×10^{-4}), the anomalous behavior of benzoic acid as compared with acetic, propionic and butyric acids disappears. Log K_{benzoic} becomes a linear function of the reciprocal of the dielectric constant between $D = 78$ and 21, and now conforms closely to the behavior of the three aliphatic acids. In Table III, p. 1257, K_{acetic} ($D = 34.3$) should read 5.62×10^{-7} instead of 5.01×10^{-7} and the second datum for propionic acid ($D = 21.0$) should read 5.33×10^{-9} instead of 5.30×10^{-9}.

(1) Lynch and La Mer, THIS JOURNAL, **60**, 1252 (1938).

(2) 6.31×10^{-5}, Brockman and Kilpatrick, *ibid.*, **56**, 1483 (1934).

DEPARTMENT OF CHEMISTRY
COLUMBIA UNIVERSITY
NEW YORK, N. Y.

RECEIVED JUNE 23, 1938

The Hydrolysis of Methyl Iodide

BY RICHARD A. OGG, JR.

The hydrolysis of methyl iodide in pure water[1] has been shown to be kinetically first order with respect to methyl iodide, and unretarded in rate by the resulting hydriodic acid. Essentially similar results have been found by the author in a brief study of methyl iodide hydrolysis in a mixture of equal volumes of anhydrous methanol and water. The solutions (some 0.02–0.08 molar in methyl iodide) were heated in sealed nitrogen-filled tubes. Reaction was followed by titration of the resulting hydriodic acid. The last stages of the reaction were complicated by formation of considerable iodine (Moelwyn-Hughes found only traces)—undoubtedly as a result of the side reaction $CH_3I + H_3O^+ + I^- \longrightarrow CH_4 + I_2 + H_2O$. (The solutions containing most iodine gave off inflammable gas on opening the tubes.) Displacement of the equilibrium

$$CH_3OH + H_3O^+ + I^- \rightleftarrows CH_3I + 2H_2O$$

to the right by the large concentration of methanol in the solvent explains the importance of the side reaction—as contrasted to the results in pure aqueous solution.

Very good first order rate constants were obtained up to some 60% completion of the reaction (iodine formation then became troublesome). At 100 and 55° the rate constants were found to be, respectively, some 3×10^{-4} (average from

(1) E. A. Moelwyn-Hughes, *Proc. Roy. Soc.* (London), **A164**, 295 (1938).

three runs, with following respective sets of constants corresponding to successive time intervals—3.1, 2.9, 3.0, 3.1, 3.2, 3.1, 3.0, 3.1; 2.9, 3.0, 2.8, 3.0) and 3.2×10^{-6} sec.$^{-1}$ (average from two runs, with following respective sets of constants—3.3, 3.4, 3.2, 3.1; 3.1, 3.0, 3.2, 3.1). The corresponding values found by Moelwyn-Hughes for the reaction in aqueous solution are 4.47×10^{-4} and 4.9×10^{-6} sec.$^{-1}$. The effect of replacing a portion of the solvent water by methanol is thus to diminish the rate of methyl iodide hydrolysis. Comparison of the figures at the respective temperatures indicates that the activation energy is but slightly affected, if at all. These results are entirely similar to the effects of solvent change on the rates of hydrolysis of secondary and tertiary alkyl halides in mixtures of ethanol and water.[2] It would appear that the hydrolyses by *neutral water* of methyl halides are kinetically similar to the corresponding reactions of secondary and tertiary halides, and that an identical intimate mechanism obtains for all of these reactions.

(2) See E. D. Hughes, *Trans. Faraday Soc.*, **34**, 185 (1938), for a review of this field.

CHEMICAL LABORATORY
STANFORD UNIVERSITY
STANFORD UNIVERSITY, CALIF.

RECEIVED JUNE 13, 1938

A New and Direct Method for the Determination of Creatine. I. Preliminary Report

BY CHARLES F. SCHAFFER

Investigations on the origin and significance of the excretion of creatine in the urine have received no general acceptance. The reason for this uncertainty is that creatine is not determined directly, but by difference. The preformed creatinine is determined by Folin's colorimetric method, and then the urine is heated with acid which converts the creatine to creatinine. The creatinine is then redetermined. The difference between this total creatinine value and that of the preformed creatinine is called creatine. The fallacies of such an analytical procedure are obvious; especially when considering that the quantitative determination of creatinine itself is made by measuring its reducing action. In fact it has been pointed out independently by Arnold,[1] Emden,[2] Hurtley,[3] Greenwald[4] and confirmed by Graham and Poulter,[5] that acetoacetic acid is capable of showing a false presence of creatine.

In attempting to formulate a copper reagent that would eliminate entirely the effect of reducing nitrogenous substances, but still retain its maximum ability to be reduced by sugars, Folin and Svedberg[6] developed one which is reduced by nitrogenous substances such as uric acid, creatine, creatinine and allantoin, but is not affected by sugar.

It was the use of this reagent which enabled Larson[7] to promulgate his colorimetric method for the determination of allantoin.

The subsequent use of this procedure for the determination of added allantoin in urine of man resulted in the recovery of excessive amounts. On investigation it was found that the substance responsible for this greatly increased reducing action was creatine.

Aware of the negligible amounts of allantoin present in human urine, it was decided that an earnest endeavor to utilize this procedure for the determination of creatine warranted investigation. It was soon discovered that by increasing the alkalinity of the copper solution, creatine demonstrated reducing properties which varied directly as its concentration and could be measured quantitatively.

Larson's procedure, slightly modified for its adaptation to creatine, is used. The determination is made by treating a portion of the filtrate of the test sample in a Folin–Wu[8] sugar tube with the ammoniacal copper solution; the alkalinity is increased by the addition of sodium hydroxide solution, and immediately it is placed in a rapidly boiling water-bath for ten minutes, cooled and the blue color, developed after the addition of acid molybdate, compared with a 1-mg. creatine standard similarly treated.

Reagents Required

Phospho-24-tungstic Acid.—It is essential that the phosphotungstic acid used be pure. Larson obtained inconsistent results in the precipitating power of eight different lots of C. P. phosphotungstic acid procured from four leading manufacturers and the results have been substantiated in this Laboratory. Basic lead acetate;[9] 5% (by weight) sulfuric acid solution; Folin ammoniacal cop-

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(1) Arnold, *Zentr. inn. Med.*, **21**, 417 (1900).

(2) Emden, *Zentr. Stoffenechael, Verdauungs-Krankheiten, N. F.*, **2**, 250–289 (1907).

(3) Hurtley, *Lancet*, **184**, 1160 (1913).

(4) Greenwald, *J. Biol. Chem.*, **14**, 87 (1913).

(5) Graham and Poulter, *Proc. Roy. Soc.* (London), **B87**, 205 (1913).

(6) Folin and Svedberg, *J. Biol. Chem.*, **70**, 418 (1926).

(7) Larson, *ibid.*, **94**, 3 (1932).

(8) Wu, *ibid.*, **43**, 197 (1920).

(9) Hawk and Bergeim, "Physiological Chemistry," Blakiston, Philadelphia, Pa., 11th ed., 1937.

per reagent;[10] 20% sodium hydroxide solution; acid molybdate reagent;[11] creatine standard: dissolve 100 mg. of creatine in water and dilute to 100 cc.

Technique.—Place 1.5 g. of phosphotungstic acid in a large Pyrex tube, 30- to 50-cc. capacity, and dissolve in 6 cc. of water. With the aid of a pipet add 4 cc. of urine sample and centrifuge until clear. Add 4 cc. of the basic lead acetate solution and centrifuge again.[12] When clear, add 6 cc. of 5% sulfuric acid and recentrifuge. Transfer 2 cc. of the resultant, clear filtrate to a Folin–Wu sugar tube. Add 2 cc. of ammoniacal copper solution and 1 cc. of 20% sodium hydroxide. Place in a vigorously boiling water-bath for ten minutes, cool, add 2 cc. of acid molybdate reagent, dilute to mark and compare immediately with a 1-mg. creatine standard similarly treated.

Observations

The phosphotungstic acid precipitates the proteins and some of the other interfering substances while the addition of lead acetate removes the excess phosphotungstic acid and the remaining interfering substances. The subsequent use of sulfuric acid precipitates the excess lead completely.

The optimum alkalinity of the medium required for the creatine to exert its most efficient reducing action necessarily detracts from the non-sugar reducing properties of the copper solution.

Normally, urine contains traces of glucose which are so minute that the error introduced by such amounts is negligible. However, when sugar is present in any appreciable amounts it must either be removed by the brief fermentation process described by Folin and Svedberg[6] and designed for use on filtrates, or the quantitative sugar determinations of Folin–Wu[11] run in conjunction with the determination of creatine. This latter method is preferred as the fermentation procedure must be regulated rather too exactly, otherwise the reducing powers are increased rather than decreased.

Recovery of Creatine Added to Urine.—Urine that had no reducing action on the copper solution or at best produced only a slight coloration which was impossible to read colorimetrically was selected and varying amounts of a standard creatine solution added.

Filtrates of these various specimens were then prepared as described above, and the determination proper performed on the filtrates.

From a series of twenty-eight different determinations recoveries ranging from 90 to 110% were obtained in contrast to recoveries of 82 to 92% employing the method of Folin.

The accompanying protocol shows a comparison of the values for creatine recovery, obtained by both the Folin and the suggested colorimetric method, when added to urine.

PROTOCOL

COMPARISON OF CREATINE RECOVERIES AFTER THE ADDITION OF A DEFINITE AMOUNT TO URINE

Urine no.	Creatine present, mg. per cc.	Recovery Folin method, mg. per cc.	Percentage error	Recovery Colorimetric method, mg. per cc.	Percentage error
1	2.6	2.5	− 3.9	2.6	0
2	3.6	3.2	−11.2	3.4	−5
3	4.6	3.8	−17.4	4.45	−3
4	1.0	0.92	− 8.0	0.97	−3
5	2.0	1.83	− 8.4	2.1	+5
6	3.0	2.57	−14.3	3.12	+4
7	1.0	0.88	−12.0	0.97	−3
8	2.0	1.74	−13.1	1.92	−4.2
9	3.0	2.38	−20.7	3.13	+4.5
10	0.6	0.49	−17.7	0.6	0

Conclusion

A preliminary report on a direct method for the determination of creatine in urine is presented. The full report is to be submitted on completion of the work.

BIOCHEMICAL AND RESEARCH LABORATORIES
THE NATIONAL DRUG COMPANY
PHILADELPHIA, PENNA.
RECEIVED MAY 13, 1938

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(10) Folin, *J. Biol. Chem.*, **82**, 88 (1929).

(11) Folin and Wu, *ibid.*, **41**, 367 (1920).

(12) Prior to the addition of the basic lead acetate, Larson recommends refrigerator incubation of the tube for one-half hour to minimize the time required for complete phosphotungstate precipitation. This procedure may be omitted as the results obtained, on final analysis of the filtrate, show very little variation.

The Common Basis of Intramolecular Rearrangements. IV.[1] A Correction: The Benzilic Acid Rearrangement

BY FRANK C. WHITMORE

Since the formulation of the working hypothesis used in this Laboratory, no facts have been found contrary to the assumption of the basis of molecular rearrangement as due to a carbon with an open sextet of electrons. However, the extreme extension of the hypothesis to include the benzilic acid rearrangement involving the addition of a proton to benzil to form a positive ion, cannot be supported. Ingold[2] has proposed the existence of an intermediate negative ion produced by the addition of hydroxyl ion to benzil and indi-

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(1) Whitmore, THIS JOURNAL, **54**, 3274 (1932); Whitmore and Stahly, *ibid.*, **55**, 4153 (1933); Whitmore and Fleming, *J. Chem. Soc.*, 1269 (1934); Wallis and Whitmore, THIS JOURNAL, **56**, 1427 (1934).

(2) Ingold, "Ann. Repts. Chem. Soc. (London)," Vol. XXV, 1928, pp. 124–134.

cated the importance of an alkaline medium in the transformation.[3] The reaction rate study conducted by Westheimer[4] indicated the existence of a bimolecular reaction between benzil and hydroxyl ion which can best be explained by the formation of the same negative ion. Recent investigation by Roberts and Urey[5] on the oxygen interchange of benzil with water of a higher concentration of H_2O^{18} indicates a more rapid exchange in alkaline than in neutral solution which is explained by the rapid, reversible addition of hydroxyl ion to form a negative ion with benzil, followed by rearrangement.

(3) Ingold, "Ann. Repts. Chem. Soc., (London)" Vol. XXX, 1933, p. 177.

(4) Westheimer, THIS JOURNAL, **58**, 2209 (1936).

(5) Roberts and Urey, *ibid.*, **60**, 880 (1938).

STATE COLLEGE, PENNA.

RECEIVED JUNE 4, 1938

COMMUNICATIONS TO THE EDITOR

THE SALT EFFECT IN THE PARAMAGNETIC CONVERSION OF *p*-HYDROGEN

Sir:

In 1934 Sachsse [*Z. physik. Chem.*, **B34**, 429 (1934); *Z. Elektrochem.*, **40**, 531 (1934)] reported that the rate constants for the conversion of *p*-hydrogen by solutions of paramagnetic ions were independent of the concentrations of these ions if the change in solubility of hydrogen with changing ionic strength were taken into account. To this is now added the fact that these rate constants are also independent of the concentration of added diamagnetic salts. The measurements were made by shaking the solutions with p-H_2 at a shaking speed in the range at which the conversion rate was independent of the shaker speed. The ratio of gas volume to solution volume was known and kept constant. The apparent rate was independent of hydrogen pressure.

Some representative data are given in the following table for which the solution volume is always 100 cc., the gas pressure *ca.* 100 mm., the concentration of manganous chloride 0.02 *M*, at room temperature.

Expt.	Molality of diamagnetic salt	$k'_{0.02} \times 10^3$	l(Ostwald)	$k(l, m^{-1}, \text{min.}^{-1})$
1	0	3.03	0.0198	7.9
2	0.3 *M* $CaCl_2$	2.75	.0173	8.2
3	0	2.15	.0198	8.0
4	1 *M* $NaNO_3$	1.65	.0158	7.7
5	2 *M* $NaNO_5$	1.41	.0127	8.2
6	0.6 *M* $BaCl_2$	1.56	.0151	7.7

In experiments 1 and 2 the gas volume is 45.1 cc.; in expts. 3 to 6 the gas volume is 64 cc. k' is the observed first order rate constant calculated by $k'_{0.02} = \frac{1}{t} \log \frac{(p\text{-}H_2)_0}{(p\text{-}H_2)_t} - k'_w$ where t is the time in minutes, $(p\text{-}H_2)_0/(p\text{-}H_2)_t$ is the rate of the initial p-H_2 concentration to that at the time t and k'_w is the correction for the conversion by pure water under the same conditions and calculated in the same way. For expts. 1 and 2 $k'_w = 0.07 \times 10^{-3}$ and for expts. 3 to 6 $k'_w = 0.05 \times 10^{-3}$. k is the velocity constant reduced to unit Mn^{++} ion concentration and corrected for the gas not in solution by the relation $k = \frac{V_g \times 2.303}{V_s \times l \times M_{MnCl_2}} \times k'$ where V_g is the gas volume, V_s the solution volume, l the Ostwald solubility of H_2 (from Seidell's "Solubilities") and M_{MnCl_2} the molality of the manganous chloride.

Thus the rate of conversion of $p\text{-}H_2 \longrightarrow o\text{-}H_2$ by Mn^{++} can be expressed by

$$\frac{-d(p\text{-}H_2)}{dt} = k(Mn^{++})\,(p\text{-}H_2)$$

where (Mn^{++}) and $(p\text{-}H_2)$ are the concentrations of Mn^{++} ion and p-H_2, respectively. There is no need to introduce any activity factor of Brönsted $f_{Mn^{++}}f_{H_2}/f_{Mn^{++}\cdot H_2}$, although the concentration of the diamagnetic salts was carried as high as 4 *M* $NaNO_3$ and 2.4 *M* $CaCl_2$ in 0.02 *M* manganous chloride. If it is incorporated it must be a constant and this is not unreasonable since the two reactants completely retain their independent identities throughout the reaction.

The effectiveness of the inhomogeneous magnetic field of the ion is independent of the ionic environment of the paramagnetic ion. This is in agreement with the observation of Sachsse that solutions of manganous sulfate and manganous chloride give the same rate constant.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF CALIFORNIA
BERKELEY, CALIFORNIA
MELVIN CALVIN

RECEIVED JULY 18, 1938

THE CATALYTIC CONDENSATION OF GRIGNARD REAGENTS WITH HYDROCARBONS

Sir:

Meyer and Tögel [*Ann.*, **347,** 55 (1906)] observed that the addition of water during the formation of the Grignard reagent from bromobenzene resulted in the formation of large amounts of biphenyl. It is also well-known that phenylmagnesium bromide does not react with bromobenzene to yield biphenyl. These facts suggested to us the possibility that this reaction might be due to the formation of free phenyl radicals, and that under suitable conditions these might condense with certain reactive molecules. This assumption was strengthened when the above reaction was carried out in the presence of a large excess of mesitylene; only a trace of biphenyl and a 13% yield of 2,4,6-trimethylbiphenyl were obtained.

We have now extended our study of this new condensation reaction to include several Grignard reagents and hydrocarbons and we are able to draw the following tentative conclusions. (1) The reaction involves the already-formed Grignard reagent. (2) *The presence of both water and metallic magnesium is necessary.* (3) Catalytic quantities of water and magnesium are sufficient, indicating that these agents serve only to initiate chain reactions. (4) A minimum amount of ether should be employed. (5) The reaction is applicable to a variety of Grignard reagents and hydrocarbons.

The following preparation of diphenylmethane from benzylmagnesium chloride and benzene is representative of the procedure now in use: 0.3 g. of magnesium turnings is allowed to react completely with 2.0 g. of benzyl chloride in 0.10 mole of ether in the usual manner. Then 1.5 moles of benzene and enough magnesium to make a total of 0.25 mole are added, followed by slow addition over a period of two hours of a mixture of one mole of benzene and enough benzyl chloride to make a total of 0.25 mole. The temperature rises to about 45° during the addition of the mixture and stirring is continued for another hour. 0.025 to 0.3 mole of water is then added (the mixture contains a little unreacted magnesium) and the mixture is stirred for another hour. The amount of water, or the rate, or the temperature at which it is added, has no marked effect on the yield. The products are isolated by standard procedures.

The following yields of condensation products have been obtained:

Grignard reagent	Hydrocarbon	Products found		Yield on basis of halide used, %
$C_6H_5CH_2MgCl$	Benzene	Diphenylmethane		29
		Dibenzyl		18
$C_6H_5CH_2MgCl$	*m*-Xylene	2,4-Dimethyldiphenylmethane		17
$C_6H_5CH_2MgCl$	Mesitylene	2,4,6-Trimethyldiphenylmethane		20
$C_6H_5CH_2MgCl$	Cyclohexane	Benzylcyclohexane		None
C_6H_5MgBr	Toluene	4-Methylbiphenyl	estimated	10
		Biphenyl		20
C_6H_5MgBr	*m*-Xylene	Dimethylbiphenyl		9
C_6H_5MgBr	Chlorobenzene	Chlorobiphenyl		5
		Biphenyl		39
C_6H_5MgBr	Cyclohexane	Biphenyl		39
		Phenylcyclohexane		None
CH_3MgI	Benzene	Toluene		0.06
		p-Xylene		.03

Further work on the problem is actively under way and we hope to publish soon the results of our findings.

GEORGE HERBERT JONES LABORATORY
THE UNIVERSITY OF CHICAGO
CHICAGO, ILLINOIS

M. S. KHARASCH
WILLIAM GOLDBERG
FRANK R. MAYO

RECEIVED JULY 21, 1938

THE ACTIVITY OF CERTAIN NICOTINIC ACID DERIVATIVES AS GROWTH ESSENTIAL FOR THE DYSENTERY BACILLUS

Sir:

Recent evidence indicates that nicotinic acid or its amide is of wide biological significance. The compound has been shown to be a part of Warburg's coenzyme, important in the treatment of human pellagra and canine black tongue, and essential for the growth of staphylococci, the diphtheria bacillus and the dysentery bacillus.

In a previous report [Koser, Dorfman and Saunders, *Proc. Soc. Exptl. Biol. Med.*, **38,** 311 (1938)] the authors have shown that 0.004 microgram per cc. will cause growth of certain members of the dysentery group in a synthetic medium otherwise unable to support growth. The essential role of nicotinic acid was demonstrated by the use of a synthetic culture medium consisting of fifteen amino acids, dextrose, and several inorganic salts. In such a medium many dysentery strains fail to grow. Upon the addition of nicotinic acid, however, development of the organisms took place. In order to test the relationship between biological activity and chemical structure we have tested a series of compounds related to nicotinic acid. The solutions were tested in decimal dilutions of molar concentration.

Pyridine-2-sulfonic acid, trigonelline, 6-methylnicotinic acid, nipecotic acid, isonicotinic acid, β-acetylpyridine, β-picoline, and pyridine were completely devoid of growth-promoting activity. The following substances showed 3+ growth (comparable to veal infusion broth) in the dilutions indicated: nicotinic acid, nicotinamide, methyl nicotinate $M \times 10^{-7}$, trigonelline amide, ethyl nicotinate, nicotinuric acid, ethyl nicotinoacetate $M \times 10^{-6}$, nicotinic acid N-methyl amide $M \times 10^{-5}$, nicotinonitrile $M \times 10^{-4}$. Picolinic acid and quinolinic acid showed activity at a dilution of $M \times 10^{-4}$ but there is some possibility that these two preparations may be contaminated with traces of nicotinic acid. They are being synthesized by reactions which will exclude the possibility of any contamination and the results of tests of their growth-promoting activity will be reported later.

We are grateful to Dr. Frank M. Strong for samples of a number of compounds tested.

This investigation was aided by a grant from the Committee of Scientific Research of the American Medical Society.

DEPARTMENT OF BIOCHEMISTRY
AND DEPARTMENT OF BACTERIOLOGY
AND PARASITOLOGY
UNIVERSITY OF CHICAGO
CHICAGO, ILL.

ALBERT DORFMAN
STEWART A. KOSER
FELIX SAUNDERS

RECEIVED JULY 15, 1938

THE CHEMILUMINESCENCE OF THE CHLOROPHYLLS, AND OF SOME OTHER PORPHYRIN METAL COMPLEX SALTS

Sir:

Recently, Helberger [*Naturwiss.*, **26,** 316 (1938)] reported a case of chemiluminescence, found in experimenting with the complex magnesium salt of phthalocyanin, and of substances with related chemical structure.

It is of considerable interest to study the chemiluminescence of porphin and of *meso* tetrasubstituted porphins, which are now synthetically accessible [Rothemund, THIS JOURNAL, **57,** 2010 (1935); **58,** 625 (1936)], and of the chlorophylls, especially with regard to the problem of photosynthesis.

We found that upon adding pure chlorophyll *a* to tetrahydronaphthalene ("Tetralin"), heated to about 125°, the red chemiluminescence is just perceptible. The intensity of the phenomenon increases with increasing temperature, exhibiting a beautiful red glow between 160 and 190°, diminishes then, and disappears, when the solution is boiled for a few minutes. Addition of more chlorophyll *a* to the hot solution causes the chemiluminescence to reappear. Chlorophyll *b* shows the same behavior. The magnesium and the zinc complex salts of porphin as well as of α,β,γ,δ-tetraphenylporphin react in the same manner, and with the same color of luminescence. The free porphyrins, porphin, and α,β,γ,δ-tetraphenylporphin, or their hemins, copper, nickel, cobalt, or silver complex salts react negative. When one adds, however, magnesium filings to a solution of α,β,γ,δ-tetraphenylporphin in tetralin, and allows the mixture to stand for some time, the chemiluminescence can be observed upon heating. No change of color or intensity of the glow takes place, if one bubbles oxygen or carbon dioxide through the hot solution. The following substances show the phenomenon, when used as solvents for porphyrin magnesium or zinc complex salts: tetrahydronaphthalene, xylene, *p*-cymene, and bromocyclohexane.

After the reaction, the solution differs spectroscopically from the unheated solution; the investigation of the reaction products from the above mentioned substances in the different solvents is in progress.

C. F. KETTERING FOUNDATION
FOR THE STUDY OF CHLOROPHYLL
AND PHOTOSYNTHESIS
ANTIOCH COLLEGE
YELLOW SPRINGS, OHIO

PAUL ROTHEMUND

RECEIVED JULY 16, 1938

THE STRUCTURE OF THE INSULIN MOLECULE

Sir:

On the basis of the Cyclol hypothesis, a structure C_2 was proposed for the insulin molecule.[1] C_2 is a cage structure consisting of a fabric carrying side chains, bent over a truncated tetrahedral framework. The only metrical parameter, *a* (a mean between C-C and C-N bond lengths), taken as 1.5 Å., defines the dimensions of C_2. C_2 molecules with axes parallel fit the rhombohedral cell of the insulin lattice given by an x-ray analysis. They can be arranged with any orientation α in the corresponding hexagonal cell, and α was necessarily left undetermined.[1] Further data, namely, Patterson–Harker diagrams, have now become available.[2]

It has been stated that these diagrams are in-

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[1] Wrinch, *Trans. Faraday Soc.*, **33**, 1368 (1937).

[2] Crowfoot, *Proc. Roy. Soc.*, (London) **164A**, 580 (1938).

compatible with the structure I proposed for insulin.[2] I have therefore made a study of the Patterson–Harker diagrams given by C_2. The skeleton of C_2 is a truncated tetrahedron with six slits whose centers give an octahedron of side $l = 8\sqrt{6a}$. All the vectors between points on its framework lie on or within a truncated octahedron of side $2l = 16\sqrt{6a} = 33.9$ Å. Postulating concentrations of atoms near these six octahedral points of the C_2 we obtain Patterson–Harker peaks for a molecule at O which lie at the corners and midpoints of the sides of the octahedron $2l$ with center at O. The figure shows the projection on the c-plane of these 18 peaks giving a hexagon with center at O, with side length 33.9 Å. There are six at its corners, six at the midpoints of its sides, and six at the midpoints of lines joining alternate corners, indicated for convenience as A, B, and C, respectively.

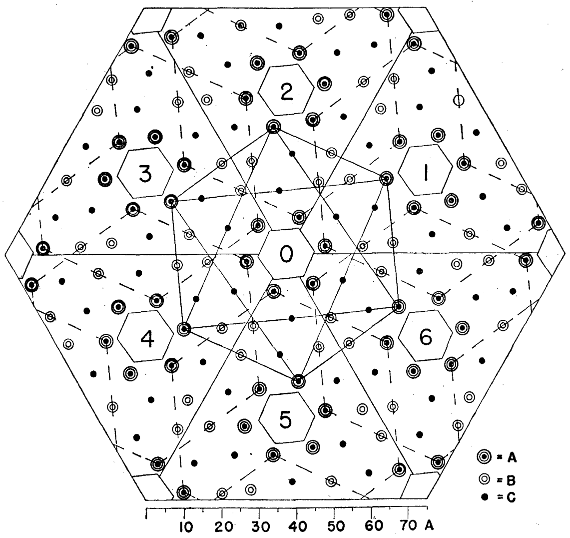

Fig. 1.—The c-plane projection of the Patterson–Harker map of the six slits of the C_2 molecule, superposed upon the corresponding projection obtained from the X-ray analysis of insulin.

We now notice that Crowfoot's c-plane projection also gives 18 peaks per molecule, reproduced in Fig. 1, which fall into a pleasing pattern of hexad, triad, and dyad sets. Superposing the C_2 hexagon on this diagram, we turn this hexagon about its center, through an increasing angle α until any of its points fall upon a Crowfoot peak. We find with $\alpha = 6°$ that all A peaks fit on A peaks, B peaks on B peaks, and C peaks on C peaks, as shown in Fig. 1.

This procedure allocates to the molecule at O, one A peak in each of the hexad sets surrounding the points 1, 2, 3, 4, 5, 6; the most remote B peak of each neighboring triad set; the nearer C peak of each neighboring dyad set. Drawing corresponding hexagons around other molecules, all the A, B, and C peaks are filled in. The six nearest A and B peaks around O are contributed, one each, by the molecules associated with the positions 1, 2, 3, 4, 5, 6, and none of them by the molecule at O.

So far the details of the skeleton and the positions of the side chains attached to the C_2 molecule have been left out of account. Nevertheless, the 18 peaks per molecule in Crowfoot's c-plane projection are given in the correct positions, on the assumption that there are concentrations of atoms at the six slits.

The full investigations will shortly be published.

LONG ISLAND BIOLOGICAL STATION
COLD SPRING HARBOR, LONG ISLAND
D. M. WRINCH

RECEIVED JULY 15, 1938

NEW BOOKS

Chemical Principles, with Particular Application to Qualitative Analysis. By JOHN H. YOE, Ph.D., Professor of Chemistry, University of Virginia. John Wiley and Sons, Inc., 440 Fourth Ave., New York, N. Y., 1937. ix + 311 pp. 29 figs. 15.5 × 23.5 cm. Price, $2.75.

A Laboratory Manual of Qualitative Analysis. By JOHN H. YOE, Ph.D., Professor of Chemistry, University of Virginia. John Wiley and Sons, Inc., 440 Fourth Ave., New York, N. Y., 1938. ix + 219 pp. 7 figs. 15.5 × 23.5 cm. Price, $2.50.

This text is a good example of the modern Leftist tendency in Qualitative Analysis. It offers the student, in a compass of 300 pages, a comprehensive and somewhat amplified review of most of the theoretical material in General Chemistry: fundamental laws, definitions and principles, chemical change, kinetic theory, states of matter, solutions, homogeneous and heterogeneous equilibrium, precipitation theory, complex ions and coördination, *p*H, oxidation–reduction, kinetics of reactions, thermo-, electro-, and photo-chemistry, atomic structure, colloids. The presentation of each topic is of necessity very brief, with a minimum of mathematics and derivations, but seems satisfactory for general review; the sections on atomic heats, the early periodic table, the gas laws, solubility and washing of precipitates, and osmotic pressure would benefit by revision and a slightly different mode of treatment. The book will provide a substantial basis for a review of chemical fundamentals, but will be criticized by some instructors as containing very little about Qualitative Analysis, being largely a repetition of the student's earlier work, and not offering any appreciable advance in chemical theory for the well-grounded student ready for a course in physical chemistry.

The accompanying Laboratory Manual supplies the basis for a large but flexible course of experimental work, with many preliminary tests in addition to the regular schemes. The method of cation analysis is a composite of the well-known Fresenius and Noyes methods, while the anion identification schemes are based on the groups of volatile, barium, silver, and soluble radicals. The use of organic reagents and spot tests is encouraged and there is a section on Dry Methods of Analysis.

ALLEN D. BLISS

Qualitative Chemical Analysis. Revised edition. By LOUIS J. CURTMAN, Professor of Chemistry, City College, The College of the City of New York. The Macmillan Company, 60 Fifth Avenue, New York, N. Y., 1938. xii + 514 pp. 44 figs. 15 × 22 cm. Price, $3.75.

A review of the first edition of this text was published in THIS JOURNAL in March, 1932 (Vol. **54**, page 1257). The second edition resembles the first edition but has been rewritten more nearly completely than most revised texts. The book consists of the usual prefaces, introduction and appendix and five major parts. The first major part, "Theory," occupies 115 pages and includes discussions of structure of atoms, valence, coördination theory, dipole moments, Brönsted's theory of acids and bases, Kohlrausch's law of independent migration, the complete ionization theory of Debye and Hückel, activity coefficient, ionic strength and all of the other topics usually discussed by texts in qualitative analysis. These ideas are made an integral part of the text, and their applications to analysis are shown. The second and fifth parts of the text furnish information regarding the metal ions and acids or anions, respectively. They include 105 and 48 pages. Besides colors of compounds and their solubilities in water, many applications of theory are made at appropriate points. For instance, solubilities of sulfides are discussed: ZnS in HCl by union of $S^=$ with H_3O^+; CuS in HNO_3 by oxidation of $S^=$ by NO_3^-; HgS in aqua regia by oxidation of $S^=$ and also formation of $HgCl_4^=$. Part three deals with problems which would occur in volumetric quantitative analysis. It includes only sixteen pages but part one contains an abundance of problems and exercises based on the other topics treated in the text. Part four, sixty pages, gives directions for preliminary experiments and a systematic analysis for metal ions. Directions for micro analysis and for setting up a system of individual reagents are included in the text. The sixteen-page table of analytical constants included in the first edition has been omitted. The subject matter is well chosen for a year's work in qualitative analysis. The arrangement is logical and the descriptions and explanations as clear and simple as truth permits. References to other books and to journals are frequent. The print is clear and errors are few. It is an improvement on the former edition as well as a modernization and a revision.

F. E. BROWN

Spectroscopy in Science and Industry. Edited by GEORGE R. HARRISON. Proceedings of the Fifth Summer Conference in Spectroscopy and its Applications. Held in Massachusetts Institute of Technology, Cambridge, Massachusetts, July 19–22, 1937. The Technology Press: John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y., 1938. vii + 134 pp. 60 figs. 19 × 25.5 cm. Price, $3.00.

This conference, held at the Massachusetts Institute of Technology in July, 1937, was probably the largest gathering of practical spectroscopists ever assembled. Thirty-six papers, twenty-nine of which appear in the present volume, comprise discussions of the most varied applications of spectroscopy. The main emphasis, quite understandably, is upon apparatus and method. A spectacular achievement in metallurgical analysis is the posting of a complete quantitative analysis for five impurities in iron by two operators within seven minutes. Absorption measurements, in the visible and in the infrared, serve for rapid analysis of mixtures difficult to separate and identify chemically; to evaluate degrees of polymerization, molecular arrangements, and reaction rates; and as aids in the solution of biochemical problems in great variety.

Unfamiliarity with modern spectroscopic methods promises to be especially disadvantageous to analysts, but the same will be true, in varying degrees, for workers in other branches of science.

GEORGE S. FORBES

Über die Bildung und den chemische Bau der Kohlen. (The Formation and Chemical Structure of Coal.) By PAUL ERASMUS, Ohlau. Verlag von Ferdinand Enke, Hasenbergsteige 3, Stuttgart W, Germany, 1938. viii + 121 pp. 16.5 × 25.5 cm. Price, RM. 10.

This is the twelfth volume of publications in the field of fuel geology, edited by Prof. W. Gothan. The author, Paul Erasmus, who was a colleague of Bergius, was killed in a laboratory accident in 1936, and the purpose of this publication, as stated by the editor in a foreword, is partly to give expression to the interesting points of view of the author, and partly to honor his memory.

That part of the work which has to do with the chemical structure of coal and which will be of greater interest to the chemist, comprises nineteen pages; the balance is devoted to a discussion of investigations of coal formation in nature.

In the part devoted to chemical structure there appear sections on the nature of hydrogen in coal, the oxygen, on the effects of hydrolysis, on the unitary character of coal, and on artificial coal. The greatest part of the chemical investigations upon which these sections are based, are stated to have been carried out in Bergius' laboratory in 1926–1930.

The point of view developed is that coal is a tridimensional polymer of relatively small aromatic and hydroaromatic units, ten carbon atoms each, linked through linear and cyclic ether oxygen bonds, and that the principal mass of the coal is essentially unitary in character. Resins, waxes, coloring materials, cuticles, and so forth, are specifically excluded from the discussion, and the findings are stated to apply chiefly to the bright coals as opposed to the durains.

In discussing the different methods of attack, solvent degradation of bright coal is stated to result in extract fractions of hydrogen–carbon ratios varying from 0.8 to 1.0, but in constant carbon–oxygen ratios of 10.0. The idea that solvent degradation may be due to partial hydrogenation is rejected. By fractional vacuum distillation of the extracts from bright coals it is said to be possible to recover 12.5% of the weight of the pure coal as a substance of composition $C_{10}H_{14}O$.

By primary hydrogenation of bright coals at 360°, a stoichiometric, easily reproducible reaction is said to take place and on the basis of twenty carbon atoms, sixteen are always found in liquid and solid products and four in the form of gases, while half the oxygen remains in organic combination and half is found as water. Based on sixteen carbon atoms the series of products formed contain from twelve to twenty-four hydrogen atoms, but the carbon–oxygen ratio is constant at sixteen to one.

Durain is looked upon as the primary hydrogenation product of bright coal and because of its higher hydrogen content, its particular value as raw material for commercial hydrogenation is pointed out.

In the section dealing with the nature of oxygen in coal, it is said that up to 50% of the oxygen in the extracts from low rank bituminous coals can be identified as carboxyl by phenylhydrazine. In the degradation products of high temperature alkali treatment, by which yields of 50% of simple products are obtained from natural and artificial bituminous coals, a large part of the oxygen is found as hydroxyl, characterized by acetylation. Hydrolysis is looked upon as taking place in two steps, the first being the opening of the oxygen-containing cycles to form hydroxyl groups, without any considerable change in molecular weight, and the second, the hydrolysis of the linear ether linkages with consequent degradation to small units. This second step is incomplete, conversions are usually 30–40% and in exceptional cases 60–80%, due to the tridimensional structure of the coal as compared with a simple linear polymer like cellulose. Crystalline bodies were obtained by the bromination of the water-soluble hydrolytic products, but no compounds were isolated.

The second part of the book, comprising ninety-four pages, is a comprehensive review of our knowledge of coal formation in nature. There are four broad headings: Humoliths, Saproliths, Fusains, and Anthracite and Graphite. Under the Humoliths are discussed decay, peat formation, the chemistry of the humic acids, moors and the transformation of various kinds of peat to brown and bituminous coals. Under Saproliths are treated the origins of the dull coals, oil shales, bitumens and petroleum, only a few pages being devoted to the last three. The usual view as to the origin of the Fusains, from forest fires, is accepted. The temperature of transformation of bituminous coals to anthracite is placed at 380° or above.

This book will be of very great interest to fuel geologists and to all those working in the field of coal chemistry. The part dealing with chemical structure is very poorly documented, and important statements and conclusions are inadequately supported by experimental data. Editor Gothan apologizes for this in a foreword, and points out that had the author lived, the experimental data would no doubt have been presented in the scientific journals. Apparently neither author nor editor had knowledge of recent American contributions in the field of the chemistry of coal.

HENRY C. HOWARD

Aanvullingen der Thermostatica. (Supplement to Thermostatics.) By Prof. Dr. J. E. VERSCHAFFELT, University of Ghent, De Sikkel, Antwerp, Belgium. 160 pp. 16 × 24.5 cm.

Instead of preparing a revised edition of his "Thermostatics" [reviewed in THIS JOURNAL, **55,** 5065 (1933)], the author has preferred to edit an appendix with corrections, in which the same division into chapters and sections is maintained as occurs in the 1933 edition of "Thermostatics." The system of symbols and the nomenclature originally proposed by the Institut International du Froid is still adhered to, although no general agreement among chemists and physicists in different countries has been attained. The significant contributions to physical sciences of the past decade have been incorporated under new section headings and some space is devoted to familiar topics previously omitted, *e. g.*, the Donnan membrane relationships. In striking contrast to the prevailing tendency of the present day toward specialization, the writer has tried to maintain a proper balance between the physical and the chemical aspects of his subject. Nevertheless, there can be no doubt that Thermostatics and its Supplement will appeal more to physicists than to chemists.

H. S. VAN KLOOSTER

Analytische Chemie der Sauerstoffsäuren des Schwefels. (Analytical Chemistry of the Oxygen Acids of Sulfur.) By Prof. DR. ALBIN KURTENACKER, German Technical Institute, Brünn. Ferdinand Enke Verlag, Hasenbergsteige 3, Stuttgart-W, Germany, 1938. ix + 216 pp. 8 figs. 16.5 × 25 cm. Price, RM. 18; bound, RM. 19.60.

This book is a very satisfactory compilation of the information that is to be had on the analytical chemistry of the oxygen acids of sulfur. Methods for the determination of sulfates, thiosulfates, sulfites, sulfides, polythionates, hyposulfites, persulfates and monopersulfates are described and in many cases these are critically discussed. Considerable space is devoted to the determination of the various types of compounds in the presence of one another, and particular attention is given to the interference of one compound in the determination of another. The effects of other substances are also discussed.

The plan of the book is to give qualitative tests for the identification of the different classes of acids of sulfur first, and then to describe quantitative methods of determination. In general, the quantitative discussion includes gravimetric and volumetric methods; in special cases, colorimetric, nephelometric, gasometric and microanalytical methods are also given.

The book carries a good subject index, and is especially rich in references to the literature, some 822 being given. It is a distinct addition to texts that deal with chemical analysis, and should find good use in any laboratory that must analyze for the oxygen acids of sulfur.

G. E. F. LUNDELL

The Analytical Chemistry of Tantalum and Niobium (Columbium). The Analysis of their Minerals and the Application of Tannin in Gravimetric Analysis. By W. R. SCHOELLER, Ph.D. Foreword by G. ROCHE LYNCH. Nordemann Publishing Company, Inc., 215 Fourth Avenue, New York, N. Y., 1937. xvi + 198 pp. 14.5 × 22.5 cm. Price, $5.50.

This monograph welds into a comprehensive analytical scheme the analytical methods developed by Doctor Schoeller and his co-workers during the past twenty years, and which have been described in some 33 original papers under the general title: "Investigations into the Analytical Chemistry of Tantalum, Niobium, and their Mineral Associates." In the welding, the old has been liberally fluxed with new material, the scope of which is by no means confined to earth acid analysis.

Of the three parts into which the monograph is divided, the first deals with primary considerations such as tantalum and niobium compounds of analytical importance, the chemical composition of tantalum and niobium minerals, alkaline and acid fluxes, the tartaric acid method for the analysis of tantaloniobate minerals, the hydrofluoric acid method for the analysis of titanoniobate minerals of the rare earths, and other methods.

The second covers quantitative separation methods involving tantalum, niobium, titanium, zirconium, tungsten, thorium, rare earths, uranium, beryllium, aluminum, and iron.

The third contains a discussion of the use of tannin as a reagent, and methods of separation and determination based on its use in the presence of mineral acid, acetate, tartrate, oxalate or ammonia. In addition to the elements just listed, these methods cover vanadium, chromium, manganese, copper, zinc, gallium, tin, and uranium. The monograph concludes with chapters on the detection of tantalum and niobium in minerals, and on the literature dealing with earth-acid analysis.

The monograph brings to fruition the work of a master in the field of earth-acid analysis. It will be found indispensable by anyone who is working in this difficult field, and will be a very worthwhile addition to the library of anyone who is interested in inorganic chemical analysis.

G. E. F. LUNDELL

Hydrophobic Colloids. Symposium on the Dynamics of Hydrophobic Suspensions and Emulsions, under the Auspices of the Colloidchemistry Section of the "Nederlandsche Chemisch Vereeniging." Held at Utrecht on the 5th and 6th of November, 1937. Reprinted from "Chemische Weekblad," 1938. Published by D. B. Centen's Uitg. Mij. N. V., Amsterdam, Holland, 1938. 180 pp. 15.5 × 23.5 cm. Price, Dutch florins 4.

The opening address of the Symposium was made by Dr. J. H. De Boer, President of the Committee on Arrangements. Professor H. R. Kruyt then gave a general introduction in which he pointed out that hydrophobic colloids had been selected for discussion at this Symposium because they are, at least ideally, the simplest of all colloids and offer an opportunity to study advantageously three important types of problems appertaining to all colloidal systems: 1. Why do the particles of a mere suspension tend to adhere to each other? (questions of attraction); 2. what must be done to prevent this? (questions of peptization); 3. what promotes coalescence? (question of flocculation).

The papers were as follows: The first, by Dr. Hamaker, described an ingenious graphical method for the study of the attractive and repulsive forces; the second, by Professor Rutgers, dealt with the electric double layer and its behavior in an external electric field; the third, by Dr. Verwey, on the double layer and stability of lyophobic colloids; the fourth, by Professor Tendeloo, on counter ion exchange with lyophobic colloids; the fifth, by Dr. Voet, on lyotropic effects in lyophobic systems; the sixth, by Dr. Overbeek, on the protective and sensitizing action of hydrophilic colloids on hydrophobic sols; the seventh, by Dr. van der Minne, consisted of (I) general remarks on emulsions, and (II) emulsification with lyophobic colloids, and the eighth, by I. H. Eilers, dealt with technical applications of base materials in the emulsified state.

After each address there is a printed discussion, often of decided interest.

The account of this Symposium, published in English, will be of great value to students of colloid chemistry, since it represents the most recent work and ideas of an active and progressive group of Dutch investigators.

ARTHUR B. LAMB

A Textbook of Qualitative Chemical Analysis. By ARTHUR I. VOGEL, D.Sc. (Lond.), D.I.C., F.I.C., Head of Chemistry Department, Woolwich Polytechnic. Longmans, Green and Company, 114 Fifth Avenue, New York, N. Y., 1937. xi + 383 pp. 14.5 × 22.5 cm. Price, $3.00.

Qualitative Analysis. By H. V. ANDERSON, B.Ch.E., M.S., Associate Professor of Chemistry, Lehigh University, and T. H. HAZLEHURST, A.B., Ph.D., Assistant Professor of Chemistry, Lehigh University. Second revised edition. Prentice-Hall, Inc., 70 Fifth Avenue, New York, N. Y., 1937. xiii + 280 pp. Illustrated. 14.5 × 21 cm. Price, $2.25.

An Elementary Course in Qualitative Analysis. By WILLIAM LLOYD EVANS, JESSE ERWIN DAY and ALFRED BENJAMIN GARRETT, The Ohio State University. Ginn and Company, 15 Ashburton Place, Boston, Massachusetts, 1938. vii + 234 pp. 21 × 27 cm. Price, $2.00.

The scope of the first of these textbooks of Qualitative Analysis is indicated by the following statement in the preface: "The ultimate object was to provide a textbook at moderate cost which can be employed by the student continuously throughout his study of the subject."

The material is divided into the following sections: The Theoretical Basis of Qualitative Analysis; Analytical Operations; Reactions of the Cations; Reactions of the Anions; Systematic Analysis of Inorganic Substances; Modification of the Systematic Analysis for Phosphate, etc.; Reactions of some Rarer Elements. The theoretical treatment is somewhat more extensive than usual, including the interionic attraction theory, some mention of the proton theory of acids and bases, electrode potentials, calculation of the electromotive force of cells, indicators, and their use for determining hydrogen ion concentrations. This treatment is in general adequate for the purpose, with the minor criticism that in some few cases reactions are explained by mechanisms which seem unnecessary at present. The descriptive material covers the reactions of most importance in qualitative analysis; a considerable number of organic reagents are included. The system of analysis for the cations is, in general, conventional; the procedures are presented in tabular form so that the manipulative directions are somewhat brief. Additional details in regard to the limitations of the methods of separation and the sensitivity of the reactions would be advantageous in a book of this scope. The acidic analysis is confined to certain group tests followed by individual confirmatory tests. The treatment of the rarer elements is brief, the reactions of some thirteen elements being covered in twenty pages.

The text by Anderson and Hazlehurst is a revision of the previous edition by Long, Anderson and Hazlehurst. In the preface to this edition the authors state that they have felt justified in making but few changes in the experimental part of the book; in consequence this review will be largely restricted to the new material. The theoretical presentation has been largely rewritten, has been separated from the related experimental procedures and is now collected in the first hundred pages; in spite of this the treatment appears to be pedagogically effective.

Acids and bases are defined as proton donors and acceptors and an analogy is drawn between the neutralization process and the electron transfer in oxidation–reduction reactions; however, the older viewpoint of the partial ionization of salts is retained. There may be in some cases too great a tendency toward over-simplification for the purpose of clarity of presentation to the student. The physical phenomena of the precipitation process are treated in considerable detail.

A few statements of chemical fact are questioned: for example, the mercurous ion is represented as being monoatomic, while both this text and that of Vogel imply that the cuprous ion is di-atomic, formulas such as $K_2Cu_2(CN)_8$ being given.

An attempt to maintain the interest of the student is made by numerous references to the industrial application of the elements and their reactions. In general, the text appears to be well worthy of consideration for elementary courses where it is not desired to emphasize the more quantitative features of either theory or laboratory practice.

It is stated in the preface that the text by Evans, Day and Garrett is designed for those students for whom elementary qualitative analysis is an integral part of their first or second year study of chemistry. It is more elementary in its approach and more distinctly a laboratory manual than the two preceding books; both the material and procedure of the course are given in considerable detail.

The cation analysis is introduced by a lecture demonstration of the group separations with tabular forms being provided wherein the student is to record his observations. Following this, experiments on the reactions of the cations are given. These are divided into Precipitation and Separation Reactions, Confirmatory Reactions, and Supplementary Reactions. These are followed by the systematic analysis which is shown by tabular outlines carrying the procedures, and by flow sheets. The procedures used are evidently designed more for simplicity of performance than analytical exactness. The anions are presented similarly and some twenty-seven constituents are included. The anion analysis consists essentially of group tests and identification of the individual constituents by separate confirmatory tests.

The theoretical material is collected in the last fifty pages of the book, and the reviewer is pleased to observe that it appears to be designed to explain the experimental phenomena which have gone before, rather than an exposition of the entire field of chemistry. This book should appeal to teachers who feel that the proper approach to qualitative analysis is through demonstration experiments and laboratory work.

The book has flexible cardboard covers and a two-ring-perforated sheet type of binding.

E. H. Swift

Combustion, Flames and Explosions of Gases. By Bernard Lewis, Ph.D., U. S. Bureau of Mines Experiment Station, and Guenther von Elbe, Ph.D., Coal Research Laboratory, Carnegie Institute of Technology, Pittsburgh, Pennsylvania. Cambridge University Press: The Macmillan Company, 60 Fifth Avenue, New York, N. Y., 1938. xv + 415 pp. 79 figs. 14.5 × 22.5 cm. Price, $5.50.

It is twenty-five years since Bodenstein first demonstrated, in the hydrogen–chlorine combination, the existence of a chain reaction. That concept has been among the most fruitful in the domain of reaction kinetics in the intervening years not only in pure science but also in the applications of science in industrial life. The present volume is an excellent exemplification of the application of the chain concept to the general field of combustion and in particular to that of hydrogen, carbon monoxide and the hydrocarbons. After a discussion of the theoretical foundations of the chain theory in Chapter 1, three chapters are devoted to the chain reactions of oxidation of the gases just mentioned. One is amazed at the complexity of phenomena revealed by the detailed analysis of processes still largely formulated in the elementary texts by simple stoichiometrically balanced equations of the type $2H_2 + O_2 = 2H_2O$. The multitude of detailed mechanisms which such an equation hides is revealed in Chapter 2. Even this oxidation is relatively simple compared with the oxidation of even the simplest hydrocarbon. The authors rightly observe that, with these latter, "there is considerably less assurance of discovering unique solutions to the various problems. In any kinetic treatment...at the present time, a certain amount of speculation is unavoidable and it is not surprising to find divergencies of opinion among investigators." The reader should not expect finality in this volume, but may well feel a deep indebtedness to the authors for their incorporation, in the first 125 pages, of the results of their own penetrating and mature consideration, over a period of years, of a great complex of material that has accrued from researches vigorously prosecuted in many important laboratories principally in Russia, Germany, England and the United States. To the assembly of those data a great mass of experiment and excellent technique has been contributed.

The remaining 250 pages of the book, however, have an equally compelling appeal. Emission spectra and ionization, ignition by sparks, the propagation of flames, the influence of vessel shape and motion variables on these flames, stationary and diffusion flames, the theory of burning velocity and detonation, these are among the chapters incorporated in Part II. Beautiful illustrations are employed to clarify the text; see especially pp. 153, 186, 189, 191, 259. Part III discusses the state of the burnt gas with important thermodynamic features properly stressed. Part IV discusses problems in technical combustion including industrial heating and internal combustion engines. It is hard to see how the mind of any chemist, physicist or engineer could not be enormously enriched and enlarged by this presentation of a subject which has always been rich in fascination to the enquiring mind from the days of the remote ancestors who made the first fires to those who daily put combustion to use either with the Bunsen flame or at the turn of the ignition key in modern motor transportation. Alternatively, the book may be read as an excellent illustration of penetrating scholarship illuminating a by no means elementary field of research.

Hugh S. Taylor

Numerical Problems in Advanced Physical Chemistry. By Dr. J. H. Wolfenden. Oxford University Press, 114 Fifth Avenue, New York, N. Y., 1938. 227 pp. Price, $2.75.

This reviewer has never before discovered any set of exercises for students that was even mildly exciting to read through, but here is one that provides very interesting reading indeed. The idea behind this unique book is to give the student of advanced physical chemistry a set of problems each of which is taken from some recently published investigation. In other words, instead of trivial exercises that are obviously merely exercises, these are problems to which some one has actually wanted to know the answers.

There are one hundred and thirty-three problems in the book, covering a very wide range of topics such as Fundamental Constants, Stoichiometry, Gaseous Equilibrium, Heterogeneous Equilibria, Thermochemistry and Thermodynamics, Conductivity of Solutions, Equilibria in Solution, Electrochemistry, Photochemistry, Molecular Structure, Crystal Structure and Radioactivity. References to the original papers from which the data for the problems were taken are given, as well as references to the appropriate parts of certain standard textbooks. In addition, each problem has a footnote containing suggestions and related information. The answers are listed at the end of the book.

Some of the problems are simple enough for use in an elementary physical chemistry course, but probably most of them are more suitable for somewhat more advanced students. They appear to be well chosen and should be of great value to graduate students and advanced undergraduates in physical chemistry.

E. Bright Wilson, Jr.

A Text-book on Crystal Physics. By W. A. Wooster, M.A., Ph.D., Lecturer in the Department of Mineralogy and Petrology, University of Cambridge. Cambridge University Press: The Macmillan Company, 60 Fifth Avenue, New York, N. Y., 1938. xxii + 295 pp. 107 figs. 14.5 × 22.5 cm. Price, $4.00.

In this book the author attempts to present the field of classical crystal physics in a form suitable for students having only an elementary knowledge of physics, mathematics and crystallography.

Tensors are introduced in the first chapter and the restrictions imposed upon the tensor components due to the invariance under symmetry operations are discussed. Much space could have been saved in the succeeding chapters if the author had included a little of the algebra of tensors. For instance reciprocal tensors are used implicitly in several sections of the book, and ought to have been defined in this first chapter.

The following chapters discuss in turn homogeneous deformation, conduction, induction, optics, piezo-electricity, pyro-electricity and elasticity.

In keeping with the assumed deficient knowledge of the reader the presentation is held on an elementary level. As a consequence the treatment is mainly descriptive, and the mathematical formulations, if given, are often sketchy and lack rigor. A discussion of Born's lattice theory was naturally outside the scope of a book of this kind. In a series of tables the author gives, however, qualitative, empirical correlations between observed properties and the atomic arrangement.

The material given in the book is well chosen and organized. While the book is not suited for students who have some knowledge of theoretical physics, it may be warmly recommended to the type of students for which it is written.

W. H. ZACHARIASEN

BOOKS RECEIVED

June 15, 1938–July 15, 1938

C. G. ANDERSON. "An Introduction to Bacteriological Chemistry." William Wood and Co., Mt. Royal and Guilford Aves., Baltimore, Md. 278 pp. $4.00.

WERNER VON BERGEN AND HERBERT R. MAUERSBERGER. "American Wool Handbook." American Wool Handbook Company, 303 Fifth Ave., New York, N. Y. 864 pp. $3.95.

ERNEST HAMLIN HUNTRESS. "Problems in Organic Chemistry." McGraw-Hill Book Co., Inc., 330 West 42d St., New York, N. Y. 270 pp. $2.25.

L. LANDAU AND E. LIFSHITZ. "Statistical Physics." Translated from the Russian by D. Schoenberg. Oxford University Press, 114 Fifth Ave., New York, N. Y. 234 pp. $6.00.

JAMES MURRAY LUCK AND CARL R. NOLLER, Editors. "Annual Review of Biochemistry. Vol. VII." Annual Reviews, Inc., Stanford University P. O., Calif. 571 pp. $5.00.

WILLIAM BUEL MELDRUM AND EARL WILLIAM FLOSDORF. "Qualitative Analysis of Inorganic Materials." American Book Company, 88 Lexington Ave., New York, N. Y. 230 pp. $2.50.

ADOLPH BERNADOTTE RINGSTROM. "The Ringstrom Three Dimensional System of the Atoms (with Atomic Musical Pitches) and the Theory of Atomic Integration." Vega Publishing Co., 1579 Milwaukee Ave., Chicago, Ill. 87 pp. $2.50.

WORTH H. RODEBUSH AND ESTHER K. RODEBUSH. "An Introductory Course in Physical Chemistry." Second edition. D. Van Nostrand Co., Inc., 250 Fourth Ave., New York, N. Y. 468 pp. $3.75.

EUGENE P. SCHOCH AND WILLIAM A. FELSING. "General Chemistry. An Introductory Course of Lessons and Exercises in Chemistry." McGraw-Hill Book Co., Inc., 330 West 42d St., New York, N. Y. 524 pp. $3.25.

JOSEPH SIVADJIAN. "La Chimie des Vitamines et des Hormones." Second edition. Gauthier-Villars, Éditeur, 55 Quai des Grands-Augustins, Paris VI^e, France. 239 pp. 50 fr.

HARRY SOBOTKA. "The Chemistry of the Sterids." The Williams and Wilkins Co., Mt. Royal and Guilford Aves., Baltimore, Md. 634 pp. $8.50.

A. THIEL, R. STROHECKER AND H. PATZSCH. "Taschenbuch für die Lebensmittelchemie." Walter de Gruyter and Co., Woyrschstrasse 13, Berlin W 35, Germany. 173 pp. RM. 8.60.

C. W. WATKEYS, Editor. "An Orientation in Science." McGraw-Hill Book Co., Inc., 330 West 42d St., New York, N. Y. 560 pp. $3.50.

ROBERT R. WILLIAMS AND TOM D. SPIES. "Vitamin B_1 (Thiamin) and its Use in Medicine." The Macmillan Co., 60 Fifth Ave., New York, N. Y. 411 pp. $5.00.

JAN ZERNDT. "Les Mégaspores du Bassin Houiller Polonais." Part II. Academie Polonaise des Sciences et des Lettres, 17 Rue Slawkowska, Kraków, Poland. 78 pp. + plates.

"Gmelins Handbuch der anorganischen Chemie. Systemnummer 22: Kalium." Lieferung 5. Verlag Chemie G. m. b. H., Corneliusstrasse 3, Berlin W 35, Germany 142 pp. RM. 19.50.

"Gmelins Handbuch der anorganischen Chemie. Systemnummer 25: Caesium." Lieferung 1. Verlag Chemie G. m. b. H., Corneliusstrasse 3, Berlin W 35, Germany. 104 pp. RM. 12.

"Gmelins Handbuch der anorganischen Chemie. System-nummer 27: Magnesium." Teil B, Lieferung 2. Verlag Chemie G. m. b. H., Corneliusstrasse 3, Berlin W 35, Germany. 130 pp. RM. 15.75.

"Gmelins Handbuch der anorganischen Chemie. System-nummer 63: Ruthenium." Verlag Chemie, G. m. b. H., Corneliusstrasse 3, Berlin W 35, Germany. 124 pp. RM. 16.50.

"Science in General Education." Report of the Committee on the Function of Science in General Education, Commission on Secondary School Curriculum. D. Appleton-Century Co., 35 West 32d St., New York, N. Y. 591 pp. $3.00.

"Tables of Reagents for Inorganic Analysis." In English, German and French. First Report of the "International Committee on New Analytical Reactions and Reagents," of the "Union Internationale de Chimie." Akademische Verlagsgesellschaft m. b. H., Sternwartenstrasse 8, Leipzig C 1, Germany. 409 pp. RM. 34; bound, RM. 36.

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[CONTRIBUTION FROM THE KENT AND GEORGE HERBERT JONES CHEMICAL LABORATORIES, UNIVERSITY OF CHICAGO]

The Catalytic Dehydrogenation of Sugar Alcohols[1]

BY J. W. E. GLATTFELD AND SOLOMON GERSHON

The preparation of aldoses by the oxidation of the corresponding sugar alcohols has been accomplished with varying degrees of success by several investigators. The published methods have not given encouraging results when applied to the preparation of some of the rare and more expensive aldoses. *l*-Galactose and *dl*-erythrose are sugars which might be made available for study if a method for accomplishing the dehydrogenation of the alcohols in a sufficiently convenient and inexpensive manner could be devised. A catalytic dehydrogenation process in which platinum is the catalyst was considered to have possibilities in this direction and the dehydrogenation of mannitol and dulcitol was attempted to test it.

Dehydrogenation of mannitol should give but one aldohexose, *d*-mannose, and one 2-ketohexose, *d*-fructose. This consideration together with the fact that the phenylhydrazone of mannose is particularly easy to separate in good yield makes mannitol an ideal alcohol for study. Fischer[2] treated mannitol with dilute nitric acid and isolated mannose phenylhydrazone and phenylglucosazone. Since then the presence of aldoses and ketoses in solutions obtained by oxidative treatment of hexitols has been verified on numerous occasions. In the case of dulcitol the aldohexoses and 2-ketohexoses theoretically possible as dehydrogenation products are *d*-galactose, *l*-galactose, *d*-tagatose, and *l*-tagatose.

With the possibilities outlined above in mind, the catalytic dehydrogenation of the two hexitols by the use of platinic oxide monohydrate as the catalyst source was undertaken. The course of the reaction and the effect of changes in the possible variants were studied first. Mannitol was used exclusively as the alcohol in this study; the data obtained are reported below under the head "Dehydrogenation Study." Procedures for the isolation of the aldoses produced from the alcohols were then investigated; the data here accumulated are reported under the head "Isolation Study." Finally the experimental work which yielded the data discussed under these two heads is reported under the head "Experimental Part."

Dehydrogenation Study

The preliminary data on the course of the reaction were obtained by analysis of the dehydrogenated mannitol solutions for total reducing material (Benedict titration), for aldose content (iodometric titration), and for acid content (titration with alkali). In order to determine the extent of oxidation of the primary products of hexitol dehydrogenation and the nature of their oxidation products, *d*-mannose and *d*-fructose were subjected to catalytic oxidation under the conditions that prevailed during the oxidation of mannitol. The data accumulated are given in Table I. In each case the dehydrogenation was carried out on a sample of 10 g. of substance in 200 cc. of water solution.

Dehydrogenation of *d*-Mannose.—The data in Table I indicate that *d*-mannonic acid was the

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(1) This article is condensed from a dissertation which was presented by Solomon Gershon in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Chicago.

(2) E. Fischer, *Ber.*, **20**, 832 (1887).

Table I

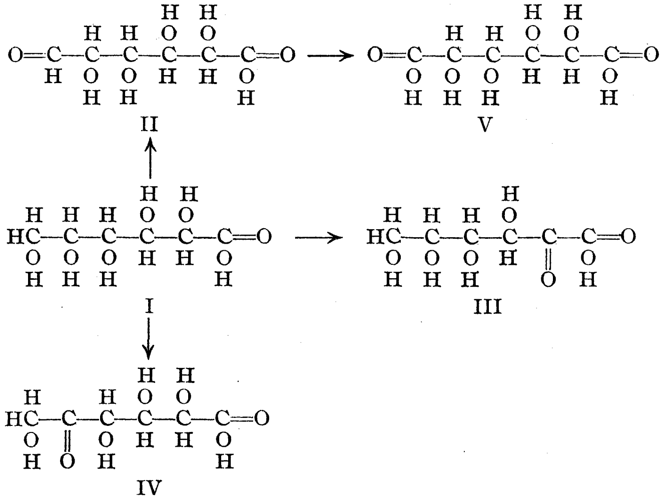
Catalytic Dehydrogenation of *d*-Mannose and *d*-Fructose

Time, hrs.	A Total red. power (calcd. as hexose) (Benedict titr.), %	100 − A Loss in total red. power, %	B Mat. oxid. to acid (calcd. as hexonic acid) (alkali titr.), %	C Aldose present (iod. titr.), %	$\frac{C}{A} \times 100$ Red. mat. present as aldose, %	D Mat. oxid. to osone. (iod. titr.), %	B + D, %
			d-Mannose				
0	100.0	0.0	0.0	100.0	100.0		
12	67.2	32.8	33.8	66.7	99.2		
24	50.0	50.0	68.9	51.5	103.0		
36	43.5	56.5	90.1	49.3	113.3		
48	35.2	64.8	103.6	41.7	118.4		
60	25.0	75.0	115.7	29.1	116.4		
72	14.0	86.0	122.3	....	....		
			d-Fructose				
0	100.0	0.0	0.0[a]			0.0	0.0
12	93.7	6.3	18.4			14.6	33.0
24	93.7	6.3	18.5			20.3	38.8
36	90.7	9.3	21.5			26.5	48.0
48	90.7	9.3	23.8			30.3	54.1
60	90.3	9.7	30.0			32.1	62.1
72	88.3	11.7	30.0			34.7	64.7

[a] This column calcd. as 2-ketohexonic acid.

only oxidation product of *d*-mannose in the early stages of the oxidation (the loss in reducing power 32.8%, twelve hours oxidation, coincided fairly well with the gain in hexonic acid content, 33.8%). Furthermore, the only reducing material present during this period was unchanged *d*-mannose (the amount of aldohexose present, as determined by iodometric titration, coincided with the total amount of reducing material present as determined by Benedict titration). As the dehydrogenation proceeded, however, the situation became more complex. A consideration of all the facts supports the conclusions that the second step in the oxidation process was the formation of *d*-mannuronic acid from *d*-mannonic acid and the third step the formation of *d*-mannosaccharic acid from *d*-mannuronic acid. The discussion below provides the basis for these conclusions.

A few of the theoretically possible primary oxidation products of *d*-mannonic acid (I) are indicated by the given formulas. *d*-Mannuronic acid (II) is a reducing alduronic acid. 2-Keto-*d*-mannonic acid (III) and 5-keto-*d*-mannonic acid (IV) are reducing keturonic acids. *d*-Mannuronic acid reduces both Benedict's solution and iodine solution whereas the two keturonic acids reduce the former but the latter only slightly, if at all. The reducing power of alduronic acids as measured by Benedict's solution is generally less than that of an equivalent weight of aldohexose[3] whereas the amount of iodine consumed in the two cases is the same. Hence, if alduronic acid were present with *d*-mannose an iodometric analysis would show more aldose, calculated as *d*-mannose, than would be indicated by a total reduction method. If keturonic acids were present with *d*-mannose, the iodometric analysis would show less aldose than would be obtained by a total reduction method. The per cent. aldose actually found by iodometric titration in the solution of *d*-mannose which had been oxidized for twenty-four hours or more


I
II
III
IV
V

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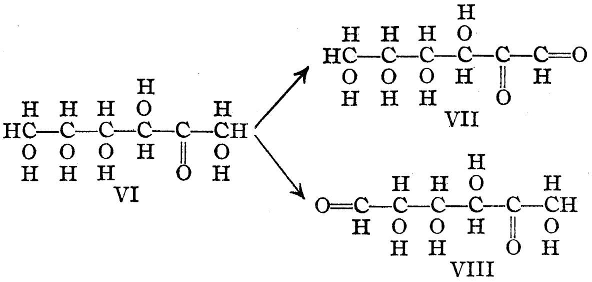
[3] H. Ohle and R. Wolter, *Ber.*, **63**, 843 (1930); F. Ehrlich and R. Guttmann, *ibid.*, **67**, 573 (1934); W. F. Goebel and F. H. Babers, *J. Biol. Chem.*, **100**, 573 (1933); Z. I. Kertesz, *ibid.*, **108**, 127 (1935)

was greater than that found by Benedict's titration (Table I). This is best explained on the assumption that *d*-mannonic acid was being oxidized to *d*-mannuronic acid. Undoubtedly some keto-mannonic acid was also formed but the amount must have been small. That *d*-mannuronic acid (II) was further oxidized to *d*-mannosaccharic acid (V) was shown by the isolation of the monohydrate of calcium *d*-mannosaccharate.

Nelson and Cretcher[4] have reported that *d*-mannuronic acid lactone reacts to some extent with alkaline iodine solutions to produce iodoform. The odor of iodoform was detected in some of the iodometric titrations carried out but no precipitation of iodoform occurred in the dilute solutions titrated. The consumption of iodine in iodoform formation would result in high values for the calculated amounts of aldose present and thus would nullify to some extent the argument presented for *d*-mannuronic acid formation. The authors, however, believe the amount of iodine consumed in iodoform formation in the dilute solutions titrated to have been so small as not to affect the reasoning to any appreciable extent. That iodoform was formed was proved by treatment of the undiluted dehydrogenated mannitol solutions with alkaline iodine solution; iodoform precipitated and was identified by melting point.

Hexoses, at elevated temperatures and in acid solution, give levulinic acid which is known to react with alkaline iodine solution to give iodoform. *d*-Glucose, *d*-mannose, *d*-galactose, and *d*-fructose were heated for twenty-four hours in a *d*-galactonic acid–lactone solution under conditions which prevailed in the hexitol oxidations. Benedict and iodometric titrations were made on the solutions before and after such treatment. No marked difference in results was observed. Levulinic acid apparently was not generated and could not, therefore, have been the source of the iodoform in the iodometric analyses.

Dehydrogenation of *d*-Fructose.—The possible six-carbon atom aldehydes that could be formed from *d*-fructose (VI) are indicated below (VII and VIII). The aldehydes as well as the corresponding acids produced by their oxidation are reducing substances. Even after seventy-two hours of oxidation the *d*-fructose solution retained 88.3% of its original reducing power. Analysis of this solution showed a 34.7% aldehyde and a 30.0% acid content. Thus 35.3% of the *d*-fructose was left unoxidized. When this solution was treated with phenylhydrazine in the cold an abundant yellow precipitate, identified as *d*-glucosazone, formed in a few minutes. The speed with which the precipitate formed indicated its source was *d*-glucosone (VII) and not *d*-fructose (VI). A 2% solution of *d*-fructose and phenylhydrazine did not produce a precipitate for twenty-five minutes while a 5% solution required ten to fifteen minutes.



Dehydrogenation of Mannitol.—The facts and conclusions recorded above aid in arriving at an interpretation of the data for the dehydrogenation of mannitol presented in Tables II and III. These data and some additional facts presented below indicate a course of reaction represented by the following scheme chart.

The first point to be noted is that the passage of air through a mannitol solution at 80–90° for thirty-five hours had practically no effect on the mannitol (Table II, 1). When platinic oxide monohydrate was added to a mannitol solution at 80–90° the mannitol was oxidized and the platinic oxide reduced to platinum (2, 3). The reaction between the oxide and mannitol was stoichiometric (4) (see Experimental Part). The passage of air through a mannitol solution which contained catalyst resulted in a dehydrogenation of the mannitol beyond the stoichiometric point. This indicates a catalytic effect of the platinum formed (5–8, etc.). Spent catalyst alone, *i. e.*, the platinum formed from the oxide in previous experiments, was without effect on mannitol (9). In the presence of air, however, the spent catalyst was a catalytic agent (10).

Experiments intended to compare oxygen with air as the oxidizing agent indicated the latter to be more efficient (11, 12). This was due to the fact that the oxide was reduced to platinum much more slowly in the presence of oxygen than in air

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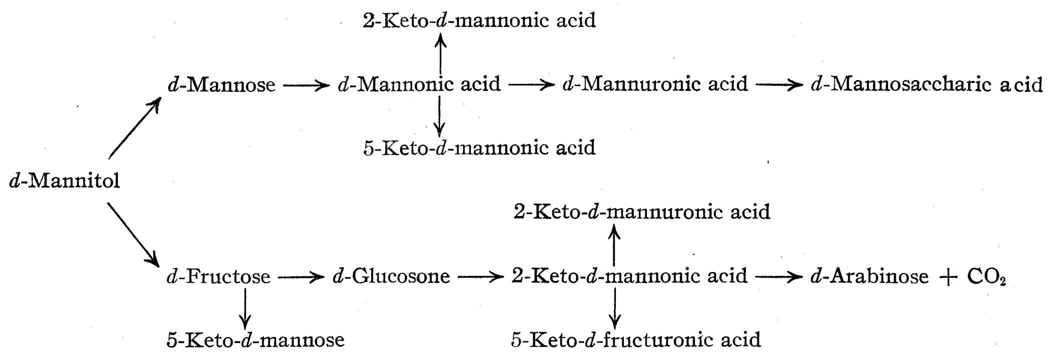
[4] W. F. Nelson and L. H. Cretcher, THIS JOURNAL, **52**, 2130 (1930).

SOME POSSIBLE OXIDATION PRODUCTS OF *d*-MANNITOL



which of course delayed the catalytic effect of the platinum. When time was allowed for the complete reduction of the oxide before the use of oxygen or air the former was more efficient. In such cases the time of reaction with oxygen was only 40–45% of that when air was used. Fifty grams of mannitol in 350 cc. of solution required the use of air for ninety-six hours in order to obtain maximum yields of mannose, whereas only fifty-five to sixty hours was required with oxygen. Twenty-five grams of mannitol in 200 cc. of solution required fifty-five hours with air but only thirty-two hours with oxygen.

The addition of the oxide in portions had no advantage. The addition of the entire amount of oxide at the start produced slightly better results because of longer contact between all of the catalyst and the solution (13b, 14). The amount of catalyst for best results depends somewhat on the amount of mannitol to be oxidized and the volume of solution (6, 7). Fifteen to 50 grams of mannitol in a 200–400 cc. volume can be dehydrogenated

TABLE II

DEHYDROGENATION OF MANNITOL

Expt.	Temp.,[a] °C.	Catalyst, g.	Mannitol in 200 cc. soln., g.	Time, hours	Conditions[b]		A, oxid. to red. mat. (calcd. as *d*-mannose) (Benedict titr.), %	B, oxid. to acid (calcd. as hexonic acid) (alkali titr.), %	A + B, %
1	80–90	0.0	5.0	35[e]	Air[c]		0.0	0.1	0.1
2	80–90	1.0	5.0	35[e]	No air		11.0		
3	80–90	0.5	5.0	35[e]	No air		9.8		
4	75	1.011	5.0	24	No air		19.1	6.7	25.8
5	80–90	1.0	5.0	35[e]	Air		41.8		
6	80–90	1.0	5.0	31[e]	Air		64.5		
7	80–90	0.5	5.0	31[e]	Air		49.1		
8	85	1.0	2.5	24	Air		37.6	65.5	103.1
9	80–90	1.0 spent	5.0	31[e]	No air		0.0		
10	80–90	1.0 catalyst	5.0	31[e]	Air		32.6		
11	60	1.0	2.5	46	Air		32.6	86.0	118.6
12	60	1.0	100 cc.	46	Oxygen		14.2	31.4	45.6
13[a]	85	4.0	5.0	2	Air, 8.6 l.		28.8	21.1	49.9
13[b]	85	4.0	5.0	8	Air, 30.0 l.		34.4	24.6	59.0
14	85	4.0[d]	5.0	8	Air, 30.0 l.		31.6	17.0	48.6
					O_2, lb.	R. p. m.			
15	27	1.0	2.5	24	30	185	5.8	1.4	7.2
16	80	1.0	2.5	24	30	185	28.0	29.9	57.9
17	80	1.0	2.5	12	25	300	20.1	9.4	29.5
18	75	0.84	2.5	32[e]	10	300	20.8	11.6	32.4
19[a]	63	1.0	2.5	45	23 air	245	18.6	7.3	25.9
19[b]	63	1.0	100 cc.	86	23 air	245	28.0	10.0	38.0

[a] Thermometer in the oil-bath for all cases except when pressure was used; in pressure work the temperature of the solution is recorded. [b] In all experiments in which air was used the air was started immediately after the catalyst was added. [c] Active bubbling of air through the solution to maintain an excess at all times. [d] Catalyst added in 1-g. portions every two hours. [e] Intermittent heating, eight hours per day.

satisfactorily with 2 g. of platinic oxide monohydrate.

The length of time required to reduce the oxide to platinum, as determined by change of color from brown to black, was dependent on the temperature and concentration of material being oxidized; the higher the temperature and the more concentrated the solution, the faster the reduction. Two grams of platinic oxide monohydrate was not reduced by 5 g. of mannitol in 200 cc. of solution after twenty-four hours of stirring at 30° whereas only forty-five minutes was required at 75°. Twenty-five grams of mannitol in 200 cc. of solution reduced 2 g. of oxide in twenty to twenty-five minutes at 80° while 15 g. required thirty to thirty-five minutes.

The optimum temperature for the catalytic dehydrogenation was 80–85° (thermometer in bath). Higher temperatures caused excessive caramelization and decomposition whereas lower temperatures necessitated longer reaction periods.

The effectiveness of the catalyst was not altered by varying its temperature of preparation. Platinic oxide monohydrate samples prepared at 400, 485, 535, and 600° all proved equally effective.

The use of oxygen or air at increased pressures, without first allowing time for the reduction of the oxide to platinum black, was less effective than oxidation at atmospheric pressure (15–19). In most cases the oxide was not reduced after twenty-four hours of agitation at the increased pressure. If sufficient time was allowed for the reduction of the oxide and pressure then applied, dehydrogenation proceeded much faster at the increased pressures than by simply bubbling oxygen or air through the solution (see Experimental Part and Table IV).

After the preliminary work discussed above, an extended study of dehydrogenation with platinum oxide and air at atmospheric pressure was made. From the data of Table III it is seen that during the first twenty-four hours mannitol was oxidized to about equal amounts of *d*-mannose and other reducing material. During the first thirty-six hours the percentage mannitol oxidized to reducing material exceeded the percentage mannitol oxidized to acid. As the concentration of the sugars increased the rate of acid formation increased, and the iodometric aldose titrations indicated increasing amounts of aldehyde. A faint iodoform odor was perceptible in the iodometric titrations of the sixty and seventy-two hour samples. Iodoform crystals were deposited when the undiluted seventy-two hour sample was treated with sodium carbonate and iodine. All oxidized mannitol solutions gave positive ketose tests and the twenty-four hour sample as well as the subsequent samples gave positive naphthoresorcin tests indicative of uronic acids.

The maximum value obtained for percentage mannitol oxidized to reducing substances, calculated as *d*-mannose, was 64.7% [Table III, (1)]. In pressure dehydrogenations the maximum value obtained was 67.7% [Table IV, (7)]. These values are higher than any previously reported value and demonstrate the possibilities of the catalytic dehydrogenation of sugar alcohols when properly controlled.

TABLE III

CATALYTIC DEHYDROGENATION OF HEXITOLS

Hexitol (15 g. in 200 cc. sol.)	Time, hrs.	A Oxid. to red. material (calcd. as aldohexose) (Benedict titr.), %	B Oxid. to acid (calcd. as hexonic acid) (alkali titr.), %	C Oxid. to aldose (iod. titr.), %	$\frac{C}{A} \times 100$ Red. mat. present as aldose, %	A + B, %
(1)Mannitol	0	0.0	0.0	0.0	0.0	0.0
	12	21.6	15.7	10.7	49.5	37.3
	24	35.9	29.8	23.1	64.3	65.7
	36	57.3	49.3	46.8	81.7	106.6
	48	64.7	76.0	59.5	92.0	140.7
	60	58.8	111.7	65.3	111.0	170.5
	72	43.5	165.0	55.4	127.4	208.5
(2)Dulcitol	0	0.0	0.0	0.0	0.0	0.0
	12	12.4	9.2	8.5	68.5	21.6
	24	19.4	24.6	13.5	69.6	44.0
	36	40.0	42.8	34.8	87.0	82.8
	48	55.2	61.6	55.2	100.0	116.8
	60	42.3	84.0	46.5	109.9	126.3
	72	29.2	104.4	31.0	106.1	133.6

Isolation Study

Mannitol.—It is apparent from the data of Table III (1) that the percentage mannitol oxidized to reducing material is in itself not a sufficient criterion of best condition for aldose isolation. A thirty-six hour sample showed 57.3% oxidation whereas a sixty-hour sample showed 58.8% oxidation to reducing material, yet the latter was contaminated with over twice as much acid as the former. Analysis of a solution might indicate 30–40% oxidation to reducing material and yet the solution might contain very little *d*-mannose, the reduction being due mainly to uronic acids. Such a solution would not be suitable for *d*-mannose isolation. The best criterion for isolation of *d*-mannose was found to be that point at which the solution showed 55–60% oxidation to reducing material and about 50% oxidation to acid.

The best yield of mannose from mannitol oxidation found recorded in the literature was that of Fenton and Jackson[5] who used hydrogen peroxide with ferrous catalyst and obtained a 42% yield of mannose as crude orange-colored phenylhydrazone. In the catalytic dehydrogenation of mannitol reported in this paper a 35.3% yield of mannose was obtained as white phenylhydrazone, which when decomposed according to the method of Herzfeld,[6] yielded a sirup which contained *d*-mannose equivalent to a 92% yield, from which in turn crystalline *d*-mannose in 50% yield was obtained calculated from the phenylhydrazone. Calculated from the mannitol the yield of *d*-mannose sirup was 32.5%, and of crystalline *d*-mannose 17.6%. The mannose was also isolated as α-methyl-*d*-mannoside, from the oxidized mannitol solutions from which the acids had been removed, in 19.9% yield and from solutions from which the acids had not been removed in 10.5% yield. The mannoside can be converted to crystalline *d*-mannose in 70% yield.[7]

After removal of the acids and of the *d*-mannose, phenylglucosazone was isolated. This was indicative of the presence of *d*-fructose. The Seliwanoff[8] ketose tests and the results of the iodometric analyses were also evidence for the presence of ketose. Calcium salts were isolated at various times from the reducing solutions. Analysis of one salt indicated it to be the monohydrate of calcium *d*-mannonate and that of another the monohydrate of calcium *d*-mannosaccharate (see below).

Dulcitol.—The analytical results obtained in the catalytic dehydrogenation of dulcitol are presented in Table III (2). The products of the reaction are of the same type as found with mannitol. Thus *dl*-galactose, *dl*-tagatose, *dl*-galactonic acid, *dl*-galactosone, 2-keto-*dl*-galactonic acid, *dl*-galacturonic acid, and mucic acid are present in the reaction solution.

The best yield of *dl*-galactose reported in the literature is that of Neuberg and Wohlegemuth[9] who used 3% hydrogen peroxide in the presence of ferrous sulfate to oxidize the dulcitol and obtained a solution which contained 40% reducing sugars. From this these authors obtained *dl*-galactose in 10% yield by direct isolation and in about 30% yield when they used phenylhydrazine. In the catalytic dehydrogenation of dulcitol herewith reported a 30% yield of *dl*-galactose, isolated as the phenylhydrazone, was obtained. Crystalline *dl*-galactose was isolated from the phenylhydrazone in 52% yield. The yield of crystalline *dl*-galactose obtained was 15.5% based on the dulcitol.

E. Votocek and co-workers[10] have reported the quantitative precipitation of *d*-galactose as 2,4-dibromophenylhydrazone monohydrate from aqueous acetic acid solution. With this fact in mind, a dulcitol solution was subjected to catalytic dehydrogenation until it showed about 50% oxidation to reducing material. *dl*-Galactose was isolated in 23.5% yield as a pink anhydrous 2,4-dibromophenylhydrazone.

dl-2,4-Dibromophenylgalactosazone and *dl*-phenylgalactosazone were isolated from the filtrates obtained after removal of the corresponding hydrazones. Mucic acid also was isolated.* Two barium salts were isolated and analyzed for barium. One contained 26.42% barium, the other 34.93% barium. Barium *dl*-galactonate contains 26.03% and the dihydrate of barium mucate contains 35.80% barium.

The salts isolated from the various reducing solutions cannot be considered pure substances even with satisfactory analyses. Barium *dl*-

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[5] H. J. H. Fenton and H. Jackson, *J. Chem. Soc.*, **75**, 1 (1899).

[6] A. Herzfeld, *Ber.*, **28**, 442 (1895); E. Abderhalden, "Handbuch der biochemischen Arbeitsmethoden," Urban and Schwarzenberg, Berlin, Vol. II, 1909, p. 74.

[7] C. S. Hudson and E. L. Jackson, THIS JOURNAL, **56**, 958 (1934).

[8] T. Seliwanoff, *Ber.*, **20**, 181 (1887); E. Abderhalden, ref. 6, p. 109.

[9] C. Neuberg and J. Wohlegemuth, *Z. physiol. Chem.*, **36**, 221 (1902).

[10] E. Votocek, V. Ettel and B. Koppova, *Bull. soc. chim.*, [4] **39**, 278 (1926).

galactonate contains 26.03% barium whereas barium *dl*-galacturonate contains 26.24%. The isolated barium salt which contained 26.42% barium did contain some of the barium *dl*-galacturonate. Its solution reduced Benedict's solution and gave a faint naphthoresorcin test.

Experimental Part

Reagents and Procedures.—(1) The platinic oxide monohydrate was prepared by the method of Adams, Voorhees, and Shriner[11] as modified by Schimpff[12] for larger amounts of catalyst. (2) The mannitol, dulcitol, and *d*-galactose were products of the Kahlbaum Chemical Company. (3) The *d*-glucose, *d*-fructose, and *d*-mannose were products of Pfanstiehl Chemical Company. (4) 2,4-Dibromophenylhydrazine was prepared from *β*-acetylphenylhydrazine by the method of Humphries and Evans.[13] The *β*-acetylphenylhydrazine was prepared by the method of A. Kaufmann.[14] (5) The naphthoresorcin was manufactured by the Eastman Kodak Company.

All iodometric analyses were made by the method developed by Cajori.[15] In all cases in which alcoholic solutions were to be analyzed, the alcohol was first removed by evaporation of the sample to a thick sirup *in vacuo* at 60–70°. Water was then added and the evaporation repeated. Iodoform formation due to the presence of the alcohol thus was avoided.

The acidimetric analyses were performed as follows. An excess of 0.1 *N* sodium hydroxide solution was added to the sample to be analyzed (phenolphthalein indicator). The solution was heated on a steam-bath for three minutes, after which time the solution still retained the pink color. An excess of 0.1 *N* hydrochloric acid was then added and the three-minute heating was repeated. The solution was then cooled and the excess acid determined by titration with standard alkali.

Tollens' naphthoresorcin[16] test for glycuronic acids was performed according to the modification of Neuberg and Kobel.[17]

1. Dehydrogenation of Mannitol

Preliminary Dehydrogenation Work.—All of the preliminary work was performed with mannitol. In all but the pressure work the solution of mannitol was made in a 500-cc. three-necked flask fitted with a mercury-seal stirrer, an efficient condenser, and an air inlet tube. The flask was immersed in a paraffin oil-bath which was heated on an electric hot plate. The temperature of the oil-bath was regulated by means of a rheostat. The conditions desired (recorded in Table II) were maintained by suitable adjustment of the rheostat, air flow, or other variables. In all cases in which the volume of air used is recorded a gasometer was used. In all cases, the air or oxygen was passed through concentrated sulfuric acid and then through a long calcium chloride tube before entrance into the reaction flask. The reaction solutions were filtered to remove platinum and then analyzed.

In the case of the test runs for which the data are presented in Table III the solutions were analyzed every twelve hours. All samples showed positive ketose tests. All samples beyond the twelve-hour sample showed positive naphthoresorcin tests.

All work performed under pressures greater than atmospheric was carried out in the hydrogenation apparatus manufactured by the Burgess–Parr Company of Moline, Illinois. The tank was filled with oxygen or air at the pressure desired. The pressure bottle was wired to maintain the reaction mixture at desired temperatures.

Stoichiometric Relationship between Catalyst and Hexitol.—Five grams of mannitol was dissolved in 200 cc. of boiled water at 75° in a three-necked flask fitted with a mercury-seal stirrer and condenser. The platinic oxide monohydrate (1.011 g.) was added with stirring. The oxide was reduced but did not settle readily after eight hours of stirring at 75°. The stirring at 75° was continued overnight, after which time the platinum settled readily and left a colorless solution. The platinum was removed by filtration and the filtrate was analyzed for total reducing material, aldose, and acid. The amount of mannitol oxidized to reducing material (calculated as *d*-mannose) was 0.953 g. (62.3% of the reducing material was aldose). This would require 0.642 g. of the platinic oxide monohydrate. The amount of mannitol oxidized to acid (calculated as monobasic acid) was 0.335 g. which would require 0.451 g. of the oxide. A total of 1.093 g. of oxide is thus theoretically necessary. This value is 0.082 g. in excess of the amount of oxide actually used and is slightly in excess of the amount accountable for by experimental error. The simplifications made in the calculation of the per cent. mannitol oxidized, however, would tend to make such small differences. There can be no doubt that the reaction is stoichiometric.

Preparation of the Phenylhydrazone of *d*-Mannose.—Fifty grams of mannitol was dissolved in 350 cc. of hot distilled water in a three-necked flask fitted with a mercury-seal stirrer, an efficient condenser, and an air-inlet tube. The flask was immersed in an oil-bath maintained at 80–85° throughout the dehydrogenation. Two grams of platinic oxide monohydrate was added. Stirring was begun and allowed to continue for thirty minutes. Oxygen was then passed through the solution rapidly enough to keep the catalyst uniformly suspended. The stirring and passage of oxygen was maintained for sixty hours (when air was used, ninety-six to one hundred hours was necessary). The platinum was allowed to settle (about ten minutes) and the solution was filtered. The filtrate and washings were concentrated to about 200 cc. at 55–60° under reduced pressure. A filtered solution of 40 g. of phenylhydrazine hydrochloride and 60 g. of sodium acetate trihydrate in 300 cc. of water (made by the application of gentle heat) was then added slowly and with stirring to the concentrated solution. A precipitate began to form in about one minute. The mixture was allowed to stand for one and one-half hours with occasional stirring. The yellow precipitate was separated by filtration and washed

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[11] Adams, Voorhees and Shriner, "Organic Syntheses," 1928, John Wiley and Sons, Inc., New York City, Vol. VIII, p. 98.

[12] G. W. Schimpff, Ph.D. dissertation, Dept. of Chemistry, University of Chicago, 1935.

[13] J. E. Humphries and R. Evans, *J. Chem. Soc.*, **127**, 1676 (1925).

[14] A. Kaufmann, *Ber.*, **42**, 3480 (1909).

[15] F. A. Cajori, *J. Biol. Chem.*, **54**, 617 (1922).

[16] B. Tollens, *Ber.*, **41**, 1788 (1908).

[17] Neuberg and Kobel, *Biochem. Z.*, **243**, 435 (1931).

with water. After it had been drained free of excess water on a Büchner funnel the precipitate was heated in about 700 cc. of acetone until the acetone boiled. The mixture was then cooled, subjected to filtration, and the solid washed with cold acetone. The phenylhydrazone of *d*-mannose was left as a fine white powder which weighed twenty-six grams. This corresponded to a 35.3% yield. The product melted with decomposition at 195–196° (corr.) and was found to be suitable for *d*-mannose isolation.

A portion of the phenylhydrazone was recrystallized twice from 95% alcohol, dried in a vacuum desiccator, and analyzed for carbon, hydrogen, and nitrogen with the results recorded below.

Anal. Calcd. for $C_{12}H_{18}O_5N_2$: C, 53.30; H, 6.71; N, 10.37. Found: C, 53.37; H, 6.53; N, 10.17.

Isolation of *d*-Mannose from Phenylhydrazone.—Twenty-five grams of the phenylhydrazone of *d*-mannose was added in small portions to a mixture of 20 g. of benzaldehyde, 25 cc. of alcohol, and 25 cc. of water which was kept hot on a steam-bath. The mixture was then refluxed for thirty minutes during which time 35 cc. of water was added. The mixture was cooled and subjected to filtration. The precipitate was triturated with small amounts of water and again separated by filtration. It was identified, after recrystallization from dilute alcohol, as the phenylhydrazone of benzaldehyde (m. p. 154.5°). The combined filtrates from the benzaldehyde phenylhydrazone were extracted with ether; the separated aqueous layer was heated with charcoal and filtered. The solution thus obtained had a volume of 225 cc. and a rotation of +2.00°. This indicates the presence of 15.2 g. of *d*-mannose (theoretical yield, 16.6 g.). The solution was evaporated to a sirup at reduced pressure and at 50°. The sirup weighed 16.5 g. and contained 91.7% mannose (Benedict titration). An optical rotation analysis showed the sirup to be 93.0% mannose.

A mixture of the sirup and 35 cc. of glacial acetic acid was warmed to 60° and maintained at 60° for one hour in order to effect complete solution of the sirup in the acid. The solution was allowed to cool slowly to room temperature and stored for one day, during which time crystals appeared. The mixture was then stored in the refrigerator for four days. The crystalline *d*-mannose was removed by filtration and washed with two 5-cc. portions of glacial acetic acid, followed by small volumes of alcohol and ether. The crystals were dried to constant weight in a vacuum desiccator which contained sodium hydroxide. The crystals then melted at 130–131° (corr) and weighed 7.0 g. This corresponded to a 50% yield of *d*-mannose. The specific rotation of the *d*-mannose was +14.9°. From the acetic acid filtrates 3.5 g. of a white sirupy mannose was precipitated by the addition of ether.

Isolation of α-Methyl-*d*-mannoside.—Fifty grams of mannitol dissolved in 350 cc. of water was oxidized with oxygen at 80–85° for fifty-five hours in the presence of 2 g. of platinic oxide monohydrate. The solution was filtered to remove platinum; the acids were removed from the filtrate with barium carbonate as described under the head "Isolation of Calcium and Barium Salts" below.

The combined alcohol filtrates obtained after the removal of the acids as barium salts were evaporated to a thick sirup *in vacuo* at 55°. The residue was kept at reduced pressure and 55° for one hour and then *in vacuo* overnight. It was then treated with 150 cc. of a 2% solution of hydrogen chloride in anhydrous methyl alcohol (acetone free). The mixture was gently refluxed for two hours on a steam-bath. Agitation was necessary during the first ten minutes to assist in the solution of the sirup. The solution was cooled somewhat, treated with 3–4 g. of charcoal, and then refluxed for thirty minutes. The solution was filtered hot. Small portions (a total of 20 cc.) of hot anhydrous methyl alcohol were used to complete the transfer. The filtrate was placed in the refrigerator for fifty hours. The crystalline mannoside was then removed by filtration and washed with a little cold absolute methyl alcohol followed by a little dry acetone. The air-dried α-methyl-*d*-mannoside melted at 189–191° (corr.), did not reduce Benedict's solution, and had a specific rotation of +79.0° at 20°. A 16.5% yield (8.8 g.) was obtained by this procedure. The filtrate was concentrated to 40 cc. at 35° *in vacuo* and placed in the refrigerator for four days. One and eight-tenths grams of crystals (m. p. 185–187°, corr.) was obtained, making a total yield of 19.9% (10.6 g.).

Isolation of Calcium and Barium Salts.—The following general procedure was used for the isolation of the calcium or barium salts from the solutions obtained by the oxidation of 25 g. of each of the oxidized hexitols. The platinum was first removed by filtration. The filtrate was treated with excess calcium or barium carbonate and the mixture maintained at 80° (thermometer in oil-bath) for one to two hours. Frequent or continuous stirring was employed throughout this heating. The excess carbonate was removed by filtration and the filtrate was concentrated at 55–60° *in vacuo* to a volume of about 50 cc. Three hundred cc. of hot alcohol was then added slowly and the mixture thoroughly shaken. The mixture was cooled and the supernatant liquid filtered. The residual gummy barium or calcium salts were treated with 25 cc. of hot water and the mixture again treated with 150 cc. of hot alcohol. After one hour the solution was again decanted through the filter. The barium or calcium salts were left behind in the form of a gum. The combined alcoholic solutions were used for aldose and osazone isolations (see below). The calcium or barium salt gums were dissolved in hot water, treated with charcoal, and the solutions filtered. Hot alcohol was added in small amounts to the hot filtrates until a permanent turbidity occurred. The solutions were then cooled and allowed to stand overnight. The salts which had crystallized out were separated from the solution by filtration, washed with 60–80% alcohol, and dried in a desiccator. The dried salts were then recrystallized by solution in hot water followed by reprecipitation with alcohol as described above. The salts thus obtained were dried in a vacuum desiccator.

Two calcium salts were thus isolated from twenty-five grams of mannitol which had been subjected to oxidation for forty-eight hours. During the recrystallization process the major portion of the calcium salt precipitated from the aqueous alcohol solution as an amorphous white solid. The filtrate from this solid deposited more salt on standing. The first salt contained 9.06% while the second contained 14.80% calcium. Calcium *d*-mannonate monohydrate contains 8.94% calcium, while calcium *d*-mannosaccharate

TABLE IV

PRESSURE DEHYDROGENATION

In all cases 25 g. of mannitol was dissolved in 200 cc. of water except in experiment 6 where 15 g. was dissolved in 100 cc. of water; the shaker was regulated at 300 rev. per min. In all cases thirty minutes of shaking at atmospheric pressure was used after each addition of catalyst. The temperature was 83°.

Expt.	Initial oxy. press., lb.	Catalyst added, g.	Time, hrs.	Press. decr., lb.	Oxid. to reducing material (calcd. as *d*-mannose) (Benedict titr.) %	Oxid. to acid (calcd. as hexonic acid) (alkali titr.) %	Yield of *d*-mannose as phenylhydrazone, %
1	40	2.0	2.0	4.6			
			5.0[a]	0.0	32.3	31.6	16.8
2a	42	2.0	2.0	5.0			
b	42	1.0	1.0	2.0	35.1	53.0	14.0
3a	42	2.0	1.0	4.8			
b	42	1.0	1.0	2.2	49.4	56.2	20.7
4a	42	2.0	1.0	4.3			
b	42	2.0	0.5	2.1	41.3	59.2	16.4
5a	42	2.0	1.0	5.5			
b	42	1.0	1.0	2.2			
c	42	1.0	1.0	1.5	44.4	73.4	5.6
6	40	2.0	2.5	4.6	39.0	56.6	11.4
7	42	2.0	2.5[b]	5.0			
			3.5 hot				
			2.5 cold				
			4.0 hot	3.0			
			22.0 hot and cold	0.2	67.7	58.3	25.4

[a] The hours listed are in addition to those listed in the same experiment. [b] The hours listed in this case are only approximate; the wire connected to the bottle snapped off twice while shaking, thus allowing the bottle to cool.

monohydrate contains 15.05% calcium. Fischer and Hirschberger[18] prepared a hydrated calcium *d*-mannonate which contained 8.78% calcium.

Isolation of Phenylglucosazone from an Oxidized Mannitol Solution.—The aqueous alcohol solution from which the calcium salts had been removed was treated with a filtered solution of 20 g. of phenylhydrazine hydrochloride and 30 g. of sodium acetate trihydrate in 150 cc. of water. The mixture was allowed to stand for one and one-half hours and then subjected to filtration. The filtrate was reserved for the isolation of glucosazone. The precipitate was washed with water, heated with 200 cc. of acetone until the latter boiled, the mixture cooled, subjected to filtration, the precipitate washed with acetone, and dried. This yield of phenylhydrazone of *d*-mannose was 20%.

The filtrate saved for glucosazone isolation was treated with 10 g. of phenylhydrazine in 10 cc. of 50% acetic acid and the solution heated on a steam-bath for two hours. The mixture was cooled and subjected to filtration. The precipitate was washed with water followed by alcohol, and dried. A yield of 9.5% glucosazone was obtained. The melting point was 206–207° (corr.). The product was recrystallized from 65% alcohol, dried, and analyzed for nitrogen.

Anal. Calcd. for $C_{18}H_{22}O_4N_4$: N, 15.64. Found: N, 15.53.

Pressure Dehydrogenations.—Twenty-five grams of mannitol was dissolved in 200 cc. of hot water in a pressure bottle. The bottle was wired and by regulation of the current a temperature of 83° was maintained. Two grams of platinic oxide monohydrate was added and the bottle shaken at 300 revolutions per minute and at atmospheric pressure for thirty minutes, when the catalyst was black. The bottle was carefully evacuated until the solution began to boil and then filled with oxygen at 42 lb. (3 atm.) pressure. The evacuation and filling were repeated three times. After the third filling, shaking was started and maintained for one hour. The pressure decreased 4.8 lb. (0.3 atm.). After one hour of agitation at the increased pressure, the catalyst activity ceased and the use of oxygen by the mannitol stopped. One gram of platinic oxide was added after the pressure had been released, the mixture was shaken at atmospheric pressure for thirty minutes followed by evacuation and filling with oxygen at 42 lb. (3 atm.) pressure as described. This time there was a decrease of 2.2 lb. (0.15 atm.) in one hour. (It is to be noted that the catalyst was added in several portions during the pressure dehydrogenations rather than in one portion as was more desirable in atmospheric pressure dehydrogenations. The cessation of catalyst activity at the increased pressures makes such a procedure necessary.) The solution was cooled for about thirty minutes and then the pressure was released and the solution filtered. The small amount of colloidal platinum was removed from the filtrate by the use of charcoal. Analysis of the filtrate from the charcoal showed that 49.4% of the mannitol had been oxidized to reducing material, calculated as *d*-mannose, and that 56.2% had been oxidized to acids, calculated as hexonic acid. The *d*-mannose was isolated as the phenylhydrazone in 20.7% yield from this solution. Table IV lists the data for other experiments with different conditions.

The main disadvantage of pressure dehydrogenations is the tendency for the oxidation to proceed beyond the aldose in the later stages of the oxidation, thus building up high concentrations of acid at the expense of aldose. As a re-

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(18) Fischer and Hirschberger, *Ber.*, **22**, 3219 (1889).

sult, the yields obtained by pressure dehydrogenation were lower than those obtained at atmospheric pressure.

2. Dehydrogenation of Dulcitol

Isolation of Mucic Acid.—The data for the results obtained in a test run in which 15 g. of dulcitol in 200 cc. of water at 80° and 2.0 g. of platinic oxide monohydrate were used, are presented in Table III (2). The solution which remained after the seventy-two hour sample had been removed deposited a crystalline substance that was identified as mucic acid by its melting point (213°, corr.) and that of its diphenylhydrazide[19] (241°, corr.).

Isolation of *dl*-Galactose with 2,4-Dibromophenylhydrazine.—Fifteen grams of dulcitol in 200 cc. of water at 80° was treated with 2.0 g. of platinic oxide monohydrate and the procedure described in the case of mannitol carried out. After thirty minutes, air was passed through the solution for forty-four hours. This solution gave positive ketose and naphthoresorcin tests and showed that 47.2% of the dulcitol had been oxidized to reducing material (calculated as *dl*-galactose) and that 48.8% had been oxidized to acid (calculated as *dl*-galactonic acid). Iodometric analysis showed that 90% of the reducing material was aldose. The solution was filtered to remove platinum and the filtrate concentrated *in vacuo* at 50° to about 35 cc. A filtered solution of 20 g. of 2,4-dibromophenylhydrazine in 140 cc. of 50% acetic acid (prepared by gentle warming) was added slowly to this concentrate. The mixture was filtered rapidly to remove a small amount of red oil which formed and the filtrate allowed to stand for three hours at room temperature. The mixture was stirred several times during this period. The precipitate was removed by filtration, washed with 100 cc. of 5% acetic acid, 25 cc. of diluted alcohol, and finally with ether. The filtrate was saved for osazone isolation. The 2,4-dibromophenylhydrazone of *dl*-galactose thus obtained was faintly pink and melted at 151–152° (corr.). The yield was 23.5%. Three recrystallizations from dilute alcohol raised the melting point to 171–172° (corr.). Charcoal was used in each recrystallization. The pure 2,4-dibromophenylhydrazone was white. It was dried at room temperature over magnesium perchlorate for two days at 20 mm. pressure and was then analyzed for nitrogen.

Anal. Calcd. for $C_{12}H_{16}O_5N_2Br_2$: N, 6.55. Found: N, 6.64.

The 2,4-dibromophenylhydrazone of *dl*-galactose was decomposed with benzaldehyde by the method of Herzfeld and yielded the 2,4-dibromophenylhydrazone of benzaldehyde and *dl*-galactose. The former melted at 103° (corr.) after several recrystallizations from dilute alcohol while the latter melted at 142–144° (corr.).

Isolation of the 2,4-Dibromophenylosazone of *dl*-Galactose.—The filtrate saved for osazone isolation was heated for two hours on a steam-bath. A black oil settled out. The mixture was cooled and about 4 g. of solid crystallized out. This was separated from the oil which remained on the bottom of the flask and was recrystallized from dilute alcohol. It was identified as the 2,4-dibromophenylhydrazide of acetic acid by its melting point, 147° (corr.).

The oil was dissolved in boiling 60% alcohol and the solution treated with charcoal, filtered, and cooled. It deposited 4 g. of a yellow precipitate which decomposed at 145–149° (corr.). This was recrystallized from dilute alcohol to which charcoal had been added and thoroughly dried over phosphorus pentoxide. The compound decomposed at 152–153° (corr.).

Anal. Calcd. for $C_{18}H_{18}O_4N_4Br_4$: N, 8.32. Found: N, 8.37.

Isolation of *dl*-Galactose with Phenylhydrazine.—Twenty-five grams of dulcitol was dissolved in 350 cc. of hot water in a three-necked flask fitted as described for mannitol. Two grams of platinic oxide monohydrate was added when the solution had reached 80°. The mixture was stirred for one hour after which air was bubbled through the solution for seventy hours. The solution then showed 60.3% of the dulcitol to have been oxidized to reducing material (calculated as *dl*-galactose) and 56.0% to acid. The solution gave positive ketose and naphthoresorcin tests. The platinum was removed by filtration and the acids were removed as barium salts by the general method described.

The alcoholic filtrate from the precipitated barium salts was concentrated at 40–50° at reduced pressure to a thin sirup which was treated with 9 g. of distilled phenylhydrazine in an equal volume of 50% acetic acid. The mixture was warmed gently a few minutes on a steam-bath, stoppered, and set aside in a dark place at room temperature for twenty-four hours. The yellow precipitate was separated by filtration and washed with a small amount of 50% alcohol. The filtrate was saved for the isolation of the *dl*-osazone. The precipitate was washed further with absolute alcohol and ether and dried. It decomposed at 144–148° (corr.). The yield of this impure phenylhydrazone was 30%. Recrystallization of the phenylhydrazone resulted in considerable loss because of solubility and because of the formation of osazone. It was therefore used without purification for the isolation of *dl*-galactose.

The crude phenylhydrazone was treated with 300 cc. of water and 12 g. of benzaldehyde. The mixture was kept on a steam-bath for thirty minutes, cooled, and subjected to filtration. The filtrate was extracted with ether several times and the separated aqueous solution was decolorized with charcoal. The solution was optically inactive. It was concentrated at 50–55° at reduced pressure to a thick sirup which weighed 5.3 g. The sirup was dissolved in hot alcohol and the solution deposited 3.8 g. of *dl*-galactose crystals, a 15.5% yield calculated from dulcitol used. The crystals were dried in vacuum over calcium chloride at 15 mm. pressure for two days. The melting point was 145° (corr.). Oxidation with nitric acid yielded mucic acid. Analysis by Benedict titration showed the material to be 98.6% *dl*-galactose. Iodometric analysis showed it to be 99.2% *dl*-galactose.

Isolation of *dl*-Phenylgalactosazone.—The filtrate set aside for osazone isolation was treated with a filtered solution of 20 g. of phenylhydrazine hydrochloride and 30 g. of sodium acetate trihydrate in 100 cc. of water. The mixture was heated on the steam-bath for one and one-half hours, cooled, and subjected to filtration. The precipitate was washed with absolute alcohol and then with ether. The dry *dl*-osazone weighed 3.5 g. indicating a 7.3% yield. It decomposed at 207° (corr.). It was recrystallized from

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[19] C. Bülow, *Ann.*, **236**, 194 (1886).

alcohol and dried *in vacuo* over calcium chloride. The compound decomposed at 208–209° (corr.).

Anal. Calcd. for $C_{18}H_{22}O_4N_4$: N, 15.64. Found: N, 15.71.

Isolation of Barium Salts.—The gummy barium salt obtained in a sixty-hour oxidation of 25 g. of dulcitol was heated with charcoal and hot water which dissolved all but 0.5 g. of material. The solution was filtered and concentrated at reduced pressure and 55° to a thin sirup. Alcohol was added very slowly to precipitate the barium salt and the mixture then warmed on a steam-bath for one hour. The mixture was cooled and subjected to filtration. The precipitate was washed with alcohol and with ether. It was dried in a vacuum desiccator for one hour, followed by two hours in an oven at 100°.

Anal. Calcd. for barium *dl*-galactonate: Ba, 26.03; for barium *dl*-galacturonate, 26.24. Found: Ba, 26.43, 26.40.

The barium salt obtained by an identical procedure in a seventy-two hour oxidation contained 34.93% barium; calculated for barium mucate dihydrate, 35.80%. Neither salt decomposed at 250° and both gave naphthoresorcin tests.

Summary

A convenient method for the catalytic dehydrogenation of sugar alcohols was developed. Mannitol and dulcitol were the hexitols studied. The advantage of the method lies in the ease of controlling the amount of hexitol dehydrogenated. The results obtained indicate that the method is most satisfactory for aldose isolation in the case of alcohols which yield but one aldose or a *dl*-aldose when dehydrogenated.

Platinic oxide monohydrate was used as the source of the platinum catalyst. The oxide acts first as an oxidizing agent.

The effect of change in the possible variants was studied.

The course of the reaction was determined by a combination of isolation of products and analytical procedures. Mannitol was oxidized to *d*-mannose and *d*-fructose. *d*-Mannose was oxidized, in the main, to *d*-mannonic acid, *d*-mannuronic acid, and finally to *d*-mannosaccharic acid. The *d*-fructose was oxidized, in the main, to *d*-glucosone and 2-keto-*d*-mannonic acid. Other products were also formed in small amounts. The products with dulcitol were similar in nature.

d-Mannose was conveniently prepared by the catalytic dehydrogenation of mannitol. The *d*-mannose was isolated from the reaction mixtures as the phenylhydrazone and as the α-methyl-*d*-mannoside.

dl-Galactose was prepared similarly from dulcitol.

The catalytic dehydrogenation method gives promise of being satisfactory for the preparation of sugars like *dl*-erythrose from the alcohol, erythritol.

CHICAGO, ILLINOIS RECEIVED JUNE 21, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

The Reductive Alkylation of Aniline

BY WILLIAM S. EMERSON AND PHILIP M. WALTERS

Although the reductive alkylation of amines is a well-known reaction,[1] it has found little application with primary aromatic amines. Clarke, Gillespie and Weisshaus,[1a] using formic acid as their reducing agent, methylated tribromoaniline with formaldehyde to give 77% of N,N-dimethyltribromoaniline. However, they obtained only polymers when aniline was used. While Skita and Keil[2] were able to prepare cyclohexylaniline from aniline and cyclohexanone in the presence of platinum and hydrogen, they did not mention their yield. Wallach[3] obtained di-*n*-amylaniline by heating valeraldehyde with phenylammonium formate, but he also gave no yield. The patent literature[4] contains references to the reductive alkylation of primary aromatic amines. In view of the importance of the reaction as a synthetic method, we felt that its possibilities with primary aromatic amines should be investigated.

The mechanism of the reaction is probably the following

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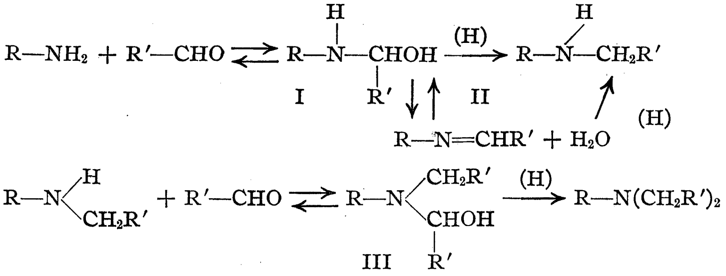
[1] (a) Clarke, Gillespie and Weisshaus, THIS JOURNAL, **55**, 4571 (1933); (b) Skita, Keil and Havemann, *Ber.*, **66**, 1400 (1933); (c) Forsee and Pollard, THIS JOURNAL, **57**, 1788 (1935).

[2] Skita and Keil, *Ber.*, **61**, 1682 (1928).

[3] Wallach, *Ann.*, **343**, 54 (1935).

[4] German Patents 376,013, 491,856, 503,113.



It cannot be said definitely that the amino alcohol (I) is reduced directly as suggested by Wallach[3] or that it is dehydrated to the Schiff base (II) before reduction. In either case the product would be the same, and it is quite possible the reaction follows both courses. Schiff bases have been reduced catalytically to secondary amines.[5]

In his study of the reaction between secondary aromatic amines and formaldehyde in the presence of hydrochloric acid, Wagner[6] found that the condensation product on immediate reduction gave the tertiary amine, while on reduction after a few hours of standing it gave the alkyltoluidine. Apparently the amino alcohol (III) which was first produced was dehydrated, forming the hydrochloride of the anhydro-benzyl alcohol as the intermediate in the rearrangement. Clarke, Gillespie and Weisshaus' results with aniline[1a] suggest that this intermediate or some rearrangement product of it polymerizes in the case of primary aromatic amines.

From a consideration of this mechanism, it was felt that in order for the reaction to be of value with primary aromatic amines, it would be necessary to employ a reducing agent powerful enough to reduce the amino alcohol (I) and a condensing agent mild enough to avoid dehydration and polymerization. For this purpose hydrogen and a catalyst seemed ideal. From a series of preliminary studies (Table I), it was found that Raney nickel as the reduction catalyst and sodium acetate as the condensing agent gave the best results.

Using this general procedure, the reaction was extended to other alkylanilines. The method as developed gave N-alkylanilines from aniline and aldehydes in 47 to 65% yields. The results are summarized in Table II.

Experimental

General Procedure.—All of the experiments were carried out in an Adams machine[7] for catalytic reduction. The catalyst was either platinum oxide[8] or Raney nickel.[9] In each case 9.3 g. (0.1 mole) of aniline was dissolved in 150 cc. of ethyl alcohol and from 0.2 to 0.5 mole of aldehyde added. This mixture, along with the catalyst, was then placed in the machine and shaken at an initial hydrogen pressure of about 50 lb. (3 atm.). When no more gas was absorbed (usually from 0.3 to 0.4 mole was taken up), the catalyst was removed by filtration and the alcohol distilled on the steam-bath. After the remaining oil had been steam-distilled, the distillate or the residue (depending on the amine) was fractionated to obtain the product.

TABLE I

ANILINE PLUS ACETALDEHYDE

Expt.	Reduction catalyst	G.	Condensing agent	G.	Product	Yield, %
1	Platinum oxide	0.1	None		Aniline	
2	Platinum oxide	.1	Gl. AcOH	7 (0.11 mole)	Polymer	Quant.
3	Platinum oxide	.2	NaOAc	1	N-Ethylaniline	41
4	Raney nickel	58	None		Mixture of amines	
5	Raney nickel	58	0.1 *N* NaOH	1 cc.	N-Ethylaniline	25
					N,N-Diethylaniline	10
6	Raney nickel	58	NaOAc	1	N-Ethylaniline	58

TABLE II

ALKYLANILINES

Aniline	Yield, %	Derivative	M. p. of derivative, °C.	Recorded m. p., °C.
Ethyl	58	Picrate	133–135	132[10]
n-Propyl	52	Acetamide	48	47–48[11]
n-Butyl	47	*p*-Bromobenzenesulfonamide	85–86	87[12]
n-Amyl	62	*m*-Nitrobenzenesulfonamide	74–75	[13]
n-Heptyl	65	*p*-Bromobenzenesulfonamide	115	[14]
Benzyl	50	Hydrochloride	210–212	214–216[15]

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[5] (a) Skita and Keil, *Ber.*, **61**, 1452 (1928); (b) Buck, THIS JOURNAL, **53**, 2192 (1931).

[6] Wagner, *ibid.*, **55**, 724 (1933).

[7] Adams and Voorhees, "Organic Syntheses," Coll. Vol. I, 1932, p. 53.

[8] Adams, Voorhees and Shriner, *ibid.*, p. 452.

[9] Covert and Adkins, THIS JOURNAL, **54**, 4116 (1932).

[10] Vignon and Evieux, *Compt. rend.*, **147**, 67 (1908).

[11] Pictet and Crepieux, *Ber.*, **21**, 1106 (1888).

[12] Marvel and Smith, THIS JOURNAL, **45**, 2696 (1923).

[13] *Anal.* Calcd. for $C_{17}H_{20}O_4N_2S$: S, 9.19. Found: S, 9.22.

[14] N,*n*-heptylaniline is a new compound; b. p. 125–130° (30 mm.); d^{20}_{20} 0.906; n^{20}_{D} 1.5080; M_D calcd. 63.3; M_D Found 63.0. *Anal.* of *p*-bromobenzenesulfonamide. Calcd. for $C_{19}H_{24}O_2NSBr$: Br, 19.5. Found: Br, 19.7 (Parr bomb).

[15] Brand, *Ber.*, **42**, 3460 (1909).

Preliminary Experiments.—These were carried out using aniline and acetaldehyde with a variety of reduction and condensation catalysts. The results are summarized in Table I.

The products were identified by their physical properties and picrates.

Alkylanilines.—Six alkylanilines were prepared using the procedure developed in preliminary experiment 6. In Table II are summarized the compounds prepared, the yields, and the method of identification. In the case of the first four alkylanilines up to 10% of the tertiary amines were produced, but no tertiary amines were found in the case of N,*n*-heptylaniline and N-benzylaniline. The reduction mixture always contained some aniline indicating the equation given above is reversible. This probably accounts for the fact that the yields range from 47 to 65%.

Summary

A procedure has been developed for the reductive alkylation of primary aromatic amines, using aldehydes in the presence of Raney nickel, hydrogen, and sodium acetate. By this method six alkylanilines have been synthesized in 47 to 65% yields.

URBANA, ILL. RECEIVED JUNE 22, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

The Reaction of Acid Anhydrides with Anils

BY H. R. SNYDER, R. H. LEVIN AND P. F. WILEY

Conjugated systems of the type —CH=N—N=CH— have not been shown to undergo the Diels–Alder condensation, but observations have been reported[1,2] which suggest that this type of reaction might be brought about under proper conditions. A study of the reaction between benzalazine and maleic anhydride was undertaken to test this idea. Heterocyclic compounds were not isolated, but the study has revealed certain facts which are of interest in connection with the general question of the reaction between acid anhydrides and anils.

When a solution of benzalazine and maleic anhydride in ordinary ether was refluxed, benzalmaleinhydrazine (I) and benzaldehyde were slowly formed. The use of ether containing dissolved water resulted in more rapid formation of the same products. With anhydrous ether solutions only a trace of benzalmaleinhydrazine was produced. The reaction therefore appears due to hydrolysis of benzalazine followed by reaction with maleic anhydride.

$$\begin{gathered}\text{(A)}\ C_6H_5CH{=}N{-}N{=}CH{-}C_6H_5 + H_2O \rightleftharpoons \\ C_6H_5CH{=}N{-}NH{-}CH(OH)C_6H_5 \rightleftharpoons \\ C_6H_5CHO + C_6H_5CH{=}N{-}NH_2 \xrightarrow{C_4H_2O_3} \\ C_6H_5CH{=}N{-}NHCOCH{=}CH{-}CO_2H \\ \text{(I)}\end{gathered}$$

Ekeley and Lefforge[3] recently reported the displacement of one or both of the benzal groups of benzalazine by treatment with acetic anhydride. By analogy with the previous interpretation of the reaction of acetic anhydride with anils,[4] they assumed the initial reaction to be the addition of acetic anhydride yielding C_6H_5-$CH{=}NN(COCH_3)CH(C_6H_5)OCOCH_3$ (II). La Parola[5] used this mechanism to account for the reaction of maleic anhydride with anils in the presence of water. In the present investigation it has been found that the rate of formation of the supposed addition product from benzalaniline and acetic anhydride is considerably increased when small amounts of acetic acid are added. The primary reaction, contrary to the assumption of Ekeley and Lefforge, is therefore addition of acetic acid. In the second step a molecule of acetic acid is liberated and may renew the cycle (B).

$$\begin{gathered}\text{(B)}\ C_6H_5CH{=}N{-}C_6H_5 + CH_3COOH \rightleftharpoons \\ C_6H_5CH(OCOCH_3)NHC_6H_5\ \text{(III)} \xrightarrow{(CH_3CO)_2O} \\ C_6H_5CH(OCOCH_3)N(COCH_3)C_6H_5\ \text{(IV)} + \\ CH_3COOH\end{gathered}$$

Compounds formed by addition of acetic acid and thioacetic acid to anils have been reported.[6–8] These substances have been formulated as containing the groupings —N(COCH₃)CH(OH)— and —N(COCH₃)CH(SH)—. The cyclization of benzalanthranilic acid, discussed later in this report, indicates the alternate mode of addition (B).

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[1] Wagner-Jauregg obtained small amounts of a crystalline substance thought to be a *bis*-pyrazolidine by refluxing a benzene solution of maleic anhydride and benzalazine [*Ber.*, **63**, 3219 (1930)].

[2] W. W. Moyer observed the formation of an apparently neutral solid by heating a mixture of benzalazine and maleic anhydride to the boiling point (private communication).

[3] Ekeley and Lefforge, THIS JOURNAL, **58**, 562 (1936).

[4] Ekeley, *et al.*, *ibid.*, **34**, 161 (1912); **35**, 282 (1913); **36**, 603 (1914); **37**, 582 (1915); **44**, 1756 (1922); *Gazz. chim. ital.*, **62**, 81 (1932).

[5] La Parola, *ibid.*, **64**, 919 (1934).

[6] Von Auwers, *Ber.*, **50**, 1599 (1917).

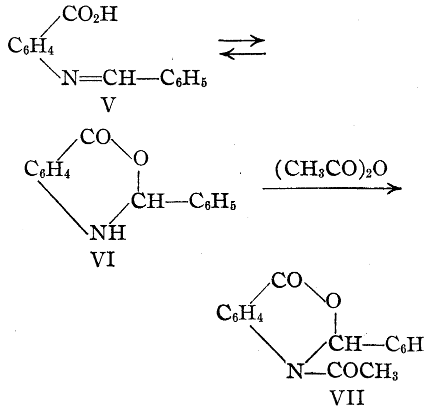
[7] Eibner, *ibid.*, **34**, 659 (1901).

[8] Galatis, *ibid.*, **66**, 1774 (1933).

Preliminary experiments indicate that a similar addition of acetic acid to the double bond in benzalazine does not occur to the same extent as in the case of benzalaniline. Thus we have so far been unable to obtain the compound (II) from benzalazine and acetic anhydride even when acetic acid was added to the mixture. However, addition of water to such a mixture brought about rapid reaction, with the production of *sym*-diacetylhydrazine and benzalacetylhydrazine in good yields. It is indicated, therefore, that the reaction observed by Ekeley and Lefforge was due to atmospheric moisture.

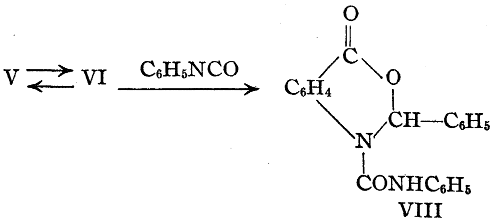
The behavior of benzalanthranilic acid is of particular interest. When this compound is heated with acetic anhydride the metoxazine derivative (VII) is formed.[4] The production of this substance might be accounted for on the basis of initial addition of acetic anhydride[4] or of acetic acid as discussed above. However, *intra*molecular addition of carboxyl group to the double bond might occcur yielding the oxazine VI which would be converted to VII by acetic anhydride.

(C)



That the metoxazine derivative (VI) may be formed from benzalanthranilic acid was proved by the reaction with phenyl isocyanate. When an equimolecular mixture of these substances was warmed a rapid reaction ensued and the expected phenylurea derivative (VIII) crystallized. Heating with dilute hydrochloric acid converted VIII into benzaldehyde and N-phenylcarbamylanthranilic acid.

(D)



Confirmation of the existence of the cyclic form of benzalanthranilic acid has been obtained by Rodebush, Buswell and Roy[9] in this Laboratory from measurement of the infrared absorption. The absorption curve of a solution of the substance in carbon tetrachloride indicated the presence of both —COOH and >N—H groups.

The reaction of benzalanthranilic acid with acetic anhydride therefore involves ring closure followed by acetylation (C). On the basis of this mechanism it might be expected that maleic anhydride, succinic anhydride or phthalic anhydride would react with benzalanthranilic acid under anhydrous conditions. However, attempts to induce such reactions under conditions similar to those employed with acetic anhydride have been unsuccessful, both in this work and that of La Parola.[5]

The production of the oxazoline observed by Galatis[8] in the reaction between *o*-benzalaminophenol and acetic anhydride may be explained on the basis of a similar cyclization.[10] The infrared absorption curve of *o*-benzalaminophenol in carbon tetrachloride solution at room temperature shows that under these conditions the compound exists entirely as the cyclic form.[9]

Experimental

Benzalmaleinhydrazine.—To 75 cc. of ether saturated with water in a glass-stoppered flask were added 5.2 g. of benzalazine and 2.5 g. of maleic anhydride. After four days the benzalmaleinhydrazine, 4.2 g. or 78% of the theoretical, was collected and washed with ether. This substance is almost insoluble in the common solvents. After purification from acetonitrile it melted at 183°.

Anal. Calcd. for $C_{11}H_{10}O_3N_2$: C, 60.55; H, 4.58; N, 12.84; neut. equiv., 218. Found: C, 60.11; H, 4.88; N, 13.06; neut. equiv., 221.

Extraction of the ethereal mother liquor with sodium bisulfite solution, followed by regeneration of benzaldehyde and treatment with phenylhydrazine gave 2.7 g. or 55% of benzalphenylhydrazine; m. p. 156–157°. Similar treatment of an ether solution of benzalazine gave no benzalphenylhydrazine.

In a parallel experiment in which no water was added to the ether employed as the solvent a very small amount, estimated as less than 0.05 g., of benzalmaleinhydrazine, was formed.

Degradation of Benzalmaleinhydrazine.—A mixture of 0.805 g. of benzalmaleinhydrazine and 150 cc. of water was heated to reflux for two hours. On cooling benzalazine

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[9] Rodebush, Buswell and Roy, unpublished work.

[10] Cyclization of a corresponding thiophenol derivative has been demonstrated by Lankelma, THIS JOURNAL, **53**, 2654 (1931).

separated and was collected. The filtrate was diluted to 250 cc. in a volumetric flask. A 50-cc. portion required 16.2 cc. of 0.0502 *N* sodium hydroxide for neutralization to phenolphthalein. The neutralized solution was shaken with 2 cc. of benzaldehyde, causing the formation of more benzalazine. The solution became acid and required an additional 16.2 cc. of the alkali for neutralization. These values are in accordance with the equations below.

$$2C_6H_5CH{=}N{-}NHCOCH{=}CHCO_2H + H_2O \longrightarrow C_4H_4O_4(\text{maleic acid}) + C_6H_5CH{=}N{-}N{=}CHC_6H_5 + NH_2NH_2{\cdot}C_4H_4O_4 \quad (1)$$

$$NH_2NH_2{\cdot}C_4H_4O_4 + 2C_6H_5CHO \longrightarrow C_6H_5CH{=}N{-}N{=}CHC_6H_5 + C_4H_4O_4 \quad (2)$$

Catalysis of the Reaction between Benzalaniline and Acetic Anhydride by Acetic Acid.—In each of two 25-cc. flasks were placed 4.5 g. of benzalaniline and 2.5 cc. of pure acetic anhydride. To one mixture was added 0.5 cc. of glacial acetic acid. The flasks were closed with corks and allowed to stand at 55–65° for eighteen hours. They were then stored at +5° in a refrigerator overnight. The reaction mixture containing acetic acid was allowed to come to room temperature and was filtered. The solid was washed with two 5-cc. portions of cold ether. The weight of the supposed addition compound (IV) was 5.0 g.; m. p. 131–132°. An attempt to recover unchanged benzalaniline from the filtrate failed. Similar treatment of the reaction mixture to which acetic acid was not added gave 1.8 g. of IV. From the mother liquor there was recovered 1.6 g. of impure benzalaniline.

The Reaction of Benzalazine with Acetic Anhydride and Water.—Attempts to prepare the addition compound (II) from benzalazine and acetic anhydride by the method used with benzalaniline failed even when the reaction period was seven days.

A mixture of 10.4 g. of benzalazine and 15.3 g. of acetic anhydride was stirred over the steam-bath and 2.5 cc. of water was added in one portion. Heating and stirring were continued for thirty minutes. From the mixture, by a modification of the procedure of Ekeley and Lefforge,[3] there was obtained 2.0 g., 34% of the theoretical, of *sym*-diacetylhydrazine and 3.0 g., 37% of the theoretical, of benzalacetylhydrazine.

Benzalanthranilic Acid and Phenyl Isocyanate.—A mixture of 5.6 g. of benzalanthranilic acid and 3.0 g. of phenyl isocyanate, protected by a calcium chloride tube, was warmed. A reaction occurred and most of the material separated as transparent crystals. The mixture was cooled and washed with about 50 cc. of benzene. The yield of crude material (VIII) was quantitative. After purification from toluene or chloroform it melted at 171°.

Anal. Calcd. for $C_{21}H_{16}O_3N_2$: N, 8.14. Found: N, 8.12.

A mixture of 0.2 g. of the oxazine (VIII), 1 cc. of concentrated hydrochloric acid and 5 cc. of water was heated to the boiling point for about five minutes. The odor of benzaldehyde was clearly evident. The insoluble solid material was separated and shaken with 5 cc. of 5% sodium hydroxide solution. Acidification of the filtered extract gave N-phenylcarbamylanthranilic acid, m. p. 180–181°.

Benzalanthranilic Acid and Maleic, Succinic and Phthalic Anhydrides.—Anhydrous equimolecular mixtures of benzalanthranilic acid and one of these anhydrides heated on the steam-bath alone or in dioxane solution, or refluxed in benzene solution, did not react. When access of moisture was not prevented, for instance, when a benzene solution of benzalanthranilic acid, with maleic anhydride or succinic anhydride, was allowed to stand in an open beaker, an almost quantitative yield of *o*-carboxymaleanilic acid or of *o*-carboxysuccinanilic acid, respectively, was obtained as demonstrated by mixed melting points made with authentic samples. The mother liquor in each case smelt strongly of benzaldehyde.

Summary

In anhydrous ether solutions benzalazine and maleic anhydride do not react. If water is present the benzalazine undergoes hydrolysis, followed by reaction with maleic anhydride to form benzaldehyde and benzalmaleinhydrazine.

The reaction between benzalaniline and acetic anhydride is catalyzed by acetic acid.

Benzalanthranilic acid undergoes cyclization by addition of the carboxyl group to the nitrogen–carbon double bond. The cyclic form reacts with phenyl isocyanate.

Certain reactions previously formulated as *direct* addition of acetic anhydride to the nitrogen–carbon double bond are better interpreted as involving (1) addition of water or carboxylic acid to the double bond followed by (2) acetylation by acetic anhydride.

URBANA, ILLINOIS

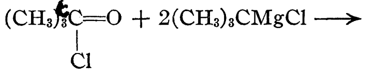
RECEIVED MARCH 28, 1938

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

The Reducing Action of *t*-Butyl Grignard Reagent on Acyl Chlorides

BY FRED L. GREENWOOD, FRANK C. WHITMORE AND HARRY M. CROOKS

In an attempt to prepare di-*t*-butyl ketone or di-*t*-butylcarbinol by the action of *t*-butylmagnesium chloride on pivalyl (trimethylacetyl) chloride it was found that the chief products are neopentyl alcohol and neopentyl pivalate resulting from the reduction of the acid chloride by the Grignard reagent.



$$(CH_3)_3C\underset{\displaystyle Cl}{\overset{}{C}}{=}O + 2(CH_3)_3CMgCl \longrightarrow$$

$$(CH_3)_3CCH_2OMgCl + 2(CH_3)_2C{=}CH_2 + MgCl_2$$

The action of *t*-butyl Grignard reagent with pivalyl chloride has been studied by the addition of the Grignard reagent to a large excess of acid chloride at a low temperature, and by the addition of the acid chloride to a large excess of the Grignard reagent at the reflux temperature of ethyl ether. Moreover, we have added isobutyryl and *n*-butyryl chlorides to a large excess of Grignard reagent at ethyl ether reflux temperature. The results are summarized in Table I.

TABLE I

Acid chloride	Ratio of $(CH_3)_3CMgCl$ to acid chloride	Products % addition	% reduction
Pivalyl[a]	1/5	32.4	8
Pivalyl[b]	4/1	1.5	94.0
Isobutyryl	5/1	63.0	20.0
n-Butyryl	4/1	71.0	9.0

[a] Grignard reagent added to acid chloride at −10°: addition product hexamethylacetone, reduction product neopentyl pivalate. [b] Acid chloride added to Grignard reagent at about 40°. Addition product was di-*t*-butylcarbinol resulting from addition of 1 mole of Grignard reagent followed by reduction; reduction product was neopentyl alcohol.

In all reactions the isobutylene formed corresponded to two moles of Grignard reagent per mole of acid chloride reduced to primary alcohol plus one mole of Grignard reagent per mole of ketone reduced to secondary alcohol. The alcohols were identified by preparation of derivatives and mixed melting points with known materials. Exception was made in the case of *n*-propyl-*t*-butylcarbinol and isopropyl-*t*-butylcarbinol which were identified by comparison of the physical constants of the substances and of their derivatives with those reported for these compounds by Haller and Bauer,[1] and by Conant, Webb and Mendum.[2] Neopentyl pivalate was identified by hydrolysis and the preparation of known derivatives of the hydrolysis products.

In all cases the Grignard reagent used was filtered and free from particles of magnesium. All attempts to find the aldehyde corresponding to the primary alcohol obtained failed.

Experimental

Preparation of the *t*-Butylmagnesium Chloride Solution.—A calibrated three-liter flask was equipped, by means of a trident, with reflux condenser, separatory funnel and mercury-sealed stirrer. To 121.5 g. of magnesium turnings (5 moles) in the flask was added 5 cc. of tertiary butyl chloride in 30 cc. of dry ether. A few drops of ethyl bromide started the reaction. When vigorous reaction had started, 300 cc. of dry ether was added and followed by the remainder of 460 g. (5 moles) of tertiary butyl chloride (b. p. 50° at 738 mm.; $n^{20}D$ 1.3859) dissolved in 1400 cc. of dry ether. The halide solution was added at such a rate that refluxing was continuous. This required about eighteen hours. Sitrring was continued for an hour after end of addition. The solution was allowed to stand overnight and then titrated by the method of Gilman.[3] The yield of reagent was 75–85%. The clear solution was filtered through two layers of cloth under pressure of dry nitrogen. The filtrate contained no particles of magnesium.

Preparation of Acid Chlorides.—Pivalic acid was prepared by carbonation of *t*-butylmagnesium chloride in 60% yield.[4] Treatment of the acid with thionyl chloride gave an 80% yield of pivalyl chloride, b. p. 70.5–71° at 250 mm., $n^{20}D$ 1.4118.

Isobutyric acid (b. p. 151° at 732 mm., $n^{20}D$ 1.3920) was prepared by alkaline permanganate oxidation of isobutyl alcohol. Isobutyryl chloride was obtained in 75% yield by the use of thionyl chloride, b. p. 90–91°, $n^{20}D$ 1.4070.

n-Butyryl chloride was obtained in 80% yield by treatment of the acid (Eastman Kodak Co.) with thionyl chloride: b. p. 101–101.5° (730 mm.); $n^{20}D$ 1.4117.

Apparatus.—The reactions were carried out in the apparatus used in the preparation of the Grignard reagent except that the system was closed and the exit gases led through the condenser to a gas-collecting carboy.

Three fractionating columns were used, all of the adiabatic, total reflux, variable take off type packed with single-turn glass helices: column 1, 1.5 × 66 cm., 12 theoretical plates; column 2, 1 × 45 cm., 9 plates; column 3, 0.9 × 53 cm., 13 plates.

Addition of *t*-Butylmagnesium Chloride to Pivalyl Chloride.—A solution of 966.5 g. of pivalyl chloride (8.0 moles) in 1 liter of dry ether was placed in the reaction flask and cooled to −10° (thermometer in the solution). To

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[1] Haller and Bauer, *Ann. chim. phys.*, [8] **29**, 313 (1913).

[2] Conant, Webb and Mendum, THIS JOURNAL, **51**, 1246 (1929).

[3] Gilman, Wilkinson, Fishel and Meyers, *ibid.*, **45**, 150 (1923).

[4] "Organic Syntheses," Vol. VIII, 104 (1928).

this was added, over a period of seventeen hours, a solution of 1.5 moles of *t*-butylmagnesium chloride in 1 liter of dry ether. During the addition the temperature was kept at −10° or below. After addition was complete the ice-bath was exchanged for a water-bath and the reaction mixture heated to 50° to drive off dissolved gases. The Grignard complex was decomposed by pouring over crushed ice, the layers were separated and the aqueous layer extracted well with ether. The combined ether layers were extracted with an excess of saturated sodium bicarbonate solution which was saved for recovery of the excess pivalic acid. The ether solution was concentrated and fractionated through Column 1. Refractionation through Column 2 yielded the following fractions:

	B. p. (740 mm.)	n^{20}_{D}	Wt., g.	Product
1	151–153	1.4175–83	67.4	Hexamethylacetone
2	153–164	1.4161–40	50.3	Mixture (?)
3	164–165	1.4033–5	14.1	Neopentyl pivalate
4	124(93 mm.)	1.4093	15.3	Pivalic anhydride

Fraction 1 was identified as hexamethylacetone by comparison of the physical constants with a known sample and then by conversion to the carbinol by sodium reduction. The resulting di-*t*-butylcarbinol was identified by means of the phenylurethan, m. p. 120.5–121°, mixed with a known sample (118.5–120°) it melted at 120–121°. Haller and Bauer reported the m. p. as 118–119°.

Fraction 3 was hydrolyzed with 25% KOH, to give an solid alcohol, which was converted to the phenylurethan, m. p. 111.5–112°. Mixed with the known derivative of neopentyl alcohol (112–112.5°) it melted at 112°. Acidification of the alkaline layer yielded an acid which gave an amide of m. p. 153–154°. Mixed with the known amide of pivalic acid (153–153.5°) it melted at 153–154°.

Fraction 4 was hydrolyzed in aqueous potassium hydroxide solution to give a solid acid which gave pivalamide. No non-acidic hydrolysis products were formed.

During the reaction 6.5 l. of isobutylene were collected in the gas carboy, 0.25 mole, a 17% yield based on the Grignard reagent used which is in accordance with the 8% yield of neopentyl trimethylacetate as reduction product.

Addition of Pivalyl Chloride to *t*-Butylmagnesium Chloride.—To a solution of 3.9 moles of *t*-butylmagnesium chloride in 2 liters of ether was added 1.1 moles of pivalyl chloride, undiluted, over a period of four and one-half hours. During this time 90 liters of gas came off consisting of about 40% ether and 55% isobutylene (slightly over two moles of isobutylene measured at 29° and 733 mm.).

After standing overnight the Grignard complex was decomposed by pouring slowly over 2 kg. of crushed ice, the layers separated and the aqueous layer steam distilled until there was no further odor of alcohol in the fresh distillate. The aqueous distillate was saturated with sodium carbonate and thoroughly extracted with ether. All ether solutions were then combined and dried. The ether was removed through Column 3 and the products fractionated through the same column.

	B. p. (737 mm.) °C.	Wt., g.	Product
1	75–100	6.0	Impure hexamethylethane
2	106–112	88.0	M. p. 50°, neopentyl alcohol
3	163–166	1.8	Semisolid, di-*t*-butylcarbinol

The phenylurethan of 2 melted at 112.5–113.5°; mixed with the known derivative of neopentyl alcohol (112–112.5°), it melted 112–113°. The α-naphthylurethan of 2 melted 98.5–99°, mixed with the known (98.5–100.5°) it melted at 98.5–99.5°.

The phenylurethan of 3 melted 120.5–121°; mixed with the known derivative of di-*t*-butylcarbinol (119–121°) it melted at 120–121°.

The yield of neopentyl alcohol was 94% while that of di-*t*-butylcarbinol was 1.5%.

Addition of Isobutyryl Chloride to *t*-Butylmagnesium Chloride.—The addition of 0.84 mole of isobutyryl chloride (89 g.) to 4.2 moles of *t*-butylmagnesium chloride in 2 liters of ether required four hours. During the reaction 1.34 moles of gas was given off which contained 93.5% isobutylene, 1.49 moles, per mole of acid chloride.

The liquid products gave the following

	B. p. (738 mm.) °C.	n^{20}_{D}	Wt., g.	Product
1	79–81	1.3910	7.5	
2	90–103		2.2	Solid, hexamethylethane
3	103–106	1.3950	12.5	Isobutyl alcohol
4	145	1.4281	82.0	*t*-Butylisopropylcarbinol

The phenylurethan of 3 melted at 83–83.5°, mixed with the known derivative of isobutyl alcohol (84–84.5°) it melted at 83–84°. The α-naphthylurethan of 3 melted at 97–97.5°, mixed with the known derivative (98–98.5°) it melted at 97–98°.

The phenylurethan of 4 melted at 86.5–87° and the α-naphthylurethan at 103–104°. Conant gives the melting point of the phenylurethan as 89° and assumes Haller and Bauer's reported value of 79° to be a misprint.

The isobutyl alcohol isolated amounted to a 20% yield based on original acid halide while the secondary alcohol accounted for 63% of the original acid chloride.

Addition of *n*-Butyryl Chloride to *t*-Butylmagnesium Chloride.—The addition of 0.98 mole of *n*-butyryl chloride to 4.0 moles of Grignard reagent dissolved in two liters of ether required five and one-half hours. During the reaction 1.1 moles of gas was given off which contained 84% isobutylene, a yield of 94% isobutylene based on the acid chloride.

The liquid products were worked up as before.

	B. p. (744 mm.) °C.	n^{20}_{D}	Wt., g.	Product
1	79–82	1.3908	7.5	
2	100–106		2	Solid, hexamethylethane
3	115–116.5	1.3993	6.5	1-Butanol
4	152–153	1.4275	90.8	*t*-Butyl-*n*-propylcarbinol

The phenylurethan of 3 melted at 62–62.5°, mixed with the known derivative of 1-butanol (62–62.5°) it melted at 62–62.5°. The α-naphthylurethan melted at 70–71°, mixed with the known derivative (71–72°) it melted at 70–71°.

The phenylurethan of 4 melted at 70.5–71.5° and the α-naphthylurethan at 113–114°. Haller and Bauer report a boiling point of 155–157° for this carbinol and a melting point of 70–71° for the phenylurethan.

The 1-butanol isolated amounted to 9% based on the acid chloride used while the secondary carbinol isolated accounted for 71% of the acid chloride.

All melting points are uncorrected.

Summary

1. The reaction of *t*-butylmagnesium chloride with a large excess of pivalyl chloride at −10° gives a 32% yield of hexamethylacetone and an 8% yield of neopentyl alcohol as its pivalic ester.

2. The reaction of a large excess of *t*-butylmagnesium chloride at about 40° with pivalyl, isobutyryl and *n*-butyryl chlorides results, respectively, in a 1.5, 63 and 71% yield of addition and in a 94, 20 and 9% yield of reduction of the acid chloride to primary alcohol.

STATE COLLEGE, PENNA. RECEIVED JUNE 4, 1938

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

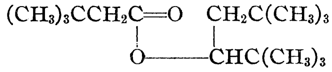
The Action of *t*-Butylmagnesium Chloride on *t*-Butylacetyl Chloride

BY FRANK C. WHITMORE AND J. W. HEYD

The preparation of *t*-butylneopentylcarbinol in quantity for use in a dehydration study involved the reaction of *t*-butylmagnesium chloride with *t*-butylacetyl chloride. An investigation of the reduction products has proved interesting when compared with the action of the same Grignard compound on trimethylacetyl chloride.[1] The addition of the acid chloride to *t*-butylmagnesium chloride produced *t*-butylneopentylcarbinol in 71% yield together with a 1% yield of neopentylcarbinol. Investigation of the products of this reaction boiling above the secondary carbinol indicates a 5% yield of *t*-butylneopentylcarbinyl *t*-butylacetate as the product of the esterification of the secondary alcohol complex with unreacted acid chloride. However, addition of *t*-butylacetyl chloride to a suitable excess of *t*-butylmagnesium chloride permitted all of the secondary carbinol to be recovered without esterification, thus raising the yield to 76%.

Addition of a slight excess of a filtered solution of *t*-butylmagnesium chloride to an ethereal solution of *t*-butylacetyl chloride, produced *t*-butylneopentyl ketone in 51% yield. In this case all of the secondary carbinol formed as reduction product underwent esterification in the presence of excess acid chloride to yield 17% of pure *t*-butylneopentylcarbinyl *t*-butylacetate. Attempts to saponify this ester by refluxing with alcoholic potassium hydroxide for seventy-one hours or by heating for fifty-six hours in a sealed tube at 90–100° were not successful. However, an authentic sample of the ester obtained from the reaction of *t*-butylneopentylcarbinol and *t*-butylacetyl chloride checked in physical constants with the reduction product and proved equally stable toward saponification under similar conditions.[2]

No reduction was obtained when *t*-butyl neopentyl ketone was treated with a solution of aluminum isopropylate in isopropyl alcohol. This inertness and the inability to form a semicarbazone or an oxime[3] are related to the steric arrangement about the carbonyl group of this ketone. The inertness of the ester is dependent on similar steric conditions.



$$\begin{array}{ll}(CH_3)_3CCH_2\underset{\displaystyle |}{C}{=}O & \underset{\displaystyle |}{CH_2}C(CH_3)_3 \\ \qquad\qquad\quad O\text{———} & CHC(CH_3)_3\end{array}$$

Experimental

Addition of *t*-Butylacetyl Chloride to *t*-Butylmagnesium Chloride.—A solution of 5.4 moles of *t*-butylmagnesium chloride in 2400 cc. of dry ether was prepared by the action of *t*-butyl chloride, b. p. 50° (732 mm.), $n^{20}D$ 1.3850, on magnesium. *t*-Butylacetyl chloride, b. p. 79° (150 mm.), $n^{20}D$ 1.4212, was prepared in 86% yield from *t*-butylacetic acid and thionyl chloride.[4] Addition of 336 g. (2.5 moles) of the acid chloride in a liter of ether to the Grignard solution (5.4 moles) was completed in three days and then the thick reaction mixture was refluxed for four days. The complex was decomposed with ice, the products extracted with ether and the solvent removed with an efficient column.[5] Fractionation of the products yielded: Fractions 1–3, 72.9 g., b. p. 34–81° (735 mm.), $n^{20}D$ 1.3520–1.3880; 4–5, 34.0 g., 81–167°, 1.4081–1.4220; 6–9, 282.3 g., 167–173°, solid; 10–11, 47.9 g., 122–208° (50–45 mm.), 1.4363–1.4450; solid residue, 15.4 g. Fractions 6–9 represent a 71% yield of *t*-butylneopentylcarbinol. A portion of the solid, by a series of fractional crystallizations, gave a pure sample of carbinol, m. p. 49.4° (corr.).

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[1] Greenwood, Whitmore and Crooks, THIS JOURNAL, **60**, 2028 (1938).

[2] Since the completion of this paper, J. S. Whitaker of this Laboratory has succeeded in partially saponifying this ester and identifying *t*-butylacetic acid as the acid fragment.

[3] Bouveault and Locquin, *Bull. soc. chim.*, [3] **35**, 642 (1906).

[4] Homeyer, Whitmore and Wallingford, THIS JOURNAL, **55**, 4209 (1933).

[5] Whitmore and Lux, *ibid.*, **54**, 3451 (1932).

A similar run using 2.25 moles of acid chloride was also completed and the material from both reactions boiling above the secondary carbinol was refractionated to give 8 fractions, 61.1 g., b. p. 90° (5 mm.), $n^{20}\mathrm{D}$ 1.4392–1.4359. Refractionation of these gave 8 fractions, 39.7 g., b. p. 90° (5 mm.), $n^{20}\mathrm{D}$ 1.4367–1.4339, which represented a 5% yield of *t*-butylneopentylcarbinyl *t*-butylacetate. The refractive index gradually approached the correct index for the synthetic ester, $n^{20}\mathrm{D}$ 1.4320. The boiling point was correct for the ester. The mol. wt. found from the depression of the f. p. of benzene is 250; calcd. 256.

The fractions of the two preparations boiling in the range of 79–168° (732 mm.), were combined and refractionated to give 2 fractions, wt. 6.9 g., b. p. 139–143°, $n^{20}\mathrm{D}$ 1.4150–1.4179. These were identified as neopentylcarbinol by means of the α-naphthylurethan, m. p. 82–83°, which gave no depression with α-naphthylurethan of known neopentylcarbinol. The yield of this reduction product was thus 1%.

An addition of 0.65 mole of *t*-butylacetyl chloride to 1.5 moles of *t*-butylmagnesium chloride produced the secondary carbinol in 76% yield with no evidence for the formation of *t*-butylneopentylcarbinyl *t*-butylacetate.

Addition of *t*-Butylmagnesium Chloride to *t*-Butylacetyl Chloride.—To a solution of 128 g. (0.95 mole) of *t*-butylacetyl chloride in 1300 cc. of ether was added one mole of *t*-butylmagnesium chloride in a liter of ether over a period of thirty-six hours. The addition complex was decomposed with ice, extracted with ether, and the product fractionated, after removal of solvent, to give: 1, 2, 54.8 g., b. p. 33–110° (728 mm.), $n^{20}\mathrm{D}$ 1.3520–1.3640; 3–6, 7.8 g., 110–158°, 1.4042–1.4125; 7–9, 18.9 g., 158–161°, 1.4135–1.4150; 10–12, 75.4 g., 161°, 1.4158–1.4160; 13–14, 15.9 g., 161–164°, 1.4167–1.4175; residue, 39.2 g. Fractions 10–12 represent a 51% yield of *t*-butyl neopentyl ketone, which did not form a semicarbazone or oxime and yielded a 2,4-dinitrophenylhydrazone with great difficulty, m. p. 123.5–124.5°.

The residue of this fractionation was combined with that of a 0.5 mole run to give 6 fractions of pure *t*-butylneopentylcarbinyl *t*-butylacetate, wt. 33 g. (17% yield), b. p. 90° (5 mm.), $n^{20}\mathrm{D}$ 1.4320, d^{20}_4 0.8553. Molecular refraction; calcd. 77.74, found 77.73. *Anal.* Calcd. for $C_{16}H_{32}O_2$: C, 75.0; H, 12.5. Found: C, 75.6; H, 12.6.

Treatment of 19.8 g. of the pure ester with 12 g. of potassium hydroxide in 60 cc. of absolute methyl alcohol at reflux temperature for seventy-one hours gave no evidence of saponification. Treatment of 16.7 g. of the ester with 20 g. of potassium hydroxide in 125 cc. of 95% ethyl alcohol in a sealed tube at 90–100° for fifty-six hours likewise gave no evidence of saponification.

Preparation of *t*-Butylneopentylcarbinyl *t*-Butylacetate.—The addition of 53 g. (0.39 mole) of *t*-butylacetyl chloride to 55.3 g. (0.35 mole) of *t*-butylneopentylcarbinol, m. p. 50–51°, gave a slight evolution of heat. The reaction mixture was refluxed for two hours, cooled, washed with 10% sodium carbonate solution, dried with anhydrous potassium carbonate and fractionated to give: 1–5, 22.2 g., b. p. 30–94° (5–7 mm.), $n^{20}\mathrm{D}$ 1.4188–1.4260; 6–8, 16.5 g., 93° (7 mm.), 1.4312–1.4316; 9–12, 36.0 g., 93° (7 mm.), 1.4318–1.4320; 13, 5.7 g., 93° (7 mm.), 1.4311; residue, 1.6 g. Fractions 6–13 represent 65% yield of the ester. A density determination on fraction 10, $n^{20}\mathrm{D}$ 1.4320, indicated d^{20}_4 0.8549. Treatment of 10 g. of the synthetic ester with 20 g. of potassium hydroxide in 120 cc. of 95% ethyl alcohol gave no indication of saponification after refluxing the mixture for seventy-two hours.

Summary

1. A study has been made of the normal addition and reduction products formed by the addition of *t*-butylacetyl chloride to *t*-butylmagnesium chloride and of those formed by the reverse addition.

2. The synthesis and physical constants of *t*-butylneopentylcarbinyl *t*-butylacetate have been described.

STATE COLLEGE, PENNA. RECEIVED JUNE 4, 1938

[CONTRIBUTION FROM THE METCALF CHEMICAL LABORATORY OF BROWN UNIVERSITY]

Photochemical Studies. XXVIII. The Photochemical Decomposition of Ethyl Methyl Ketone by Wave Lengths from 1850–2000 Å.

BY VICTOR R. ELLS AND W. ALBERT NOYES, JR.

Ethyl methyl ketone, in common with other ketones, absorbs in the near ultraviolet, the approximate limits being 2400 and 3200 Å. No discrete structure could be found in this region,[1] although fluorescence may be excited, at least by the 3130 Å. line of mercury. However, recent work[2] on the fluorescence of acetone has raised the question as to whether the ketones or some of their decomposition products are mainly responsible for the emission of fluorescent radiation.

The photochemical decomposition of ethyl methyl ketone in the near ultraviolet has been investigated by Norrish and Appleyard.[3] The products of the reaction were found to be carbon monoxide and approximately equal amounts of ethane, propane and butane, together with small amounts of ethylene and acetaldehyde. In the

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[1] Duncan, Ells and Noyes, THIS JOURNAL, **58**, 1454 (1936).

[2] Matheson and Noyes, *ibid.*, **60**, 1857 (1938).

[3] Norrish and Appleyard, *J. Chem. Soc.*, 874 (1934).

analogous decomposition of acetone at room temperature, biacetyl has been shown to be one of the main products.[4]

The second region of absorption in ketones occurs just below 2000 Å. and may be investigated also with the aid of quartz apparatus. At these wave lengths acetone gave approximately equal amounts of hydrocarbon (ethane) and carbon monoxide,[5] indicating thereby that little or no biacetyl is formed. However, the quantum yield for the decomposition did not approach unity, apparently, as the pressure was lowered, thus leading to some difficulties in the theoretical interpretation of the results.

The present work was undertaken with the object of ascertaining whether ethyl methyl ketone behaves in a manner analogous to acetone in the region of 1850 to 2000 Å. or whether the quantum yield is higher. The entire question of the adiabatic transfer of polyatomic molecules between energy states rests on a very insecure theoretical foundation and the introduction of such an idea[6] was made only because of the apparent difficulty in accounting by more rational means for the fate of all of the absorbed energy.

As will be seen it is not necessary, for ethyl methyl ketone, to use unorthodox ideas for the explanation of the experimental facts, at least in the wave length region studied.

Experimental Procedure and Results

(a) The Determination of Diketones among the Reaction Products in the Near Ultraviolet.—Since it is quite important to know all of the reaction products in order to arrive at a proper estimate of the quantum yield, it was decided first to ascertain whether diketones are produced upon irradiation of ethyl methyl ketone in the near ultraviolet region.

Reactions were carried out in a Pyrex cell with plane window using as a light source a capillary mercury arc.[7] The wave lengths were greater than 3000 Å. and the absorption was due almost entirely to the group of lines near 3130 Å.

The ethyl methyl ketone was synthesized by the acetoacetic ester synthesis. Ethyl acetoacetate was added to the proper amount of sodium metal dissolved in ethyl alcohol to form the sodium compound of the enol form. Methyl iodide was added and the mixture refluxed for several hours until it no longer gave an alkaline reaction. The alcohol was distilled off, water added and the ethyl methylacetoacetate extracted with diethyl ether. After purification by fractional distillation, the ethyl methylacetoacetate was hydrolyzed with 10% sodium hydroxide and the ethyl methyl ketone distilled off. In addition to fractional distillation, the ethyl methyl ketone was purified by formation of the bisulfite compound which was decomposed by potassium carbonate to reform the ketone. Fused potassium carbonate was used as the final drying agent. The boiling point of the final material was 79.4 ± 0.2°.

The ethyl methyl ketone was kept flowing through the reaction cell by immersing traps in water at different temperatures. After irradiation for a period of sixty to one hundred hours, liquid air was placed on one of the traps and the non-condensable gases collected by means of a Toepler pump, after which they were analyzed for carbon monoxide by the method of Blacet and Leighton.[8]

The condensed liquids were removed from the system and treated with hydroxylamine hydrochloride, nickel chloride and ammonium hydroxide solutions to quantitatively precipitate the diketones as nickel glyoxime salts. The precipitates were filtered through Gooch crucibles and weighed. Although a method has been developed by Johlin[9] for separating some of the possible salts, the small amount of precipitate (1–3 mg.) rendered this impracticable, so that an average molecular weight of 316.9 was taken.

Four runs were made showing that the following percentages of carbon monoxide appeared as diketones among the reaction products: 11.7, 9.9, 11.3, 10.6; average 10.9. It is apparent, therefore, that diketones are formed upon irradiation of ethyl methyl ketone in the near ultraviolet and this fact must be taken into account in obtaining a final theory of the mechanism of the reaction.

(b) The Determination of the Quantum Yield at 1850–2000 Å.—The light source has been described[5] and consisted of a spark between rotating aluminum disks. The group of lines from 1855 to 1990 Å. was separated by focal isolation. In this region ethyl methyl ketone shows several bands[1] and a weak continuous absorption.

The method of gas analysis used for the products was essentially that described by Manning[10] and used in the work on acetone.[5] After irradiation, the ethyl methyl ketone and products were, as far as possible, condensed with liquid air and the residual gases (carbon monoxide, ethane and methane, if present) were pumped off with a Toepler pump and measured with a McLeod gage. Prolonged pumping and several evaporations and recondensations were necessary to effect removal of the ethane. The analysis of this fraction was carried out exactly as described.[10] No ethylene was found in these gases, indicating that the Type II decomposition of ethyl methyl ketone described by Norrish and Appleyard[3] does not seem to be very important in this wave length region.

A second fraction of reaction products was next removed by replacing the liquid air by a solid–liquid pentane mixture at about −155°. This fraction would contain propane and butane as well as any acetaldehyde and carbon dioxide which might have been formed. This fraction was burned with oxygen using the hot platinum wire as previously described.[10]

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[4] Barak and Style, *Nature*, **135**, 307 (1935); Spence and Wild, *ibid.*, **138**, 206 (1936); *J. Chem. Soc.*, 352 (1937).

[5] Howe and Noyes, THIS JOURNAL, **58**, 1404 (1936).

[6] Norrish, Crone and Saltmarsh, *J. Chem. Soc.*, 1456 (1934).

[7] Heidt and Daniels, THIS JOURNAL, **54**, 2381, 2384 (1932).

[8] Blacet and Leightan, *Ind. Eng. Chem.*, *Anal. Ed.*, **3**, 266 (1931); Blacet, Leighton and McDonald, *ibid.*, **5**, 272 (1933).

[9] Johlin, THIS JOURNAL, **37**, 892 (1915).

[10] Manning, *ibid.*, **56**, 2589 (1934).

In all cases an excess of carbon monoxide was found, indicating superficially, as with acetone,[5] that diketones were not formed. However, it has been emphasized by Norrish and his co-workers[6] that the hydrocarbons are quite soluble in the condensed ketones and that some difficulty is encountered in effecting their removal.

To further test the possibility of diketone formation, the spectrum of biacetyl was photographed in the far ultraviolet.[11] An intense band at 57,295 cm.$^{-1}$, which is well removed from any bands of ethyl methyl ketone,[1] could be used for the identification of biacetyl. Other bands also furnished confirmatory evidence for the formation of this compound. A series of photographs was made with known pressures of biacetyl and a comparison of the spectra of the reaction products, from which carbon monoxide and ethane had been removed, with these standards permitted a very rough estimate to be made of the amount of biacetyl produced. No estimate of the amounts of the other possible diketones could be made, so that the three were assumed to be present in equal amounts. Moreover, some diketones would be formed during the photographing of the spectrum so that no great accuracy is claimed for the amount of diketones formed. One band at 58,086 cm.$^{-1}$ which appeared on some of the spectra may have been due to one of the other diketones.

The hydrogen bromide actinometer was used, as previously,[5] for the determination of the number of quanta absorbed. Runs made with the purpose of obtaining proof for the existence of biacetyl were made in an all quartz cell and the results agreed with those obtained in the cell with windows attached by wax.

Table I shows the analysis of the gases formed during reaction.

TABLE I

COMPOSITION OF REACTION PRODUCTS

Ketone pressure, mm.	Carbon monoxide (mm. in anal. app.)	Hydrocarbons, mm.	% Carbon monoxide	Ethane, mm.	Propane, mm.	Butane, mm.
70	0.0222	0.0197	53.0	0.0062	0.0066	0.0069
62	.0140	.0089	61.1	.0026	.0034	.0029
58	.0129	.0099	56.6	.0036	.0035	.0028
25	.0182	.0157	54.0	.0056	.0054	.0047
14	.0224	.0227	49.7	.0079	.0071	.0077
4	.0114	.0099	53.5	.0032	.0035	.0032
11	.0176	.0135	56.6	.0049	.0045	.0041

From the data in Table I it is seen that the average ratio ethane:propane:butane is 1:1.03:0.95, so that the relative amounts of these hydrocarbons agree very closely with those reported by Norrish and Appleyard[3] in the near ultraviolet.

Table II presents data on the number of molecules of carbon monoxide produced per quantum absorbed by ethyl methyl ketone.

In order to estimate how much biacetyl was formed, the spectrum of this substance was photographed in a 15-cm. tube at pressures which were estimated on a McLeod gage. As little as 0.0001 to 0.0002 mm. was sufficient to cause the 57295 cm.$^{-1}$ band to be recognizable.

After irradiation of ethyl methyl ketone, the liquids were condensed with liquid air and the carbon monoxide and ethane were pumped off. The trap, which was fitted with a small bulb which could be broken by a magnetic hammer, was sealed off and attached to the cell in front of the spectrograph. The trap was immersed in dry ice–ether mixtures during the photographing of the spectrum. The vapor pressure of biacetyl is about 0.01 mm. at −70° and about 0.004 mm. at −77°.

The volume of the cell used for photographing the spectrum was about 0.13 of the volume in which the gases were measured in the quantum yield determinations. If the three diketones are formed in equal amounts, multiplying the number of molecules of biacetyl by six will give the number of molecules of ethyl methyl ketone which have disappeared during irradiation due to diketone formation. Multiplication of the approximate pressure of biacetyl in the absorption cell by 0.77 gives the pressure of ethyl methyl ketone which would have disappeared in the larger volume.

Table III gives rough estimates of the extent of the diketone reaction in four runs.

The order of magnitude of the fraction of the reaction which leads to diketone formation seems to be the same as in the near ultraviolet, but the data are too inaccurate to permit a definite statement on this point to have much meaning.

It should be mentioned in passing that similar experiments were performed on acetone after the conclusion of this work to ascertain whether biacetyl was formed in sufficient quantity to make a correction necessary on the previous work.[5] No biacetyl could be detected in this case, but this matter is worthy of a more thorough investigation.

Since biacetyl is formed to a considerably less extent from acetone in the near ultraviolet as the temperature is increased it was decided to make quantum yield determinations at higher temperatures. Moreover, Winkler[12] studied the photochemical decomposition of acetone from 60 to 400°, at wave lengths 2200 to 3200 Å. and found methane and ketene among the products, the ketene being detected by effects observed by Ross and Kistiakowsky.[13] The quantum yield which was 0.3 at 60° increased to 1 at 160°.

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[11] Ells, THIS JOURNAL, **60**, 1864 (1938).

[12] Winkler, *Trans. Faraday Soc.*, **31**, 761 (1935).

[13] Ross and Kistiakowsky, THIS JOURNAL, **56**, 1112 (1934).

TABLE II

NUMBER OF MOLECULES OF CARBON MONOXIDE PRODUCED PER QUANTUM ABSORBED

Run	Ketone press., mm.	Molecules CO $\times 10^{-17}$	Intensity (arbitrary units)	Incident quanta $\times 10^{-17}$	Fraction absorbed	Absorption coeff.[a] k	Quantum yield
27	90	0.605	18.2	0.94	0.92	0.028	0.70
24	52	.753	20.0	1.20	.77	.029	.81
20	30	1.113	15.9	1.86	.79	.053	.76
23	25	1.113	19.2	1.72	.83	.072	.77
21	24	0.589	18.4	1.06	.79	.065	.71
29	24	1.064	19.1	1.83	.77	.061	.76
18	22	1.178	23.2	2.66	.57	.039	.77
22	16.5	1.113	18.0	1.91	.77	.088	.76
14	14	4.388	20.4	6.66	.85	.135	.77
17	11	3.448	18.8	6.32	.72	.11	.76
19	8	1.636	18.3	2.97	.69	.15	.79
25	6	0.982	20.7	1.57	.82	.29	.76
31	5	1.505	19.6	2.50	.78	.30	.77
15	4	2.233	17.1	5.40	.58	.22	.71
26	1.75	0.605	20.2	1.30	.63	.63	.74
33	1.00	.654	17.9	1.71	.47	.63	.82
28	0.75	.392	17.6	1.60	.30	.47	.83
30	.73	.982	18.6	3.63	.31	.51	.87
32	.34	.245	18.8	2.55	.115	.60	.84
34	.09	.196	17.2	4.25	.052	.59	.88
35[b]	.017	.098	17.6	....	(.010)	(.60)	(1.2)
46[b]	.018	.196	17.8	....	(.010)	(.60)	(1.1)
36[c]	18	1.685	22.2	3.14	.71	....	0.75

[a] The absorption coefficient is calculated from the equation—kp (mm.) = $\ln_e$ (*fraction transmitted*). It is quite evident that Beer's law is not obeyed for the radiation used, thus indicating that more than one wave length is being absorbed. [b] The quantum yield in these runs is calculated using the same k (0.60) as found in Run 34. Since the fraction absorbed is thus probably too low, the quantum yields are probably too high. [c] This run was made in the all quartz cell referred to above.

TABLE III

EXTENT OF THE DIKETONE REACTION

Run	Ketone pressure, mm.	Estimated pressure biacetyl (abs. cell)	Press., CO, mm.	Equiv. press. of ethyl methyl ketone (in anal. app.)	Approx. quantum yield of diketone reaction
46	0.018	0.0001	0.0012	0.0001	0.06
45	13	.0020	.0250	.0016	.05
44	14	.0085	.0890	.0070	.06
47	43	.0012	.0080	.0009	.08

In the present work on ethyl methyl ketone runs were made from 100 to 200°. No thermal decomposition was found, but methane was formed photochemically. No method of testing for ketenes was practicable. Table IV presents the data.

TABLE IV

QUANTUM YIELD AT ELEVATED TEMPERATURE

Run	Ketone press., mm.	Temp., °C.	Quantum yield of CO formation	Fraction absorbed	Ratio CO/CH_4	Quantum yield of CH_4 formation
47	43	105–110	0.79	0.60	4.2	0.19
41	4.75	160–165	.79	.36	4.0	.20
42	45	160–165	.85	.74	2.2	.38
48	43	195–200	.71	.59	1.5	.47

The amount of methane seems to increase both with increasing temperature and with increasing pressure. In run 47 a spectroscopic test was made for biacetyl and only a trace was found. This might have been produced during the photographing of the spectrum.

Discussion

It is quite evident from the data in Tables II and III together that as the pressure is lowered the over-all quantum yield for the disappearance of ethyl methyl ketone in the wave length region 1850–2000 Å. approaches unity. The highest value observed experimentally is about 0.95 and this is well within the experimental error of 1.00.

At higher pressures the yield decreases, so that the average of runs conducted at pressures over 20 mm. is 0.83 (allowing 0.08 for the biacetyl reaction).

Since Beer's law is not obeyed, it is necessary to allow for at least two and probably more different types of absorption. Thus we may write down the following primary processes

$$I_1 \quad K + h\nu = K_1 \quad (1)$$

$$I_2 \quad K + h\nu = CH_3CO + C_2H_5 \quad (2)$$

$$I_3 \quad K + h\nu = C_2H_5CO + CH_3 \quad (3)$$

where K represents a molecule of ethyl methyl ketone and K_1 an excited molecule. The active molecules may fluoresce, may dissociate or may be deactivated by collision. No fluorescence could be detected in the visible, in contradistinction to the behavior in the near ultraviolet.[1] With acetone, also,[5] no fluorescence excited by these wave lengths could be detected. Therefore we may write the following reactions for K_1:

$$k_1 \quad K_1 + K = K + K \qquad (4)$$
$$k_2 \quad K_1 = CH_3CO + C_2H_5 \qquad (5)$$
$$k_3 \quad K_1 = C_2H_5CO + CH_3 \qquad (6)$$

If, now, none of the free radicals recombine to give ethyl methyl ketone, we arrive at the following expression for the quantum yield of ketone decomposition

$$\Phi = \frac{1}{I_1 + I_2 + I_3}\left[I_2 + I_3 + \frac{I_1}{\frac{k_1(K)}{k_2 + k_3} + 1}\right] \qquad (7)$$

Since the relative values of I_1, I_2 and I_3 change with pressure, the quantitative application of equation (7) would have little meaning. It is evident, however, that it may be made to fit the data on quantum yields. According to this equation the yield should become one at zero pressure and this seems to be true. At higher pressures the variation of quantum yield will depend upon the relative magnitudes of the absorption coefficients for the three primary processes as well as on the magnitudes of k_1, k_2 and k_3. Little more can be said concerning the variation of over-all quantum yield from the data at room temperature.

There may be a slight tendency for the amount of biacetyl to increase with the pressure, the tendency of this substance to dissolve in the ethyl methyl ketone being a factor which might prevent the increase from becoming more noticeable. This could be explained easily on the basis of the higher optical absorption and consequently greater chance of reaction between free radicals.

If (1), (2) and (3) are the only primary processes (the simultaneous splitting off of both alkyl groups would not be impossible), the following equations must be considered

$$CH_3CO = CH_3 + CO \qquad (8)$$
$$C_2H_5CO = C_2H_5 + CO \qquad (9)$$
$$CH_3CO + CH_3CO = (CH_3CO)_2 \qquad (10)$$
$$CH_3CO + C_2H_5CO = CH_3COCOC_2H_5 \qquad (11)$$
$$C_2H_5CO + C_2H_5CO = (C_2H_5CO)_2 \qquad (12)$$
$$CH_3 + CH_3 = C_2H_6 \qquad (13)$$
$$CH_3 + C_2H_5 = CH_3CH_2CH_3 \qquad (14)$$
$$C_2H_5 + C_2H_5 = C_4H_{10} \qquad (15)$$

As the temperature is increased, methane could be formed by

$$CH_3 + CH_3COC_2H_5 = CH_4 + C_4H_7O \text{ (free radical)} \qquad (16)$$

Rice and Herzfeld[14] ascribe a heat of activation of 15,000 cal. to the analog of (16) in acetone. The free radical could split off an ethyl or a methyl group to give ketene or methyl ketene. For this reaction Rice and Herzfeld give an activation energy of 48,000 cal., so that it would become important only at high temperatures.

The fact that equal quantities of the hydrocarbons ethane, propane and butane have been found in this work as well as by Norrish and Appleyard[3] is quite interesting. Presumably these reactions occur through the formation of quasi-molecules which must be stabilized by collision with a third body. That a statistical equilibrium is not established is evident since there is not twice as much propane as of either of the others. The number of binary collisions for (13), (14) and (15) will be in the ratio 1.00:0.87:0.83. With equal concentrations of the free radicals, the same steric factors, molecular diameters and activation energies, the rates of formation and hence the quantities produced should be in this same ratio. Assuming the same activation energies, the steric factors (or molecular diameters) must increase in the reverse order. This might imply that the more complex the quasi-molecule the greater the chance of a suitable *three-body collision*, a not unexpected result.

Reactions (8) and (9) involve small heats of reaction and for (8) Rice and Herzfeld give a heat of activation of 10,000 cal. This accounts for the fact that little diketone is formed at the higher temperature.

Summary

1. Photochemical decomposition of ethyl methyl ketone in the near ultraviolet (largely with the 3130 Å. line of mercury) leads to the production of diketones, approximately 11% of the reaction going in this way at room temperature.

2. The quantum yield of carbon monoxide formation from ethyl methyl ketone at room temperature with wave lengths from 1850 to 2000 Å. increases from about 0.70 to about 0.88 as the pressure decreases from 90 mm. to 0.1 mm.

3. Diketones are formed in this region of the spectrum. The formation of biacetyl has been shown spectroscopically.

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[14] Rice and Herzfeld, THIS JOURNAL, **56**, 284 (1934).

4. The total quantum yield of ethyl methyl ketone decomposition with wave lengths below 2000 Å. is nearly one at low pressures when allowance is made for diketone formation.

5. At higher temperatures some methane is formed, but at room temperature the principal hydrocarbons are ethane, propane and butane in approximately equal amounts.

6. Possible secondary reactions have been discussed.

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Studies on Aging and Properties of Precipitates. XXIII. The Postprecipitation of Ferrous Sulfide with Cupric Sulfide

By I. M. Kolthoff and Frank S. Griffith[1]

Böttger and Druschke[2] found that iron is found in a precipitate of copper sulfide when the latter is formed under such conditions that no precipitation of iron sulfide alone occurs. Even when the copper sulfide was precipitated from solutions which were 2 *N* in nitric, hydrochloric or sulfuric acid, iron was found in the precipitate. In the present paper it is shown that iron sulfide is not *co*-precipitated but *post*-precipitated with cupric sulfide.

Experimental

The materials used were c. p. products. The stock ferrous sulfate solution was kept in 0.1 *N* sulfuric acid, the latter inhibiting the air oxidation. A fresh solution was prepared frequently. Concerning the method of treatment of the solutions with hydrogen sulfide reference is made to previous papers.[3]

After shaking in an atmosphere of hydrogen sulfide for a given period of time the solutions were filtered and the precipitate washed with 0.1 *N* hydrochloric acid which had been saturated with hydrogen sulfide. The filtrate and washings were evaporated to a volume of 25–50 ml., thus removing the hydrogen sulfide, 5 ml. of 5 *N* hydrochloric acid was added and any ferric iron formed reduced with a slight excess of stannous chloride. After the further classical treatment the ferrous iron was titrated with 0.05 *N* potassium dichromate using sodium diphenylamine sulfonate as indicator. In those cases in which the amount of iron removed from solution was very small the iron was determined in the washed precipitate. The latter was dissolved, the iron oxidized and precipitated with ammonia. The precipitate was dissolved, the iron reduced to the ferrous state and titrated with 0.005 *N* potassium dichromate.

Experimental Results

In order to get an impression of the order of magnitude of the precipitation of iron, various preliminary experiments were carried out. One hundred ml. of solution containing 5 mmol. of cupric sulfate and 1.25 mmol. of ferrous sulfate and being 1.55 *N* in sulfuric acid (after precipitation of copper 1.65 *N*) was treated with hydrogen sulfide for fifteen minutes, filtered, and the iron determined in the precipitate. Only 0.05 mg. of iron or 0.07% of the original amount was found in the precipitate. The experiment was repeated with the solution heated to 95° before saturating with hydrogen sulfide; 0.19 mg. of iron (0.27%) was found in the precipitate. A similar set of experiments was run with the solution being 0.53 *N* in sulfuric acid (after precipitation of copper sulfide 0.63 *N*): precipitation at room temperature, 0.42 mg. of iron in precipitate (0.60%); precipitation started at 95°, 0.75 mg. of iron in precipitate (1.07%). The amounts of iron found in the precipitates (room temperature) are about one-fifth of those expected from the results of Böttger and Druschke. However, these authors do not state the time of precipitation; it is shown later that the amount of iron entering the precipitate increases with the length of time of contact with the copper sulfide.

Evidence of Postprecipitation: Effect of Time before Filtration, Concentration of Acid and of Temperature.—In the following experiments a mixture was used containing 5 mmol. of copper sulfate and 1.25 mmol. of ferrous sulfate in 100 ml. In some of the experiments the iron was present during the precipitation of the copper sulfide, in others it was added one or two minutes after precipitation of the copper. Hydrogen sulfide was bubbled through continuously during the course of the experiments; in the one-month experiments the gas outlet, after a few hours, had a fine capillary. The flasks were shaken continuously except in the one-month experiments. After the period of shaking given in Table I the filtrates were analyzed for iron.

From the fact that the extent of precipitation of the iron is about the same, regardless of whether the copper sulfide is precipitated in the presence of iron or the iron is added after precipitation of copper, it follows conclusively that we are dealing with a phenomenon of postprecipitation. The amount of postprecipitation decreases rapidly with

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[1] From a thesis submitted by Frank S. Griffith to the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Doctor of Philosophy, June, 1937.

[2] W. Böttger and K. Druschke, *Ann.*, **453**, 315 (1927).

[3] I. M. Kolthoff and D. R. Moltzau, *J. Phys. Chem.*, **40**, 779 (1936); Kolthoff and Griffith, *ibid*., **42**, 531 (1938); see also thesis of junior author.[1]

TABLE I

POSTPRECIPITATION OF IRON SULFIDE. EFFECT OF TIME, ACID AND TEMPERATURE

Temp. after addition of iron, °C.	Concn. of H_2SO_4 after pptn. of Cu, *N*	Iron added before or after pptn. of Cu	Iron in precipitate in % after			
			15 min.	4 hours	4 days	1 month
25	0.25	Before	0.4	0.8	1.0	
25	.25	After	.4	.8	...	..
25	.125	Before	.8	3.3	5.0–5.8	5.5
25	.125	After	1.0	4.0	...	..
75[a]	.252	Before	2.1	3.6	4.5–5.0	
75[a]	.252	After	2.0	4.0	...	..
75[a]	.125	Before	6.4	7.3	9.5–10.0	
75[a]	.125	After	5.0	7.0	...	
98[a]	.125	Before	10.2		12.5	14.5
95[b]	.25	Before	...	9.5–9.8	...	..
95[b]	.125	Before	...	16–18		

[a] Temperature is given at beginning of experiment after precipitation of copper sulfide. No further heat was applied.
[b] The suspension was reheated to 95° four times during the course of an experiment.

increasing sulfuric acid concentration. The rate of postprecipitation and probably also the amount of postprecipitation increases with the temperature. It is doubtful whether distribution equilibrium of iron between solution and solid has been attained in any of the experiments. The copper sulfide ages with time and, as will be shown later, its effect upon the postprecipitation of iron decreases with increasing age.

Precipitation at Higher Temperatures.—When higher temperatures were *maintained* the rate of postprecipitation was found to be much greater. Experiments were carried out with solutions of the same composition as those in Table I, the acid concentration being 0.125 *N*. The following are a few typical figures: temperature 50°; precipitated after one hour 7.0%, after four hours 8.0%, after thirty hours 9.6% of iron. Temperature 90°, precipitated after forty-five minutes 13 to 14% of iron, after twelve hours 15 to 16%. Apparently, most of the postprecipitation occurs during the first fifteen to thirty minutes.

Effect of Varying the Iron and Acid Concentrations.—In the following experiments 100 ml. of solution was taken containing 5 mmol. of copper sulfate and varying amounts of ferrous sulfate and sulfuric acid. The solutions were heated to the boiling point, put on the shaker in the air-bath at 95° and hydrogen sulfide was passed through for one hour. At the time these experiments were performed it was believed that the iron sulfide was present in the solid phase in the form of a solid solution. The experiments were made with the intention of determining the distribution coefficient of the iron sulfide between the liquid and solid phases. From the results given in Table II it is seen that the amount of iron postprecipitated increases with increasing iron concentration of the solution and decreases markedly with increasing acid concentrations, but the value of the distribution coefficient of the iron sulfide calculated from the results was not found to be constant. From the analytical view-point it is of interest to mention that no postprecipitation of iron is found at room temperature from solutions being at least 0.5 *N* in hydrochloric or 1 *N* in sulfuric acid, when filtration is made soon after the precipitation of copper.

TABLE II

EFFECT OF CONCENTRATION OF IRON AND OF ACID

Concn. of H_2SO_4 after pptn. of CuS, *N*	Concentration of $FeSO_4$ Original	Concentration of $FeSO_4$ Final *M*	Fe in ppt., %	Fe in ppt., mmol.
0.125	0.0013	0.00079–.00083	39 to 36	0.051–0.046
.125	.013	.0113	12.5 to 13	.16 – .17
.250	.0013	.00115	11	.014
.250	.013	.0121–.0123	6.5 to 5.2	.085– .067
.250[a]	.0130		8.6	.11
.250	.1295	.1275	1.4 to 1.5	.19 – .18

[a] Ten millimoles of copper sulfide instead of five.

Postprecipitation of Iron Sulfide with Aged Copper Sulfide.—At room temperature it was found to make little difference whether the iron was present during the precipitation of copper sulfide or added a few minutes afterward. At higher temperatures, however, the amount of iron found postprecipitated was always less (3 to 4%) when the iron was added after precipitation of the copper sulfide, indicating a rapid aging of copper sulfide at elevated temperatures. In order to study the effect of aging more systematically experiments were carried out in the following way. The acidified copper solution was introduced in an Erlenmeyer flask closed by a rubber stopper with two holes. Through one hole passed the inlet tube of the hydrogen sulfide; through the other a tube sealed to an ampoule containing 10 ml. of acid iron solution. The bottom of the ampoule had been blown thin in order to facilitate breaking. It was provided with a small hole in the neck which served as an exit for the gas. The copper solution was heated to the boiling point, and kept there for at least five minutes to bring the iron solution in the ampoule to the same temperature. After this time the flask was placed in a box maintained at 90°, and hydrogen sulfide passed through the copper solution. The mixture was shaken for the time specified in Table III as the "age of CuS" after which time the iron solution was added by punching a hole in the bottom of the ampoule with a glass rod. After shaking for fifteen minutes more the mixture was filtered and the filtrate analyzed for iron. The mixture contained 5 mmol. of copper sulfide, and 1.25 mmol. of ferrous sulfate in 100 ml.; the sulfuric acid concentration after adding the iron solution was 0.125 *N*.

Table III

Effect of Aging of Copper Sulfide at 95°

Age of CuS	0	2 min.	7 min.	20 min.	4 hours	17 hours	36 hours
Fe in ppt., %	12.5	9	6.0	5.5	2.0	0–1	0

The copper sulfide ages rapidly at 95° and becomes much less effective in its promotion of the precipitation of iron sulfide. Kolthoff and Pearson[4] showed that aged copper sulfide is more effective than the fresh product in causing the postprecipitation of zinc sulfide. The mechanism of the zinc postprecipitation is quite different from that of iron sulfide. The zinc sulfide separates from supersaturated solution as a separate phase; the iron, on the other hand, is removed from a solution undersaturated with respect to ferrous sulfide.

The rapid aging of cupric sulfide at 95° explains why it is not possible to attain distribution equilibrium of the iron in the long period experiments. Thus, working at 95° it was not possible to obtain more than 16 to 18% of the iron in the precipitate under conditions specified in Table I (final acidity 0.125 *N*). When, on the other hand, the copper solution was added slowly to the acid ferrous sulfate solution which was kept at 95° and saturated with hydrogen sulfide it was possible to obtain a precipitate containing 23 to 25% of the iron (final conditions as above).

All results reported so far indicate that the iron sulfide in the solid phase is present either as a solid solution or in the form of a chemical compound. X-ray investigations, kindly carried out by Mr. M. L. Fuller[5] of the New Jersey Zinc Co., Palmerton, Penna., by the power method with a mixed precipitate revealed the lines of copper sulfide and of chalcopyrite, $CuFeS_2$. Apparently, then, the speed of formation of copper sulfide is greater than that of chalcopyrite. The former, however, is not stable in the presence of ferrous iron and hydrogen sulfide in the solution, and at not too high acidities, it is slowly transformed into chalcopyrite.

Solubility of Ferrous Sulfide.—It has been stated before in this paper that the iron sulfide is postprecipitated with copper sulfide from solutions in which the solubility product of iron sulfide is not exceeded. Since the solubility of most slightly soluble sulfides depends much upon the degree of perfection and crystal modification it was decided to determine the solubility of iron sulfide aged under various conditions. Bruner and Zawadski[6] determined the solubility of ferrous sulfide by passing hydrogen sulfide through solutions of ferrous sulfate until equilibrium was reached and by dissolving ferrous sulfide in dilute acid. As an average they obtained in solutions saturated with hydrogen and ferrous sulfides a value of $[Fe^{++}]/[H^+]^2$ of 3.4×10^4. Moser and Behr[7] dissolved in 0.01 *N* sulfuric acid a product which had been precipitated at room temperature and aged for eighteen hours. Using the value of Noyes and Sherrill[8] for the second dissociation constant of sulfuric acid a value of $[Fe^{++}]/[H^+]^2$ of 5.5×10^4 is calculated from their data.[9]

The determination of the solubility of both fresh and well-aged iron sulfide was attempted. The following products were used:

Product 1: Fresh.—A solution of 30 g. of ferrous sulfate and 100 g. of ammonium acetate in 100 ml. of water was kept saturated with hydrogen sulfide at room temperature for one hour. A portion of the precipitate was washed four times with 0.012 *N* hydrochloric acid using the centrifuge for separating liquid and solid.

Product 2.—A solution of 28 g. of ferrous sulfate and 15 g. of sodium acetate in 100 ml. of water was kept saturated with hydrogen sulfide for eighteen hours at room temperature and the precipitate collected.

Product 3.—A molar solution of ferrous sulfate was saturated with hydrogen sulfide at 0°, the bottle containing the suspension was closed by a rubber stopper held by a wire and placed on the sand-bath at 80° for ten days (final *p*H was 2.30). The product was composed of black crystals sufficiently large to be seen by the naked eye.

An excess of the iron sulfide was shaken with acid, which previously had been saturated with hydrogen sulfide, for eight hours or longer. The sulfide was then allowed to settle or was centrifuged and the clear solution siphoned out of the flask by means of hydrogen sulfide under pressure from the Kipp generator. The hydrogen ion activity of the solution was determined colorimetrically or by means of the glass electrode and the iron content after filtration was determined by the dichromate method. The results are given in Table IV.

Table IV

Solubility of Iron Sulfide of Various Age in Acid at 25° (Direct Method)

Product used	Age	HCl, *N*	*p*H	Ml. 0.05 *N* $K_2Cr_2O_7$ for titrn. 50 ml. of soln.	$[Fe^{++}]/[H^+]^2$
1	Fresh	0.012	3.50 3.60[a]	5.75–5.46	8.3×10^4
1	Fresh	.012	3.60[b]	6.05	9.7×10^4
2	18 hrs., r. t.	.012	3.45[a]	6.33	5.0×10^4
3	10 days 80°	.025	3.19[b]	13.46	3.2×10^4
3	10 days 80°	.025	3.23[b]	12.20	3.5×10^4
3	10 days 80°	.025	3.18[b]	12.85	2.9×10^4
3	10 days 80°	.025	3.13[b]	11.95	2.2×10^4
3	10 days 80°	.025	3.20[b]	11.80	2.0×10^4

[a] Measured colorimetrically with tetrabrom phenol blue.

[b] Measured with the glass electrode.

It should be mentioned that an error of 0.05 in *p*H causes an error of 20% in the value of the quotient $[Fe^{++}]/[H^+]^2$. The value obtained with product 2 (5.0×10^4) which was prepared according to the directions of Moser and Behr[7] is in good agreement with that calculated from these authors' figures (5.5×10^4). From the results in Table IV it is seen that the solubility of iron sulfide depends little upon the age of the product, the value of $[Fe^{++}]/[H^+]^2$ being about 9×10^4 for a fresh product and about 3×10^4 for drastically aged products.

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[4] I. M. Kolthoff and E. A. Pearson, *J. Phys. Chem.*, **36**, 549 (1932).

[5] The authors take this occasion to thank Mr. Fuller for his valuable coöperation.

[6] L. Bruner and J. Zawadski, *Z. anorg. allgem. Chem.*, **65**, 143 (1909).

[7] L. Moser and M. Behr, *ibid.*, **134**, 49 (1924).

[8] M. S. Sherrill and A. A. Noyes, This Journal, **48**, 1861 (1926).

[9] Kolthoff, *J. Phys. Chem.*, **35**, 2711 (1931), in calculating this ratio from Moser and Behr's data made a mistake in that he failed to take into account the decrease of the concentration of the strong acid by the dissolved iron sulfide.

It was also attempted to reach solution equilibrium from the other side. One hundred milliliters of 0.125 *M* ferrous sulfate was placed in a flask which was shaken continuously while a slow stream of hydrogen sulfide was passed through. If the time of precipitation was longer than seven days, the flask was stoppered after that time and allowed to stand without further shaking.

TABLE V

SOLUBILITY OF IRON SULFIDE AFTER PRECIPITATION

Time of pptn.	Temp., °C.	*p*H	Ml. of 0.05 *N* $K_2Cr_2O_7$ for titrn. of 10 ml. of soln.	$[Fe^{++}]/[H^+]^2$
20 hours	25	3.01	23.68	1.2×10^5
70 hours	25	2.94	23.64	9.0×10^4
7 days	25	2.64	23.33	2.2×10^4
1 month	25	2.00	20.90	1.0×10^3
20 hours	90	2.60	23.28	1.9×10^4
70 hours	90	2.31	27.65	5×10^3

The solubility of iron sulfide at 90° in solutions saturated with hydrogen sulfide seems to be slightly less than that at room temperature. The figures indicate that the postprecipitation of iron sulfide with copper sulfide even at higher temperature (Tables I, II and III) cannot be a separation of the former in the pure form.

In order to substantiate this conclusion in an unequivocal way the following experiment was carried out. One hundred ml. of 0.0125 *M* ferrous sulfate in 0.125 *N* sulfuric acid was saturated with hydrogen sulfide and heated to the boiling point, whereupon some of the well-aged, crystalline product No. 3 of iron sulfide was added. The mixture was shaken for one hour at 90° while hydrogen sulfide was passed through the flask. The filtrate and washings required 41.9 ml. of 0.05 *M* potassium dichromate, whereas the original iron solution required only 26.00 ml. Thus, some of the iron sulfide had gone into solution. If cupric sulfide instead of the well-aged iron sulfide had been added (Tables I, II) some of the iron would have been removed from solution. This conclusion is in agreement with the results of the X-ray analysis, which showed that the iron is present in the precipitate in the form of chalcopyrite.

That the postprecipitated iron sulfide is incorporated in the copper sulfide precipitate was also shown by experiments in which mixed precipitates were extracted with 0.2 *N* hydrochloric acid. Hardly any of the postprecipitated iron was extracted. Even upon washing at room temperature with 1 and 3 *N* hydrochloric acid (saturated with hydrogen sulfide) it was impossible to extract all of the iron. A hot extraction with 3 *N* acid removed all of the iron.

Finally, experiments were made in which zinc and mercuric sulfides instead of cupric sulfides were used as promoting agents of the precipitation of iron in acid solution. In agreement with Böttger and Druschke[2] it was found that these sulfides did not cause the precipitation of any iron at room temperature and at 80° at an acidity of 0.125 *N* sulfuric acid, even after seventeen hours of shaking.

Summary

1. Iron sulfide is postprecipitated with cupric sulfide from acid solutions which are undersaturated with regard to pure ferrous sulfide. The postprecipitated iron sulfide is difficultly extracted with 3 *N* hydrochloric acid. The presence of $CuFeS_2$ in the mixed precipitate was shown by X-ray analysis.

2. The rate of postprecipitation is small at room temperature but large at 70–95°. Due to aging of the cupric sulfide it is difficult to attain the true state of equilibrium.

3. The amount of postprecipitated iron increases with increasing ferrous iron concentration and decreasing hydrogen ion concentration and increasing amounts of cupric sulfide.

4. The promoting effect of cupric sulfide upon the precipitation of iron sulfide decreases rapidly upon aging at 90°.

5. The solubility of fresh iron sulfide expressed by the ratio of $[Fe^{++}]/[H^+]^2$ in solution saturated with hydrogen sulfide was found to be 9×10^4 at room temperature, that of mildly or drastically aged products 5 to 3×10^4.

MINNEAPOLIS, MINN.

RECEIVED MAY 4, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NEW YORK UNIVERSITY]

The Ternary Systems Sodium Iodate–Sodium Chlorate–Water and Potassium Iodate–Potassium Chlorate–Water at 25 and 50°

BY JOHN E. RICCI

Introduction.—The results of studies of ternary systems involving either sodium iodate or sodium chlorate indicated that it would be interesting to investigate the system sodium iodate–sodium chlorate–water. Sodium iodate, for example, is known to exhibit a rather marked tendency to form double compounds with other sodium salts, such as sodium chloride, bromide, iodide, nitrate and sulfate.[1] Sodium chlorate, on the other hand, has been found so far to form only one double salt, namely, $NaClO_3 \cdot 3Na_2SO_4$.[2] The present solubility measurements on the system sodium iodate–sodium chlorate–water were made for the purpose of extending the information on the two series of salts, alkali iodates and alkali chlorates, and to investigate any possible compound formation or solid solution taking place between the two specific salts at these temperatures. The system potassium iodate–potassium chlorate–water was studied simultaneously, both to extend the measurements to the corresponding potassium salt system and, by taking advantage of the more certain attainment of equilibrium in the latter system, to use it as a check on the analytical method needed for the investigation of the more troublesome sodium salt system. The results of the phase rule study of these systems, at 25 and 50°, indicate no compound formation in either combination, and no solid solution for any of the solid phases, within the limits of experimental accuracy.

Materials and Methods.—The sodium and potassium iodates were recrystallized C. P. material, dried at 100–110°. Analysis by titration with standard sodium thiosulfate (standardized against very pure potassium iodate), showed them both to be 100.0% pure. The chlorates were high grade C. P. material, powdered and dried at 150–200°.

The procedure for the solubility determinations was in general that usually described for similar phase rule investigations. Densities of saturated solutions, reported for the 25° isotherms, were determined by means of pipets calibrated for delivery. Temperatures were controlled to ±0.01°.

For the analysis of the saturated solutions, the iodate was determined by treatment with excess of potassium iodide and a limited amount of acetic acid, and titration of the liberated iodine by means of standard thiosulfate solution. Tests showed this method for the determination of iodate in the presence of large amounts of chlorate to be very exact. The procedure was to treat the iodate–chlorate solution, diluted to 50–60 ml., with 5–6 g. of potassium iodide and 2 ml. of glacial acetic acid, and to titrate at once with thiosulfate. In such low acidity the interference due to oxidation of iodide by even large amounts of chlorate, proves to be altogether negligible, while the reaction of the iodate is complete and rapid. Employing this acidity throughout, very small amounts (0.1 to 0.3 g.) of sodium iodate were titrated in the presence of up to 20 g. of sodium chlorate, the determination proving exact in every case (the average error being one part in three thousand).

A similar procedure was described by Barneby,[3] who, however, tried it in the presence of much smaller amounts of chlorate only.

The total dissolved solid was determined by evaporation to dryness, and the chlorate salt then calculated by difference.

No difficulty was encountered in the solubility determinations for the potassium salt system. The usual procedure—preparation of complexes of exact composition, analysis of the filtered saturated solution and identification of solid phases by algebraic extrapolation of the tie-lines connecting these two compositions—proved satisfactory and very accurate. To ensure attainment of equilibrium, the mixtures were stirred for periods of five to nine days, and the equilibrium checked by repeated analysis of the solution. The mean error of the extrapolation of tie-lines to the compositions of the pure phases was only 0.09%, verifying the applicability of the titration method employed and the dependability of the experimental procedure in general.

The attainment of solubility equilibrium in the sodium iodate–sodium chlorate system is much slower. Complexes of exact composition can be prepared only from anhydrous sodium iodate, while the stable phase for this salt, for the whole of the 25° and part of the 50° isotherm, is the monohydrate, $NaIO_3 \cdot H_2O$. The hydration of sodium iodate, however, particularly in the presence of high concentrations of other salts, is extremely slow in reaching completion. In every case in which the original sodium iodate was seeded with monohydrate crystals in the presence of dissolved sodium chlorate, even though the solid phase formed was always quite obviously the correct hydrate from its very distinctive appearance, nevertheless the mathematical extrapolation of tie-lines through the points representing saturated solution and total complex was always such as to indicate that the remaining solid contained about 1% either of sodium chlorate (in solid solution) or of unchanged anhydrous sodium iodate. This was observed repeatedly even for mixtures stirred for as long as sixty days (at 25°). Many experiments were

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[1] Ricci, THIS JOURNAL, **56**, 295 (1934).

[2] Ricci and Yanick, *ibid.*, **59**, 491 (1937).

[3] Barneby, *ibid.*, **38**, 330 (1916).

made with this procedure, the results of which, however, are not included in the tables here presented, inasmuch as it was proved subsequently that the apparent deviation of the composition of the solid phase from that of pure $NaIO_3 \cdot H_2O$ was due simply to lack of equilibrium or incomplete hydration, and that there is in reality no formation of mixed crystals at all at the temperatures studied.

The procedure finally employed to obtain equilibrium results for this system, wherever the solid phase is $NaIO_3 \cdot H_2O$, involved the addition of the component sodium chlorate to mixtures already containing the completely hydrated $NaIO_3 \cdot H_2O$ and water, obtained by stirring sodium iodate and water, seeded with the monohydrate, for several days. As the composition of the total complex could not be known with any accuracy in such a procedure, the wet residue was analyzed in every case, and the solid phase then identified by algebraic extrapolation through saturated solution and wet residue. A check on the attainment of equilibrium was again made and the minimum time allowed (six days at 25°) was found to be sufficient; the analysis of one solution, stirred for six days, gave 1.52% $NaIO_3$ and 43.00% $NaClO_3$; after nineteen more days, 1.52% $NaIO_3$ and 42.98% $NaClO_3$.

For all other solid phases in both systems, at the temperatures studied, equilibrium was readily attained from the original complexes of exact composition, and the phases were regularly identified by ordinary algebraic extrapolation through solution and total complex. At 50° in the sodium salt system, metastability for either anhydrous or hydrated sodium iodate can be maintained easily, in the first case by starting with anhydrous sodium iodate and not seeding, and in the second case by following the procedure described above, hydrating the sodium iodate completely before addition of sodium chlorate.

TABLE I

SYSTEM KIO_3–$KClO_3$–H_2O

Saturated solution Wt. % KIO_3	$KClO_3$	Density	Original complex Wt. % KIO_3	$KClO_3$	Solid phase
		—25°—			
8.45	0.00	1.043			KIO_3
7.05	2.31	1.070	20.00	2.00	KIO_3
5.85	5.31	1.082	19.04	4.58	KIO_3
5.43	6.78	1.091	18.00	6.54	$KIO_3 + KClO_3$
5.44	6.79	1.092	12.48	12.54	$KIO_3 + KClO_3$
5.44	6.81	1.089	6.99	17.92	$KIO_3 + KClO_3$
5.42	6.81	1.086	5.01	19.00	$KIO_3 + KClO_3$
5.43	6.80	1.090(av.)			$KIO_3 + KClO_3$
2.92	7.31	1.068	2.52	20.02	$KClO_3$
0.00	7.90	1.048			$KClO_3$
		—50°—			
13.21	0.00				KIO_3
10.87	3.71		27.07	3.03	KIO_3
8.76	8.58		25.06	7.00	KIO_3
7.26	13.76		22.04	11.54	$KIO_3 + KClO_3$
7.27	13.77		14.03	18.93	$KIO_3 + KClO_3$
7.27	13.77		7.98	24.12	$KIO_3 + KClO_3$
7.27	13.77(av.)				$KIO_3 + KClO_3$
5.27	14.31		4.48	27.04	$KClO_3$
2.41	15.11		2.03	28.17	$KClO_3$
0.00	15.78				$KClO_3$

Results.—The results for the system KIO_3–$KClO_3$–H_2O are shown in Table I and Fig. 1; those for the system $NaIO_3$–$NaClO_3$–H_2O in Tables II and III and Figs. 2 and 3.

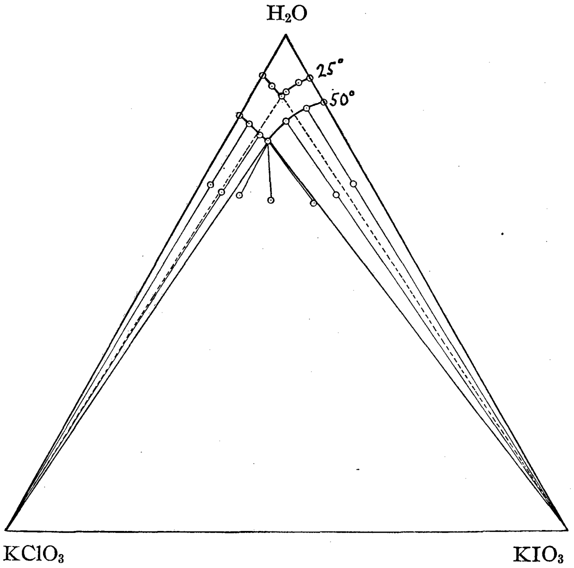

Fig. 1.—System KIO_3–$KClO_3$–H_2O at 25 and 50°.

TABLE II

SYSTEM $NaIO_3$–$NaClO_3$–H_2O AT 25°

Saturated solution Wt. % $NaIO_3$	$NaClO_3$	Density	Wet residue Wt. % $NaIO_3$	$NaClO_3$	Solid phase
8.57	0.00	1.075			$NaIO_3 \cdot H_2O$
4.51	8.36	1.098	25.12	6.33	$NaIO_3 \cdot H_2O$
3.14	16.50	1.146	24.91	12.39	$NaIO_3 \cdot H_2O$
2.43	24.67	1.204	27.37	17.78	$NaIO_3 \cdot H_2O$
1.97	32.57	1.273	29.77	22.53	$NaIO_3 \cdot H_2O$
1.69	38.66	1.332	28.02	27.40	$NaIO_3 \cdot H_2O$
1.52	42.99		10.00	38.96 (total complex)	$NaIO_3 \cdot H_2O$
1.46	44.56	1.396	28.04	31.48	$NaIO_3 \cdot H_2O$
1.39	46.37	1.404	23.40	35.03	$NaIO_3 \cdot H_2O$
1.33	48.13	1.425	28.22	33.83	$NaIO_3 \cdot H_2O$
1.30	49.19	1.440	24.57	36.50	$NaIO_3 \cdot H_2O$
			Original Complex		
1.29	49.42	1.445	5.99	46.94	$NaIO_3 \cdot H_2O + NaClO_3$
1.29	49.40		9.98	44.97	$NaIO_3 \cdot H_2O + NaClO_3$
1.29	49.32	1.441	8.0	47.0	$NaIO_3 \cdot H_2O + NaClO_3$
1.29	49.44	1.446	4.99	50.49	$NaIO_3 \cdot H_2O + NaClO_3$
1.29	49.32	1.444	5.0	54.0	$NaIO_3 \cdot H_2O + NaClO_3$
1.29	49.40		2.05	56.23	$NaIO_3 \cdot H_2O + NaClO_3$
1.29	49.38	1.444(av.)			$NaIO_3 \cdot H_2O + NaClO_3$
1.16	49.52	1.444	1.01	55.95	$NaClO_3$
0.00	50.14				$NaClO_3$

In the potassium salt system the only solid phases found are the pure anhydrous salts themselves; the algebraic extrapolation of tie-lines indicates, at both temperatures, no solid solution formation on either side of the diagram.

Similarly, in the sodium salt system, no compound formation is found, and the salts again

TABLE III

SYSTEM $NaIO_3$–$NaClO_3$–H_2O AT 50°

Saturated solution Wt. %		Wet residue Wt. %		
$NaIO_3$	$NaClO_3$	$NaIO_3$	$NaClO_3$	Solid phase[b]
13.49	0.00			$NaIO_3 \cdot H_2O$
7.67	10.02	36.02	6.81	$NaIO_3 \cdot H_2O$
5.69	16.56	37.87	10.26	$NaIO_3 \cdot H_2O$
4.91	20.61	31.69	14.17	$NaIO_3 \cdot H_2O$
3.23	33.33	32.49	22.22	$NaIO_3 \cdot H_2O$
2.41	43.71	31.24	29.29	$NaIO_3 \cdot H_2O$
2.12	48.95	31.48	32.99	$NaIO_3 \cdot H_2O$ (m)
1.92	53.20	27.13	38.23	$NaIO_3 \cdot H_2O$ (m)
1.87	54.58	32.29	36.23	$NaIO_3 \cdot H_2O$ (m) + $NaClO_3$
		Original Complex		
1.87	54.61	12.0	54.0	$NaIO_3 \cdot H_2O$ (m) + $NaClO_3$
1.87	54.59(av.)			$NaIO_3 \cdot H_2O$ (m) + $NaClO_3$
2.50	43.41	17.99	36.52	$NaIO_3$ (m)
(2.2	45.)[a]			$NaIO_3$ + $NaIO_3 \cdot H_2O$
2.14	47.86	17.01	40.58	$NaIO_3$
1.75	53.83	16.99	45.48	$NaIO_3$
1.71	54.69	11.99	53.97	$NaIO_3$ + $NaClO_3$
1.68	54.74	2.99	61.01	$NaIO_3$ + $NaClO_3$
1.69	54.71(av.)			$NaIO_3$ + $NaClO_3$
1.26	54.98	1.01	63.96	$NaClO_3$
0.00	55.74			$NaClO_3$

[a] By interpolation. [b] (m) = Metastable.

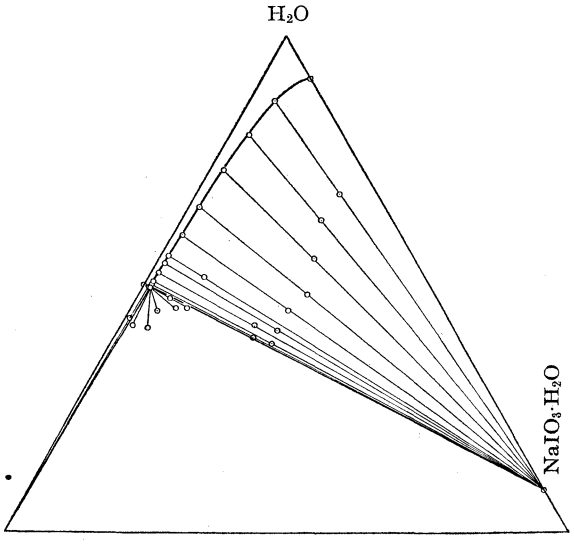

Fig. 2.—System $NaIO_3$–$NaClO_3$–H_2O at 25°.

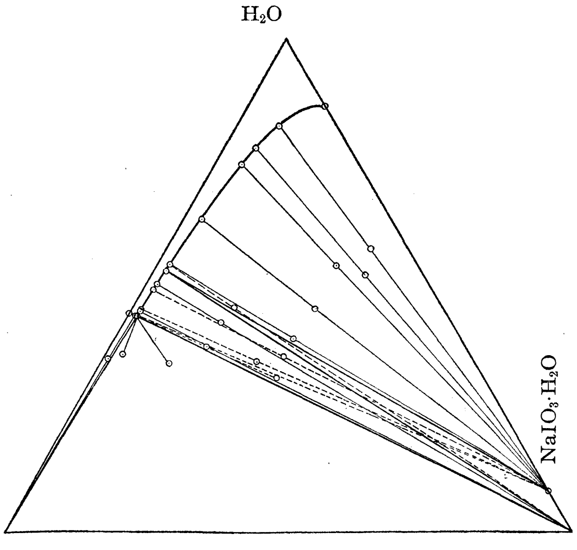

Fig. 3.—System $NaIO_3$–$NaClO_3$–H_2O at 50°.

exist in the pure state, without the formation of mixed crystals, within the limits of the accuracy of the algebraic extrapolation of tie-lines. For the case of the phases anhydrous sodium chlorate and anhydrous sodium iodate, this accuracy is quite high, since the extrapolation is performed through the accurately analyzed solution and the composition of a total complex of exact preparation. The mean absolute deviation from purity for these solid phases, as indicated by the extrapolations for both temperatures, was 0.026%, the algebraic mean being less than 0.004%. For the monohydrate of sodium iodate as solid phase, the extrapolation was by means of the saturated solution and the composition of the wet residue. At 25°, at which temperature the wet residue can be analyzed quite accurately, the mean absolute deviation of the extrapolated tie-lines from the point representing $NaIO_3 \cdot H_2O$ was 0.14%, the mean algebraic error being only −0.03%. At 50°, however, a wet residue cannot be analyzed so accurately, due to evaporation during sampling; as a consequence the absolute average error of extrapolation at this temperature was 0.38%, the algebraic average, however, being only −0.08%.

It can be said, therefore, that for all phases and at both temperatures the salts exist in the pure state, without formation of mixed crystals.

Anhydrous sodium iodate exists as a stable solid phase for the system $NaIO_3$–$NaClO_3$–H_2O at 50°, at high concentrations of sodium chlorate, even though the transition temperature between anhydrous and monohydrated sodium iodate in the binary system with water is 23.4° above this temperature. At the same time the solubility curve of the monohydrate can be followed continuously to a metastable isothermally invariant point, at which the solid phases are $NaClO_3$ and $NaIO_3 \cdot H_2O$. The two solubility curves, however—that for anhydrous and that for hydrated sodium iodate—are so nearly parallel and close together that it would be very difficult to determine their point of crossing directly. It can be estimated, nevertheless, from the concentration of sodium iodate along the two curves, that the isothermally invariant point representing equilibrium between the two forms of the iodate must have the approximate composition 2.2% $NaIO_3$ and 45% $NaClO_3$. At higher concentrations of sodium chlorate the anhydrous sodium iodate has the lower solubility and is therefore the stable phase. These relationships are indicated in the table of results for this isotherm, but cannot be shown with any clearness in the figure.

Summary

Solubility measurements are given for the two ternary systems KIO_3–$KClO_3$–H_2O and $NaIO_3$–$NaClO_3$–H_2O at 25 and 50°. Neither compound formation nor solid solution is observed for either system at these temperatures. In the 50° isotherm of the system $NaIO_3$–$NaClO_3$–H_2O, anhydrous sodium iodate is found to exist as a stable phase over a limited range of the solubility curve at high concentrations of sodium chlorate.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF KANSAS]

The Solubility of Halides in Anhydrous Acetic Acid

BY ARTHUR W. DAVIDSON AND WILBERT CHAPPELL

It was reported by Benrath,[1] as early as 1905, that a large number of chlorides are appreciably soluble in glacial acetic acid and may be crystallized unchanged from such solutions. Quantitative data on the solubility of halides in this solvent are limited, however, to the still earlier work of Étard[2] on mercuric chloride, the studies of Menschutkin on systems of acetic acid with calcium chloride, magnesium bromide and iodide,[3] and antimony chloride and bromide,[4] and the recent determination by Scholl, Hutchison and Chandlee[5] of the solubility of barium chloride in pure acetic acid and in the presence of various concentrations of sodium bromide.

The present paper includes solubility data, over a wide range of temperature, for sodium, potassium, ammonium, barium, strontium, cupric and mercuric chlorides, as well as for mercuric bromide and iodide. Of these salts, strontium chloride proved to be by far the most soluble at room temperature, and mercuric chloride to have the greatest solubility at the boiling point of the solvent. Experiments with cadmium chloride showed the solubility of this salt to be too small to be measured.

Method

Preparation of Materials.—Pure anhydrous acetic acid was prepared as described in previous papers of this series. All the salts used, except mercuric bromide and iodide, were purified by recrystallization and dried to constant weight under suitable conditions. Mercuric bromide and iodide were prepared by precipitation, and were dried for several days at 110 to 115°.

Determination of Solubility.—In every case except for the chlorides of barium and strontium, the synthetic method, as described in previous papers, was used. Duplicate determinations, with the usual precautions, were made of the equilibrium temperatures. The values given are believed to be correct to within 1° in the case of ammonium chloride and the mercuric halides, and to within 3° elsewhere, even in the case of cupric chloride, which gives a very steep temperature–concentration curve.

For barium and strontium chlorides the analytical method was used for determining solubilities. About 100 cc. of the solvent was placed in contact with an excess of the solid solute in a tightly stoppered bottle, which was then maintained at the desired temperature in a suitably adjusted thermostat. After equilibrium had been reached, filtered samples were withdrawn by means of a pipet with a bit of cotton fitted over its tip, and the chlorine content of each sample was determined by the usual gravimetric method.

Analysis of Solid Phases.—The solids to be analyzed were separated from their saturated solutions by filtration with gentle suction, rapidly pressed between dried pieces of porous tile, and allowed to remain over pellets of sodium hydroxide in a desiccator, for a few minutes only. Samples were then weighed as quickly as possible, and their chlorine content was determined in the usual way.

Results

Cupric, Sodium, Potassium and Ammonium Chlorides.—In the tables given below, S denotes the mole percentage of solute, and T the corresponding equilibrium temperature. These data are presented graphically in Fig. 1.

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[1] Benrath, *J. prakt. Chem.*, [2] **72**, 228 (1905); see also Davidson, THIS JOURNAL, **50**, 1890 (1928).

[2] Étard, *Ann. chim. phys.*, [7] **2**, 555 (1894).

[3] Menschutkin, *Z. anorg. Chem.*, **54**, 89 (1907).

[4] Menschutkin, *J. Russ. Phys.-Chem. Soc.*, **43**, 1785 (1911).

[5] Scholl, Hutchison and Chandlee, THIS JOURNAL, **55**, 3081 (1933).

I. Cupric chloride

S	T
Solid phase $CuCl_2$	
0.0081	35
.0150	50
.0163	62
.0218	75

II. Sodium chloride

S	T
Solid phase NaCl	
0.076	30
.081	41
.085	45
.097	54
.105	60
.115	68
.130	76
.145	84
.166	92

III. Ammonium chloride

(a) Solid phase $HC_2H_3O_2$	
0	16.60
0.053	16.53
(b) Solid phase NH_4Cl	
0.053	21
.065	25
.084	32
.095	38
.110	43
.134	53
.150	58
.178	65
.209	72
.224	77
.259	84
.282	87
.312	92
.348	98

IV. Potassium chloride

(a) Solid phase $HC_2H_3O_2$	
0.168	16.45
(b) Solid phase KCl	
0.157	24
.170	30
.188	39
.207	47
.229	55
.239	59
.257	63
.272	70
.295	76
.336	87
.367	93

In the case of the alkali chlorides, the solid phases that separated from the saturated solution were shown, by analysis, to be the unsolvated salts. In the case of the copper salt it was impossible to obtain sufficient solid for an accurate analysis, but the brownish-yellow color of the crystals indicated that they probably consisted of unsolvated cupric chloride.

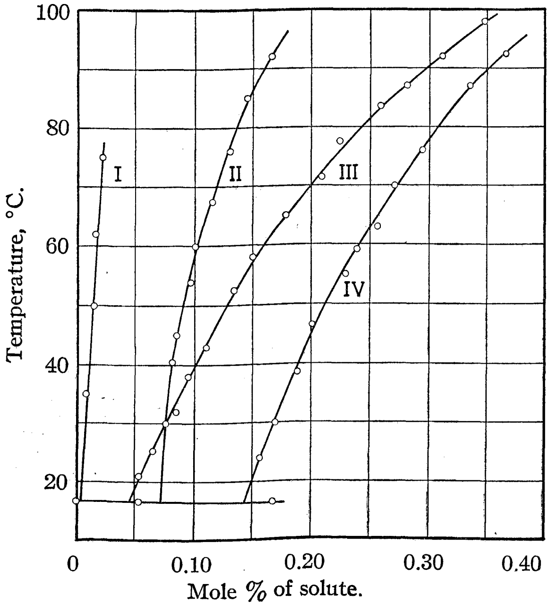

Fig. 1.—Solubility curves for $CuCl_2$ (I), NaCl (II), NH_4Cl (III) and KCl (IV) in anhydrous acetic acid.

Because of the extremely slow rate at which the alkali chlorides dissolve in acetic acid at low temperatures, there was room for some doubt as to whether or not the temperatures at which disappearance of crystals was observed, corresponded to true equilibrium. In order to check this point, analyses were made on solutions which had been maintained at 30°, with continuous agitation, for ten days, after having been heated to 100° for an hour in contact with excess solute. The solubility values so obtained, in mole %, are compared below with those obtained by interpolation from the preceding tables. It will be noted that the agreement, even at this low temperature, is fairly good. Incidentally, the value given by Eichelberger[6] for the solubility of ammonium chloride (temperature not specified) corresponds to 0.078 mole %.

	NaCl	NH_4Cl	KCl
Solubility, synth.	0.076	0.076	0.170
Solubility, anal.	.073	.080	.175

Barium and Strontium Chlorides.—The solubility of barium chloride is too low to be determined accurately by the synthetic method. Analysis of solutions saturated by contact with excess solid for a week at 30 and at 45° gave, respectively, 0.0077 and 0.0100 mole % of solute. The figure given by Scholl, Hutchison and Chandlee[5] (p. 3084) for the solubility at 25° is equivalent to 0.0059 mole %.

Preliminary experiments with strontium chloride immediately revealed that its solubility in acetic acid rapidly diminishes with increasing temperature. An attempt was made to determine the solubility by noting the temperature at which the last of the solid phase just disappeared, on *cooling* the solution; the crystals dissolved too slowly, however, for concordant results to be obtained by this method. Accordingly, a saturated solution was prepared at about 15°, and transferred to a thermostat at the desired temperature. An abundant crop of crystals was formed, and equilibrium was attained after agitation of the mixture for twelve hours. That portion of the freezing point curve in which acetic acid was the solid phase, however, was obtained by the determination of equilibrium temperature in the usual manner.

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[6] Eichelberger, THIS JOURNAL, **56**, 799 (1934).

The data are tabulated below, and plotted in Fig. 2.

STRONTIUM CHLORIDE–ACETIC ACID

S	*T*	*S*	*T*
(a) Solid phase $HC_2H_3O_2$		(b) Solid phase $SrCl_2$	
0	16.60	1.67	98.9
0.55	16.32	2.22	83.0
1.09	16.05	3.28	60.0
1.81	15.68	4.04	45.0
3.07	15.05	5.12	30.0
3.93	14.50	6.11	19.0
5.11	13.65		

Analysis of solid phase (b) showed it to be unsolvated. It will be noted that the solubility of the salt at 20° is almost four times as great as at 100°; up to the present, this is the only case of retrograde solubility to have been observed in an acetic acid system.[7]

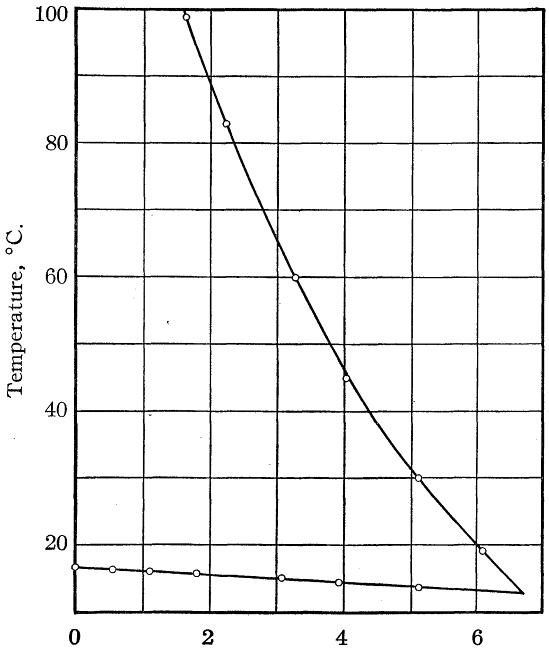

Fig. 2.—System $SrCl_2$–$HC_2H_3O_2$.

Mercuric Halides.—Unlike the alkali chlorides, the mercuric halides were found to dissolve rather rapidly in acetic acid, so that saturation equilibria were readily attained in these systems. It is noteworthy that when a solution of mercuric iodide, saturated at 100°, was suddenly chilled to about 60°, the crystals deposited consisted of the metastable yellow variety of the salt; when the mixture was stirred, this gradually changed to the stable scarlet form. The intense color of the latter greatly facilitated the accurate determination of equilibrium temperatures.

The data are tabulated below, *S* and *T* having

I. Mercuric iodide

S	*T*
Solid phase HgI_2	
0.011	31
.021	47
.030	56
.045	67
.065	76
.097	90
.134	100
.192	110

II. Mercuric bromide

(a) Solid phase $HC_2H_3O_2$	
0.194	16.50
(b) Solid phase $HgBr_2$	
0.261	25
.287	32
.350	41
.413	51
.477	58
.650	71
.707	75
.860	86
.998	92
1.13	97
1.29	103
1.50	110

III. Mercuric chloride

S	*T*
(a) Solid phase $HC_2H_3O_2$	
0	16.60
0.270	16.45
.477	16.35
(b) Solid phase $HgCl_2 \cdot 2HC_2H_3O_2$	
0.477	17
.680	24
.936	30
1.06	33
1.19	36
(c) Solid phase $HgCl_2$	
1.15	40
1.30	46
1.46	53
1.61	60
1.81	66
2.01	72
2.22	78
2.42	84
2.74	92
3.05	97
3.55	106
4.21	117

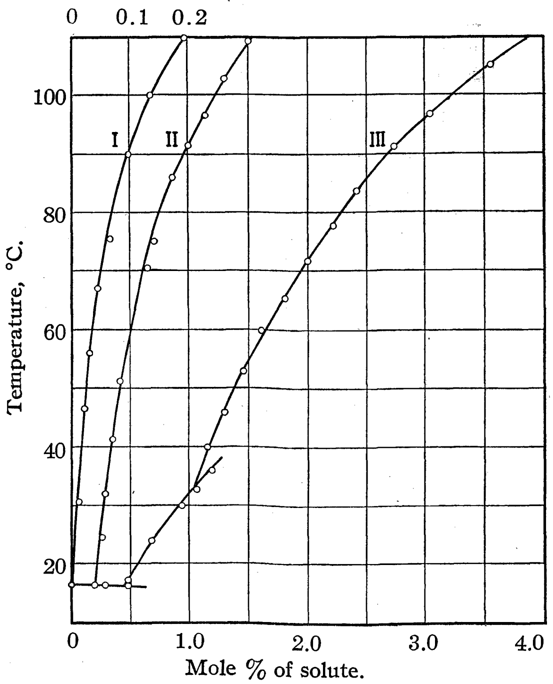

Fig. 3.—Solubility curves for HgI_2 (use upper concentration scale), $HgBr_2$ (II) and $HgCl_2$ (III) in anhydrous acetic acid.

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(7) The solubility of strontium chloride in water shows no such trend. In aqueous solution, however, the solid phases in equilibrium with the saturated solution, at least up to 200°, are hydrates, not the unsolvated salt. See Menzies, THIS JOURNAL, **58**, 934 (1936).

the same significance as before, and are presented graphically in Fig. 3.

In series I, the solid phase was shown to be unsolvated by the fact that a 1-g. sample did not impart any appreciable acidity to the water in which it was suspended. In II, analysis for bromine gave a result in accord with the composition of the unsolvated salt.

Benrath[1] (p. 237) reported that mercuric chloride may be recrystallized unchanged from glacial acetic acid. The course of the solubility curve here obtained, however, clearly indicated the existence of two distinct solid phases of the solute, with a transition point at 33°. The mean of two analyses[8] of the solid phase III (b) gave Cl, 17.68% (calcd. for $HgCl_2 \cdot 2HC_2H_3O_2$, 18.11%); while the mean of three analyses of solid phase III (c) gave Cl, 25.61% (calcd. for $HgCl_2$, 26.12%). Phase (b), then, is evidently a disolvate, which has not been reported previously. The solubility values presented in series III (b) and III (c) are, for the most part, considerably lower than those of Étard,[2] who represented the solubility curve throughout this region as a straight line, and overlooked the presence of a solvate.

Discussion

For purposes of comparison, the solubilities at 30° of the nine halides here studied have been brought together in Table I.

TABLE I

SOLUBILITY OF HALIDES IN ANHYDROUS ACETIC ACID AT 30°

Salt	Mole %	Moles per 1000 g. solvent	Salt	Mole %	Moles per 1000 g. solvent
$CuCl_2$	0.0070	0.0012	$SrCl_2$	5.12	0.899
NaCl	.075	.0125	$HgCl_2$ (disolvate)	0.936	.157
NH_4Cl	.080	.0133			
KCl	.175	.0292	$HgBr_2$	.284	.047
$BaCl_2$	.0077	.0013	HgI_2	.011	.0018

As might have been expected from their high melting points and small tendency toward solvation in this relatively slightly polar solvent, the first five of these salts are but slightly soluble in acetic acid. No explanation can be offered at present for the highly anomalous behavior of strontium chloride, whose differential heat of solution, at saturation, must be negative. The greater solubility of mercuric chloride, as compared to the alkali chlorides, is probably due to the lower melting point of the former and its greater tendency toward solvation. This salt is almost as soluble in acetic acid as in water, while mercuric bromide and iodide, especially the latter, are distinctly *more* soluble in acetic acid than in water.

Freezing point depression data, which were available over a wide concentration range in the case of strontium chloride, were used to calculate values of the freezing point divergence function, j, for these solutions. The value of j was found to remain practically constant, for molalities between 0.1 and 0.7, at 0.72. Such constancy in the value of j is in accord with previous observations for this solvent,[9] and its magnitude for this salt is almost identical with that found for the same concentration range in the case of strontium acetate.[10]

Summary

1. Solubility data over a wide range of temperature have been obtained for cupric, sodium, potassium, ammonium, strontium and mercuric chlorides, and mercuric bromide and iodide, and at 30 and 45° for barium chloride, in anhydrous acetic acid.

2. Strontium chloride has been found to exhibit retrograde solubility in this solvent.

3. The new solvate $HgCl_2 \cdot 2HC_2H_3O_2$ has been isolated and analyzed.

LAWRENCE, KANSAS RECEIVED JUNE 27, 1938

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[8] In these and other analyses of mercuric halides, mercuric ion was removed by precipitation as mercuric oxide, before the precipitation of the halide ion.

[9] Davidson and Geer, THIS JOURNAL, **60**, 1211 (1938).

[10] Davidson and Chappell, *ibid.*, **55**, 3531 (1933).

[CONTRIBUTION FROM THE JOHNS HOPKINS UNIVERSITY]

The Calculation of the Ionization Constants of Inorganic Oxygen Acids from their Structures

BY ALEXANDER KOSSIAKOFF[1] AND DAVID HARKER

Introduction

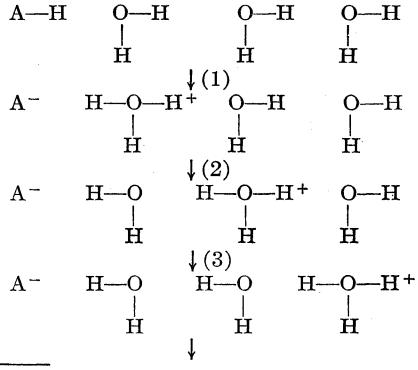
In a given solvent, the free energy of ionization of an acid is directly related to its atomic configuration. The object of this paper is the formulation of a theoretical approach to the evaluation of this relationship. Due to the importance which is generally attached to theoretical calculations correlating physical properties with the structures of molecular systems, it is hoped that the treatment presented here will prove of general interest.

The complicated nature of most acid molecules and of highly polar solvents renders a rigorous calculation of the free energy of ionization impracticable, if not entirely impossible. However, if the treatment is limited to non-resonating oxygen acids a number of reasonable assumptions may be made which facilitate a direct calculation of this quantity. The method of evaluation given here depends on the resolution of the free energy of ionization into one part which is essentially constant for all acids in a given solvent, and another part which depends strongly on the structure of the acid. The constant part constitutes a parameter in the equation; the variable part can be explicitly calculated from structural data. Having determined the parameter from the experimental ionization constant of a single acid, the constants of other acids are uniquely determined. The procedure is simple and direct, enabling a calculation of the ionization constant of an inorganic oxygen acid to be made in a short time with an average accuracy of ±0.8 in log K.

Previous Work.—The wide variation found in the ionization constants of acids has aroused the interest of many investigators. The majority of these have contented themselves with making purely qualitative observations. G. Oddo[2] noted that the ratio of oxygen to hydrogen atoms in an oxygen acid was related to its strength. Hantzsch and Langbein[3] observed that the strength of an acid increased with the number of oxygen atoms per replaceable hydrogen and with the negativity of the central atom. Similar qualitative correlations have been made by a number of other authors.[4]

The problem has been treated quantitatively by Smallwood[5] and by van Arkel and Carriere.[6] Smallwood calculated the relative strengths of some organic acids on the basis of dipole interaction. Since carboxylic acids are resonating systems, it is impracticable to check Smallwood's calculations by the method of this paper. Van Arkel and Carriere attempted to calculate the strengths of acids from the assumption that the charge distribution in the acid molecule is determined by the ions formed by the separate atoms. This assumption is not in agreement with the known structures for most of these molecules, and it is consequently not surprising that the treatment does not lead to results in agreement with experiment. It may be noted that neither Smallwood nor van Arkel and Carriere have considered the properties of the solvent.

Mechanism of Ionization.—There is good evidence that the ionization of an acid takes place through the transfer of the proton from the anion to a water molecule followed by the subsequent exchange of protons between water molecules.[7] The absence of free protons in solution, together with the abnormally large mobility of hydronium ion, provide ample justification for this picture. As will appear later, the mechanism involving proton exchanges is extremely valuable in simplifying the calculation of acid strength. The process may be symbolized thus



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[1] American Can Co. Fellow, Johns Hopkins University.

[2] G. Oddo, *Gazz. chim. ital.*, **52**, I, 56 (1922).

[3] A. Hantzsch and W. Langbein, *Z. anorg. allgem. Chem.*, **204**, 193 (1932).

[4] R. Oda, S. Namamoto, *J. Soc. Chem. Ind., Japan.*, **35**, Suppl. 543 (1932); H. S. Simms, THIS JOURNAL, **58**, 1239 (1936); T. M. Lowry, *Chemistry & Industry*, **42**, 1048 (1926).

[5] H. M. Smallwood, THIS JOURNAL, **54**, 3049 (1932).

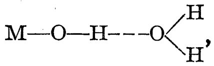
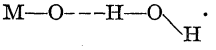
[6] A. E. van Arkel and Carriere, *Chem. Weekblad*, **33**, 182 (1936).

[7] J. D. Bernal and R. H. Fowler, *J. Chem. Phys.*, **1**, 515 (1933).

and so forth. This process removes the proton from the anion and reorients the water molecules in the immediate vicinity of that oxygen on the anion from which the proton has been removed. Thus, there is no extensive displacement of water, but there is a certain amount of reorientation. It will be seen from the subsequent discussion that a calculation of the free energy change involved in this process is a good approximation to the total free energy of ionization of an acid.

By confining our attention to non-resonating oxygen acids of the non-metallic elements, we are enabled to make approximations which permit the calculation of their free energies of ionization. Oxygen acids—those in which the removable proton is attached to an oxygen atom—comprise a large majority of the inorganic acids, and consequently the limitation of the treatment to this class causes no great loss in scope. The lack of knowledge concerning the energetics of resonating systems requires the elimination of the acids of boron, carbon, and nitrogen from the present treatment. A careful consideration of the ionization process for the non-resonating oxygen acids makes the following assumptions reasonable:

1. The forces between a proton and an acid ion are due to an electron-pair bond with the nearest oxygen atom and to the electrostatic field of the ion.
2. The hydroxyl electron-pair bond is the same for all acids. Variations in strength from one acid to another are due solely to changes in the electrostatic field and symmetry of the ion.
3. Acid and anion molecules form hydrogen bridges to adjacent water molecules, and orient the more distant water molecules by their electrostatic fields. These effects constitute the hydration of the molecules.

The first assumption is based on the fact that exchange forces diminish rapidly with distance and, therefore, will be extremely small between non-bonded atoms. The second assumption is reasonable due to the similarity of the binding of the central atom to the oxygens in the various acids. The third assumption is an expression of the geometry of hydration of anions and acid molecules. Hydroxyl groups rigidly orient the water molecules surrounding them thus:  $\mathrm{M{-}O{-}H{-}{-}{-}O}\langle^{\mathrm{H}}_{\mathrm{H}}$, non-hydroxyl oxygen thus:  $\mathrm{M{-}O{-}{-}{-}H{-}O}\backslash_{\mathrm{H}}$.

Analysis of the Free Energy of Ionization.—Consider an elementary ionization process, in which a particular proton is transferred from a given acid molecule to a particular water molecule. The reversible work done on the system is the sum of the work done in each of the following processes.

1. Rupture of the O–H bond in the acid molecule.
2. Formation of the O–H bond in hydronium ion, H_3O^+.
3. Removal of the proton from the electrostatic field of the anion.
4. Reorientation of the water molecules.
5. Compression of the water molecules.
6. Change in volume of the system against atmospheric pressure.

Let A_1 to A_6 represent the reversible work done on the system in the processes 1 to 6, respectively. The work done on the system, ΔA, is given by the expression

$$\Delta A = \Delta F - \Delta(PV)$$

At constant pressure $\Delta(PV) = -A_6$, the work done against atmospheric pressure. Therefore, the free energy change, $\Delta F'$, for the elementary ionization process, defined above, may be written

$$\Delta F' = A_1 + A_2 + A_3 + A_4 + A_5 \qquad (1)$$

Assumption 2 implies that A_1 is constant for all the acids considered, and A_2 does not depend upon the acid involved.

A_5 is the change in the compression work during ionization. T. J. Webb,[8] in his calculation of the free energy of hydration of ions, has evaluated the compression work, W_c, in terms of the radii and charges of monatomic ions. For a univalent ion of radius 1.5 Å., W_c is calculated to be 1 kcal. It increases as the square of the charge for a monatomic ion. However, for a polyatomic ion containing widely separated centers of charge, W_c will increase approximately with the first power of the total charge. The polyatomic anions of the oxygen acids are cases intermediate between these two extremes. The increase of W_c with the charge of the acid anion will be, therefore, considerably less than second power. The deviations from constancy in A_5 for the large complex anions under consideration should not exceed 0.5 kcal. The error involved in assuming A_5 to be constant is, consequently, small enough to obviate the necessity of its calculation for each acid.

Since A_1, A_2, and A_5 are essentially constant for

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[8] T. J. Webb, This Journal, **48**, 2589 (1926).

the acids under consideration, we make the approximation that

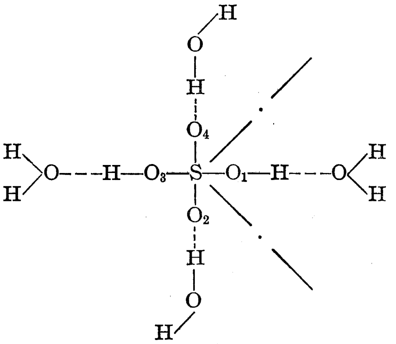
$$A_1 + A_2 + A_5 = C \qquad (2)$$

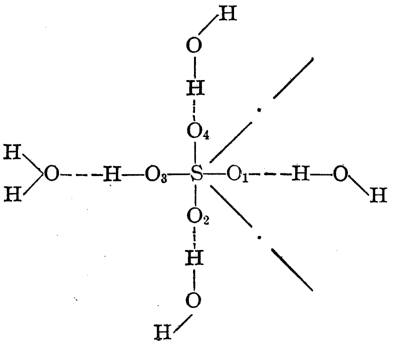
where C depends only on the temperature. Consequently

$$\Delta F' = A_3 + A_4 + C \qquad (3)$$

The Calculation of $A_3 + A_4$.—It is now necessary to show that $A_3 + A_4$ may be calculated by computing the work done in removing a proton from the anion by successive transfers between water molecules. It has been noted that this process reorients the water molecules in the immediate vicinity of that oxygen in the anion from which the proton has been removed. It remains to be shown that this work constitutes practically the entire work of reorientation resulting from the ionization process and, therefore, that A_4 is indeed included in the calculation.

The molecules of oxygen acids are, in general, complex structures, the peripheries of which consist of strongly orienting groups. The assumption has been made that these groups (oxygen and hydroxyl groups) rigidly orient the water molecules surrounding them in a definite way. The consequence is that upon ionization, which changes one hydroxyl group in the molecule into a free oxygen, only the water molecules surrounding this hydroxyl are reoriented. As an example consider H_2SO_4, which changes upon ionization into HSO_4^-. The molecules in the immediate neighborhood will be arranged thus





The main reorientation takes place in the solid angle including O_1, the waters surrounding O_2, O_3, and O_4 maintaining their original orientations. Obviously, the first two proton transfers produce the total change in orientation of the nearest neighboring waters. While subsequent transfers will not reorient all the more distant water molecules, the energy of reorientation of those water molecules which are neglected in the process is small, due to the much greater dielectric constant at large distances and to thermal agitation. Since a rigorous calculation of the total orientation effect would result in only a small correction, and would be extremely involved, the approximation is justified that the proton transfer mechanism calculation includes practically all of the reorientation energy which depends on the structure of the acid.

We write, therefore, the work required to remove the proton from the electrostatic field of the anion, A_3, plus that required to reorient the water molecules, A_4, to a sufficient approximation, as the sum

$$A_3 + A_4 = W_1 + W_2 + W_3 + W_4 + \ldots = \Sigma W_i \qquad (4)$$

where W_i is the change in potential energy accompanying the ith proton transfer. Webb[8] has shown that a calculation of the electrical work involved in a process of this type leads to a term in the free energy change (ΔF) rather than to a term in the internal energy change (ΔE).

The calculation will consist in the evaluation of the W_i's using the familiar formula for the change in mutual potential energy of two particles with charges q_1 and q_2 as the distance between them changes from r_1 to r_2

$$\Delta V = \int_{r_1}^{r_2} \frac{q_1 q_2}{\epsilon r^2}\, dr \qquad (5)$$

where ϵ is the dielectric constant.

In order to apply the formula, we must investigate the charge distribution in the anion and the dielectric properties of the medium.

Distribution of Charge.—There is considerable evidence that in an electron-pair bond between non-metallic atoms the two electrons are shared approximately equally.[9] Since the molecules of the acids under consideration are held together by single electron-pair bonds, we assign to each atom all its non-bonding and half its bonding electrons for the purpose of calculating its effective charge.[10]

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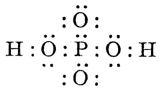
(9) L. O. Brockway and H. O. Jenkins, THIS JOURNAL, **58**, 2036 (1936).

(10) L. Pauling, *ibid.*, **53**, 1367 (1931).

The numerical value of this charge will be equal to the atomic number of the atom minus the number of electrons assigned to it. This number has been called the "formal charge."

Let us take $H_2PO_4^-$ as an example. The Lewis structure of this ion is



$$\begin{array}{c} :\ddot{O}: \\ H:\underset{..}{\ddot{O}}:\ddot{P}:\underset{..}{\ddot{O}}:H \\ :\underset{..}{\ddot{O}}: \end{array}$$

The phosphorus atom has a formal charge of 15 − 14 = +1, the two "free" oxygens each have a charge of 8 − 9 = −1, all other atoms have zero formal charge.

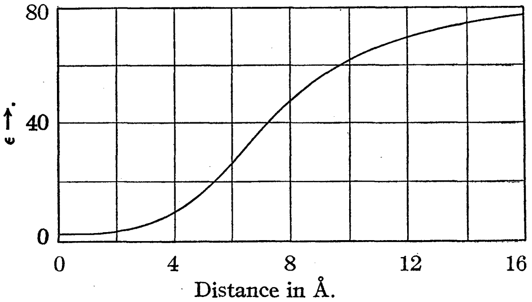


Fig. 1.

In general, the actual charge distribution in a molecule is only approximately represented by the formal charges assigned to its atoms. In addition to the single ionic structure $M^+—O^-$, the doubly covalent structures $M=O$ and completely ionic structures $M^{++}O^=$ must be taken into account in any exact calculation of the energy of the M–O bond. The effects of these two additional bond types on the charge distribution will be in opposite directions, and, therefore, will partially cancel. Moreover, since we shall make calculations only for oxygen acids of the elements in the last three columns of the periodic table (not including the first row), we feel that due to the similarity in the central atoms the small differences between the actual charge distributions and those given by the formal charge method should all be approximately equal. Since there is already a parameter C in the calculated free energy, this uniform difference can be appropriately included in the parameter.

The excellent agreement between the experimental and the calculated free energies of ionization leads us to believe that the actual charge distribution for the acids considered can deviate only slightly from that given by the "formal charge" method.

Dielectric Constant.—The dielectric constant of a solvent in the immediate neighborhood of a charged particle, such as an ion, has an abnormally low value due to the electrical saturation effect produced by the orientation of the solvent dipoles by the field. By the application of the Langevin theory to this problem, Debye[11] has calculated the effective dielectric constant of water as a function of the distance from a univalent ion. The result is shown in the graph, Fig. 1.

It is significant that the dielectric constant remains at a value of 3.0 up to a distance of about 2 Å. from the charged particle. Since the first proton transfer occurs within a distance of 1.8 Å. from the nearest free oxygen atom (which determines the value of ϵ in this region), the change in potential energy, W_1, of the proton during this transfer should be calculated using a constant value of 3.0 for ϵ. For W_1, equation (5) now reduces to the simple form

$$W_1 = \Sigma_j \frac{q_j e}{3.0}\left(\frac{1}{r_{j1}} - \frac{1}{r_{j2}}\right) \qquad (6)$$

where j refers to the jth atom in the anion.

Since the subsequent proton transfers occur at larger distances from the ion, where ϵ is much greater, their contribution to ΣW_i is small compared to W_1. Consequently, deviations of the dielectric constant at distances of over 2 Å. from the ion from the values predicted by Debye will not seriously affect the result.

The Calculation of the Free Energy of Ionization, ΔF, from $\Delta F'$.—It is now necessary to consider the relation between the free energy change $\Delta F'$ and ΔF which is defined in terms of the measured ionization constant

$$\Delta F = -RT \ln K$$

where, for an acid HA

$$K = \frac{(A^-)(H_3O^+)}{(HA)}$$

It will be shown that the difference between $\Delta F'$ and ΔF consists of two terms: one independent of the nature of the acid, the other depending only upon the symmetry of the acid and anion molecules.

In the process to which $\Delta F'$ refers, it is implied that a particular proton is transferred from an acid molecule to a particular position on a certain water molecule; in the reverse process it is im-

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(11) M. P. Langevin, *Ann. chim. phys.*, [8] **5**, 70 (1905); P. Debye, "Marx' Handbuch der Radiologie," Akademische Verlagsgesellschaft, Leipzig, 1925, Vol. VI, pp. 618–680; "Polar Molecules," Chemical Catalog Co., New York, N. Y., 1929.

plied that a particular proton is transferred from a hydronium ion to a certain free oxygen on an anion. ΔF, however, refers to a process in which this differentiation between equivalent positions is not made.

That term in the difference between the two quantities which arises from the equivalence of positions on water molecules, and of protons in hydronium ions, is dependent on the concentration of the solution, but not on the nature of the acid. Inasmuch as ionization constants are generally extrapolated to infinite dilution, this term is constant and can be absorbed in the parameter.

The term in the difference between $\Delta F'$ and ΔF which varies with the nature of the acid can be calculated as follows: Let n_H be the number of equivalent hydrogens on the acid molecule and n_O the number of equivalent oxygens in the anion. Accordingly, in K'—calculated from the relation, $\Delta F' = -RT \ln K'$—the acid concentration to be used is $n_H(\mathrm{HA})$ and the anion concentration is $n_O(\mathrm{A}^-)$. Therefore, disregarding factors independent of the nature of the acid

$$K' = \frac{n_O(\mathrm{A}^-)(\mathrm{H_3O}^+)}{n_H(\mathrm{HA})} = \frac{n_O}{n_H} K$$

Consequently

$$\begin{aligned} \Delta F &= -RT \ln K' + RT \ln \frac{n_O}{n_H} \\ &= \Delta F' + RT \ln \frac{n_O}{n_H} \\ &= \Sigma W_i + RT \ln \frac{n_O}{n_H} + C \qquad (7) \end{aligned}$$

The Numerical Computation of ΔF.—The first step in the calculation of the work involved in the various proton transfers is the construction (on paper) of a scale model of the hydrated acid molecule. The correct distances between atoms and the bond angles are obtained from published results of X-ray and electron diffraction investigations.[12] The electrostatic energy of the proton in the acid molecule is calculated, and from this is subtracted its energy in a position adjacent to the oxygen in the nearest water molecule. This is the work W_1. The work involved in the subsequent proton transfers is calculated in an analogous manner.

We have taken the O–H–O hydrogen bridge distance to be 2.70 Å. and the O–H bond distance to be 0.95 Å. Each proton transfer, therefore, moves the proton a distance 0.80 Å. along the hydrogen bridge.

To evaluate C we take the experimentally determined free energy of ionization of a single acid for which both the structure and the ionization constant are well known. We have chosen H_3PO_4 for this purpose. From this one experimental free energy we are enabled to calculate uniquely the ionization constant of any non-resonating oxygen acid for which the structure is known. Conversely, if a number of structures can be written for a given acid, the experimental value of the ionization constant allows us to choose the true one.

The crystal structures of BPO_4 and KH_2PO_4 have shown the system PO_4 to be tetrahedral. The average P–O distance from these and other measurements is 1.53 Å. Taking the P–O–H angle as 110° we can construct a scale model for the molecule H_3PO_4.

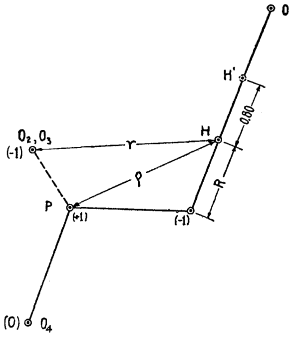

Fig. 2.—O_2 and O_3 out of plane of fig. Formal charges given in parentheses. O_3 and O_4 are hydroxyl oxygens.

By the use of equation (6) we find for the first proton transfer

$$W_1 = \frac{1.44 \times 10^{13} e^2}{3.0} \left[\left(\frac{1}{R_1} - \frac{1}{R_2}\right) - \left(\frac{1}{\rho_1} - \frac{1}{\rho_2}\right) + \left(\frac{1}{r_1} - \frac{1}{r_2}\right)\right]$$

$$= 52.4 - 12.4 + 4.9 = 44.9 \text{ kcal.}$$

Subsequent proton transfers contribute 1.2 kcal. more (calculated by the use of equation (5)), so that $\Sigma W_i = 46.1$ kcal. Since there are three equivalent protons in H_3PO_4 and two equivalent free oxygens on $H_2PO_4^-$, $RT \ln \frac{n_O}{n_H} = RT \ln \frac{2}{3} = -0.2$ kcal. Experimentally $-RT \log K$ for H_3PO_4 in water at 298.1°K. is 2.9 kcal. From these data we can evaluate the parameter C in equation (7).

$$2.9 = 46.1 - 0.2 + C \qquad C = -43.0 \text{ kcal.}$$

Since W_1, which is very easy to compute, turns

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[12] *Zeitschrift für Kristallographie*, Ergänzungsband (Strukturbericht) I, II, III, Akademische Verlagsgesellschaft, Leipzig.

TABLE I

Acid	d[a]	W_1	W_i	$RT \ln \frac{n_O}{n_H}$	$\Delta F'$	ΔF	$-\log K_1$	$-\log K$	$-\log K_{\text{obsd.}}$ Tables[14]	
H_4GeO_4	1.59	52.4	53.7	−0.8	9.8	9.9	7.2	7.3	8.6	
H_3PO_4	1.53	44.9	46.1	− .2	2.9	2.9	2.1	2.1	2.1[b]	
$H_2PO_4^-$	1.53	49.8	51.7	+ .2	8.2	8.9	6.0	6.5	7.2	
$HPO_4^=$	1.53	55.6	58.0	+ .6	14.3	15.6	10.5	11.4	11.9	
H_3PO_3	1.53	44.9	46.1	.0	3.1	3.1	2.3	2.3	1.6	
$H_2PO_3^-$	1.53	49.8	51.6	+ .6	8.6	9.2	6.3	6.7	6.7	
$H_4P_2O_7$	1.53[c]	44.4	45.6	− .6	2.0	2.0	1.5	1.5	0.9	
$H_3P_2O_7^-$	1.53	46.3	47.6	+ .6	5.1	5.2	3.7	3.8	2.0	
$H_2P_2O_7^=$	1.53	52.0	53.8	− .4	9.8	10.4	7.2	7.6	6.7	
$HP_2O_7^{\equiv}$	1.53	53.9	55.9	+1.1	13.2	14.0	9.7	10.3	9.4	
H_3AsO_4	1.66	45.4	46.6	−0.2	3.4	3.4	2.5	2.5	2.3	
$H_2AsO_4^-$	1.66	49.4	51.3	+ .2	7.8	8.5	5.7	6.2	7.0	
$HAsO_4^=$	1.66	54.6	56.8	+ .6	13.4	14.4	9.8	10.5	9.2	
H_3AsO_3	1.66	52.4	53.7	− .6	10.0	10.1	7.3	7.4	9.2	
HSO_4^-	1.50	43.3	44.9	+ .8	2.3	2.7	1.7	2.0	1.7	1.9[15]
H_2SO_3	1.50	44.8	46.1	.0	3.0	3.1	2.2	2.3	1.9	
HSO_3^-	1.50	50.0	52.0	+ .6	8.8	9.6	6.4	7.0	5.3	7.0[16]
H_2SeO_3	1.73	45.6	46.9	.0	3.8	3.9	2.8	2.9	2.3	
$HSeO_3^-$	1.73	49.2	51.0	+ .6	8.0	8.6	5.9	6.3	8.1	
H_2TeO_3	1.84[d]	46.0	47.3	0	4.2	4.3	3.1	3.1	2.5	
$HTeO_3^-$	1.84	49.2	51.0	+ .6	8.0	8.6	5.9	6.3	7.7	
H_6TeO_6	1.97[d]	52.4	53.7	−1.1	9.5	9.6	7.0	7.0	6.2	7.7[16]
$H_5TeO_6^-$	1.97	55.0	56.5	−0.4	12.8	13.1	9.4	9.6	10.4	11.2[16]
HOCl	1.54	52.4	53.7	.0	10.6	10.7	7.8	7.8	6.2	7.4[17]
$HClO_2$	1.54	45.0	46.2	+ .4	3.6	3.6	2.6	2.6	..	2.0[18]
HIO_3	1.80	39.3	41.0	+ .6	−1.9	−1.4	−1.4	−1.0	0.7	
H_5IO_6	1.93	46.2	47.3	− .4	4.0	3.9	2.9	2.9	1.6	

[a] d = central atom-oxygen distance. [b] The parameter, C, is determined by this value. [c] The P–P distance in $H_4P_2O_7$ = 3.12 Å. [d] Since the Te covalent radius is 0.04 Å. greater than that for I,[13] this distance has been added to the experimentally determined I–O distances to obtain the Te–O distances in corresponding compounds.

out to be a good approximation to ΣW_i, we have thought it worth while to evaluate a parameter C_1 for the simpler calculation by means of the relation

$$\Delta F_1 = W_1 + RT \ln \frac{n_O}{n_H} + C_1 \qquad (8)$$

and to list values of $-\log K_1$ calculated from ΔF_1 to show the relatively good results obtainable in this way.

$$2.9 = 44.9 - 0.2 + C_1 \qquad C_1 = -41.9 \text{ kcal.}$$

Having fixed the parameter in our equation, it can be used for the prediction of the free energy of ionization of other acids. For instance, for the second ionization step of H_3PO_4 (the ionization of $H_2PO_4^-$) ΣW_i is found to be 51.7 kcal., and $RT \ln \frac{n_O}{n_H} = RT \ln \frac{3}{2} = +0.2$ kcal. Adding C, $\Delta F = 8.9$ leading to a value of $-\log K = 6.5$ as compared to be experimentally determined value of 7.2.

Numerous other acids have been treated in the same way as $H_2PO_4^-$ and the results are set forth in Table I. In Fig. 3 $-\log K$ (observed) is plotted against $-\log K$ (calculated). A line of unit slope appears in the plot on which all points would fall if the agreement were perfect. The horizontal distance from a point to the line is numerically equal to the deviation of the calculated from the experimental result.

The agreement of the calculated with the observed values is quite striking in view of the simplicity of the calculation. While the acids included are all oxygen acids of the elements in the last four columns of the periodic table, the elements considered range from chlorine, whose properties are typically non-metallic, to tellurium, which is a metalloid. Moreover, the ion acids, such as HSO_4^-, fit nicely into the scheme. The quantities calculated represent differences between large numbers, making the resulting agreement all the more encouraging.

The values of $-\log K$ (calculated) for the first

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(13) L. Pauling and M. L. Huggins, *Z. Krist.*, **87**, 205 (1934).

(14) Landolt-Börnstein, "Physikalisch-chemische Tabellen," Erganzungsband II, 1931.

(15) W. J. Hamer, THIS JOURNAL, **56**, 860 (1934).

(16) H. T. S. Britton and R. A. Robinson, *Trans. Faraday Soc.*, **28**, 531 (1932).

(17) J. W. Ingram and Morrison, *J. Chem. Soc.*, 1200 (1933).

(18) Barnett, Thesis, University of California, 1935.

ionization step, for which the assumptions should be most nearly valid, show a mean absolute deviation of about 0.8 from $-\log K$ (observed). This means an average agreement of the calculated with the experimental ionization constants within a factor of 6. When the ion acids are included, the total mean absolute deviation in $-\log K$ is 0.9, or an average agreement of the ionization constants within a factor of 8. There seems to be no trend in the deviations, notwithstanding the fact that there is only one parameter to be determined from experimental data.

Prediction of Structures.—In case several reasonable atomic configurations can be postulated for a given acid, the true one usually can be chosen by comparing the strength calculated for each of these structures with the experimental value, since the calculated strength is very sensitive to change in the structure of the acid. In general, the strength corresponding to one structure agrees closely with the observed value, while the strengths corresponding to the other structures differ from that observed by far more than the error of the method. Calculations of this type have been made for a number of such acids and the results appear in Table II.

It is seen that the structures $Ge(OH)_4$, $HPO(OH)_2$, $As(OH)_3$, $Te(OH)_6$, and $IO(OH)_5$ give calculated ionization constants in good agreement with those observed. The alternate structures, on the other hand, lead to completely unreasonable values. The correct structures of phosphorous, arsenious,[12] telluric,[19] and periodic[20] acids have been determined previously by other methods; this calculation merely confirms these results. We believe that our result provides the first evidence concerning the structure of germanic acid.

Strong Acids.—There are a number of oxygen acids which are completely ionized in aqueous solution. The calculated values of $-\log K$ for these acids are all negative, in general agreement with experiment (see Table III). The theory predicts that in any hydroxylated solvent, such as alcohol, the free energies of ionization of non-resonating oxygen acids will differ from those in aqueous solution only by a change in the parameter C. The relative strengths of the acids would be the same as in water, the change being an additive constant in the expression for $-\log K$.

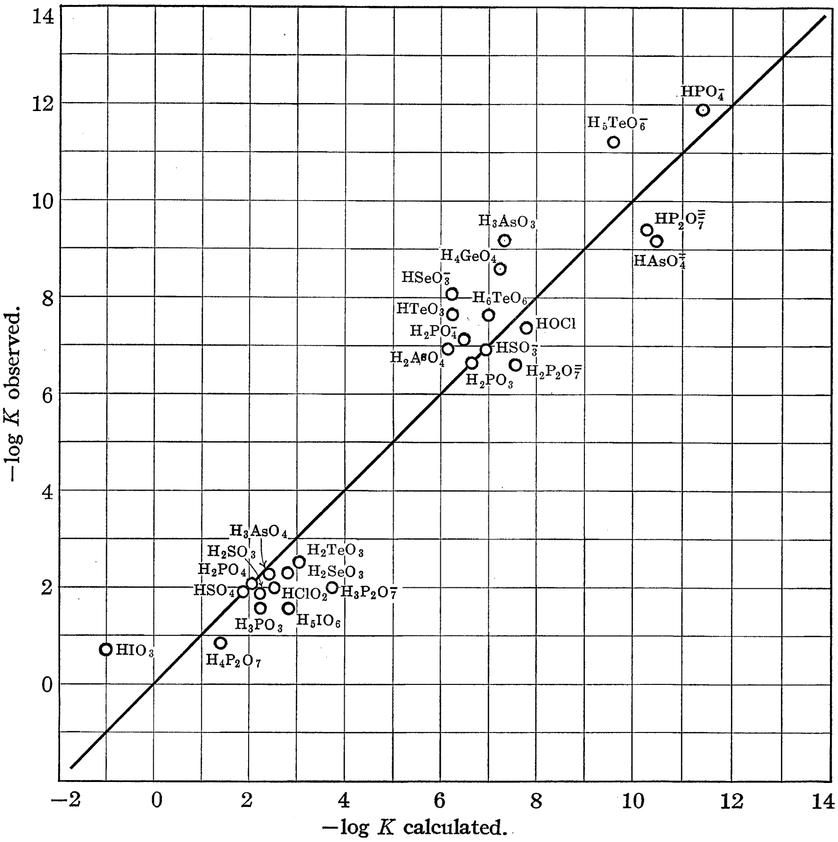

Fig. 3.—$HPO_4^=$, $HTeO_3^-$, $H_2AsO_4^-$, $H_2PO_3^-$, H_3PO_4, etc.

At present there are insufficient data on the strengths of these acids in non-aqueous solvents to permit a reliable evaluation of C. However, we have tabulated the results of the calculations for some of these acids so that, when the data become available, we may compare our results with experiment. The results of these calculations appear in Table III.

Oxygen Acids of First Row Elements.—Boric, carbonic, nitric, nitrous, and the carboxylic acids have atomic configurations which permit more than one electron structure to be written either

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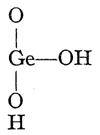
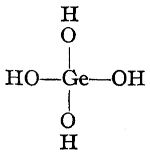
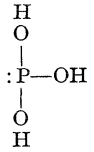
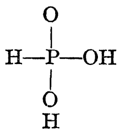
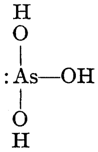
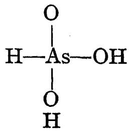
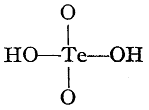
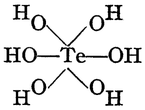
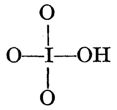
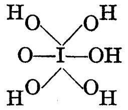
(19) L. M. Kirkpatrick and L. Pauling, *Z. Krist.*, **63**, 502 (1926).

(20) L. Helmholz, THIS JOURNAL, **59**, 2036 (1937).

TABLE II

Acid	Structure I	Structure II	$-\log K_{\text{calcd.}}$ I	$-\log K_{\text{calcd.}}$ II	$-\log K_{\text{obsd.}}$	Difference I	Difference II
Germanic[a]			2.6	7.3	8.6	−5.0	−1.3
Phosphorous			7.4	2.3	1.6	+5.8	+0.7
(2nd)			11.9	6.7	6.7	+5.2	0.0
Arsenious			7.4	2.8	9.2	−1.8	−6.4
Telluric			−1.2	7.0	7.7	−7.4	−0.7
(2nd)			2.0	9.6	11.2	−8.4	−1.6
Periodic			−4.8	2.9	1.6	−6.4	+1.3

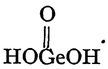
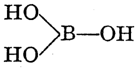
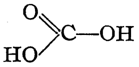
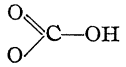
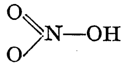
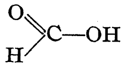
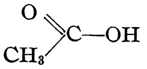
[a] The calculation does not exclude the possibility of a carbonic acid structure for germanic acid:  $\mathrm{HO}\overset{\overset{\mathrm{O}}{\|}}{\mathrm{Ge}}\mathrm{OH}$. However, double bonds to elements in the second row of the periodic table are rare, and have never been found for third row elements. Together with crystal structure data for GeO_2, this fact makes the existence of the double bonded structure for germanic acid extremely improbable.

TABLE III

Acid	d	W_i	$RT \ln n_O/n_H$	ΔF	$-\log K_{\text{calcd.}}$
H_2SO_4	1.50	38.7	+0.2	−4.1	−3.0
$H_2S_2O_6$	1.50[a]	38.7	−0.4	−4.7	−3.4
$HS_2O_6^-$	1.50[a]	41.6	+1.1	−0.3	−0.2
$HClO_4$	1.54	32.7	+0.8	−9.9	−7.3
$HClO_3$	1.54	38.7	+0.6	−3.7	−2.7

[a] The S–S distance in $H_2S_2O_6$ = 2.01 Å.

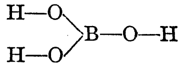
TABLE IV

Acid	Classical structure	$-\log K_{\text{calcd.}}$	$-\log K_{\text{obsd.}}$	Difference
Boric		7.4	9.2	−1.8
Carbonic		7.5	6.5	+1.0
(2nd)		12.2	10.4	+1.8
Nitric		−0.1	≪0	...
Nitrous	O=N—OH	7.8	3.3	+4.5
Formic		7.8	3.7	+4.1
Acetic		7.8	4.7	+3.1

for the acid molecule, or for the anion, or for both. This fact makes it impossible to assign a unique formal charge to each atom and, consequently, the calculation of the ionization constants of these acids cannot be made by the method of this paper. However, we can calculate the ionization constant corresponding to any one electron structure and compare it with the experimental result. If the true charge distribution is close to that used in the calculation, the calculated and observed ionization constants should be in good agreement.

The ionization constants of these acids, calculated on the basis of their classical structures, all turn out to be smaller than the observed values, except for the case of H_3BO_3. While the deviations may be considered to be within the error of the calculation for carbonic acid and bicarbonate ion, the deviations for nitric, nitrous, and the carboxylic acids are far outside the error of the calculation. Measurements of absorption spectra[21] and bond distances[12] for these latter substances indicate the absence of localized double bonds, and therefore the classical structures should not be expected to lead to true ionization constants.

The resonance phenomenon accounts not only for the absence of localized double bonds but also for the decrease in the work of ionization. Resonance in the acid molecule decreases the negative charge on the hydroxyl oxygen. The removal of the proton increases the resonance of the system, thereby producing a further decrease in the work of ionization. Thus, the presence of this effect may well account for the magnitude and direction of the differences between the calculated and observed ionization constants of these acids.

The case of boric acid deserves special mention in view of the interest attached to the type of bonding present in boron compounds. The structures of a large number of boron compounds have been determined recently.[22–26] It has been assumed generally that the boron halides (except perhaps BF_3) possess double bond resonance of the graphite type. On the other hand, boron trimethyl has been shown by Lévy and Brockway[25] to have a structure containing three coplanar single bonds (sp^2). Evidence as to the type of bonding present in boric acid can be obtained from its ionization constant. The ionization constant calculated from the planar, single bond structure,  $\begin{matrix}H{-}O\\ H{-}O\end{matrix}\!\!>\!B{-}O{-}H$ agrees with experiment within the error of the calculation, showing that the sp^2 structure is a good approximation to the true one. The deviation between the calculated and observed values is in the opposite direction from the deviations observed for acids exhibiting double bond resonance and, therefore, indicates that such resonance is absent or very small in the structure of boric acid. The calculation points to the presence of ionic structures such as $(OH)_2B^+(OH)^-$, although the deviation is not great enough compared to the error of the experiment to justify an estimate of the importance of these structures.

Acknowledgment.—We are deeply indebted to Dr. Joseph E. Mayer, of this department, and to Dr. Linus Pauling and Mr. Henri Lévy, of the California Institute of Technology, for many constructive suggestions and criticisms which were extremely valuable in the preparation of this paper.

Summary

The calculation of the ionization constants of inorganic oxygen acids has been carried out on the basis of reasonable assumptions concerning the structures of the acid molecules and the mechanism of ionization. Most of the calculated ionization constants agree with the experimental ones to within a factor of 8.

1. The free energy of ionization has been shown to consist of a term depending only on the structure of the acid and a term depending only on the solvent and the temperature. The constant term has been evaluated from the ionization constant of a single acid of known structure.
2. The ionization constants of a large number of acids have been evaluated, and have been found to agree well with experimental values.
3. On the basis of the calculation the structures of a number of acids have been determined from their known strengths.
4. The effect of resonance on the strength of acids has been discussed.

BALTIMORE, MD. RECEIVED APRIL 18, 1938

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(21) A. Hantzsch, *Ber.*, **50**, 1422 (1917).

(22) L. Pauling and S. Weinbaum, *Z. Krist.*, **87**, 181 (1934).

(23) S. H. Bauer and L. Pauling, THIS JOURNAL, **58**, 2403 (1936).

(24) S. H. Bauer, *ibid.*, **59**, 1906, 1804 (1937).

(25) H. A. Lévy and L. O. Brockway, *ibid.*, **59**, 2085 (1937).

(26) W. H. Zachariasen, *J. Chem. Phys.*, **5**, 919 (1937).

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

Glycofuranosides and Thioglycofuranosides. III. New Crystalline Furanosides of *d*-Galactose and *l*-Arabinose

BY JOHN W. GREEN[1] AND EUGENE PACSU

In Part I of this series[2] the synthesis of β-ethylgalactofuranoside by the reaction of the ethylmercaptal of the sugar with mercuric chloride in alcohol solution under neutral conditions was described. The isolation of the α-isomer[3] in crystalline form was also presented. This method has now been extended with success to other alcohols and also to the pentose *l*-arabinose. Three new β-alkylgalactofuranosides and two α-alkylarabinofuranosides have been prepared in crystalline form, and they are listed with their physical properties in Table I.

These substances, with the exception of β-benzylgalactofuranoside, are very hygroscopic. The yields are mostly low, as the presence of even a small amount of the other isomer seems to hinder crystallization very strongly. The β-propylgalactofuranoside crystallizes spontaneously, with a good yield. The α-methyl *l*-arabinofuranoside sirup was crystallized by seeding with its mirror image, crystalline α-methyl-*d*-arabinofuranoside.[4]

Galactose ethylmercaptal reacts quite slowly with benzyl alcohol and the resulting sirup has a smaller negative rotation than those of the other reaction sirups.

Attempts to prepare an intermediate thioarabinofuranoside, analogous to the thioglucosides,[2,5] failed, so the formation of the arabinofuranosides must be similar to that of the galactofuranosides.

As shown in Table I, the rotations of all these furanosides agree satisfactorily with the rotations calculated on the basis of Hudson's isorotation rules.

The $B_{(1-4)}$ value for the galactofuranosides was calculated from the molecular rotations for α- and β-ethylgalactofuranosides; the respective A_x values for the galactofuranosides were calculated from the molecular rotations of the galactopyranosides. The $B_{(1-4)}$ value for the *l*-arabinofuranosides was calculated from the molecular rotation of α-methyl-*d*-arabinofuranoside; the respective A_x^0 values for the *l*-arabinofuranosides were calculated from the molecular rotations of the *l*-arabinopyranosides.

Experimental

Preparation of β-Methylgalactofuranoside.—A mixture of 5.7 g. of galactose ethylmercaptal, 10.9 g. of mercuric chloride (2 moles), 5 g. of yellow mercuric oxide, and 3 g. of drierite was shaken with 60 cc. of absolute methyl alcohol for four hours at room temperature. The mixture was filtered, the filtrate treated with 5 cc. of pyridine and kept at 0° for two hours. The pyridine-mercuric chloride was filtered off and the filtrate evaporated *in vacuo* at 40° to a sirup. The sirup was dissolved in cold water, the solution filtered and neutralized with a few drops of sodium hydroxide solution to phenolphthalein, then evaporated *in vacuo* at 40° to a sirup. After several evaporations from absolute ethyl alcohol, the sirup was extracted with dry ether on a shaking machine. About four liters of solvent was used and the resulting solution was distilled off from a bath at 40–50°. The sirup left was dissolved in a small amount of absolute methyl alcohol and the solution filtered and concentrated to a hard sirup in a vacuum desiccator over calcium chloride. The sirup, rotating −83° in water solution, was then kept in an icebox and after one month changed to a solid crystalline mass.

The latter was dissolved in 100 cc. of warm ethyl acetate and the solution seeded at 0°. Crystals were slowly deposited in the form of hard buttons. On further recrystallization from ethyl acetate pure crystals were obtained: yield 20%; m. p. 63–65°, $[\alpha]^{20}\text{D}$ −108° (0.0500 g. substance, 3 cc. of water solution, 2-dm. semi-micro tube, rotation 3.60° to the left). The crystals did not reduce Fehling's solution and were quite hygroscopic. The mother liquor slowly deposited more crystalline material.

Anal. Calcd. for $C_7H_{14}O_6$: C, 43.3; H, 7.2. Found: C, 43.1; H, 7.1.

Preparation of β-Propylgalactofuranoside.—A mixture of 5.7 g. of galactose ethylmercaptal, 10.9 g. of mercuric chloride (2 moles), 5 g. of yellow mercuric oxide, and 3 g. of drierite was shaken with 60 cc. of absolute *n*-propyl alcohol for five hours at room temperature. The mixture was filtered and worked up as in the preparation of the methylgalactofuranoside. The ether extraction solution was distilled on a water-bath at 40–50° and the residue crystallized spontaneously.

The crystalline material was recrystallized from 30 cc. of dry ethyl acetate, when a crop of 2.8 g., with specific rotation −96° in water solution, was obtained. On further crystallization from 30 cc. of ethyl acetate, a crop of 1.00 g. of needle-like crystals was obtained, whose rotation did

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[1] Research Assistant on Special Funds from the Rockefeller Foundation.

[2] Green and Pacsu, THIS JOURNAL, **59**, 1205 (1937).

[3] Green and Pacsu, *ibid.*, **59**, 2569 (1937).

[4] The authors are indebted to Miss Edna Montgomery and Dr. C. S. Hudson for the seed crystals of α-methyl-*d*-arabinofuranoside.

[5] (a) Schneider and Sepp, *Ber.*, **49**, 2054 (1916); (b) Schneider, Sepp and Stiehler, *ibid.*, **51**, 220 (1918); (c) Schneider, Gille and Eisfeld, *ibid.*, **61**, 1244 (1928).

TABLE I

Substance	Mol. wt.	M. p., °C.	$[\alpha]^{20}_D$ in H_2O	Mol. rot. in H_2O	A_x	$B_{(1-4)}$	$[\alpha]^{20}_D$ calcd.
β-Methylgalactofuranoside	194	63–65	−108	−20,950	19,110	−1150	−104.4
β-Propylgalactofuranoside	222	89–90	−100	−22,200	20,710	−1150	− 98.5
β-Benzylgalactofuranoside	270	80–81	− 96	−25,920	25,800	−1150	− 99.0
α-Methylarabinofuranoside	164	. . .	−125	−20,500	−18,810	−1360	−123.0
α-Ethylarabinofuranoside	178	48–49	−116	−20,650	−19,830	−1360	−119.0

not change on further recrystallization: yield of pure material 23%; m. p. 89–90°; $[\alpha]^{20}_D$ −100° (0.0500 g. substance, 3 cc. of water solution, 2-dm. semi-micro tube, rotation 3.32° to the left). The crystals did not reduce Fehling's solution and were fairly hygroscopic.

Anal. Calcd. for $C_9H_{18}O_6$: C, 48.7; H, 8.1. Found: C, 48.9; H, 7.9.

Preparation of β-Benzylgalactofuranoside.—A mixture of 5.7 g. of galactose ethylmercaptal, 10.9 g. of mercuric chloride (2 moles), 5 g. of yellow mercuric oxide, and 3 g. of drierite was shaken with 60 cc. of benzyl alcohol for ten hours at room temperature. The mixture was filtered and the filtrate diluted with 480 cc. of petroleum ether (b. p. 30–60°) and 120 cc. of benzene, then extracted[6] with four 60-cc. portions of water. The bulk of the mercuric chloride precipitated at this stage in the separatory funnel and was filtered off. The water solutions were combined, filtered, extracted with a little ether to remove any benzyl alcohol, and finally treated with 1 cc. of pyridine. A small amount of pyridine–mercuric chloride was filtered off, the solution neutralized with a few drops of sodium hydroxide solution to phenolphthalein, and evaporated *in vacuo* at 40° to a sirup. The latter was evaporated several times with absolute ethyl alcohol.

The sirup, rotating −40° in water solution, crystallized after five to six weeks in a desiccator at room temperature, and from a solution in 25 cc. of dry ethyl acetate 1.25 g. of crystals was obtained, rotating −70° in water solution. After three recrystallizations from ethyl acetate 0.65 g. of pure crystals was obtained: yield 12%; m. p. 80–81°; $[\alpha]^{20}_D$ −96° (0.0500 g. substance, 3 cc. of water solution, 2-dm. semi-micro tube, rotation 3.20° to the left). The crystals were very fine needles, were only faintly hygroscopic and did not reduce Fehling's solution.

Anal. Calcd. for $C_{13}H_{18}O_6$: C, 57.7; H, 6.8. Found: C, 57.7; H, 6.7.

Preparation of α-Methyl-*l*-arabinofuranoside.—A mixture of 5.1 g. of *l*-arabinose ethylmercaptal, 10.9 g. of mercuric chloride (2 moles), 5 g. of yellow mercuric oxide, and 3 g. of drierite was shaken with 60 cc. of absolute methyl alcohol for two hours at 25°. The reaction proceeded very fast and liberated some heat. The mixture was filtered and worked up as above for methylgalactofuranoside, and the sirup extracted with ether.

The sirup obtained rotated −96° in water solution and, upon seeding with a trace of crystalline α-methyl-*d*-arabinofuranoside, solidified in two days. From 25 cc. of dry ethyl acetate solution, 0.45 g. of pure crystals was deposited slowly at 0°. The rotation did not change on further recrystallization from 100 cc. of dry ether: yield 14%; m. p. not taken due to extreme hygroscopic nature of crystals; $[\alpha]^{20}_D$ −125° (0.0400 g. substance, 3 cc. of water solution, 2-dm. semi-micro tube, rotation 4.16° to the left). The crystals are extremely hygroscopic and devoid of action toward Fehling's solution.

Anal. Calcd. for $C_6H_{12}O_5$: C, 43.8; H, 7.3. Found: C, 43.7; H, 7.3.

Preparation of α-Ethyl-*l*-arabinofuranoside.—A mixture of 5.1 g. of *l*-arabinose ethylmercaptal, etc., as immediately above, was shaken for two hours with 60 cc. of absolute ethyl alcohol at 25°. The mixture was filtered, etc., and extracted with ether in the usual way. The sirup, which rotated −79° in water solution, changed into a crystalline mass after four months over phosphorus pentoxide.

The product was dissolved in 10 cc. of dry ethyl acetate and 0.9 g. of crystals was deposited at 0°. These crystals rotated −116° in water solution and further recrystallizations did not change this value; yield 24%; m. p. 48–49°; $[\alpha]^{20}_D$ −116° (0.2055 g. substance, 10 cc. of water solution, 2-dm. semi-micro tube, rotation 4.77° to the left). The crystals were very hygroscopic and did not reduce Fehling's solution.

Anal. Calcd. for $C_7H_{14}O_5$: C, 46.96; H, 7.86. Found: C, 46.9; H, 7.7.

Summary

β-Methyl-, β-propyl-, and β-benzylgalactofuranoside, and α-methyl- and α-ethyl-*l*-arabinofuranoside have been obtained in the crystalline state, by reaction of the ethyl mercaptal of the two sugars with mercuric chloride in a neutral solution of the respective alcohol. The rotations of the new compounds agree well with the values calculated from Hudson's rules of isorotation.

PRINCETON, NEW JERSEY

RECEIVED JULY 1, 1938

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[6] Purves and Hudson, THIS JOURNAL, **59**, 53 (1937).

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF CALIFORNIA]

Sulfophenylarsonic Acids and Certain of their Derivatives. I. *p*-Sulfophenylarsonic Acid

BY J. F. ONETO

In a recent paper Barber[1] suggests that the Bart reaction appears not to be applicable to aminophenylsulfonic acids due to the strongly negative group present.

This investigation was undertaken with the object of preparing derivatives of a number of sulfo- and sulfonamidophenylarsonic acids and of studying the application of the Bart reaction in the preparation of the parent compounds.

p-Sulfophenylarsonic acid was first prepared by Hewitt, King and Murch[2] through application of the Leuckardt xanthate method[3] to arsanilic acid. The product thus obtained was purified by recrystallization from water. This is a very unsatisfactory method because of the extreme solubility of the acid. Voegtlin[4] refers to *p*-sulfophenylarsonic acid as being so freely soluble in water at any *p*H that it is very difficult to obtain the acid in pure form.

Sodium *p*-sulfophenylarsonic acid was prepared in this Laboratory in 28% yields by application of the Bart reaction to sulfanilic acid. The free acid, obtained from the sodium salt through the barium salt stage, was purified readily by dissolving in the least amount of boiling 80% acetic acid and precipitating the acid in glistening, colorless needles by the addition of boiling glacial acetic acid. The work of Hewitt and coworkers was repeated and the acid thus obtained purified in the same manner with satisfactory results.

With the piperidine salt of N-pentamethylenedithiocarbamic acid,[5] sodium *p*-sulfophenyldiiodoarsine forms a well-defined, crystalline, piperidine salt of *p*-sulfophenylarsylene N-pentamethylenedithiocarbamate.

Sodium *p*-sulfophenylarsine oxide, containing three molecules of water, was obtained by hydrolysis of the corresponding bromo-arsine with sodium hydroxide. This product forms a crystalline silver salt when its hot aqueous solution is treated with a solution of silver nitrate.

Experimental Part

Sodium *p*-Sulfophenylarsonic Acid.—A mixture consisting of 76 g. of sulfanilic acid, 28 g. of anhydrous sodium carbonate and 400 cc. of water was diazotized at 0° with 100 cc. of 37% hydrochloric acid and a solution of 32 g. of sodium nitrite in 160 cc. of water in the usual manner. The diazo solution was coupled at 10–15° with an alkaline arsenite solution prepared by dissolving 80 g. of sodium hydroxide, 98 g. of arsenic trioxide and 1.2 g. of copper sulfate in 1000 cc. of water. After standing for two days, the reaction mixture was concentrated to 350 cc., thoroughly cooled and the precipitate of inorganic salts removed by filtration. The filtrate was heated to boiling, made acid to congo red paper with 37% hydrochloric acid and then allowed to stand at room temperature for twenty-four hours. The heavy, granular precipitate which consisted chiefly of sodium *p*-sulfophenylarsonic acid was partially purified by repeatedly boiling with decolorizing carbon in aqueous solution, concentrating the solution to a small volume and precipitating the sodium salt by the addition of 95% alcohol; yield 60 g. Thirty grams of the material thus obtained was dissolved in 125 cc. of boiling water and 30 g. of sodium chloride was added to the boiling solution. Colorless, crystalline sodium *p*-sulfophenylarsonic acid started to precipitate almost immediately. The mixture was cooled in ice, filtered and the product washed with cold, saturated sodium chloride solution, then with small portions of cold 80% alcohol and finally with acetone. Eighteen grams of product was obtained sufficiently pure for analysis.[6] It is insoluble in alcohol and acetic acid, exceedingly soluble in water.

Anal. Calcd. for $C_6H_6O_6AsSNa$: As, 24.64. Found: As, 24.36.

Barium *p*-Sulfophenylarsonic Acid.—Ten grams of sodium *p*-sulfophenylarsonic acid was dissolved in 30 cc. of boiling 0.7% hydrochloric acid. To the hot solution was added 20 cc. of a saturated solution of barium chloride. The barium salt started precipitating at once from the hot solution in the form of colorless needles. After cooling, the product was filtered, washed first with cold 0.7% hydrochloric acid, then with water and finally with acetone. The material thus obtained, which was sufficiently pure for analysis, is relatively soluble in water; yield 9.5 g.

Anal. Calcd. for $C_{12}H_{12}O_{12}As_2S_2Ba$: As, 21.42; Ba, 19.64. Found: As, 21.09; Ba, 19.64.

***p*-Sulfophenylarsonic Acid.**—Five grams of barium *p*-sulfophenylarsonic acid was dissolved in 100 cc. of boiling water and the barium was precipitated from the hot solution by adding the calculated amount of 0.1 *N* sulfuric acid. After removal of the barium sulfate, the filtrate was allowed to evaporate at room temperature. The residue was purified by dissolving in the least amount of boiling

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(1) Barber, *J. Chem. Soc.*, 2048 (1930).

(2) Hewitt, King and Murch, *ibid.*, 1369 (1926).

(3) Leuckardt, *J. prakt. Chem.*, **41**, 179 (1890).

(4) Voegtlin, *Physiol. Rev.*, **5**, 91 (1925).

(5) Blicke and Oakdale, THIS JOURNAL, **54**, 2993 (1932).

(6) A halogen analysis indicated the presence of 0.7% sodium chloride.

80% acetic acid and then treating the hot solution with boiling glacial acetic acid. The *p*-sulfophenylarsonic acid crystallized in the form of colorless, glistening needles; yield 2.5 g. When heated, the product gradually darkens but remains solid up to 300°. It is insoluble in ether, acetone and benzene; soluble in alcohol.

Anal. Calcd. for $C_6H_7O_6AsS$: As, 26.56. Found: As, 26.51.

Sodium *p*-Sulfophenyldiiodoarsine.—Ten cc. of 50% hydriodic acid was added to a hot solution of 2 g. of sodium *p*-sulfophenylarsonic acid in 5 cc. of water. The crystalline iodoarsine began precipitating immediately. The mixture was filtered after cooling thoroughly and the product washed first with glacial acetic acid and then with acetone. The yield was 2 g. after recrystallizing from 80% acetic acid. It is insoluble in cold glacial acetic acid and alcohol but readily soluble in water. When heated the compound liberates vapors of iodine.

Anal. Calcd. for $C_6H_4O_3AsI_2SNa$: As, 14.75; I, 49.98. Found: As, 14.65; I, 49.76.

Sodium *p*-Sulfophenyldibromoarsine.—A solution prepared from 10 g. of sodium *p*-sulfophenylarsonic acid, 30 cc. of water, 20 cc. of 48% hydrobromic acid and a trace of hydriodic acid was saturated with sulfur dioxide at room temperature. The mixture was then concentrated on the steam-bath to about 20 cc., chilled in ice and the product removed by filtration; 8.5 g. of sodium *p*-sulfophenyldibromoarsine was obtained after recrystallizing from glacial acetic acid–ethyl acetate mixture. The product is readily soluble in alcohol and water.

Anal. Calcd. for $C_6H_4O_3AsBr_2SNa$: As, 18.10; Br, 38.62. Found: As, 18.07; Br, 38.36.

The Piperidine Salt of *p*-Sulfophenylarsylene N-Pentamethylenedithiocarbamate.—To a hot soluiton of 0.5 g. of sodium *p*-sulfophenyldiiodoarsine in 13 cc. of 50% alcohol there was added a hot solution of 0.5 g. of the piperidine salt of N-pentamethylenedithiocarbamic acid in 25 cc. of alcohol. The colorless needles which formed were removed by filtration and washed repeatedly with cold 95% alcohol. The product weighed 0.3 g. and when heated decomposed at 230–232°. The compound is insoluble in ether, acetone and benzene.

Anal. Calcd. for $C_{23}H_{36}O_3N_3AsS_5$: As, 11.75. Found: As, 12.01.

Sodium *p*-Sulfophenylarsine Oxide.—Five grams of sodium hydroxide was added to as olution of 15 g. of sodium *p*-sulfophenyldibromoarsine in 100 cc. of water and the solution boiled under a reflux condenser for fifteen minutes. The solution was then cooled, made acid to congo red paper with 37% hydrochloric acid and allowed to evaporate at room temperature. After several days a heavy mass of large colorless crystals was obtained which weighed 8 g. The product, containing three molecules of water, was purified by dissolving in water, concentrating the solution in a desiccator over sulfuric acid to a small volume and recovering the crystalline residue.

Anal. Calcd. for $C_6H_4O_4AsSNa\cdot 3H_2O$: As, 23.11. Found: As, 23.00.

The product effloresced at room temperature and was completely dehydrated by heating to 200° for four hours in an oil-bath under reduced pressure.

Anal. Calcd. for $C_6H_4O_4AsSNa$: As, 27.74. Found: As, 27.81.

On adding 10 cc. of 0.25 *N* silver nitrate solution to a hot solution of 0.52 g. of sodium *p*-sulfophenylarsine oxide in 10 cc. of water, a silver salt of *p*-sulfophenylarsine oxide crystallized on slight cooling; yield 0.5 g.

Summary

The preparation of sodium *p*-sulfophenylarsonic acid by the Bart reaction and a method for the purification of the free acid have been described. The following derivatives and salts have been prepared: barium *p*-sulfophenylarsonic acid, the piperidine salt of *p*-sulfophenylarsylene N-pentamethylenedithiocarbamate, sodium *p*-sulfophenyldiiodo and -dibromoarsine and sodium *p*-sulfophenylarsine oxide.

SAN FRANCISCO, CALIF.

RECEIVED JUNE 20, 1938

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

The Cleavage of the Carbon Chain of α-Methyl-*d*-lyxopyranoside by Oxidation with Periodic Acid[1]

BY W. DAYTON MACLAY AND C. S. HUDSON

The known α-methyl-*d*-lyxoside (m. p. 108–109°, $[\alpha]^{20}D$ + 59.4° in water)[2] has been shown by Hirst and Smith[3] through methylation methods to be a pyranoside and it is regarded as the alpha form because it is more dextrorotatory than *d*-lyxose ($[\alpha]^{20}D$ −14°, final); under this classification its structure is (I). It is to be expected that the oxidation of this substance by periodic acid will proceed in the manner that has been demonstrated in the case of the alpha forms of the methyl pyranosides of *d*-xylose and *d*-arabinose[4] to produce the dialdehyde (II); the latter substance, on oxidation by bromine water in the presence of strontium carbonate, should be oxi-

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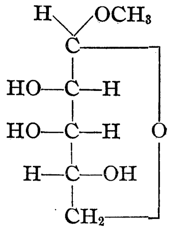
[1] Publication authorized by the Surgeon General, U. S. Public Health Service.

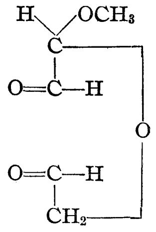
[2] Phelps and Hudson, THIS JOURNAL, **48**, 505 (1926).

[3] Hirst and Smith, *J. Chem. Soc.*, 3147 (1928).

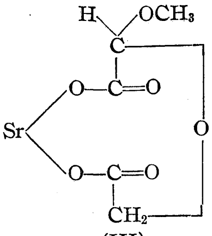
[4] Jackson and Hudson, THIS JOURNAL, **59**. 994 (1937).



(I)
α-Methyl-*d*-lyxopyranoside



(II)
D′-Methoxy-diglycolic aldehyde



(III)
Strontium D′-methoxy-diglycolate

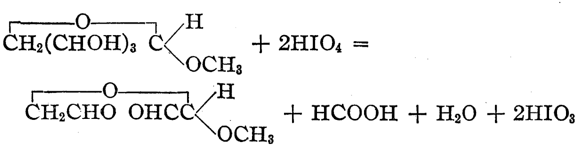
dized to the strontium salt (III), which has been obtained from the xylose and arabinose pyranosides. The experiments have borne out these expectations fully and the crystalline strontium salt, which has been obtained in a yield of 76%, proves to be identical with that which results from the xylose and arabinose *α*-methyl pyranosides. The result therefore confirms the conclusion from methylation data that the lyxoside is a pyranoside and also proves that it is of the alpha classification, as was previously inferred from the comparison of its rotation with that of lyxose.[5]

TABLE I

COMPARISON OF OXIDATION PRODUCTS OF *α*-METHYL-*d*-LYXOSIDE WITH THOSE OF *α*-METHYL-*d*-ARABINOSIDE AND *α*-METHYL-*d*-XYLOSIDE

Substance	Methyl glycoside $[\alpha]^{20}_D$	Dialdehyde $[\alpha]^{20}_D$	Dibasic acid $[\alpha]^{20}_D$	Strontium salt $[\alpha]^{20}_D$
α-Methyl-*d*-lyxoside	+59.4	+124.1	−12.8	−54.7
α-Methyl-*d*-arabinoside[4]	−17	+124.2	−12.7	−55.5
α-Methyl-*d*-xyloside[4]	+154	+125.2	−12.1	−55.5

The oxidation of the methyl-lyxopyranoside by periodic acid follows the reaction equation that has been found to hold for the xylose and arabinose methyl-pyranosides,[4] namely



$$\overbrace{\mathrm{CH_2(CHOH)_3\,C}}^{\mathrm{O}}\genfrac{}{}{0pt}{}{\diagup \mathrm{H}}{\diagdown \mathrm{OCH_3}} + 2\mathrm{HIO_4} =$$

$$\overbrace{\mathrm{CH_2CHO\ \ OHCC}}^{\mathrm{O}}\genfrac{}{}{0pt}{}{\diagup \mathrm{H}}{\diagdown \mathrm{OCH_3}} + \mathrm{HCOOH} + \mathrm{H_2O} + 2\mathrm{HIO_3}$$

Experimental

Oxidation of *α*-Methyl-*d*-lyxopyranoside with Periodic Acid.—To a solution of 1.3583 g. of pure *α*-methyl-*d*-lyxoside in 60 cc. of water was added 28.27 cc. of 0.615 *M* periodic acid solution (2.1 molecular equivalents). The solution was quickly diluted to 100 cc. and the rotatory changes observed at about 20°. From an initial specific rotation of +59.4° the rotation rapidly increased during the first ten minutes and became practically constant at the end of twenty-five minutes. After standing at 20° for twenty-one hours the solution had a specific rotation of +124.1° (referring to the dialdehyde). Five cubic centimeters of the solution was analyzed for periodic acid and the result showed that one mol of the lyxoside had consumed 1.988 mols of periodic acid, which conforms with the equation previously stated.

The free methoxy-diglycolic aldehyde (II) was obtained in a sirupy form by following the procedure used by Jackson and Hudson in the isolation of the dialdehyde resulting from the periodic acid oxidation of other methyl pentopyranosides. To the sirupy dialdehyde, dissolved in 330 cc. of water, 25 g. of strontium carbonate and 2 cc. of bromine were added and the mixture was shaken for five hours. After standing at room temperature for an additional eighteen hours the excess bromine was removed by aeration and the strontium carbonate by filtration. The bromide ions were removed by shaking with 17 g. of silver carbonate, the silver ions precipitated by hydrogen sulfide and the excess hydrogen sulfide removed by aeration. The solution was concentrated *in vacuo* in a bath at 60° to a volume of 10 cc., when crystallization of the strontium methoxy-diglycolate trihydrate commenced: yield, 1.8 g. (76%). Recrystallized three times from 8 parts of water the substance was obtained in the form of needle-like crystals exhibiting a rotation of −43.7° (*c*, 0.8; *l*, 4).

Anal. Calcd. for $C_5H_6O_6Sr \cdot 3H_2O$: C, 19.75; H, 3.98; OCH_3, 10.21; Sr, 28.85; H_2O, 17.79. Found: C, 19.86; H, 4.11; OCH_3, 10.14; Sr, 28.62; H_2O, 17.73.

Anhydrous strontium methoxy-diglycolate was obtained by heating the trihydrate at 100° *in vacuo* for four hours. Its solution in water gave a specific rotation of −54.7° (*c*, 1.2; *l*, 4).

Anal. Calcd. for $C_5H_6O_6Sr$: C, 24.03; H, 2.42. Found: C, 24.01; H, 2.61.

Summary

The oxidation of *α*-methyl-*d*-lyxoside by periodic acid yields a dialdehyde which, on oxidation by bromine water in the presence of excess strontium carbonate, forms the same crystalline strontium D′-methoxy diglycolate trihydrate (76% yield) that has previously been obtained from the *α*-methyl-pyranosides of *d*-arabinose and *d*-xylose. The result confirms the conclusion of Hirst and Smith from methylation data that the lyxoside is a pyranoside, and proves that it is an *α*-form.

WASHINGTON, D. C. RECEIVED JUNE 24, 1938

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[5] I have expressed some years ago the view that the lyxoside is a furanoside because of a certain anomaly in its optical rotation [*ibid.*, **52**, 1689 (1930)] but the methylation data of Hirst and Smith[3] show that it is a pyranoside and their conclusion is now confirmed by the results of the periodic acid oxidation.—C. S. HUDSON.

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, No. 173]

Cleavage of the Carbon Chain of Glycosides by Oxidation with Lead Tetraacetate[1]

BY W. S. McCLENAHAN[2] WITH R. C. HOCKETT

The glycol-splitting power of lead tetraacetate has been used in several instances to prepare carbohydrate derivatives.[3] In these cases it has been the practice to mask certain hydroxyl groups of a polyhydric alcohol so that no pair of free hydroxyl groups would remain on adjacent carbon atoms except at the position where the carbon chain is to be broken and aldehyde groups produced. Difficulties in preparing such derivatives have seriously limited the extension of this type of synthesis.

Since *cis* glycols are reported to be oxidized much more rapidly than *trans*[4,5] it was thought that a compound containing both types of diol structure might, when treated with an equimolar quantity of lead tetraacetate, be split preferentially at the *cis* position to such an extent that the masking of groups would be unessential. In this respect α-methyl-*d*-mannopyranoside (I)[6] seemed of particular interest since its oxidation with lead tetraacetate might be expected to produce a mixture of (II) and (III) containing a high percentage of the former; hydrolysis of the product would then give a considerable quantity of the difficultly accessible tetrose, *d*-erythrose.

However, Criegee[7] has found that lead tetraacetate produces *two* moles of formaldehyde from glycerol, which can occur only by the further oxidation of the glycolaldehyde first formed; since both (II) and (III) contain an alpha-hydroxyaldehyde grouping, they would probably be capable of further oxidation to a common product (IV). No information exists regarding the rates of such reactions. Karrer and Pfaehler[8] have oxidized α-methyl-*d*-glucoside (V) with lead tetraacetate, but although this would also be expected to produce (II) and (III), the glycoside contains no *cis* glycol structure and its oxidation therefore provides no evidence regarding possible preferential attack at such a position. The products isolated by these workers fail, moreover, to show unequivocally the ultimate fate of the dialdehydes.

Our experiments with the oxidation of α-methyl-*d*-mannoside by somewhat less than an equimolar quantity of lead tetraacetate have provided strong evidence, however, that the product formed is largely (IV), since nearly half the mannoside was recovered unchanged after all the tetraacetate had been consumed, and hydrolyzed portions of the product yielded large quantities of glyceraldehyde osazone. These observations indicate that wherever the initial fission may have occurred, the secondary oxidation of hydroxyaldehyde (II) or (III) is even more rapid and consumes additional oxidizing agent faster than does the unattacked methylmannoside remaining in the mixture. Finally, oxidation of the product with bromine water in the presence of strontium carbonate gave a strontium salt (VI) which was identical in all measured properties with that obtained by Jackson and Hudson[9] when they oxidized α-methyl-*d*-mannopyranoside with periodic acid followed by strontium hypobromite.

The investigation was extended to other glycosides, and in each case the final product corresponded to that obtained by Jackson and Hudson[9] or Maclay and Hudson[10] from the same compound (Table I).

The results show that the method for determining ring structures and alpha and beta configurations of glycosides as developed by Jackson and Hudson may be carried out with lead tetraacetate as well as with periodic acid. The former may be preferable for compounds more soluble in water; the latter, for derivatives more soluble in organic solvents.

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[1] This paper represents part of a thesis submitted by William S. McClenahan to the Graduate School of the Massachusetts Institute of Technology in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] Louis Francisco Verges Fellow in Chemistry in 1936–1937 and 1937–1938.

[3] Von Vargha, *Ber.*, **68**, 18 (1935); Appel, *J. Chem. Soc.*, 425 (1935); Steiger and Reichstein, *Helv. Chim. Acta*, **19**, 1016 (1936).

[4] Criegee, *Ber.*, **64**, 260 (1931).

[5] Criegee, *ibid.*, **65**, 1770 (1932); Criegee, Kraft and Rank, *Ann.*, **507**, 159 (1933).

[6] The configuration of the groups about an asymmetric carbon atom is not conceived, in itself, to restrict the possibility of free rotation about the carbon–carbon bonds; *e. g.*, it is not appropriate to look upon the hydroxyls of active tartaric acids as fixed either in *cis* or *trans* position despite the fact that conventional projectional formulas make them appear so. On the other hand, where a ring structure exists as in a glycoside or in cyclohexanediol, conventional considerations indicate that the rotation around carbon–carbon bonds is prevented and hydroxyl groups bear a fixed relation to one another in space which moreover is determined by the configurations of the asymmetric carbons.

[7] Criegee, *Ann.*, **495**, 211 (1932).

[8] Karrer and Pfaehler, *Helv. Chim. Acta*, **17**, 363 (1934).

[9] Jackson and Hudson, THIS JOURNAL, **59**, 994 (1937).

[10] Maclay and Hudson, *ibid.*, **60**, 2059 (1938).

Table I[11]

Glycoside	Dialdehyde by HIO_4(9) $[\alpha]^{20}D$	Dialdehyde by $Pb(OAc)_4$ $[\alpha]^{20}D$	Dibasic acid by HIO_4(9) $[\alpha]^{20}D$	Dibasic acid by $Pb(OAc)_4$ $[\alpha]^{20}D$	Strontium salt by HIO_4(9) $[\alpha]^{20}D$	Strontium salt by $Pb(OAc)_4$ $[\alpha]^{20}D$
α-Methyl-*d*-mannoside	+119.5	+132[a]	+26.3	+25.2[b]	−53.0	−52.2
α-Methyl-*d*-glucoside	+121.1	+170[a]	+26.0	+24.7[b]	−52.9	−50.7
β-Methyl-*d*-arabinoside	−123.7	..	+12.5	+11.9	+55.7	+55.0
α-Methyl-*d*-lyxoside	..	..	..	−11.5	..	−56.6[c]

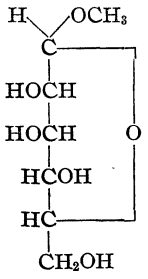
[a] Calcd. from rotation of aqueous solution after oxidation, on the basis of 100% yield of dialdehyde (IV).

[b] Determined by liberating the acid (c = *ca.* 1%) from its anhydrous salt with an equivalent quantity of hydrochloric acid.

[c] Recrystallized to constant rotation (c = 1.2108). The values for other salts were determined after one or two recrystallizations.

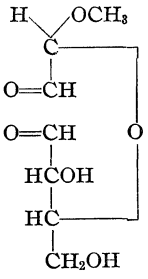
The reaction of lead tetraacetate with glycosides is slow in acetic acid and by-products resembling acetates frequently formed. This could be prevented by substituting chloroform for acetic acid as the solvent, which greatly accelerates the reaction.

Preliminary studies have also been made concerning the rates of oxidation of the various glycosides. These have proved very useful in determining the quantities of lead tetraacetate to be used and the time required for the different reactions. These experiments will be reported in a separate communication.

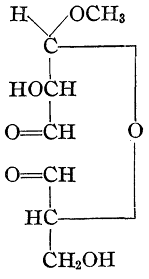


(I)

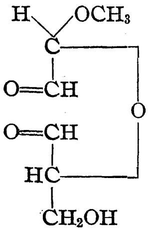
α-Methyl-*d*-manno-pyranoside



(II)

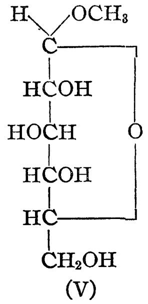


(III)



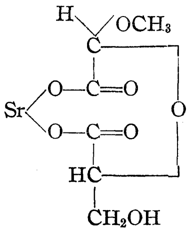
(IV)

D′-methoxy-D-hydroxymethyl-diglycolic aldehyde



(V)

α-Methyl-*d*-gluco-pyranoside



(VI)

Strontium D′-methoxy-D-hydroxymethyl diglycolate

We are indebted to Doctors C. S. Hudson and E. L. Jackson of the National Institute of Health for a sample of strontium D′-methoxy-D-hydroxymethyl diglycolate for purposes of comparison.

Experimental

Lead Tetraacetate.—A mixture of 530 cc. of glacial acetic acid and 115 cc. of acetic anhydride was heated to 75° in a 1-liter, 3-necked Pyrex flask provided with an electric stirrer and a thermometer. To this was added 150 g. of dry red lead in six portions. The solution was allowed to become colorless between successive additions, and the temperature was kept below 90°. When the reaction was complete the slightly turbid solution was decanted from a small amount of undissolved red lead and allowed to cool in a closed vessel. The white, crystalline lead tetraacetate was filtered off on a Büchner funnel, washed with a little glacial acetic acid, and was stored in a desiccator over phosphorus pentoxide. These operations could be carried out in the open air if performed rapidly. The product weighed about 60–70 g. and was not recrystallized for use in these experiments.

Oxidation of α-Methyl-*d*-lyxopyranoside.—Three grams (0.0183 mole) of dry lyxoside (of rotation +59.4°) was added to 150 cc. of dried chloroform ($CaCl_2$) in a 500-cc. 3-necked flask, and during the course of an hour 17.5 g. (0.0395 mole) of dry lead tetraacetate was added in small portions with continuous mechanical stirring. The temperature remained below 35° at all times. Stirring was continued for two hours after the last addition. The chloroform solution was then decanted from the nearly insoluble lead diacetate and the chloroform was removed under reduced pressure. The residue was taken up in water, which formed a precipitate of brown lead dioxide, and an excess of hydrogen sulfide was passed into the mixture. The lead diacetate was also dissolved in water and treated with hydrogen sulfide separately. After filtration and aeration the first solution gave a strong Fehling's test, the second only a slight one. The two were combined, concentrated under reduced pressure to a sirup, and reconcentrated several times after addition of sulfur-free toluene to remove all acetic acid. The resulting sirup was diluted to 500 cc., and 20 g. of strontium carbonate and 3 cc. of bromine were added. The flask was shaken until the bromine dissolved, then placed in the dark at room temperature and occasionally shaken during the first hour. After eighteen hours nearly all reducing power had disappeared. The bromine was removed by aeration, and

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(11) All rotations reported in this paper represent specific rotations of the D line of sodium by aqueous solutions at 20°; c is concentration in grams per 100 cc. of solution, and l is the tube length in decimeters.

the excess strontium carbonate was filtered off and washed with cold water. The filtrate and washings were shaken with silver carbonate until free from bromide ion; the solids were then filtered off and washed. Silver was removed from the filtrate as the sulfide. After filtration and aeration, a slight acidity was neutralized to phenolphthalein with strontium hydroxide solution. The solution was then filtered through carbon and concentrated under reduced pressure to 50 cc., filtered, and the concentration continued to 10 cc. The addition of a few drops of alcohol caused a turbidity which increased slightly after a few hours at room temperature. After filtering, the addition of a little more alcohol caused crystallization to begin. Several crops of fine needles were obtained by alternately adding alcohol and chilling; yield of trihydrate of the salt, 3 g. or 54%. After four recrystallizations of the salt[12] from 8 parts of water the rotation of the anhydrous substance became constant at −56.6° (*c*, 1.2108; *l*, 2).[11] The corresponding free acid rotated −11.5° (*c*, 0.9648; *l*, 4).[11]

Anal. Calcd. for $C_5H_6O_6Sr{\cdot}3H_2O$: H_2O, 17.8. Found (loss in wt. at 105° *in vacuo*); 17.6. Calcd. for $C_5H_6O_6Sr$: Sr, 35.01. Found: Sr, 34.94.

Oxidation of β-Methyl-*d*-arabinopyranoside.—The procedure was the same as reported for α-methyl-*d*-lyxoside. The yield of strontium salt was 65%. The anhydrous substance rotated +55.0° (*c*, 1.0080; *l*, 2).[11] The corresponding free acid rotated +11.9° (*c*, 0.8390; *l*, 1).[11]

Anal. Calcd. for $C_5H_6O_6Sr{\cdot}3H_2O$: H_2O, 17.8. Found (loss in wt. at 105° *in vacuo*): 17.6. Calcd. for $C_5H_6O_6Sr$: Sr, 35.01. Found: Sr, 34.32.

Oxidation of α-Methyl-*d*-mannopyranoside.—This oxidation proceeds more rapidly than in the previous cases so the total reaction time was reduced to one and a half hours. The yield of strontium salt (IV) was 55% after correcting for a small amount of mannoside which was recovered unchanged. The anhydrous form rotated −52.2° (*c*, 0.6280; *l*, 4).[11] The corresponding free acid rotated +25.2° (*c*, 1.044; *l*, 1).[11]

Anal. Calcd. for $C_6H_8O_7Sr{\cdot}2H_2O$: H_2O, 11.41. Found: (loss in wt. at 105° *in vacuo*), 12.18. Calcd. for $C_6H_8O_7Sr$: Sr, 31.25. Found: Sr, 31.08.

Oxidation of α-Methyl-*d*-glucopyranoside.—The total reaction time was three and a half hours, and the yield of strontium salt (VI) was 59% after correcting for a small amount of unchanged glucoside. The anhydrous salt rotated −50.7° (*c*, 0.6492; *l*, 2).[11] The corresponding free acid rotated +24.7° (*c*, 1.1440; *l*, 4).[11]

Anal. Calcd. for $C_6H_8O_7Sr{\cdot}2H_2O$: H_2O, 11.41. Found: (loss in wt. at 105° *in vacuo*), 11.8. Calcd. for $C_6H_8O_7Sr$: Sr, 31.25. Found: Sr, 31.13.

Summary

1. Several methyl-pyranosides have been oxidized with lead tetraacetate in glacial acetic acid and in chloroform solutions.

2. There has been observed in each case cleavage of the carbon chain with elimination of one carbon and formation of a dialdehyde through the consumption of two moles of oxidizing agent per mole of glycoside.

3. Further oxidation of these dialdehydes with strontium hypobromite has led to isolation of strontium salts of dibasic acids identical with those produced by Jackson and Hudson and Maclay and Hudson through the action of periodic acid and strontium hypobromite on the same methyl-glycosides.

4. In the case of α-methyl-*d*-mannoside it has been shown that in acetic acid at room temperature the removal of carbon three from the first fission product proceeds at a more rapid rate than does the initial cleavage.

CAMBRIDGE, MASS. RECEIVED JUNE 24, 1938

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[12] Mother liquors from this salt developed growths of mold during several weeks' exposure to the laboratory air. A small quantity of a water-insoluble organic compound containing strontium was found as a product.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

The Coupling Action of the Grignard Reagent. VI. A New Synthesis of Hexaalkylbenzils

BY REYNOLD C. FUSON AND JOSEPH CORSE

The coupling action of the Grignard reagent on halogen compounds has been shown to take place according to the general equation $2RMgX + 2R'X \longrightarrow R{-}R + R'{-}R' + 2MgX_2$.[1] The reaction seems to be conditioned largely by the activity of the halogen atom in the R′X molecule. In fact, similar results are obtained when the alkyl halide is replaced by other types of halogen compounds, notably certain metal halides such as cupric chloride[2] and silver bromide.[3] The metals suffer reduction—a change which is analogous to coupling. It would appear that any halogen compound in which the halogen atom is loosely bound might serve to bring about such effects.

It occurred to us that the halogen atoms of

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[1] Fuson, THIS JOURNAL, **48**, 2681 (1926).

[2] Krizewsky and Turner, *J. Chem. Soc.*, **115**, 559 (1919).

[3] Gardner and Borgstrom, THIS JOURNAL, **51**, 3375 (1929); Gardner, Joseph and Gollub, *ibid.*, **59**, 2583 (1937).

acyl halides should possess sufficient activity for this purpose. However, experience has shown that these react with Grignard reagents to give ketones or carbinols, and it is reasonable to suppose that addition to the carbonyl group takes precedence over other possible types of reactions. By the introduction of steric hindrance, however, it is possible to reduce the rate of the addition reaction and so favor any tendency there may be to undergo coupling.

To test this suggestion, we have made 2,4,6-trimethylbenzoyl chloride and 2,4,6-triethylbenzoyl chloride and treated them with solutions of methylmagnesium iodide. The results verified our prediction; both alkylation and coupling occurred. By analogy with similar types of reactions the equations for the alkylation and the coupling would be as follows

$$\text{Coupling: } 2R_3C_6H_2COCl + 2CH_3MgI \longrightarrow R_3C_6H_2COCOC_6H_2R_3 + C_2H_6 + 2MgICl$$

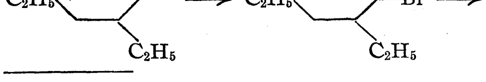
$$\text{Alkylation: } R_3C_6H_2COCl + CH_3MgI \longrightarrow R_3C_6H_2COCH_3 + MgICl$$

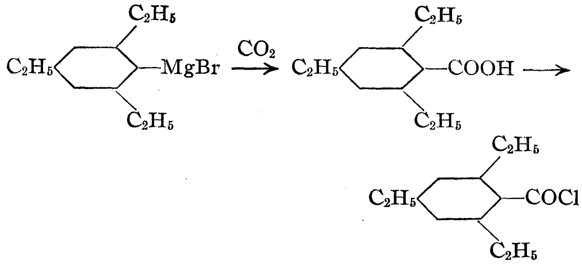
Alkylation alone occurred when the acid chloride was added to the solution of the Grignard reagent. In order to bring about coupling it was necessary to add the reagent to a dilute ether solution of the acid chloride. Under these conditions the yields of hexamethylbenzil and hexaethylbenzil were 39 and 32%, respectively. The alkylation products, acetomesitylene and 2,4,6-triethylacetophenone, were obtained in yields of 35 and 38.5%, respectively.

As a synthetic method for the preparation of hexamethylbenzil this is far superior to those of Kohler and Baltzly,[4] Gray and Fuson[5] and Fuson, Matuszesky and Gray.[6] It is somewhat more convenient than the method of Arnold and Fuson.[7] The hexaethylbenzil had not been made previously.

The work with triethylbenzene derivatives was greatly facilitated by the fact that this hydrocarbon has recently been made readily available by the excellent method of Norris and Rubinstein.[8]

The 2,4,6-triethylbenzoyl chloride was made by the following series of transformations





2,4,6-Triethylacetophenone, the product which accompanied the hexaethylbenzil, had been reported previously by Kunckell[9] but was not characterized. In the present work this ketone and its dinitro and benzal derivatives were synthesized and characterized.

Experimental Part

2,4,6-Triethylacetophenone.—A mixture of 162 g. of 1,3,5-triethylbenzene, 500 cc. of carbon disulfide and 300 g. of anhydrous aluminum chloride was placed in a 2-liter three-necked flask equipped with dropping funnel, stirrer and reflux condenser leading to a gas absorption trap. The mixture was heated to reflux and 101 g. of acetic anhydride was added over a period of one and one-half hours, the rate of addition being adjusted to keep the mixture boiling slightly. The mixture was stirred for an additional hour and allowed to stand for three hours. It was decomposed by pouring into 2 kg. of cracked ice to which 100 cc. of concentrated hydrochloric acid had been added. The layers were separated and the aqueous portion was extracted twice with 100-cc. portions of carbon disulfide. The extracts were added to the separated layer and the combined liquid was dried with calcium chloride. The solution was then filtered and the solvent removed on the steam-bath. The ketone distilled at 115–118° (5 mm.). The yield was 163 g. or 80% of the theoretical amount; n^{20}_D 1.5097; d^{20}_4 0.9475.

Anal. Calcd. for $C_{14}H_{20}O$: C, 82.26; H, 9.86. Found: C, 82.20; H, 9.79.

3,5-Dinitro-2,4,6-triethylacetophenone.—To 15 cc. of fuming nitric acid cooled to 0° was added 1 g. of 2,4,6-triethylacetophenone. The mixture was allowed to stand for ten minutes and then was poured into 50 g. of chipped ice. The precipitate was collected on a filter and recrystallized from aqueous alcohol. The yield of dry product was 1.3 g. or 90% of the theoretical amount. The compound crystallizes from alcohol in needles which melt at 112–113°.

Anal. Calcd. for $C_{14}H_{18}O_5N_2$: C, 57.13; H, 6.16. Found: C, 57.05; H, 6.06.

Benzal-2,4,6-triethylacetophenone.—A solution of 2.8 g. of sodium hydroxide in 22 cc. of water was made in a 50-cc. flask. To this was added 10 g. of 2,4,6-triethylacetophenone, 30 cc. of 95% ethyl alcohol and 5.8 g. of freshly distilled benzaldehyde. The flask was placed on the shaking machine for eighteen hours. The mixture was then diluted with 10 cc. of water and cooled. The crystalline product was separated and washed with 15 cc. of cold 80% alcohol. The yield of crude product was 14.2 g. or 90% of

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(4) Kohler and Baltzly, THIS JOURNAL, **54**, 4015 (1932).

(5) Gray and Fuson, *ibid.*, **56**, 739 (1934).

(6) Fuson, Matuszesky and Gray, *ibid.*, **56**, 2099 (1934).

(7) Arnold and Fuson, *ibid.*, **58**, 1295 (1936).

(8) Norris and Ingraham, *ibid.*, **60**, 1421 (1938).

(9) Kunckell, *Ber. deut. pharm. Ges.*, **23**, 188 (1913).

the theoretical amount. The compound crystallizes in slightly tinted prisms which melt at 66°.

Anal. Calcd. for $C_{21}H_{24}O$: C, 86.24; H, 8.28. Found: C, 86.14; H, 8.25.

2,4,6-Triethylbromobenzene.—Three hundred and twenty-four grams of 1,3,5-triethylbenzene was added to 200 cc. of carbon tetrachloride in a 2-liter three-necked flask equipped with a stirrer, dropping funnel and reflux condenser which was attached to a gas absorption trap. Ten grams of powdered iron was added and the mixture cooled to 0°. The flask was protected from light as much as possible and 320 g. of bromine dissolved in 200 cc. of carbon tetrachloride was added with vigorous stirring over a period of five hours. The reddish-brown solution was allowed to stand overnight. It was then washed twice with 500-cc. portions of water, once with 500 cc. of 10% sodium hydroxide and with water until the aqueous layer was neutral to litmus. The carbon tetrachloride solution was dried with calcium chloride, filtered and the carbon tetrachloride removed by distillation. The residue was then refluxed one-half hour with an alcoholic solution of sodium hydroxide prepared from 400 cc. of 95% ethyl alcohol and 20 g. of sodium. The solution turned dark red and some sodium bromide precipitated. After standing overnight the solution was diluted with 1 liter of water and the bromide layer separated. The aqueous portion was extracted with three 200-cc. portions of carbon tetrachloride which were added to the halide layer The carbon tetrachloride layer was dried with calcium chloride, filtered and solvent removed on the water pump. The remaining solution was fractionated with the oil pump. Three hundred and forty grams of product boiling at 96–99° (2–3 mm.) was obtained. The yield amounted to 70% of the theoretical; $n^{20}{}_{D}$ 1.5366; $d^{20}{}_{4}$ 1.2076.

Anal. Calcd. for $C_{12}H_{17}Br$: C, 59.76; H, 7.11. Found: C, 59.89; H, 7.06.

2,4,6-Triethyl-3,5-dinitrobromobenzene.—Five grams of 2,4,6-triethylbromobenzene was added to 50 cc. of fuming nitric acid cooled to 0°. The mixture was allowed to stand at room temperature for twenty minutes and then poured into 250 cc. of water. The precipitate was collected and recrystallized from alcohol, giving needles which melt at 78.5–79°. The yield amounted to 4.6 g. or 67% of the theoretical.

Anal. Calcd. for $C_{12}H_{15}O_4N_2Br$: N, 8.46; Br, 24.13. Found: N, 8.66; Br, 23.72.

2,4,6-Triethylbenzoic Acid.[10]—Twelve and one-half grams of magnesium turnings was placed in a 1-liter three-necked flask equipped with stirrer, reflux condenser and dropping funnel. A solution of 120.5 g. of 2,4,6-triethylbromobenzene in 200 cc. of dry ether was then added at such a rate that, after the reaction started, gentle refluxing ensued. The addition of reagent takes about two and one-half hours. Stirring was continued for an additional hour, with heating the last twenty minutes. The mixture was then cooled in an ice–salt bath to −5°, and small pieces of dry ice were added cautiously. Care was taken not to add very large pieces because considerable heat is produced in spite of the coldness of the dry ice. After the reaction had spent its force and no appreciable heating took place on addition of dry ice, 50 to 75 g. of dry ice was added and the ice–salt bath removed. The mixture was allowed to come up to room temperature unaided and was then poured into 300 cc. of ice water containing 40 g. of ammonium chloride and 20 cc. of concentrated hydrochloric acid. The ether layer was separated and the aqueous layer washed twice with 100-cc. portions of 0.25 normal hydrochloric acid. The ether was then extracted with one 200-cc. and two 100-cc. portions of 10% sodium hydroxide solution. These were combined, made acid and the precipitate collected. The precipitate was dissolved in a 10% potassium bicarbonate solution. This solution was then extracted with 200 cc. of ether, the aqueous layer separated and boiled a little to remove dissolved ether. The aqueous solution was then cooled and made acid with dilute hydrochloric acid. The yield amounts to 68 g. or 66% of the theoretical. After recrystallization the acid melted at 113–113.5°.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.71; H, 8.86.

3,5-Dinitro-2,4,6-triethylbenzoic Acid.—One gram of 2,4,6-triethylbenzoic acid was mixed with 20 cc. of fuming nitric acid and warmed on the steam-bath for thirty minutes. The yellow solution was then poured into 100 cc. of ice water and allowed to stand. The crystals were collected and after recrystallization from ligroin the melting point was 128.5–129°, as compared with 128–129° in the literature.[10]

2,4,6-Triethylbenzoyl Chloride.—To 51.5 g. of 2,4,6-triethylbenzoic acid in a 200-cc. modified Claisen flask, 51 g. of phosphorus pentachloride was added in small portions. When all the phosphorus pentachloride had been added and the reaction subsided, the mixture was warmed slightly for five minutes. The phosphorus oxychloride was removed by the water pump and the acid chloride was then distilled. The acid chloride boiled at 112–113° (4–5 mm.); the yield was 47 g. or 83% of the theoretical amount; $n^{20}{}_{D}$ 1.5182; $d^{20}{}_{4}$ 1.0424.

Anal. Calcd. for $C_{13}H_{17}OCl$: Cl, 15.78. Found: Cl, 15.54.

2,4,6-Triethylbenzamide.—To 40 cc. of concentrated aqueous ammonia was added 3.4 g. of 2,4,6-triethylbenzoyl chloride. The mixture was shaken for one hour. The precipitate was then collected and recrystallized from aqueous alcohol. The yield was 2.6 g. or 83% of the theoretical amount. The melting point was 148–150°, and after recrystallization rose to 154.5–155.5°. The literature[10] gives 155–156°.

2,4,6,2′,4′,6′-Hexaethylbenzil.—To a solution of 28.3 g. of 2,4,6-triethylbenzoyl chloride in 200 cc. of absolute ether placed in a 1-liter three-necked flask equipped with stirrer, reflux condenser and dropping funnel, was added 200 cc. of 1.35 molar methylmagnesium iodide solution. The Grignard reagent was added at a regular rate over a two-hour period, and the solution was stirred vigorously. The reaction mixture was then decomposed with an ice–ammonium chloride solution. The ether layer was separated and washed with water twice. The aqueous portion was extracted with two 100-cc. portions of ether, which were added to the ether layer. This ether solution was dried with anhydrous sodium sulfate, then filtered, the ether removed on the steam cone and the residue distilled

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[10] Gattermann, Fritz and Beck, *Ber.*, **32**, 1123 (1899).

with the oil pump. Nine and eight-tenths grams of 2,4,6-triethylacetophenone came over at 112–114° (4–5 mm.). The distillation slowed up and was discontinued at this point. After standing overnight at room temperature, the flask contained yellow crystals. These were removed, filtered and washed with a little 85% alcohol. On recrystallization from petroleum ether, 7.75 g. of product was obtained. The yields of diketone and monoketone were 32.5 and 38.4%, respectively.

The monoketone was identified by means of a mixed melting point of its benzal derivative with an authentic specimen. The diketone crystallized in golden-yellow prisms melting at 75–75.5°.

Anal. Calcd. for $C_{26}H_{34}O_2$: C, 82.49; H, 9.06. Found: C, 82.53; H, 9.01.

2,4,6,2′,4′,6′-Hexamethylbenzil.—The Grignard reagent prepared from 23.7 g. of methyl iodide and 4.06 g. of magnesium diluted to 200 cc. with absolute ether was added with vigorous stirring over a period of seventy minutes to 10.95 g. of 2,4,6-trimethylbenzoyl chloride dissolved in 200 cc. of absolute ether. The reaction mixture was then decomposed and treated in a manner similar to that described for the triethyl compound. The yield of acetomesitylene was 3.44 g. and that of the benzil was 3.45 g., or 35 and 39%, respectively. The acetomesitylene was converted to the benzal derivative which was identified by means of a mixed melting point with an authentic specimen. The dimesityl diketone was likewise identified by comparison with an authentic specimen.

When the acid chloride was added to the solution of the Grignard reagent, it was not possible to isolate any benzil from the reaction products. Instead, acetomesitylene was formed in 88% yields.

Summary

2,4,6-Trimethylbenzoyl chloride and 2,4,6-triethylbenzoyl chloride are coupled by the action of methylmagnesium iodide to give, respectively, 2,4,6,2′,4′,6′-hexamethylbenzil and 2,4,6,2′,4′,6′-hexaethylbenzil.

URBANA, ILLINOIS RECEIVED MAY 23, 1938

[CONTRIBUTION FROM THE CHEMICAL DIVISION OF THE PROCTER & GAMBLE COMPANY]

A Phase Study of the System Sodium Palmitate–Sodium Chloride–Water at 90°

BY ROBERT D. VOLD[1] AND R. H. FERGUSON

It is the aim of this paper to present a complete equilibrium diagram of the system sodium palmitate–sodium chloride–water at 90° with greater precision than that which has characterized any previous published account of a similar system of soap, inorganic electrolyte and water. Especial emphasis is directed to the support of the interpretation of those parts of the diagram where the curd phase[2] is shown.

The practical soap maker has long been familiar with curd soap as an intermediate, distinctive form, differing markedly in its properties from neat soap, the usual finished product of the soap boiling process. However, the first clear concept of curd as a separate and discontinuous phase from neat soap, and of the relations of both these forms of soap to the other coexisting phases is of recent origin. This concept has been developed in a remarkable group of papers by McBain,[3] dealing with the properties and behavior of soap. In these papers both the experimental results and the imagination exhibited in the interpretation are of the first importance in the whole field of soap chemistry.

Inevitably, however, the evidence is not equally convincing with respect to all parts of the diagram constructed by McBain and his co-workers. For example, it is possible to derive conflicting views[4] relating to the presence of definite hydrates in the system at high temperatures, and the early dew-point results[5] do not support the existence of the three-phase invariant equilibrium, neat soap–curd phase–lye. In fact no definite constancy of phase composition has been clearly established hitherto for this equilibrium.

In general, the results of the present work, involving careful, systematic vapor pressure measurements of the system at 90°, are in agreement with McBain's conception of the equilibrium diagram. There are some quantitative divergencies, as may be noted by comparing the McBain diagrams with Fig. 6 below. In particular we have obtained definite proof that crystalline curd phase of sodium palmitate exists at 90° as a distinct phase different from neat soap, and that the neat–

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[2] The term *curd phase* will be used herein to refer to a homogeneous solid phase. In the literature, in addition to this meaning, the word curd has been used to describe variously a heterogeneous mixture of solid soap and other phases, any cooled and solidified soap system, and the upper curdy layer of soap in the soap kettle.

[3] Alexander, "Colloid Chemistry," Vol. I, Chapter by McBain; bibliography, McBain, Lazarus and Pitter, *Z. physik. Chem.*, **A147**, 87 (1930).

[4] Ostwald and Erbring, *Kolloid-Beihefte*, **31**, 345–346 (1930).

[5] McBain and Salmon, *J. Chem. Soc.*, **119**, 1374 (1921).

curd phase–lye equilibrium at this temperature is invariant. Contrary to the hypothesis of McBain, Lazarus and Pitter we find no evidence for the existence of stoichiometric hydrates of sodium palmitate at 90°.

Experimental

(a) **Methods Used.**—The solid nature of the systems encountered in highly concentrated soaps makes it virtually impossible to employ the method of phase separations developed by Ferguson and Richardson[6] for delimiting middle soap equilibria. Middle soap, while exceedingly gummy, is not as difficult to push to a condition of separation from other phases as is curd phase in the upper concentrated region of the diagram. Accordingly the phase separation method was used only to determine the boundaries of the middle soap and nigre fields.

For the various equilibria relating to curd phase and to check phase boundaries in the neat and middle soap fields an isopiestic vapor pressure method was devised. Essentially the method was adapted from that described by Collins and Menzies,[7] and has the advantage that it is independent of subjective visual observation of the appearance of the system, and is unaffected by whether or not the different phases present separate nicely or remain in intimate admixture.

A dew-point vapor pressure method was also employed in certain instances as discussed below.

(b) **Vapor Pressure Relations.**—The use of vapor pressure data to determine phase equilibrium diagrams is based directly on the requirements of the phase rule. A condition of invariance results whenever two condensed phases are simultaneously present in a binary system at constant temperature. Under such conditions the vapor pressure must remain constant despite changes in total composition, and thus give rise to flat portions in the vapor pressure–composition curve. The compositions at the ends of such "flats" give points on the phase boundaries of the two soap phases in equilibrium with each other.

In the ternary system soap–salt–water, at constant temperature, three condensed phases must be present before the pressure is independent of the total composition. In this case, however, the compositions at the ends of the flat in the vapor pressure curve give points on boundary lines connecting the compositions of the three phases present instead of giving the phase compositions themselves as in the binary system. This is equivalent to saying that "flats" in the vapor pressure curves in a ternary system are indicative of and specify the positions of triangles in the equilibrium diagram.

The composition at which transition from a one-phase to a two-phase region occurs in the ternary system at constant temperature may be determined from the vapor pressure–composition curve, since it is marked by a definite change in slope. This arises from the fact that in the one-phase region the rate of change of vapor pressure is directly dependent on the total composition, whereas in the two-phase region it is determined by the change of the compositions of the individual phases themselves.

Where lye (the technical name for any solution of electrolyte containing but little soap) is present, tie-line directions can be deduced from vapor pressure data. At equilibrium the partial pressure of water must be the same over all phases in the system. Consequently, the composition of a lye phase can be determined from the observed pressure in conjunction with standard recorded values for the vapor pressure of salt solutions, provided the solubility of sodium palmitate in the lye is not sufficient to change its vapor pressure appreciably. Lines drawn between the known composition of the total system and the composition of the equilibrium lye determined in this manner give the tie line upon which the composition of the equilibrium soap phase must lie.

That this procedure is valid in the present system was demonstrated by direct analyses of several lye layers which showed that sodium palmitate is practically insoluble in fairly concentrated salt solutions at 90°. Furthermore, it was found that the vapor pressure of systems consisting of curd phase, saturated lye and solid salt agreed exactly with that in the literature for the vapor pressure of a saturated salt solution at 90° and with our own values for the dew-point of saturated salt solution.

(c) **Procedure.**—In the more dilute systems phase boundaries were determined by methods of phase separation and analysis similar to those used with commercial soap systems.[8] In a few cases analyses were made of the partially separated phases, thus obtaining tie line directions. In all cases the visual appearance of the equilibrium systems was noted carefully in order to identify the phases present and facilitate interpretation of the vapor pressure curves.

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[6] Ferguson and Richardson, *Ind. Eng. Chem.*, **24**, 1329 (1932).

[7] Collins and Menzies, *J. Phys. Chem.*, **40**, 379 (1936).

[8] Ferguson, *Oil & Soap*, **14**, 115 (1937).

Studies by this (separation) technique were actually carried out at 100° instead of at 90°. The results were calculated to 90° for incorporation with the results of vapor pressure studies by use of temperature coefficients of phase boundary concentrations deduced from McBain's equilibrium diagrams at 90 and 100°. That no appreciable error is introduced by this procedure is evident since (a) the phase boundary concentrations for these phases—nigre, middle soap and neat soap—change but slowly with temperature, thus making the total correction small, and (b) for these phases the results obtained by McBain at 100° agree within 2% with those obtained in our study.

Phase equilibria in the more concentrated systems were deduced from vapor pressure curves as described above. After considerable preliminary work it was found that satisfactory results were obtained when 10-cc. portions of sulfuric acid solution were equilibrated with 1-g. soap samples in a closed system. During the experiment the acid concentration remains essentially constant while the soap system gains or loses water as required to make its vapor pressure the same as that of the acid.

In this work soap systems and sulfuric acid solutions were measured into the respective legs of an inverted Y-shaped Pyrex tube of about one inch (2.5 cm.) diameter. The tubes were then chilled in a salt–ice mixture and sealed off under vacuum from a water pump. After immersion in an oil-bath held at 90 ± 0.2° for a sufficient period to establish equilibrium (usually about five days) the two legs of the tube were simultaneously plunged into ice water thus preserving the compositions present at 90°. In this operation care was taken to make the level of the ice water the same as the level of the soap and acid in the respective legs in order to minimize distillation of water either into or out of the soap sample during the quenching process. The tube was then broken open and the contents of the two legs analyzed. The water content of the soap system was determined from the loss of weight on heating the *whole* sample to constant weight at 105°. The concentration of the sulfuric acid solution was determined by titration of a known weight of solution with standard alkali. Vapor pressures were obtained from the sulfuric acid concentrations of a plot of Collins'[9] vapor pressure results for such solutions at 90°.

A very large number of experiments was carried out with both binary and ternary systems over the whole composition range to test the validity of this method of vapor pressure determination as applied to soap systems and to establish the accuracy of the results. That the isopiestic method is satisfactory for use with soap systems is evident from the following experimental generalizations based on this work.

(1) Any two soap–water systems, one of higher and the other of lower water content, reach the same final concentration when sealed up in separate tubes with an acid of aqueous vapor pressure between the vapor pressures of the original soap systems.

(2) Duplicate soap samples sealed up in different tubes with the same acid reach the same equilibrium concentration at 90° even though one is brought to 90° by heating up from room temperature and the other by cooling down from 103°.

(3) Although the relative amounts of soap system and sulfuric acid were varied fivefold in some cases, the same vapor pressure and soap concentration were reached at equilibrium in all instances.

(4) Vapor pressures of salt solutions at 90° determined by the isopiestic method are in satisfactory agreement with the literature values, and with our dew-point determinations.

(5) Soap systems of widely differing initial concentration came to the same final concentration within a maximum deviation of ± 0.6% when equilibrated with the same acid. Some of the data on which this conclusion is based appear in Table I.

The reliability of the methods of analysis used was verified by analyzing samples of known composition and also by comparison of results with those obtained by analyses of samples for real soap content by standard methods.

To prove the absence of any systematic errors in the isopiestic vapor pressure method which conceivably could have led to erroneous vapor pressure–composition curves with resultant misconception of the nature of the phase equilibria involved, the vapor pressures of sodium palmitate–water systems at 90° were redetermined using an entirely independent method. For this purpose a dew-point method was used patterned after that described by McBain and collaborators.[10]

Use of the dew-point method for the determination of vapor pressures in the present work rests on the fact that the partial pressure of water vapor from a soap system at 90° is the same as that of pure water at some lower temperature. The temperature of pure water having the same vapor pressure as the soap system at 90° is given by the temperature at which dew just begins to form on a polished metal tube suspended in a closed space above the soap system. The vapor pressure of the soap system of known composition is then found simply from standard tables giving the vapor pressure of water at the dew-point temperature.

The technique of our determinations was essentially the same as that described by McBain, and modified by Ferguson and Vold.[11] The apparatus consisted of a glass tube closed at top and bottom with monel metal plates. These were equipped with circular grooves in which rubber washers were placed, and were held tightly against the glass by means of four "tie bolts." The top plate had a threaded hole through which the dew-point tube proper could be screwed down tightly against a rubber washer. The dew-point tube itself was a chromium-plated copper tube whose temperature could be varied by forced circulation of water from an auxiliary bath.

Extraordinary precautions were required to obtain accurate rather than merely reproducible results by this method. Soap samples (about 15-g. systems) were homogenized by heating to 295° in sealed tubes in a rotating autoclave prior to studying them in the dew-point apparatus. It was shown experimentally that the composition of the sample in the dew-point apparatus did not change during the time of the experiment. This is important since a small change in total composition may give rise to a

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[9] Collins, *J. Phys. Chem.*, **37**, 1191 (1933).

[10] McBain, Bull and Staddon, *ibid.*, **38**, 1075 (1934).

[11] Ferguson and Vold, *Oil & Soap*, in press.

surface layer of sufficiently different composition from the bulk of the sample to cause a serious error in the dew-point. At least fifteen hours was allowed for attainment of equilibrium since preliminary experiments showed that in many cases shorter periods of time were inadequate.

The validity of the technique finally evolved was confirmed by several tests. The vapor pressure of salt solutions at 90° determined by this dew-point method agreed within 1 mm. with the values listed in the "International Critical Tables."[12] In several experiments the equilibrium temperature was approached from higher and lower temperatures without causing any change in the observed dew-point of the soap sample at 90°. Finally, it was shown with several samples that the dew-point remained unchanged for periods of time running up to a week in the apparatus at 90°.

As appears from the results shown in Fig. 1, vapor pressures determined by the dew-point technique agree within the experimental error of that method with those obtained by the isopiestic method. Both series of experiments for systems containing NaP and H_2O alone, *i. e.*, along the left axis of the ternary phase diagram, show a step in the vapor pressure–composition curve, thus furnishing proof of the simultaneous presence of curd phase and neat soap as distinct phases.

It is of interest that the same result is obtained despite the fact that homogenized samples were used in the dew-point experiments whereas soap systems used in the isopiestic experiments had never been heated much above 105° and were used directly without preliminary equilibration. This fact would seem to show that we are dealing with the same equilibrium solid phase in both cases despite the difference in initial treatment.

(d) **Materials.**—The sodium palmitate used in these experiments was prepared by neutralizing (to phenolphthalein) a hot alcoholic solution of palmitic acid with a nearly saturated carbon dioxide-free aqueous solution of sodium hydroxide. The resulting soap was dried at 130–140°.[13] The palmitic acid was Eastman best product. The two lots used to prepare the sodium palmitate at different times during the course of the experimental work had the following characteristics.

Iodine value	0.09	0.05
Incipient fusion	61.5	61.9
Complete fusion	62.6	63.0
Molecular weight (by titration)	260	261

Sodium palmitate–water samples of the same composition made up from the two different preparations of sodium palmitate had the same vapor pressure.

Coleman and Bell C. P. sodium chloride was used throughout.

(e) **Results.**—The vapor pressure data obtained for the sodium palmitate–water system at

TABLE I

VAPOR PRESSURE OF SODIUM PALMITATE–WATER SYSTEMS AT 90°

Tube	Original % soap	% soap at equil.	Vapor press., mm.	Av. % soap at equil.	Av. vapor press., mm.	Phases present
E_5B	15.0	17.7	523			Nigre
E_4A	24.0	29.1	521			Middle soap and nigre
E_4B	28.0	31.1	521			
E_3A	33.8	37.7	519	37.7	519	Middle soap
E_3B	37.9	37.6	519			
1X	51.8	52.2	510			Middle soap and neat soap
21X	54.8	55.9	510			
21Y	51.8	54.7	510			
2X	64.0	56.3	510			Middle soap and neat soap
2Y	59.8	54.0	510			
22X	64.0	52.5	510			
22Y	59.8	52.3	510			
23X	67.8	60.8	505			Neat soap
23Y	. .	60.3	505	60.6	505	
9A	62.7	60.9	505			
9B	57.3	60.8	505	60.9	505	
5RY	74.0	67.6	497			Neat soap
4X	73.4	68.4	495			Neat soap
4Y	68.2	67.8	495	68.1	495	
24X	73.4	68.1	495			
24Y	68.2	68.0	495	68.1	495	
5X	79.6	68.4	495			
5Y	74.0	69.4	495	68.9	495	
25X	79.6	68.0	495			
25Y	74.0	68.2	495	68.1	495	
1B	73.3	69.9	491			Neat soap
6X	80.9	73.3	481			Neat soap
6Y	77.2	73.4	481	73.4	481	
26X	80.9	71.6	481			
26Y	77.2	72.4	481	72.0	481	
5A	77.5	74.0	481			
5B	80.6	73.4	481	73.7	481	
4B	90.0	73.2	479			Neat soap
8A	88.8	73.9	477			
8B	83.2	73.2	478	73.4	478	
14A	76.1	74.2	474			Neat soap
14B	84.0	74.3	474	74.3	474	
7A	93.2	86.9	471			Neat soap and curd phase
7B	85.7	85.5	471			
16A	76.2	79.3	472			
16B	81.2	80.4	471			
17A	83.0	80.8	471			
17B	95.0	83.2	471			
13A	86.8	92.1	467			Curd phase
13B	93.3	93.0	466	92.5	467	
12A	89.1	92.7	463			Curd phase
12B	94.5	92.3	462	92.5	463	
27X	85.3	93.0	458			Curd phase
7Y	81.1	93.0	458	93.0	458	
9X	90.3	93.6	436			Curd phase
9Y	93.9	93.2	436	93.4	436	
29X	90.3	93.4	436			
29Y	93.9	93.5	436	93.5	436	
28Y	86.5	94.5	410			Curd phase
38Y	86.5	95.2	410	94.9	410	
6A	95.3	96.3	381			Curd phase
6B	100.0	96.2	380	96.3	380	
11A	91.3	95.4	381			
11B	96.0	95.9	380	95.7	380	
10B	94.8	98.2	328			Curd phase

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(12) "International Critical Tables," Vol. III, 1928, p. 370.

(13) A dilatometric investigation of sodium palmitate has indicated the existence of more than one form of anhydrous solid soap, and additional liquid crystalline phases. Transitions from one phase to another may be slow (or incomplete) with the result that the modification obtained may depend on the experimental conditions of the preparation. The curd phase under discussion in this paper always contained some water; it formed spontaneously in the system and so must be the stable equilibrium solid phase at this temperature. Furthermore, equilibria involving curd phase at 90° were shown experimentally to be perfectly reversible. Hence, it is difficult to imagine that the results obtained with aqueous systems at this temperature are subject to any uncertainty arising from possible differences in the initial crystalline modification of the anhydrous sodium palmitate.

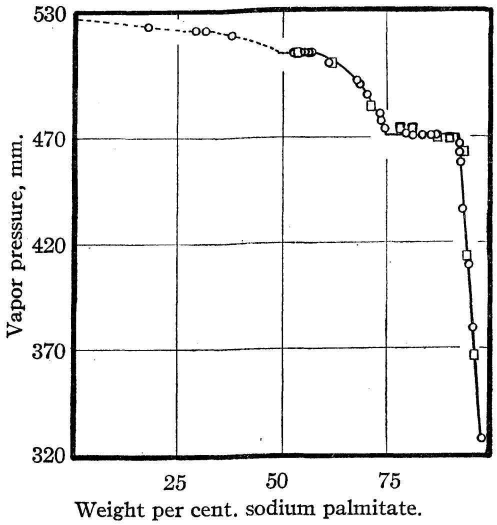

Fig. 1.—The vapor pressure of sodium palmitate–water systems at 90°: ○, points by the isopiestic method; □, points by the dew-point method.

90° are assembled in Table I. To conserve space the data for ternary systems are shown graphically in Figs. 2, 3, 4 and 5. The compositions at which phase changes occur, deduced from the vapor pressure curves and from the phase analysis and delimiting experiments, are given in Table II.

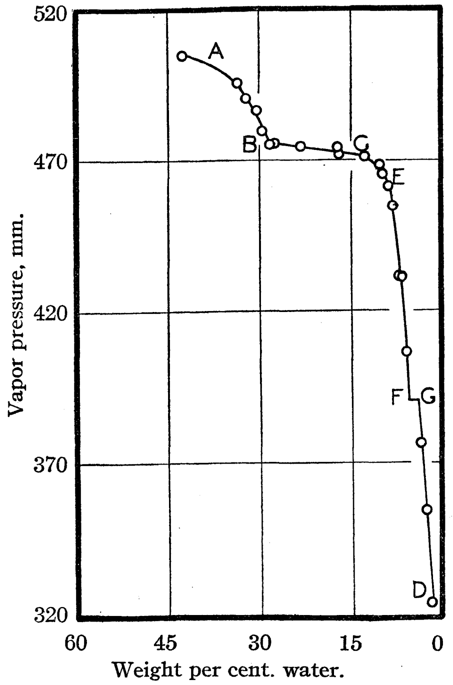

Fig. 2.—The vapor pressure of sodium palmitate–sodium chloride–water systems at 90°: sodium chloride concentration equals 0.80% sodium palmitate concentration.

In Fig. 1 the partial pressure of water vapor is plotted as a function of composition for the sodium palmitate–water system at 90°. The three flats in the curve correspond respectively to the coexistence of middle soap–nigre, middle soap–neat soap and neat soap–curd phase. The compositions of the phases in equilibrium, determined from the ends of the flats in the vapor pressure curve in the case of middle soap–nigre and middle soap–neat equilibria, are in good agreement with the values found directly by the delimiting method. The flat for the neat soap–curd phase equilibrium constitutes conclusive experimental proof of the existence of these two forms of soap as independent phases.

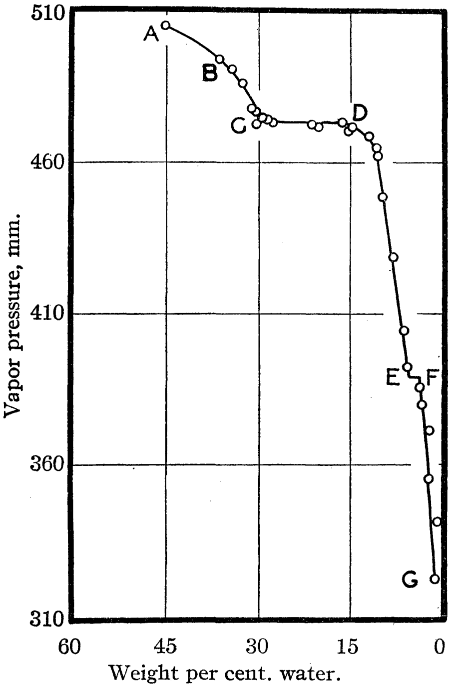

Fig. 3.—The vapor pressure of sodium palmitate–sodium chloride–water systems at 90°: sodium chloride concentration equals 1.22% sodium palmitate concentration.

Figure 2 shows the change in partial pressure with change in water content for systems in which the ratio of salt concentration to soap concentration is held constant at 0.0080. The application of phase rule principles to this curve, coupled with visual observation of the phases present, leads to the following interpretation. Above 28.5% water (point B) neat soap is present. Between 28.5% and 12.5% water (B to C) neat soap and curd phase are present. Since three condensed phases are required for a condition of invariance in a ternary system at set temperature, the pressure is not constant but changes slowly with the total composition. After all the neat soap has disappeared (point C) curd phase alone remains and the pressure falls more rapidly with further decrease in water content. At 9.0% water (point E) a two-phase region, curd phase–lye, is again entered with a resultant slight change in slope of the vapor pressure curve. Between 5.1 and 3.9% water (points F and G) the vapor pressure remains constant, thus showing three condensed phases are present in the system. These are curd phase, saturated lye and solid salt. Below 3.9% water only the two solids, curd phase and crystalline salt, remain and the vapor pressure decreases rapidly and continuously with further decrease in water content.

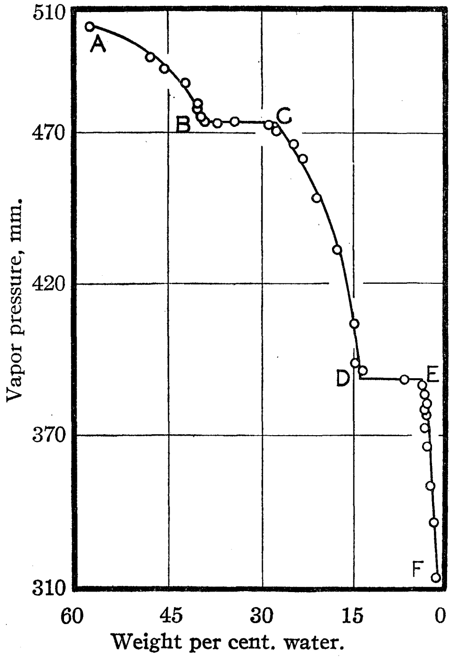

Fig. 4.—The vapor pressure of sodium palmitate–sodium chloride–water systems at 90°: sodium chloride concentration equals 5.27% sodium palmitate concentration.

The change from curd phase to curd phase–lye, evidenced by the inflection in the curve at E, is so slight that it was identified as such only after subsequent work determining the equilibrium diagram had shown the necessity for its existence. The compositions at the ends of flats, indicative of the presence of three condensed phases, are much more accurately determined than are the compositions of inflections representing transitions from one-phase to two-phase regions.

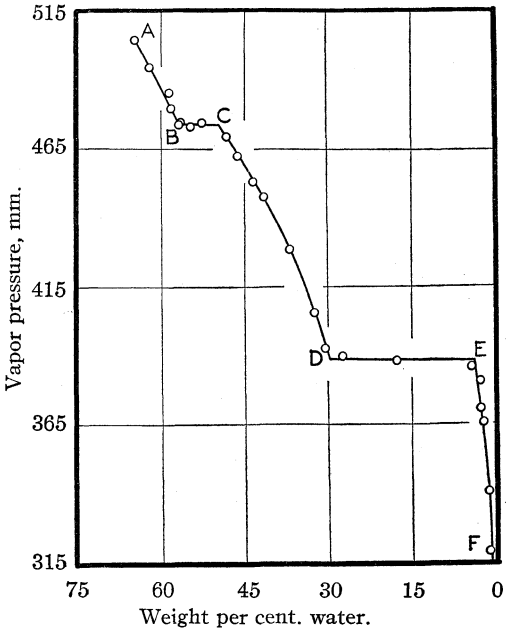

Fig. 5.—The vapor pressure of sodium palmitate–sodium chloride–water systems at 90°: sodium chloride concentration equals 17.70% sodium palmitate concentration.

Figures 3, 4 and 5 show the results at higher relative salt concentrations where progressive decrease in water content results in the formation of two different three-phase equilibria. The compositions at the ends of the higher flat in each curve represent the range within which neat soap, curd phase and lye exist in equilibrium with each other. The lower flat determines the composition range of coexistence of curd phase, saturated lye and solid salt.

The phase equilibrium diagram at 90° is shown in Fig. 6. This diagram is simply a modification of the customary Gibbs triangle for representation of the equilibria in ternary systems and is especially convenient in representing soap systems. Ordinates show the weight per cent. of sodium palmitate and abscissas the weight per cent. of sodium chloride, the per cent. water being obtained by difference. A straight line, passing through the origin and any given composition, represents the compositions of all systems which can be obtained by altering the water content of the original system.

The experimental data on which the equilibrium diagram is based are assembled in Table II. The compositions of the curd phase and neat soap corners of the curd phase–neat soap–lye triangle were determined within about 2% by comparison of the vapor pressure curves for systems with salt to soap concentration ratios of 0.008 and 0.012. On the first curve (Fig. 2) the compositions of curd phase and neat soap at the inflection points (C and B) lie just outside the triangular area; on the second curve (Fig. 3) corresponding points (D and C) lie just inside this area. The composition limits of the neat soap–middle soap–nigre and neat soap–nigre–lye triangles at 90° were obtained indirectly from values for these points at 100°. These compositions at 100° were corrected for the 10° decrease in temperature by the same relative amounts deduced for corresponding points in phase rule diagrams of the system: tallow soap–sodium chloride–water at 100 and 80°.[14] Use also was made of McBain's data showing the change in the isotropic solution boundary in the sodium palmitate–sodium chloride–water system from 100 to 90°.

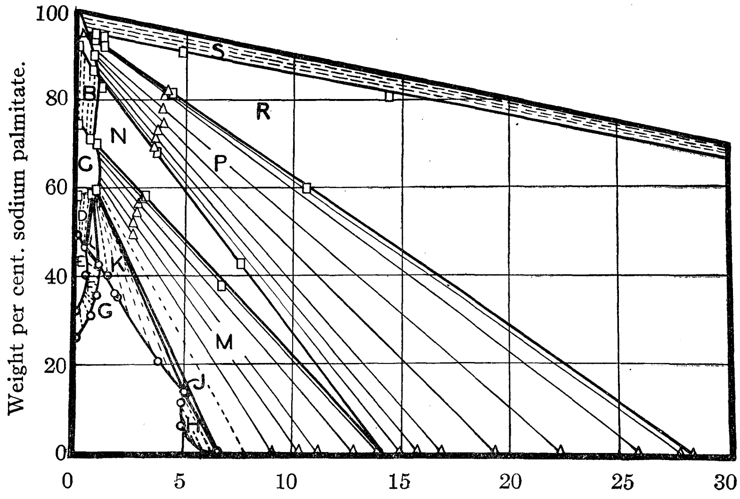

Fig. 6.—The system sodium palmitate–sodium chloride–water at 90°: ○, points from delimiting experiments; □, points from vapor pressure data; △, points from tie line determinations. A, curd phase; B, curd phase–neat; C, neat; D, neat–middle; E, middle; F, middle–nigre; G, nigre; H, nigre–lye; J, neat–nigre–lye; K, neat–nigre; L, middle–neat–nigre; M, neat–lye; N, neat–curd phase–lye; P, curd phase–lye; R, curd phase–lye–salt; S, curd phase–salt.

The following considerations establish the validity of the present experimental results. Theoretically two of the lines forming the boundaries of the neat soap–curd phase–lye triangle should converge to a point on the lye axis corresponding to a lye composition above which curd phase is in equilibrium with lye and below which neat soap is in equilibrium with lye. It is clear from Fig. 6 that the experimental points do fall nicely on straight lines which intersect exactly at a point on the water–salt axis. In all cases the same vapor pressure (473–474 mm.) was found experimentally for all systems having compositions within the triangle.

In the curd phase–saturated lye–solid salt equilibrium theoretically one of the lines forming the sides of the triangle should run to the point representing pure salt and another to the composition of a saturated lye solution (28.4%). As appears in Fig. 6 the experimental points do define two straight lines which satisfy these requirements. Here again the same vapor pressure was found experimentally for all systems within the triangle regardless of wide variations in total composition. Furthermore, the value found for this vapor pressure, 389 mm., is in good agreement with the literature value for the vapor pressure of a saturated salt solution at 90°.[12]

The accuracy of the results by the analytical and phase-delimiting method for equilibria involving fluid soap phases is attested by their self-consistency. Furthermore, the boundaries obtained by this method are in relatively good quantitative agreement with those obtained by McBain[3] by an entirely different method.

Discussion

(a) Description of Phases.—Descriptions of the physical nature of equilibria involving liquid and liquid crystalline soap phases have already been given in considerable detail for several systems, notably tallow soap–sodium chloride–water,[6,15] potassium oleate–potassium chloride–water[16] and potassium laurate–lauric acid–water.[17] Since the corresponding phases in the sodium palmitate–sodium chloride–water system at 90° closely resemble those referred to above, it will be unnecessary to describe them here in detail.

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(14) Unpublished data obtained in this Laboratory.

(15) Ferguson, *Oil & Soap*, **9**, 4–8 (1932).

(16) McBain and Elford, *J. Chem. Soc.*, 424 (1926).

(17) McBain and Field, THIS JOURNAL, **55**, 4786 (1933).

More attention will be devoted to equilibria involving curd phase since these have not been so adequately described.

As appears in Fig. 6 sixteen different equilibrium conditions are possible at 90°, the particular state of any given system being determined by the relative amounts of soap, salt and water present. Inspection of the phase diagram shows the concentration limits for the existence of these various equilibria.

1. Nigre, or isotropic solution of soap and salt (Field G), is a single homogeneous phase, despite its colloidal nature and capacity for existing as mobile liquid, thick viscous liquid or even elastic transparent jelly.

2. Middle soap (Field E) is also a single phase of variable composition, a liquid crystalline solution. It combines the mechanical properties of a stiff fluid having a pronounced yield value[18] with certain of the optical properties of a crystal. Generally it occurs as clear gummy lumps of very great viscosity.

3. Neat soap (Field C), a single phase of variable composition, is another liquid crystalline solution. It is more turbid and at 90° in this system is less viscous than middle soap.

4. Curd phase (Field A) is another single phase of continuously variable composition. It is a crystalline form of solid soap. When formed in the presence of neat soap it is characterized by

TABLE II

EQUILIBRIUM DATA FOR THE SYSTEM NaP–NaCl–H_2O AT 90°. A. PHASE BOUNDARY DATA FROM VAPOR PRESSURE RESULTS

Phases	Composition, % NaP	Composition, % NaCl
Points on the neat soap boundary	58.0	0.00
	71.4	.57
	74.5	.00
Points on the curd phase boundary	92.5	.00
	90.3	.72
	86.8	.69
	100.0	.00
Points on the neat–lye edge of the neat–curd phase–lye triangle	37.3	6.60
	58.0	3.06
	70.1	0.86
Points on the curd phase–lye edge of the neat–curd phase–lye triangle	42.9	7.60
	68.4	3.60
	83.0	1.03
Points on the curd phase–lye edge of the curd phase–lye–salt triangle	59.9	10.6
	81.7	4.30
	92.4	1.14
	94.2	0.76
Points on the curd phase–salt edge of the curd phase–lye–salt triangle	81.0	14.4
	91.2	4.81
	94.8	1.17
	95.2	0.77

B. PHASE BOUNDARY DATA FROM PHASE RULE REQUIREMENTS AND EXTENSION OF RESULTS FROM VAPOR PRESSURES

Description of point	Composition, % NaP	Composition, % NaCl	Source of data
Lye apex of neat–curd phase–lye triangle	0	14.3	Vapor pressure of flat confirmed by intersection of sides of triangle
Saturated lye	0	28.4	"I. C. T." data
Solid salt	0	100	Visual observation; assumes no solid solution formation by NaCl
Neat soap in equilibrium with curd phase and lye	70.8	0.65	Intermediate between composition on neat soap boundary just outside the neat–curd–lye triangle and composition just inside the triangle (see Figs. 2 and 3)
Curd phase in equilibrium with neat soap and lye	85.0	.90	Intermediate between composition on curd phase boundary just outside the neat curd–lye triangle and composition just inside the triangle (see Figs. 2 and 3)
Curd phase in equilibrium with lye and solid salt	95.5	.30	Intersection of sides of curd–lye–salt triangle

C. DATA FOR EQUILIBRIA INVOLVING FLUID SOAP PHASES

Phases	Composition % NaP	Composition % NaCl
Points on middle soap boundary	32.0	0
	40.0	0.4
	49.0	0
Points on isotropic solution boundary	6.0	4.9
	11.2	4.9
	13.7	5.0
	20.5	3.8
	35.1	1.9
	35.5	1.8
	40.0	1.4
	40.0	0.8
	35.5	.9
	31.0	.7
	26.0	.0
Apices of neat–middle–nigre triangle	59.0	.7
	46.5	.4
	42.5	1.0
Apices of neat–nigre–lye triangle	59.5	0.8
	13.5	5.1
	0	6.6

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[18] McBain and Watts, *J. Rheology*, **3**, 437 (1932).

TABLE II (*Concluded*)

D. TIE LINE DIRECTIONS DETERMINED FROM TOTAL SYSTEM COMPOSITIONS AND VAPOR PRESSURES

1. Systems in which NaCl concentration = 5.27% soap Concentration. (NaP)

Total system % NaCl	Total system % NaP	Vapor pressure, mm.	Lye phase, % NaCl
	Phases in equilibrium: neat soap–lye		
2.58	49.2	495	9.1
2.59	51.7	491.5	10.3
2.74	54.5	487	11.2
2.83	56.4	480	12.8
2.98	56.7	478	13.2
3.02	57.5	475.5	13.9
	Curd phase–lye		
3.38	67.5	473	14.4
3.49	69.5	471	14.9
3.58	71.7	567	15.7
3.66	73.5	462	16.8
3.97	74.9	449	19.3
3.92	78.3	432	22.3
4.05	81.2	407.5	25.9
4.16	82.5	392	27.8

2. Systems in which NaCl concentration = 17.70% NaP concentration.

Total system % NaCl	Total system % NaP	Vapor pressure, mm.	Lye phase, % NaCl
	Neat soap–lye		
4.88[a]	32.7	495	9.1
5.44[a]	36.3	486	11.4
6.80	35.2	480	12.8
6.60	37.1	474.5	14.1
	Curd phase–lye		
7.80	44.3	470	15.1
8.12	46.0	463	16.55
8.55	48.6	454	18.3
8.80	49.6	448.5	19.4
9.50	53.7	430	22.6
10.2	57.9	406	26.1
10.5	59.3	393	27.8

[a] In these systems salt concentration was only 15% of soap concentration.

the presence of long, lustrous fibers and tufts of shorter, finer fibers. We have obtained these fibers in lengths up to two or three centimeters.

Analysis of fibers in the binary system shows that they consist of neutral soap and water, thus proving that their development is not due to the formation of acid soap. Expulsion of water by drying to constant weight at 105° results in no change in the appearance of the fibers nor are they affected by cooling from 90° to room temperature. Fibers developed in binary systems of sodium palmitate–water were no different in appearance from those formed in the ternary system.

Plates 1, 2 and 3 are typical of the appearance of these fibers. Plate 1 shows a mixture of macroscopic curd phase fibers and neat soap. Plates 2 and 3 are photomicrographs of curd phase fibers at successively higher magnifications. They illustrate the similarity in form between the large fibers visible to the unaided eye and the finer ones visible with the microscope. This same structural form also has been observed in the ultramicroscope.[19]

Curd phase formed without contact with neat soap, as by diffusion of water vapor into anhydrous sodium palmitate, does not develop visible fibers. Under these circumstances the appearance is that of a white solid of granular formation.

5. Two-phase equilibrium between nigre and middle soap (Field F). It is of interest here that addition of salt to the soap solution actually results in an increase in the solubility of the soap.

6. Two-phase equilibrium between nigre and neat soap (Field K). Here increased salt concentration in the soap solution results in a rapid decrease in the solubility of the soap, the saturation phase being liquid crystalline neat soap.

7. Two-phase equilibrium between nigre and lye (Field H). At low soap concentrations sufficient increase in salt concentration results in separation into two isotropic liquid phases.

8. Two-phase equilibrium between neat soap and lye (Field M). Reasonably good separations of molten liquid crystalline neat soap over isotropic lye occur throughout this range of concentrations.

9. Two-phase equilibrium between neat soap and middle soap (Field D). This is a very difficult field in which to obtain separation of phases.

10. Two-phase equilibrium between neat soap and curd phase (Field B). Complete separation of phases was never attained in this range, although a fairly good degree of segregation was obtained in a centrifuge. Even systems of total composition such that they were mostly neat soap appeared to the naked eye to consist primarily of fibrous solid material.

11. Two-phase equilibrium between curd phase and lye (Field P). As the total soap concentration is increased, the appearance of the curd phase changes from a feathery white solid, covered with a fuzz of fine whiskers, to a damp granular solid of no pronounced structure. Sometimes a clear lye layer separated below the soap

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(19) McBain, Darke and Salmon, *Proc. Roy. Soc.* (London), **A98**, 395 (1921).

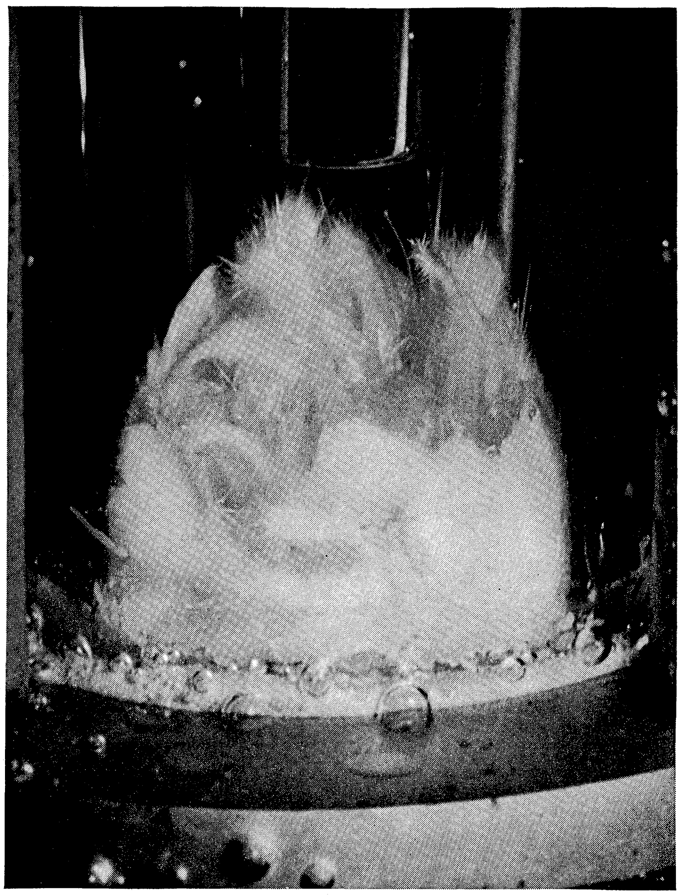

Plate 1.—Macroscopic fibers at 90°: NaP–H_2O system, 76.9% NaP after a few days at 90°.

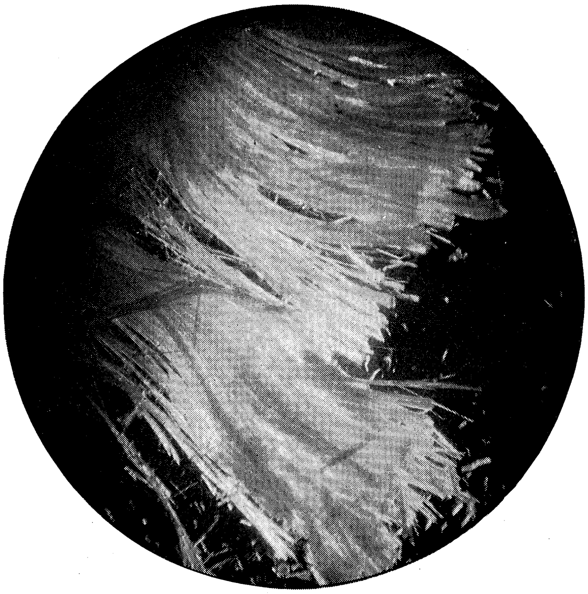

Plate 2.—Photomicrograph of macroscopic curd fibers: NaP–H_2O system, about 76% NaP, polarized light ×13, crossed Nicols.

Plate 3.—Photomicrograph of macroscopic curd fibers: reflected light ×42.

layer; at other times all the lye was mechanically enmeshed in the curd phase forming a macroscopically homogeneous mass.

12. Two-phase equilibrium between curd phase and solid salt (Field S). The appearance of these systems is very similar to the soap layers found in the region of curd phase–lye equilibria. As the water content is decreased the soap gradually becomes drier and changes from a loosely caked solid to a granular dry free-flowing solid. In most cases crystals of salt can be seen mixed with the soap.

13. Three-phase equilibrium between neat soap, middle soap and nigre (Field L). (Separations have been obtained in certain commercial soap systems.[6])

14. Three-phase equilibrium between neat soap, nigre and lye (Field J). The relatively low soap content of the neat soap separating in the sodium palmitate system compared to that separating in this region in systems of ordinary commercial soaps is of technical interest.

15. Three-phase equilibrium between neat soap, curd phase and lye (Field N). As in the case of curd phase–neat soap equilibria, systems in this composition range usually developed pronounced macroscopic soap fibers. Occasionally a small amount of lye settled out beneath the soap layer but in general these systems appeared macroscopically homogeneous despite the actual presence of three phases.

16. Three-phase equilibrium between curd phase, saturated lye and solid salt (Field R). Here again most of the salt and lye are enmeshed in the curd phase forming a damp mass of white solid. Sometimes crystals of free salt were observed.

(b) **Comparison with Previous Work.**—The present results are in agreement with McBain's general concept of curd phase existing in true reversible equilibrium with neat soap and lye. In the fields of nigres, middle soap, neat soap, middle soap–nigre, middle soap–neat soap–nigre, neat soap–nigre, neat soap–nigre–lye and neat soap–lye our results by phase analysis and delimiting methods are in satisfactory quantitative agreement with McBain's results obtained by extrapolation from observations of temperatures at which phase changes occurred in systems of varying composition.

In the equilibria involving solid soap phases there are considerable discrepancies between the present results obtained by the vapor pressure method and the older work. For instance, our results show that the presence of small amounts of salt in curd phase actually increases the amount of water it can contain before "melting" to neat soap, whereas McBain tentatively drew the phase boundary as though the water content of curd phase decreased on addition of salt. However, this is not a difference in kind but only of degree. It is not surprising inasmuch as previous diagrams of the equilibria involving curd phase were derived from a few scattered incidental observations by a process of reasonable deduction rather than from systematic experimental data. The upper apex of our curd–lye–salt triangle is considerably different from McBain's. This may be due to a difference in the soap used, in the method of preparation of the soap before determining the vapor pressure, or to a systematic error in the older vapor pressure work.

(c) **Nature of Curd Phase.**—The present work, in agreement with the first work of McBain and collaborators, shows that curd phase in this system consists of sodium palmitate associated with varying amounts of salt and water. On the basis of the fact that at room temperature quite different amounts of water can be contained in the curd phase, McBain[3,10] tentatively assumed the existence of definite sodium palmitate hydrates. Contrary to this hypothesis all the present work favors the view that the curd phase of sodium palmitate at 90° is a single phase of continuously variable composition.

Let us consider the vapor pressure—composition curve for the binary system, sodium palmitate–water, at 90°. If there is a stoichiometric hydrate, application of the phase rule in its usual form necessitates a flat in the vapor pressure curve corresponding to the equilibrium between anhydrous sodium palmitate and the hydrate. Actually the vapor pressure of curd phase at 90° was found to decrease continuously with decrease in water content.

Points on the curd phase boundary could not be obtained directly by phase analysis or delimiting experiments because of incomplete separation of phases. However, in many cases tie-line directions could be ascertained by analysis even though the composition of the uncontaminated soap phase at the end of the tie-line remained unknown. All tie lines involving curd phase extrapolated to points of continuously variable composition on the curd phase boundary. If curd phase consisted of one or more definite hydrates these tie-lines would have had to converge to the points representing the compositions of the hydrates. In this connection it might also be mentioned that in an earlier paper McBain[5] himself has commented on the fact that the water content of soap curd appears to vary continuously with the concentration of the electrolyte used to salt it out.

Summary

An isopiestic vapor pressure method has been developed which is suitable for studying soap systems at high temperatures and high soap concentrations where the usual methods based on observation of phase changes or analysis of phases are inapplicable due to non-separation of phases. By means of vapor pressure measurements in a pure single soap system at 90°, it has been demonstrated (a) that curd phase can exist in true reversible equilibrium with neat soap, and that the two are separate phases; (b) that no stoichiometric hydrates occur in the system at 90°, the curd phase varying continuously in water content.

The complete equilibrium diagram has been drawn for the system sodium palmitate–sodium chloride–water at 90°.

The formation and appearance of curd fibers have been described.

IVORYDALE, OHIO RECEIVED JUNE 3, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY]

The Preparation of Some Higher Alkylglucosides

BY C. R. NOLLER AND W. C. ROCKWELL

The following records the preparation and some properties of *n*-hexyl-, *n*-octyl-, *n*-nonyl-, *n*-decyl- and *n*-dodecylglucoside. These compounds were synthesized in order to make available for physical-chemical investigations pure surface-active compounds of known constitution that have suitable solubility characteristics and do not ionize in aqueous solutions.

The method of synthesis was essentially that of Fischer and his co-workers,[1] namely, the condensation of acetobromoglucose with the appropriate alcohol and hydrolysis of the tetraacetyl derivative to the alkyl glucoside. One important change was made in the method of deacetylating the tetraacetates, namely, the replacement of hydrolysis using barium hydroxide or ammonium hydroxide by catalytic transesterification[2] with methyl alcohol and sodium methoxide. In this way the time of hydrolysis is greatly reduced and the isolation of the pure glucoside is simplified.

It will be noted from the tables that while the melting points of the tetraacetyl derivatives are fairly sharp, those of the alkyl glucosides especially from octyl up are over a very wide range. This was noted by Fischer and Helferich,[1] who stated that they were unable to explain the phenomenon. We have noted that during a melting point determination the solid changed to a semi-transparent state at the lower temperature noted. On further raising the temperature little change took place until the higher temperature was reached when sharp melting to a clear liquid occurred. It appears to us that the lower temperature marks the transition from the solid to the liquid–crystal state and the higher temperature the transition from the liquid–crystal to the liquid state.

n-Hexylglucoside is very soluble in water and its aqueous solutions show little tendency to foam on shaking. As the length of the alkyl group increases the foam-producing ability is greatly increased, the nonyl-, decyl- and dodecylglucosides giving very stable foams. The solubility in water decreases, the dodecylglucoside being only sparingly soluble in cold water but readily in hot water. Cetylglucoside was reported by Fischer and Helferich[1] as being insoluble in water.

It was not determined whether these glucosides are hydrolyzed by emulsion but the work of Fischer and Helferich and the observed negative rotations would indicate that they are β-glucosides.

Experimental

Pentaacetylglucose and Acetobromoglucose.—When pentaacetylglucose was prepared according to the proced-

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[1] Fischer and Raske, *Ber.*, **42**, 1465 (1909); Fischer and Helferich, *Ann.*, **383**, 68 (1911).

[2] Fischer and Bergmann, *Ber.*, **52**, 852 (1919); Zemplén and Pacsu, *ibid.*, **62**, 1613 (1929).

ure of Fischer,[3] using 100-g. quantities of glucose, charring took place due to the heat of the reaction. This was obviated by adding the glucose in portions of about 10 g. at such a rate that the temperature did not rise above 110°. Glucose hydrate may be used instead of the anhydrous glucose recommended by Fischer without changing the yield or quality of the product.

Considerable trouble was encountered in the preparation and storage of acetobromoglucose. Of the various procedures reported in the literature and modifications which were tried, the method of Freudenberg, Noe and Knopf[4] gave the best results.

Tetraacetylalkylglucosides.—A mixture of 0.15 mole of the pure alcohol, 0.02 mole of acetobromoglucose, 200 cc. of absolute ether and 0.025 mole of freshly prepared, dry silver oxide[5] in a tightly stoppered flask was shaken mechanically for two hours. At the end of this time a small sample gave no precipitate when tested with silver nitrate solution. The ether solution was filtered through a thin layer of diatomaceous earth on a Büchner funnel, the ether evaporated and the excess alcohol removed by steam distillation. Upon cooling the residue in the flask, the crude tetraacetylglucoside congealed and was filtered and crystallized from dilute aqueous methyl alcohol. The products frequently came down as a milky emulsion which crystallized on cooling in an ice-bath. The yields varied from 40 to 60% of the calculated amount. The properties and analyses of the individual compounds are given in Table I. The specific rotations were determined in methyl alcohol solution.

TABLE I

TETRAACETYLALKYLGLUCOSIDES

Alkyl radical	M. p., °C.	$[\alpha]^{25}D$	Saponification equivalent Calcd.	Found
n-Hexyl	51–52.5	−22.4	108.1	106.7
n-Octyl	53–54	−21.7	115.1	116.5
n-Nonyl	39.5–40.5	−20.9	118.6	118.4
n-Decyl	47.5–48.5	−21.5	122.1	123.0
n-Dodecyl	58.5–59.5	−18.8	129.1	131.0

Alkylglucosides.—To a solution of 0.01 mole of tetraacetylalkylglucoside in 100 cc. of absolute methyl alcohol was added 2 cc. of a 0.1 *N* solution of sodium methylate in methyl alcohol. The solution was boiled for one-half hour under a reflux condenser protected by a calcium chloride tube and the methyl alcohol then removed under reduced pressure. The sirupy residue was taken up in hot ethyl acetate and on cooling in a freezing mixture the glucoside crystallized and was filtered and washed with petroleum ether. Considerable difficulty was encountered in crystallizing the crude glucosides since there was a tendency to separate as a gel. The dodecylglucoside crystallized best from water. The properties and analyses of the glucosides are given in Table II, the rotations being determined in methyl alcohol solution. The analyses for glucose were made by hydrolyzing the sample with dilute sulfuric acid and determining iodimetrically the amount of glucose formed. We are indebted to Mr. S. Kinsman for the rotations and analyses of the alkylglucosides.

TABLE II

ALKYLGLUCOSIDES

Alkyl radical	M. p., °C.	$[\alpha]^{25}D$	% glucose after hydrolysis Calcd.	Found
n-Hexyl	88–91	−33.7	68.1	68.9
n-Octyl	65–99	−30.3	61.6	62.2
n-Nonyl	65–118	−28.8	58.8	58.3
n-Decyl	75–130	−27.8	56.2	56.3
n-Dodecyl	77–137	−24.7	51.7	51.2

Summary

n-Hexyl-, *n*-octyl-, *n*-nonyl-, *n*-decyl- and *n*-dodecylglucosides and their tetraacetates have been prepared in a pure state. Aqueous solutions of the glucosides from octyl through dodecyl foam on shaking but dodecylglucoside is only slightly soluble in cold water. These glucosides should be of value in physical-chemical investigations where a non-ionizing surface-active substance is desired.

STANFORD UNIVERSITY, CALIF. RECEIVED MAY 25, 1938

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(3) Fischer, *Ber.*, **49**, 584 (1916).

(4) Freudenberg, Noe and Knopf, *ibid.*, **60**, 241 (1927).

(5) Helferich and Klein, *Ann.*, **450**, 225 (1926).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

A Method of Distinguishing Primary, Secondary and Tertiary Aliphatic Acids

BY FRANK C. WHITMORE AND HARRY M. CROOKS, JR.

Whitmore and Laughlin[1] found that when certain aliphatic acids were treated with phosphorus pentoxide at temperatures in the neighborhood of 150° the relative yields of carbon monoxide and carbon dioxide were dependent upon the character of the alkyl group attached to the carboxyl carbon. Their results indicated this as a possible method of distinguishing between primary, secondary and tertiary acids RCH_2COOH, $RR'CHCOOH$ and $RR'R''CCOOH$. In the present study this has been confirmed and extended to cover fifteen aliphatic acids other than those reported by Whitmore and Laughlin. The studies have included six primary acids, eight secondary acids and five tertiary acids.

In the case of primary acids, the gaseous products totaled 5–13% of the theoretical amount required by complete loss of the carboxyl group, the ratio of carbon dioxide to carbon monoxide increasing, with increase in molecular weight of the acid, from 5:1 to a 13% yield of carbon dioxide with no carbon monoxide. With secondary acids, the yield of carbon monoxide increased from 9 to 30% and the yield of carbon dioxide decreased from 1.7 to 0.5% with increase in molecular weight of acid. With tertiary acids, the carbon monoxide yield increased from 55 to 90% with increase in molecular weight of acid, only traces of carbon dioxide being formed.

A method for distinguishing between secondary and tertiary acids is especially important in view of the confusion about the two acids, $C_{11}H_{23}CO_2H$, obtained by the oxidation of triisobutylene.[2] From their speeds of esterification they were thought to be tertiary although one later was proved to be secondary. The present method distinguishes them definitely, the dineopentylacetic acid forming 30% CO and 0.5% CO_2 while the isomeric methyl-*t*-butylneopentylacetic acid gives 90% CO and 0.2% CO_2.

All reactions were run at the same temperature (155–160°). The yield of gas is probably dependent on this factor. Thus, Kipping[3] obtained 30–60% yields of ketone and presumably a corresponding yield of carbon dioxide, by treating primary acids with phosphorus pentoxide at 200–220°.

In all cases, a heavy tar was formed in the reaction.

Experimental

The apparatus used consisted of a three-necked, 200-cc., round-bottomed flask fitted with a gas inlet tube, a dropping funnel and a reflux condenser. Gases from the reaction were led through the condenser to a calibrated gas collecting carboy. The system was so assembled that all parts could be flushed out with nitrogen. In the case of acids solid at room temperature a procedure was devised permitting introduction of the solid in small portions without opening the system.

Gas analyses were made with a standard Orsat apparatus using 10% sodium hydroxide solution for carbon dioxide and cuprous chloride in hydrochloric acid for carbon monoxide.

Procedure.—Approximately one-tenth mole runs of each acid were made. For this, 25 g. of phosphorus pentoxide was weighed into the reaction flask, the acid placed in the dropping funnel, the apparatus assembled and tested for leaks. The apparatus was then swept out with from three to five liters of dry nitrogen with the gas-collecting carboy disconnected. The carboy was connected and the bath surrounding the flask heated to 100–110°. The acid was then added slowly (about forty minutes for 0.1 mole) to the hot oxide. After all the acid was added the bath temperature was raised to 155–160° and held at that point

DESCRIPTION OF ACIDS USED

Acid	B. p.		$n^{20}D$	Source
	°C.	Mm.		
n-Caproic	114	740	1.4163	Mallinckrodt Chem. Wks.
Isocaproic			1.4150	Eastman Kodak Co.
t-Butylacetic	96	25	1.4107	[a]
Methylneopentylacetic	119	20	1.4242	[a]
n-Caprylic			1.4280	Eastman Kodak Co.
Stearic	U.S.P.X.			Baker Chemical Co.
Diethylacetic	119	731	1.4132	[b]
Methyl-*n*-propylacetic	191	735	1.4140	[b]
Diallylacetic	113	11	1.4520	[c]
Di-*n*-propylacetic	120	16	1.4239	[d]
Di-*n*-butylacetic	143	16	1.4328	[d]
Dineopentylacetic	m. p. 88–89°			[d]
Trimethylacetic	m. p. 35°			[e]
Ethyldimethylacetic	100	23	1.4141	[e]
Diethylmethylacetic	134	50	1.4250	[e]
Triethylacetic	m. p. 39°			[e]

[a] From oxidation of diisobutylene; to be published later. [b] From Dr. F. A. Karnatz, this Laboratory; malonic ester synthesis. [c] From Dr. D. M. Jones, this Laboratory. [d] From Dr. P. A. Lasselle, this Laboratory; hydrolysis of corresponding nitriles. [e] Addition of carbon dioxide to corresponding Grignard compound.

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(1) Whitmore and Laughlin, THIS JOURNAL, **54**, 4462 (1932).

(2) Conant and Wheland, *ibid.*, **55**, 2499 (1933); Whitmore and Laughlin, *ibid.*, **56**, 1128 (1934); Whitmore and Wilson, *ibid.*, **56**, 1397 (1934).

(3) Kipping, *J. Chem. Soc.*, **57**, 532, 980 (1890); **63**, 452 (1892).

for an hour to ensure complete reaction. During this time the mass in the reaction flask became black and gummy.

The flask was allowed to cool to room temperature and then the excess of pentoxide was hydrolyzed by adding 30–60 cc. of water through the dropping funnel (air excluded). When hydrolysis was completed, the gaseous contents of the flask were swept into the carboy with 2 liters of dry nitrogen and the total gas analyzed for carbon dioxide and carbon monoxide.

The results are given in tabular form. The data for *n*-butyric, isobutyric, trimethylacetic and methyl-*t*-butylneopentylacetic acids, determined previously,[1,4] were included for purposes of comparison.

Acid	% CO	% CO_2
Primary		
n-Butyric	1.1	5.5
n-Caproic	0.9	6.3
Isocaproic	.8	.77
t-Butylacetic	.5	5.3
n-Caprylic	.14	9.9
Stearic	.0	13.0
Secondary		
Isobutyric	8.8	1.7
Diethylacetic	26.0	1.6
Methyl-*n*-propylacetic	21.7	1.6
Di-*n*-propylacetic	27.5	0.6
Diallylacetic	17.6	.5
Di-*n*-butylacetic	24.6	.5
Methylneopentylacetic	26.6	.8
Dineopentylacetic	30.0	.5
Tertiary		
Trimethylacetic	55.0	0.2
Ethyldimethylacetic	68.0	.0
Diethylmethylacetic	84.5	.6
Triethylacetic	77.5	.0
Methyl-*t*-butylneopentylacetic	90.0	.2

Summary

Fifteen aliphatic acids have been treated with phosphorus pentoxide at 150–160° and the yields of carbon monoxide and carbon dioxide recorded.

On the basis of the yield and composition of the gaseous products of this reaction a method of discriminating between acids having a primary, secondary or a tertiary alkyl group attached to the carboxyl carbon is proposed.

STATE COLLEGE, PENNA. RECEIVED JUNE 27, 1938

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(4) Whitmore and Laughlin, THIS JOURNAL, **56**, 1128 (1934).

[CONTRIBUTION NO. 384 FROM THE FOOD RESEARCH DIVISION, BUREAU OF CHEMISTRY AND SOILS, UNITED STATES DEPARTMENT OF AGRICULTURE, AT THE DEPARTMENT OF PHARMACOLOGY, STANFORD UNIVERSITY SCHOOL OF MEDICINE]

Studies on Phenothiazine. IV. Potentiometric Characterization of Thionol

BY FLOYD DEEDS AND C. W. EDDY

In a previous report[1] we have described a simple method for the conversion of phenothiazine to thionol (hydroxyleucophenthiazone). We have pointed out that thionol is a reversible oxidation–reduction system and reported the potential of the system under conditions when the ratio of the concentration of the oxidant to the concentration of the reductant was unity. This paper is concerned with details of the potentiometric studies of the system thionol–leuco thionol.

All oxidation–reduction potentials were measured with bare platinum electrodes, the saturated calomel half cell being used as the working standard of reference. Two platinum electrodes were used in each measurement and no potential reading was accepted as final until the two electrodes agreed within 0.1 mv. when the system was well poised. When the concentration of one component was low relative to that of the other, a discrepancy of not more than 0.5 mv. was considered indicative of equilibrium. Before using the electrodes they were cleaned in aqua regia, washed thoroughly, and their behavior checked in 0.001 *M* ferri–ferrocyanide solution in which the concentration of oxidant and reductant was equal. All potentials were measured with a Leeds and Northrup type K potentiometer placed in the grid circuit of a General Electric FP 54 tube as shown in the accompanying diagram.

Measurements were made in an air-bath at a temperature of 21–22°. Potentials were measured in an atmosphere of pure nitrogen which was passed over heated copper gauze to remove all traces of oxygen. The leuco base of thionol was prepared by reduction of thionol with platinized asbestos and a stream of hydrogen freed of oxygen by passage over heated platinized asbestos. When reduction was completed the solution of leuco base was freed of hydrogen with a stream of oxygen-free nitrogen. The stream of nitrogen also served to force the solution of leuco thionol through a sintered glass filter to remove the asbestos and to transfer the solution to an oxygen-free buret. Since the measured amount of solution of oxidant (10 cc.) placed in the titration vessel and the solution treated for reduction to the leuco base were aliquots of the same thionol solution, the ratio of oxidant to reductant after each addition of reductant from the buret was determined readily.

For the determination of the curve relating the potential to the ratio of reductant to oxidant a solution of thionol

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[1] F. DeEds and C. W. Eddy, THIS JOURNAL, **60**, 1446 (1938).

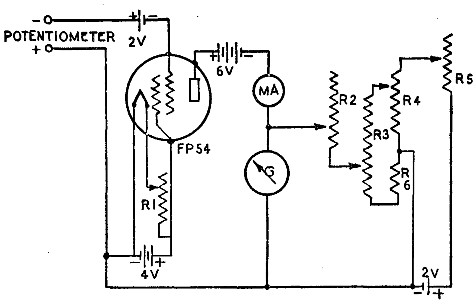

Fig. 1.—Diagram of static vacuum tube voltmeter: G, L. & N. galvanometer 0.025 m. a. per mm. scale division; R$_1$, 50-ohm rheostat; R$_2$, 200-ohm variable resistance; R$_3$, 700-ohm potentiometer; R$_4$, 400,000-ohm potentiometer; R$_5$, 500,000-ohm rheostat; R$_6$, 10,000-ohm resistance; MA, microammeter.

in a phosphate buffer of *p*H 6.57 was prepared by volatilizing a chloroform solution of thionol from the heated buffer during constant mechanical stirring. The concentration of thionol was approximately *M*/4600. The sigmoid curve showing the variation in potential from 0–75% reductant is given in Fig. 2, and the data obtained on the two platinum electrodes are given in Table I.

TABLE I

TITRATION OF 10 CC. OF BUFFERED THIONOL WITH BUFFERED LEUCO THIONOL [*p*H 6.57]

Leuco thionol, cc.	Reduction, %	E_h, obsd., v.	E_h, calcd., v.	Diff., v.
0.00		0.2462		
.50	4.76	.2277	0.2269	+0.0008
1.00	9.09	.2193	.2180	+ .0013
2.00	16.66	.2110	.2090	+ .0020
3.00	23.07	.2057	.2037	+ .0020
4.00	28.57	.2018	.2000	+ .0018
5.00	33.33	.1987	.1971	+ .0016
7.00	41.17	.1940	.1928	+ .0012
8.00	44.44	.1917	.1911	+ .0006
10.00	50.00	.1882		.0000
11.00	52.38	.1867	.1870	− .0003
13.00	56.52	.1839	.1843	− .0004
15.00	60.00	.1818	.1830	− .0012
20.00	66.66	.1762	.1793	− .0031
25.00	71.42	.1719	.1764	− .0045
30.00	75.00	.1677	.1740	− .0063
40.00	80.00	.1605	.1703	− .0098

It has been shown by Clark and Cohen[2] that at constant *p*H the relation of potential to the ratio of reductant to oxidant is given by the equation

$$E_h = E_0' - \frac{RT}{nF} \ln \frac{[Sr]}{[S_0]}$$

where E_h is the observed potential referred to the normal hydrogen electrode.

$$E' = E_h \text{ when } \frac{[Sr]\text{, the concentration of reductant}}{[S_0]\text{, the concentration of oxidant}} = 1$$

R is the gas constant.
T is the absolute temperature.
F is one faraday.
n is the number of electrons exchanged when one molecule of oxidant is changed to one molecule of reductant, or *vice versa*.

At a temperature of 21° this electrode equation may be given numerical form

$$E_h = E_0' - \frac{0.05833}{n} \log \frac{[Sr]}{[S_0]}$$

In the reports of Clark, including that on methylene blue, the value of n was found to be 2. Since thionol is very closely related to methylene blue, we have assumed $n = 2$ in our studies. Using this value we have solved the electrode equation for E_h for all values of the ratio $[Sr]/[S_0]$. Comparison of the calculated values with the observed is shown in Table I.

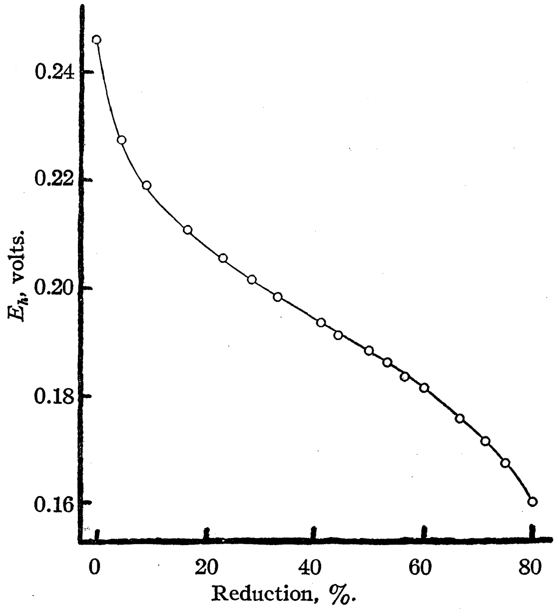

Fig. 2.—Relation between electrode potential and percentage reduction when *p*H is constant at 6.57: titration of thionol with leuco thionol at *p*H 6.57.

Comparison of the observed and calculated values for E_h shows that the difference is appreciable as the ratio $[Sr]/[S_0]$ becomes smaller or greater than unity. We do not believe that this error is due to the assumption that $n = 2$, but rather to the fact that leuco thionol is photosensitive. In other experiments to be reported in another paper, the agreement between observed and calculated E_h values was much closer, the maximum difference being 0.0011 v. in a single instance. The deviation reported does not invalidate the conclusion that thionol–leuco thionol is a reversible oxidation–reduction system nor does

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[2] W. M. Clark and B. Cohen, *U. S. Pub. Health Repts.*, **38**, 666 (1923).

it detract from the significance of the potential when $[Sr]/[S_o] = 1$ and the system is well poised.

The photosensitivity of the leuco thionol was demonstrated by the following experiment. A solution of thionol was reduced to the leuco base with platinized asbestos and hydrogen. A portion of the colorless solution was transferred to each of two oxygen-free Pyrex vessels. One of these was kept in the dark as a control for six days, and the other subjected to irradiation under a sun lamp. A pronounced red color developed in the irradiated vessel. At the end of six days the solution in the control vessel was colorless, but after two hours of exposure under the skylight in the laboratory a definite red coloration was noticeable. The rapidity with which the leuco thionol was converted to the red thionol under the influence of irradiation with the appropriate wave length of light suggested the feasibility of following the photosensitive action potentiometrically. At the same time advantage was taken of the opportunity to observe the effect of conversion of leuco thionol to thionol upon hydrogen ion concentration under strict anaerobic conditions.

A solution of thionol in distilled water was prepared and reduced to leuco thionol as previously described. The reduction vessel was then swept free of hydrogen with a stream of oxygen-free nitrogen which also served to force the solution of leuco thionol through a sintered glass filter into an oxygen-free vessel provided with a glass electrode for detecting potential changes due to alteration in *p*H and a bare platinum electrode for measuring of oxidation–reduction potential changes. The vessel was wrapped with black paper provided with a flap which could be raised for purposes of irradiation. The source of light for irradiation was an argon-filled glow lamp, which emits a wave length of light fairly efficient in converting leuco thionol to thionol. Throughout the course of the potential measurements the solution was stirred by a stream of oxygen-free nitrogen.

The time–potential curves of two such experiments are presented in Fig. 3. Since small increments of thionol induced by irradiation of leuco thionol produce large changes in the oxidation–reduction ratio, the irradiation in the early part of the experiment was limited to five-minute periods. Later when the rate of change of the ratio was small continuous irradiation was resorted to.

The change in potential registered by the bare platinum electrode is in harmony with the observation that as irradiation was prolonged the intensity of red color, due to increasing concentration of thionol, increased. The potential changes are due chiefly to a change in oxidation–reduction potential but not entirely so, for the solution was intentionally unbuffered to permit detection of *p*H changes. In the experiment at a temperature of 26° where the data are designated by circles the glass electrode registered a change of 64 mv., or somewhat more than one *p*H unit in the direction of increased acidity. At the same time the platinum electrode registered a change of 288.2 mv. The quantitative aspects of the experiment cannot be emphasized in the absence of exact knowledge of the molar concentration of the leuco thionol solution. The important points are the demonstration of the photosensitivity of leuco thionol, and the fact that conversion to thionol is accompanied by an increase in hydrogen ion concentration in unbuffered solutions. Clark, Cohen and Gibbs[3] have called attention to the photosensitivity of methylene white. These authors state: "We are not sure that the absence of visible coloration can be regarded as proof that there did not take place changes too small for positive identification but large enough to have a significant part in cumulative errors. Indeed, our titration curves often have the form which would result from the presence of very small percentages of oxidant in a solution treated as if it were completely reduced." Similarly, in the present study of thionol–leuco thionol inspection of Table I shows that the difference between the observed and calculated values of E_h might well be accounted for by the presence of small amounts of oxidant in the solution of reductant as the result of photodynamic action.

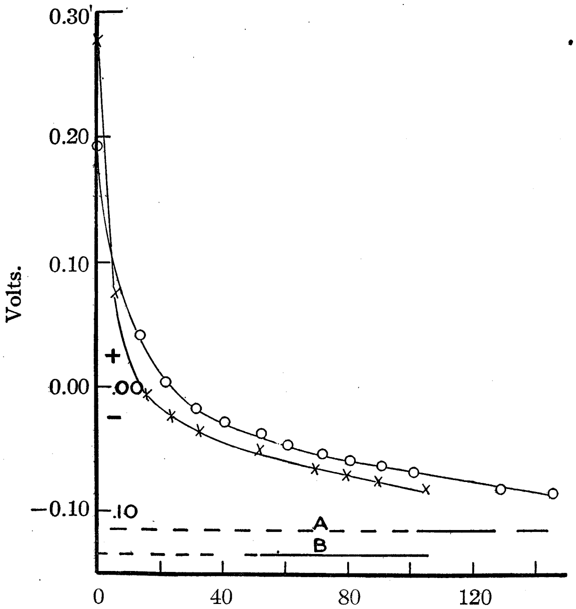

Fig. 3.—Time–potential curve showing change in oxidation–reduction potential due to photosensitivity of leuco thionol: A, length of dash indicates time of irradiation for experiment plotted with circles; B, length of dash indicates time of irradiation for experiment plotted with crosses.

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(3) W. M. Clark, B. Cohen and H. D. Gibbs, *U. S. Pub. Health Repts.*, **40**, 1131 (1925).

Because of the presence in the system thionol-leuco thionol of OH and NH groups, which may be capable of ionization, the system may be characterized further by a determination of the curve relating pH to the potential when $[Sr]/[S_0] = 1$. The curve was determined in the following manner. An approximately 0.2 M solution of phosphoric acid was titrated with an approximately 0.2 M solution of sodium hydroxide, and the change in pH followed with glass electrode measurements. The resulting curve relating pH to cc. of sodium hydroxide added was plotted on a large scale. From this curve the amount of sodium hydroxide required to bring a given amount of phosphoric acid to a given pH was determined. On the basis of such information a series of buffers was prepared and their exact pH values then determined with the hydrogen electrode. A chloroform solution of thionol was prepared by dissolving 0.1 g. in 100 cc. Five cc. of this chloroform solution was added slowly to 75 cc. of each buffer heated and mechanically stirred until all the chloroform was volatilized. The buffer solution of thionol was cooled and made up to 100 cc. with additional buffer. This procedure did not modify the pH of the buffers except in the case of the two most alkaline buffers used. The exact pH of these two buffer solutions of thionol was determined by duplicating the procedure in the absence of thionol and measuring their values with the hydrogen electrode. These buffers originally had values of 8.89 and 10.69 which were shifted to 8.70 and 9.90, respectively. A portion of each thionol solution was reduced as previously stated, and, under anaerobic conditions, 10 cc. of the reductant added to 10 cc. of the oxidant. The potentials were measured as before using two bare platinum electrodes. Final readings were recorded when the two electrodes were in substantial agreement. The data are given in Table II and presented in the form of a curve in Fig. 4.

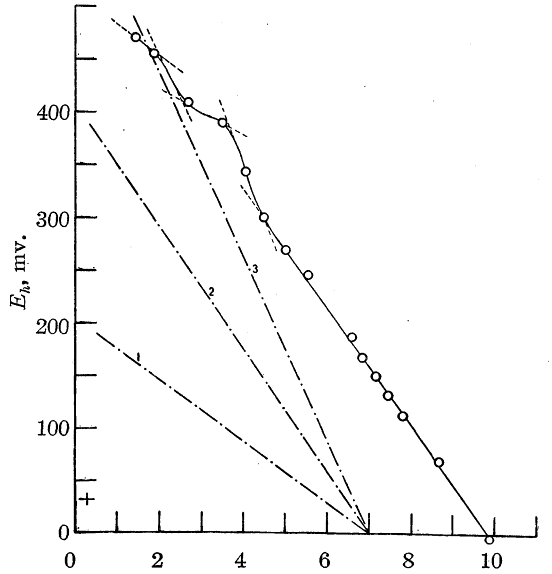


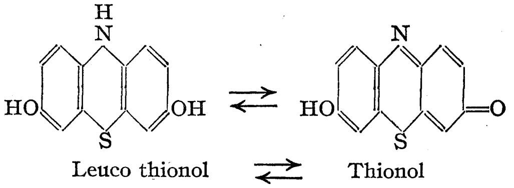
Fig. 4.—Relation between electrode potential and pH when total oxidant and total reductant are equimolecular: thionol, E_0' *vs.* pH.

TABLE II

VARIATION OF E_0' WITH pH, $T = 21°$

pH	$E_h = E_0'$, v.	
	Electrode 1	Electrode 2
1.42	+0.4712	+0.4725
1.85	+ .4573	+ .4579
2.65	+ .4105	+ .4105
3.47	+ .3917	+ .3917
4.03	+ .3450	+ .3450
4.47	+ .3021	+ .3023
4.99	+ .2710	+ .2710
5.53	+ .2482	+ .2477
6.57	+ .1882	+ .1882
6.84	+ .1687	+ .1687
7.14	+ .1515	+ .1515
7.44	+ .1333	+ .1333
7.78	+ .1132	+ .1132
8.70	+ .0700	+ .0700
9.90	− .0041	− .0038

The deflections of the curve in Fig. 4, in terms of ionizable groups, may be interpreted as follows. Each point on the curve designated by a circle represents the potential of a mixture of oxidant and reductant in equal concentrations at a definite pH value. As will be seen from the formula for leuco thionol there are two hydroxyl groups and an NH (3) capable of ionization. The formula for the oxidant shows that there is one hydroxyl group capable of ionization and a double bonded oxygen which may ionize if hydration occurs. For convenience of interpretation the broken lines 1, 2 and 3 radiating from a pH value of 7 in Fig. 4 represent slopes or $-\mathrm{d}E/\mathrm{d}p\mathrm{H}$ values of 29.2, 58.3 and 87.5 mv. per unit of pH, respectively, at 21°. It will be seen that between pH



values of 4.47 and 9.90 the observed potentials fall on a line, the slope of which approximates that of line 2. Between *p*H values 4.47 and 3.47 the potentials fall on a line approximately parallel to line 3. The potentials at *p*H values of 3.47 and 2.65 fall on a line approximately parallel to line 1. From *p*H 2.65 to 1.85 the slope of the curve once more approximates that of line 3. The dotted line extensions of the straight line portions of the curve give intersections corresponding to *pK* values of 3.16×10^{-3}, 2.24×10^{-4}, and 3.39×10^{-5}.

As has been shown in the papers by Clark and co-workers, deflections in the E_0':*p*H curve denote the presence of detectable dissociations either in the oxidant or reductant, or in both. To determine whether a particular dissociation occurs in the oxidant or reductant these authors made use of a principle which Hall, Preisler and Cohen[4] stated as follows: "In the E_0':*p*H curve, the bend with a convexity in the direction of negative e. m. f. always corresponds to a dissociation in the reductant; and, vice versa, a deflection with a concavity toward negative e. m. f. denotes a dissociation in the oxidant. That is, when the change in slope (defining slope as $-\mathrm{d}E/\mathrm{d}p\mathrm{H}$) is negative, the dissociation causing the change is assignable to the reductant; when the change is positive, the corresponding dissociation belongs to the oxidant." Therefore at *p*H 4.47 the dissociation is assignable to the reductant and likely due to the NH group. At *p*H 3.65 the change in slope involves two ionizable groups in the oxidant. Since the change in slope occurs suddenly both groups have the same or very nearly the same dissociation constant. At *p*H 2.5 the change in slope involves the two ionizable groups in the reductant. Here again the change in slope occurs suddenly, suggesting that both groups have the same dissociation constant, as might be expected from the symmetrical placement of the hydroxyl groups in the molecule.

Development of an equation relating the potential of the fixed ratio of thionol to leuco thionol with change in hydrogen ion concentration failed to yield a set of calculated E_0' values showing satisfactory agreement with the observed values. This failure to correlate the physical chemical findings with the structural formulas for thionol and leuco thionol might be attributed to inaccurate *pK* values traceable to errors caused by the photosensitivity of the leuco thionol. However, the attempt to explain the deflections of the E_0':*p*H curve requires the assumption that both hydroxyl groups of the reductant have the same *pK* value, and that the double bonded oxygen of the oxidant undergoes hydration and subsequent ionization. Therefore an explanation for the deflections of the E_0':*p*H curve was sought on some basis other than ionizable groups.

The close relationship of thionol to α-phenazine and pyocyanine studied by Michaelis[5] and Friedheim and Michaelis[6] suggested the possibility that the system thionol–leuco thionol might be characterized by the existence of a semiquinone in the *p*H range from 0 to 4. Evidence for the existence of a semiquinone should be obtainable both colorimetrically and electrometrically.

Colorimetric tests for the presence of a semiquinone were made at *p*H values of 1.00, 1.21, 1.47, 1.85, 3.06, and higher. At *p*H values of 3.06 and higher reduction of thionol with stannous chloride, titanium trichloride, or platinized asbestos and hydrogen gas gave a change of color which proceeded directly from red to colorless, and was reversed directly to red by the addition of hydrogen peroxide. At the lower *p*H values of 1.00, 1.21, 1.47, and 1.85 reduction by the above methods gave a color change from red through purple to blue, light green and finally colorless. Reoxidation with hydrogen peroxide reversed the order of color change. The more acid the reaction the more pronounced the intermediate colors and the greater the ease with which partial reduction characterized by the intermediate colors could be maintained over a period of time. These observations are in conformity with the behavior to be expected in the presence of a semiquinone.

Attempts to confirm this colorimetric evidence with potential measurements have failed, a major difficulty being the instability of the potentials in the extreme acid range.

Nevertheless, the difficulties encountered in seeking an explanation of the deflections in the E_0':*p*H curve do not invalidate the curve, which was found to be reproducible, nor do they detract from the usefulness of the curve as discussed in a succeeding paper.[7]

It is of interest to compare the potential of this

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[4] W. L. Hall, P. W. Preisler and B. Cohen, *ibid.*, Supplement No. 71 (1928).

[5] L. Michaelis, *J. Biol. Chem.*, **92**, 211 (1931).

[6] E. Friedheim and L. Michaelis, *ibid.*, **91**, 355 (1931).

[7] F. DeEds, C. W. Eddy and J. O. Thomas, *J. Pharmacol. Exptl. Therapeutics*, in press.

thiazine, thionol, with the values given by Clark[3] for two other thiazines, Lauth's violet and methylene blue. At *p*H 7 the E_0' for thionol is 0.158, for methylene blue 0.011, and for Lauth's violet 0.062 at *p*H 6.967, and 0.045 at *p*H 7.517, which gives 0.061 at *p*H 7 by interpolation. These values place thionol appreciably closer to the oxygen electrode than the other two thiazines, being about midway between 1-naphthol-2-sulfonate-indophenol and 2,6-dichlorophenol-indo-*o*-cresol. This is in agreement with the observation that spontaneous oxidation of leuco thionol exposed to air occurs more slowly than is the case with methylene white at the same *p*H. Likewise, the reducing power of a given sample of urine is more readily demonstrated with thionol than with methylene blue.

Summary and Conclusions

1. The potentiometric characteristics of thionol have been determined.
2. Colorimetric evidence for the existence of a semiquinone has been submitted.
3. The three thiazines, methylene blue, Lauth's violet and thionol have been compared with regard to their position on the oxidation–reduction scale.

SAN FRANCISCO, CALIF. RECEIVED JUNE 15, 1938

[COMMUNICATION NO. 675 FROM THE KODAK RESEARCH LABORATORIES]

Oxidation Processes. XII.[1] The Autoxidation of Hydroquinone and of the Mono-, Di- and Trimethylhydroquinones

BY T. H. JAMES, J. M. SNELL AND A. WEISSBERGER

A study of the primary reaction in the autoxidation of hydroquinone is severely complicated by the presence of secondary reactions involving nuclear hydrogens. In order to avoid such complications, we investigated the autoxidation of durohydroquinone.[1] In this compound, the four nuclear hydrogens of hydroquinone are replaced by methyl groups. This prevents secondary reactions, which complicate the hydroquinone autoxidation. Hydrogen peroxide and duroquinone could be shown to be the reaction products, and it was further observed that duroquinone exerts a marked catalytic effect upon the reaction. In order to apply these results to the autoxidation of hydroquinone, we have investigated the autoxidation of the intermediate members of the homologous series, namely, toluhydroquinone, the three xylohydroquinones, and ψ-cumohydroquinone (trimethylhydroquinone) and we have extended previous observations on the oxidation of hydroquinone itself.

Materials[2]

***p*-Benzoquinone**, twice sublimed; m. p. 116°.

Hydroquinone, recrystallized from benzene, or three times from water slightly acidified with hydrochloric acid; m. p. 172°. No kinetical difference between these samples and the original material was detected.

Toluquinone, recrystallized from ligroin (b. p. 70–90°), and sublimed at 100°.

Toluhydroquinone, recrystallized from toluene; m. p. 127–128°.

Dimethylquinones were made from the corresponding xylidines, as follows.

The xylidine (61 g., 0.5 mole) was dissolved in 200 ml. of concentrated sulfuric acid and 1000 ml. of water, and a solution of 60 g. of sodium bichromate in 150 ml. of water was slowly run in, with stirring, at a temperature below 10°. The mixture was left standing in a cool place for twenty-four hours, and then 80 g. of bichromate in 240 ml. of water was added in the same manner. After another twenty-four hours, the precipitate was collected, washed with water, and the filtrate extracted with ether. The combined precipitate and ether solution was steam distilled. The distillate was half saturated with sodium chloride, cooled, the quinone collected, and the filtrate extracted with ether. The combined precipitate and ether extract residue was recrystallized from petroleum ether or ligroin and sublimed.

2,5-Dimethylquinone.—Yield 40%; m. p. 124–124.5°.

2,5-Dimethylhydroquinone was prepared according to Conant and Fieser[3]; recrystallized from ethanol, yield 46%; m. p. 210–212°.

2,6-Dimethylquinone.—Yield 10%; m. p. 72–73°.

2,6-Dimethylhydroquinone was prepared analogously to the 2,5-dimethylhydroquinone;[2] recrystallized from water (Norite), yield 60%; m. p. 153–154°.

2,3-Dimethylquinone.—From 3-amino-1,2-dimethylbenzene; yield 8%; m. p. 59–60°.

2,3-Dimethylhydroquinone.—The solution of the quinone (0.6 g.) in 25 ml. of 25% ethanol was reduced at 0° with sulfur dioxide for one hour; yield 17%; m. p. 224–225°.

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[1] Part XI: T. H. James and A. Weissberger, THIS JOURNAL, **60**, 98 (1938).

[2] All materials the origin of which is not stated are Eastman grades.

[3] Conant and Fieser, THIS JOURNAL, **45**, 2199 (1923).

3-Amino-1,2-dimethylbenzene.[4]—Forty-eight grams of 3-nitro-1,2-dimethylbenzene was reduced with 56 g. of iron powder in 150 ml. of water containing 10 ml. of concentrated hydrochloric acid, followed by stirring and heating on the steam-bath for three hours, followed by steam distillation: yield 70%; b. p. 109–111° at 22 mm. The acetyl derivative was recrystallized from toluene; m. p. 133–134°.

3-Nitro-1,2-dimethylbenzene.—*o*-Xylene (100 g.) was run slowly into a mixture of 600 g. of fuming nitric acid (sp. gr. 1.52) and 200 g. of glacial acetic acid, with rapid stirring, at 20–25°. Stirring was continued at this temperature for one hour, the mixture poured into water, extracted with benzene and washed.

The isomers were separated by fractional distillation through a 17-cm. Widmer column at 12 mm. Fractions were collected at intervals of 3–4°, between 113 and 126°, cooled in an ice–salt bath and crystals collected. The filtrates were refractionated; yield of 3-nitro-1,2-dimethylbenzene, b. p. (12 mm.) 113–116°, 48 g., 37%; 4-nitro-1,2-dimethylbenzene, b. p. (12 mm.) 125–126°, 35 g., 27%.

2,3,5-Trimethylquinone (ψ-Cumoquinone).—The method of L. I. Smith[5] was not used because no pseudocumidine of satisfactory quality was available. Instead, isoduridine was oxidized with elimination of the methyl group[6] in the para position to the amino group. Isoduridine was prepared from isodurene through the monobromo derivative.[7]

Bromoisodurene was prepared closely following the procedure for the bromination of durene[4]; yield, 61 g., 77%; b. p. 148–149° at 30 mm.

Nitrobromoisodurene.—Sixty-one grams of bromoisodurene in 280 g. of chloroform was added to 226 g. of concentrated sulfuric acid, cooled to 0°, and, with rapid stirring, a mixture of 22 g. of fuming nitric acid (sp. gr. 1.52) and 55 g. of chloroform was run in from a dropping funnel, at about 5°. After stirring had been continued for five minutes, 500 ml. of chloroform was added to dissolve the solid reaction product. The chloroform layer was separated and washed with sodium carbonate and with water, and the chloroform distilled off until the residue (about 125 cc.) started to crystallize. An equal volume of methyl alcohol was added, the mixture was cooled in ice and the crystals were filtered off and washed with methyl alcohol; yield, 49 g., 66%; m. p. 168–173°. Calcd. for $C_{10}H_{12}NO_2Br$: N, 5.44; Br, 31.0. Found: N, 5.35; Br, 31.4.

2-Amino-1,3,4,5-tetramethylbenzene (Isoduridine).—The method employed by Willstätter and Kubli[4] for the preparation of duridine did not eliminate the halogen from the isodurene derivative. To crude nitrobromoisodurene (49 g.) in 600 ml. of boiling glacial acetic acid and 100 ml. of concentrated hydrochloric acid was added, with boiling and stirring, 50 g. of zinc dust in small portions. When the reaction slowed down, an additional 50 g. of zinc dust and 50 ml. of hydrochloric acid were added, and boiling and stirring continued for one hour. The solution was cooled, the crystals filtered off, the filtrate concentrated until crystals formed (about 150 ml.) diluted with water and hydrochloric acid and the resulting precipitate combined with the main product.

The crude bromoisodurene hydrochloride was debrominated with a solution of 160 g. of potassium hydroxide in 375 ml. of water and 600 ml. of 95% ethyl alcohol, with 125 g. of zinc dust and 1 g. of mercuric chloride with boiling and stirring overnight. This was usually sufficient for reduction, but in one case it was necessary to continue boiling for an additional twenty-four hours, adding more alkali (100 g.), water (250 ml.), and zinc (50 g.), with 1 g. of mercuric chloride.

The reaction mixture was steam distilled and the distillate, which contained insoluble oil, was collected. The amine was salted out and extracted with ether. The yield of isoduridine, b. p. (16 mm.) 134–136°, was 18.5 g., 66%, based on the nitrobromoisodurene. The acetyl derivative was recrystallized from alcohol, m. p. 219–220°.[8]

2,3,5-Trimethylquinone (ψ-Cumoquinone).—Isoduridine (18.5 g.) in 1500 ml. of water and 170 ml. of concentrated sulfuric acid was oxidized below 5° with 44 g. of sodium bichromate crystals in 150 ml. of water, added slowly from a dropping funnel with rapid stirring. After one hour, the mixture was kept in a cool place for twenty hours. Then an additional 34 g. of sodium bichromate in 80 ml. of water was added as before at 5° and the mixture stirred at room temperature for twenty-four hours. It was worked up as mentioned; yield of pure quinone 1.27 g., m. p. 28.5–29.5°.

2,3,5-Trimethylhydroquinone (ψ-Cumohydroquinone) was prepared analogously to the 2,5-dimethylhydroquinone,[3] using the residue of the petroleum ether filtrate from the quinone purification. About 3 g. was warmed on the steam-bath with a solution of 5 g. of stannous chloride in 45 ml. of 2 *N* hydrochloric acid. The colorless solution was cooled, filtered, and the product recrystallized from 30% ethanol and from toluene; colorless needles, m. p. 171–173°, 1.86 g.; combined yields of pure quinone and hydroquinone, 17%, based on the isoduridine.

Tetraethylquinone.—We are indebted to Professor L. I. Smith, of the University of Minnesota, for a sample of this material; m. p. 58–59°.

Tetraethylhydroquinone.—The quinone (1.14 g.) was reduced in alcohol (15 ml.) with stannous chloride (25 g.) in concentrated hydrochloric acid (6 ml.) on the steam-bath. Water (30 ml.) was added to the colorless solution, cooled, and the crystals washed with a little water; recrystallized from toluene; yield 0.8 g., 67%; m. p. 170.5–171.5°.

Durohydroquinone Monomethyl Ether.—Durohydroquinone (3.2 g.) was heated in a nitrogen-filled sealed tube with 4.6 g. of methyl iodide and 50 cc. of absolute ethanol, in which 0.46 g. of sodium had been dissolved, for two hours in a steam-bath. The contents were poured into 100 ml. of water, filtered, and the precipitate extracted with 75 ml. of boiling benzene. The insoluble material consisted of 0.8 g. of durohydroquinone. The residue of the solution was stirred under nitrogen with 50 cc. of warm (2 *N*) sodium hydroxide, and cooled and filtered. Hydrochloric acid precipitated colorless crystals which were recrystallized from ligroin: yield, 0.7 g., 19.5%; m. p. 115–116°. The alkali-insoluble material consisted of durohydroquinone dimethyl ether and a little duroquinone.

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.3; H, 8.9. Found: C, 73.1; H, 8.8.

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(4) Noelting and Forel, *Ber.*, **18**, 2611 (1885).

(5) Smith, THIS JOURNAL, **56**, 472 (1934).

(6) Noelting and Baumann, *Ber.*, **18**, 1152 (1885).

(7) Willstätter and Kubli, *ibid.*, **42**, 4157 (1909).

(8) Noelting and Baumann give 210–211°, *ibid.*, **18**, 1149 (1885).

TABLE I

Chemical	Amount, mmol.	Solution	Time of oxidation, min.	Ml. O_2 abs.	Ml. O_2 ev.	$\frac{100\ O_2\ \text{ev.}}{O_2\ \text{abs.}}$
Hydroquinone	0.5	Water	50	5.3	0.9	17
	.5	Water[a]	46	5.2	3.1	60
Toluhydroquinone	.25	20% ethanol	50	4.8	2.4	50
o-Xylohydroquinone	.25	20% ethanol-water	16	3.6	3.3	92
	.25		60	5.6	4.6	82
m-Xylohydroquinone	.25	20% ethanol		5.8	3.8	66
p-Xylohydroquinone	.25	20% ethanol	50	6.0	4.3	70
ψ-Cumohydroquinone	.125	20% ethanol	30	2.9	2.5	86

[a] Oxidation in presence of 0.2 g. of 2-methylbenzothiazole-metho-*p*-toluenesulfonate.

The other materials were identified with or prepared according to the same methods as those described in the preceding paper of this series.[1]

Reaction Products

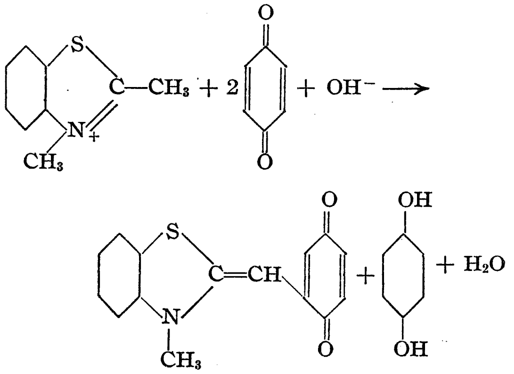
Tests for hydrogen peroxide in the autoxidized solutions were positive. With the xylohydroquinones and ψ-cumohydroquinone, the procedure described for durohydroquinone was used. This method failed in the case of hydroquinone itself, supposedly because the reaction between peroxide and quinone[9] was too rapid. The test was therefore carried out after hydroquinone (0.11 g.) had been oxidized in aqueous borate buffered solutions (50 ml.) containing 2-methylbenzothiazole-metho-*p*-toluenesulfonate (0.3 g.). The latter acted as a quinone acceptor (see formula (1)), forming a water-insoluble reaction product, and the filtered solution gave a positive peroxide test (perchromate reaction).

Peroxide was determined quantitatively by measuring the oxygen evolved when aqueous 0.1 *M* potassium permanganate solution was added in excess to the autoxidized solutions buffered at *p*H 7.6–8.0. Acidulated permanganate could not be used in many cases, since carbon dioxide was formed in the reaction between the acid permanganate and the quinone. Control experiments showed that neutral permanganate did not cause evolution of gas on addition to the buffered (*p*H 7.8–8.0) solutions of hydroquinone, quinone, or hydroxyquinone.

A representative example of the results of the peroxide tests is given in Table I.

ψ-Cumoquinone and the *xyloquinones* were extracted from the oxidized solutions of the corresponding methylhydroquinones with benzene and identified by melting point determinations.

Proof that *quinone* was formed in the autoxidation of *hydroquinone* itself was obtained by making use of the reaction of quinone with 2-methylbenzothiazole-metho-*p*-toluenesulfonate. According to our colleague Dr. L. G. S. Brooker,[10] these substances react in alkaline solution with formation of [(3-methyl-2(3)-benzothiazolylidene)-methyl]-*p*-benzoquinone


(1)

This is in agreement with our observation that the addition of 2-methylbenzothiazole-metho-*p*-toluenesulfonate to an alkaline solution of hydroquinone increases the oxygen absorption through the regeneration of hydroquinone. In the case of ψ-cumohydroquinone, the total oxygen absorption increased from 1 to 2 moles. The experiments were carried out in aqueous borate buffered solutions (50 cc.) at *p*H 8.2.

(1) Hydroquinone (0.25 mmol.), oxidized in the presence of an excess of 2-methylbenzothiazole-metho-*p*-toluenesulfonate (1.0 mmol.), yielded a blue-violet precipitate.

(2) Quinone, added to a buffered 2-methylbenzothiazole-metho-*p*-toluenesulfonate solution, yielded a blue-violet precipitate.

(3) Hydroquinone which had absorbed 1 mole of oxygen yielded, on addition of methylbenzothiazole-metho-*p*-toluenesulfonate, a green solution without a precipitate.

(4) Quinone, which had stood for some time in the alkaline solution in the presence of excess hydrogen peroxide, yielded, on addition of methylbenzothiazole-metho-*p*-toluenesulfonate, a green solution without a precipitate.

(5) Hydroxyquinone, added to the methylbenzothiazole-metho-*p*-toluenesulfonate solution, yielded a green solution of the same appearance.

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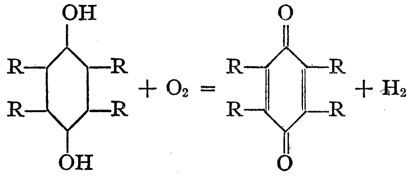
(9) Reinders and Dingemans, *Rec. trav. chim.*, **53**, 209 (1934).

(10) Private communication; see also F. Kröhnke and H. Schmeiss, *Ber.*, **70**, 1728 (1937).

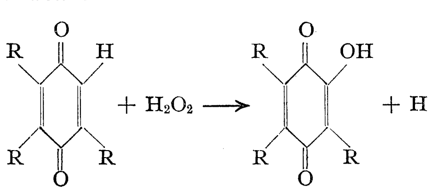
Precipitates (1) and (2) were filtered off, washed, dried, and dissolved in ethanol. The absorption spectra of the resulting solutions were measured.[11] They were identical, having a maximum absorption at 620 mμ and a minimum at 420–460 mμ. A solution prepared from hydroxyquinone and methylbenzothiazole-metho-*p*-toluenesulfonate gave an entirely different spectrum with a maximum absorption at 450–460 mμ, a small minimum at 540–550 mμ, and another slight maximum at 620–630 mμ.

The analogy between hydroquinone and its homologs makes it unlikely that the *formation* of quinone and hydrogen peroxide with the former is due to an interference of the methylbenzothiazole-*p*-toluenesulfonate. These experiments therefore generalize the results reported in the preceding paper and show that the *first products in the autoxidation of hydroquinone and its homologs are the corresponding quinones and hydrogen peroxide.* The general equation for the first step in the autoxidation of hydroquinone and its mono-, di, tri-, and tetramethyl homologs can thus be written



(2)

where R represents alkyl groups or hydrogen. The experiments (3–5) show further that quinone reacts with the hydrogen peroxide with formation of hydroxyquinone. It appears safe to generalize that if at least one of the R's is hydrogen, the further reaction



(3)

(3) takes place, and polymerization of the hydroxyquinone provides for the formation of "humic acids."[12]

Kinetics

The apparatus and general procedure employed in the study of the kinetics were those described in the preceding papers of this series. All experiments, unless otherwise specified, were carried out at 20.00 ± 0.03°, and with a total solution volume of 50.0 ml. The aqueous buffers were prepared from 25.0 ml. of 0.15 *M* borax plus 0.8 *M* boric acid, or 25.0 ml. of 0.5 *M* disodium phosphate and 0.2 *M* monosodium phosphate. Because of the slight solubility of some of the compounds in water, 20% ethanol solutions were used in some of the experiments. In these experiments the buffer was prepared from 10.0 ml. of 0.2 *M* disodium phosphate and sufficient 0.1 *M* hydrochloric acid to give the desired *p*H value. Measurements of *p*H were made on the completed solutions by means of a calibrated glass electrode.

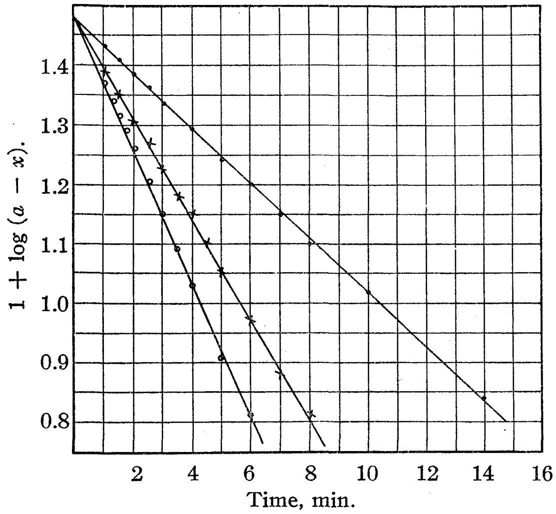


Fig. 1.—Oxidation of xylohydroquinone phosphate buffer, *p*H 7.75: —·—·— *o*-xylohydroquinone; —x—x— *p*-xylohydroquinone; —o—o— *m*-xylohydroquinone.

The data were analyzed as follows: log $(a - x)$ was plotted against t for each set of data (a is the theoretical oxygen uptake if 1 mole of oxygen is absorbed per mole of the hydroquinone; x, the volume absorbed at time t (minutes)). The slope of the resulting curve was then determined for various values of x. If the rate of oxygen uptake is governed by a first-order equation, the slope will be independent of x, and its value, k_{10}, multiplied by 2.3, will give the first-order reaction constant (k). In the case of the xylohydroquinones, k_{10} was constant throughout the greater part of the reaction (Fig. 1). The autoxidation of toluhydroquinone and of hydroquinone likewise follows the first-order equation for oxygen uptakes to 50–70% mole. Beyond this, compli-

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[11] We are indebted to Mr. E. Richardson for the absorption measurements.

[12] Eller and Koch, *Ber.*, **53**, 1469 (1920).

cations arise which are due to further oxidation of the primary reaction products.

The use of the theoretical oxygen uptake a is suggested by the results with durohydroquinone in combination with the observations about the reaction products reported above. After 1 mole of oxygen has been absorbed, further uptake is much slower with ψ-cumohydroquinone and the dimethyl hydroquinones so that a break in the ml. O_2/t curve occurs. (For *m*-xylohydroquinone, the character of this subsequent reaction was substantiated by the fact that a mixture of equal molecular portions of the quinone and of hydrogen peroxide absorbed oxygen at the same rate as the oxidized solution of the hydroquinone at the same *p*H.) The oxygen values where the breaks in the ml. O_2/t curves occur check well with the theoretical values. This is shown in Table II.

Table II

Total Amounts of Oxygen Absorbed (N. T. P.)

Compound	O_2 Absorbed	Theoretical
ψ-Cumohydroquinone	5.45	5.6
p-Xylohydroquinone	2.75	2.8
m-Xylohydroquinone	2.7	2.8
o-Xylohydroquinone	2.7	2.8

The differences between observed and theoretical values obviously are caused by the action of hydrogen peroxide on the hydroquinones. With toluhydroquinone and with hydroquinone itself, the difference in the reaction rates between the initial and the subsequent reaction is less pronounced. It is sufficient, however, as mentioned above, to produce a straight line on our plots for about 70 and 50%, respectively, of an oxygen uptake of one mole.

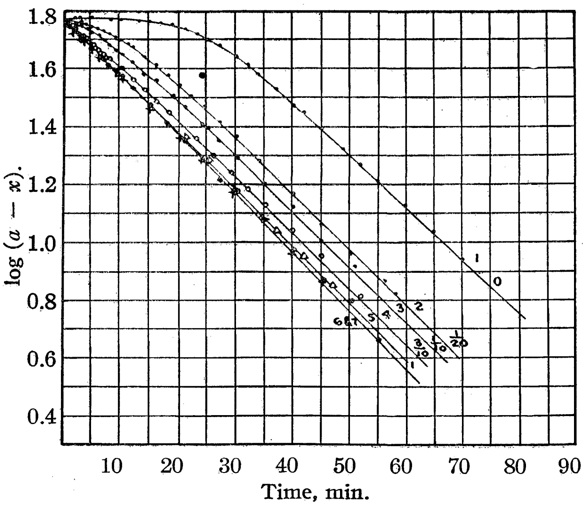

Fig. 2.—Oxidation of ψ-cumohydroquinone. Effect of added ψ-cumoquinone on $^1/_4\,M$ mol. of ψ-cumohydroquinone: Curve 1, no added ψ-cumoquinone; Curve 2, $^1/_{80}\,M$ mol.; Curve 3, $^1/_{40}\,M$ mol.; —○—○— 4, $^3/_{40}\,M$ mol.; —Δ—Δ— 5, $^3/_{20}\,M$ mol.; —·—·— 6, $^1/_4\,M$ mol.; —x—x— 7, $^1/_2\,M$ mol.

For **the autoxidation of cumohydroquinone,** which will be considered first, 20% ethanol was used as solvent because of the low solubility of the material. A phosphate buffer was employed for most of the work, although check runs were made in a buffered borate solution. The buffers used kept the *p*H of the solutions constant within 0.02 unit throughout the entire course of the oxidation.

The reaction exhibits a pronounced *induction period*, as shown in curve 1 of Fig. 2. The slope of the curve attains a maximum, and this constant value is maintained throughout the remainder of the oxidation, in conformity with the kinetics of a first-order reaction.

The induction period does not appear to be due to the presence of an inhibitor. Successive purifications of the ψ-cumohydroquinone gave no significant change, and identical oxidation curves were obtained when the ethanol normally used was replaced by a sample obtained from an entirely different source and purified according to the method of Danner and Hildebrand.[13] Moreover, the induction period persisted if the solutions were prepared, mixed, and stored for one hour in an atmosphere of pure nitrogen before oxidation was begun.

The induction period is shortened by the addition of ψ-cumoquinone to the reaction mixture at the start of the oxidation, and it is eliminated completely if about 0.15 mmol. of *ψ-cumoquinone* is added to the 0.25 mmol. of ψ-cumohydroquinone used in these experiments Thus, it appears that the ψ-cumoquinone formed during the autoxidation acts as a catalyst. Other quinones, phenosafranin and indophenol, also eliminate the induction period.

In Fig. 3, values of k_{10} obtained from curve 1 of Fig. 2 are plotted against the corresponding amounts of oxygen absorbed. In the same figure, the initial values of k_{10} obtained from curves 2–7 (Fig. 2) are plotted against the amounts of ψ-cumoquinone added. The close similarity of the curves confirms the fact that the governing factor in the acceleration is the ψ-cumoquinone. The slight difference between the two curves is

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(13) Danner and Hildebrand, This Journal, **44**, 2827 (1922).

explained by the action of the hydrogen peroxide upon the ψ-cumoquinone in the experiments recorded by curve 2.

The dependence of k_{10} upon the initial amounts of ψ-cumohydroquinone present is given in Table III.

TABLE III

DEPENDENCE OF k_{10} UPON THE INITIAL CONCENTRATION OF ψ-CUMOHYDROQUINONE; PHOSPHATE BUFFER, *p*H 7.40

Total volume of solution	50.0	50.0	100.0	50.0
Mmol. ψ-cumohydroquinone	0.50	0.25	0.25	0.125
Mmol. O_2 absorbed	k_{10}	k_{10}	k_{10}	k_{10}
0.005	0.0014	0.0014	..	0.0012
.010	.0028	.0026	0.0012	.0025
.015	.0042	.0044	.0020	.0044
.020	.0057	.0058	.0026	.0052
.040	.0102	.0100	.0046	.0110
.060	.0135	.0133	.0065	.0145
.080	.0170	.0170	.0094	.0172
.100	.0175	.0176	.0110	.0175
.200	.0175	.0176	.0170	..

With a constant volume of solution, the induction period disappears in all cases after the *same amount* of oxygen has been absorbed. The elimination of the induction period does not depend upon the ratio of ψ-cumoquinone to ψ-cumohydroquinone, but it depends either on the absolute amount or on the concentration of the ψ-cumoquinone. The data obtained when a total volume of 100 ml. was employed instead of the customary 50 ml. showed that the *concentration* of the ψ-cumoquinone is the essential factor.

The observation that the quinone eliminates the induction period in the autoxidation of ψ-cumohydroquinone is analogous to our results with durohydroquinone.[1] At variance with the case of durohydroquinone, however, an initial velocity which might be interpreted as that of the uncatalyzed reaction, is not indicated by the curves in Fig. 3 which go through the origin. A more important difference consists in the dependence of the reaction velocity on the concentration of the quinone. With durohydroquinone, the reaction rate rises linearly with the concentration of the quinone; *with ψ-cumohydroquinone, however, the catalytic influence drops with increasing concentration of the quinone until a further addition becomes irrelevant* (see Fig. 3).

Duroquinone, upon standing in an alkaline solution, gradually loses its power of catalyzing the autoxidation of durohydroquinone. The rate of this loss, which is probably due to self condensation of the quinone, is too low to be of significance in the experiments recorded in the previous paper.[1] In order to determine whether a similar, but more rapid, loss occurring in the case of ψ-cumoquinone could account for the fact that its catalytic effect reaches a limiting value, experiments were carried out where the mixture of ψ-cumohydroquinone and ψ-cumoquinone was allowed to stand for varying times in an atmosphere of pure nitrogen before oxidation was started. Some of the results are recorded in Table IV.

TABLE IV

1/8 mmol. ψ-Cumohydroquinone, 1/8 mmol. ψ-Cumoquinone

Time elapsing before start of oxidation	Volume oxygen absorbed, 20°, 760 mm.				
Oxidation time, min.	15 sec.	30 min.	74 min.	75 min.[a]	0[b]
2	0.40	0.40	0.40	0.40	..
4	.80	.75	.70	.70	0.03
7	1.22	1.10	1.00	1.13	.10
12	1.80	1.52	1.45	1.70	.40
15	2.02	1.80	1.68	1.95	.68
20	2.35	2.10	2.00	2.30	1.13
75	2.95	2.95	2.95	..	2.90

[a] Quinone alone stood in alkaline solution. [b] No quinone added.

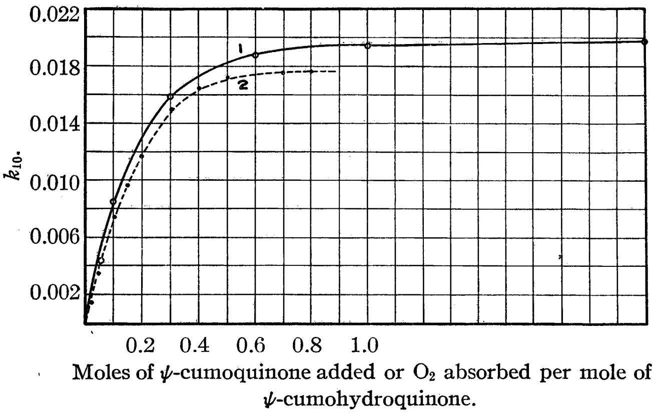

Fig. 3.—Quinone catalysis of the autoxidation of ψ-cumohydroquinone: —○—○— 1, ψ-cumoquinone added; — —•— —•— — 2, from oxidation curve.

Only very little loss occurred in the catalytic activity of ψ-cumoquinone which stood in alkaline solution for the length of time required for completion of the normal autoxidation of ψ-cumohydroquinone. The peculiar behavior of ψ-cumoquinone is therefore due to other causes.

The dependence of the maximum value of k_{10} upon the pH of the solution is shown in Table V. The maximum velocity of the reaction varies with the square of the hydroxyl-ion concentration, and plot of log k_{10} against *p*H gives a straight line of slope 2.0.

Table V

Dependence of k_{10} upon the Hydroxyl-Ion Concentration; 0.25 Mmol. ψ-Cumohydroquinone

*p*H	k_{10}	2+log k_{10}
7.84	0.140	1.15
7.64	.056	0.75
7.48	.0252	.40
7.40	.0180	.26

The *p*H values given in the first column were measured by means of a glass electrode placed in solutions of the buffer which contained all the ingredients of the solution used in oxidation measurements except the ψ-cumohydroquinone and alcohol. The latter was replaced by an amount of water sufficient to give the same total volume. The *p*H values may therefore be wrong in their absolute amounts, but their gradation is right, since no significant effect on the oxidation velocity is observed when successive amounts of water are replaced by alcohol in experiments with hydroquinone, using the same phosphate buffer as that employed in the present case (see page 2091).

Table VI shows the *variation of k_{10} with the partial pressure of oxygen* for three *p*H values.

Table VI

0.25 Mmol. ψ-Cumohydroquinone. Dependence of k_{10} upon Partial Pressure of Oxygen

O_2 abs./ψ-Cumohydroquinone	*p*H 7.84		*p*H 7.64		*p*H 7.40	
	O_2	Air	O_2	Air	O_2	Air
0.02	0.016	0.013	0.0030	0.0026	0.0014	0.0012
.05	.034	.022	.0090	.0075	.0035	.0024
.10	.060	.028	.0175	.0107	.0070	.0040
.15	.076	.032	.0250	.013	.0095	.0046
.20	.090	.034	.0325	.0144	.0118	.0052
.30	.110	.035	.0425	.0135	.0150	.0048
.40	.126	.035	.0480	.0135	.0163	.0046
.50	.130	.035	.0520	.0135	.0172	.0046

Although the accuracy with which k_{10} can be determined in the early stages of the oxidation is low, the data show that the dependence of the rate of autoxidation upon the oxygen pressure increases as the reaction progresses. It did not quite attain a direct proportionality, however, in these experiments.

The autoxidation of the xylohydroquinones, toluhydroquinone, and hydroquinone itself follows the first-order law with respect to the concentration of the dihydroxy compound. This is demonstrated both by the straight line obtained in a log $(a-x)$, t plot and by the independence of the reaction constant upon the initial concentration of the hydroquinone over tenfold variations in concentration. The autoxidation rate varies linearly with the concentration of the oxygen (Table VII).

Table VII

Dependence of k upon Partial Pressure of Oxygen

Borax buffer, 0.25 mmol. hydroquinone, 20% ethanol

	o-Xylohydroquinone	*m*-Xylohydroquinone	*p*-Xylohydroquinone
Pure oxygen	0.024	0.045	0.042
Air	.0051	.0095	.0089
Ratio	4.71	4.73	4.72

The dependence of the rate of autoxidation upon the hydroxyl-ion concentration of the solution has been a subject of some dispute. Euler and Brunius, and Reinders and Dingemans observed a dependence upon the square of the hydroxyl-ion concentration. La Mer and Rideal found a relationship between the first power of the reaction rate and the 1.5 power of the hydroxyl-ion concentration. St.-Maxen claimed a first-power relationship.[1] We have found a dependence upon the square of the hydroxyl-ion concentration for the following materials: durohydroquinone, ψ-cumohydroquinone, *o*-, *m*-, and *p*-xylohydroquinone, toluhydroquinone, and hydroquinone.

These data are summarized in Fig. 4, in which log k is plotted against *p*H. The slope of each line is very nearly 2.0. All data given are for aqueous solutions. Two series of buffers were used, phosphate and borate. The ionic strengths were kept as nearly as possible constant in each series. Measurements of *p*H were made on the complete solutions with a glass electrode. The fact that, in every case, the slope measured is slightly less than 2.0 can be understood on the assumption that the singly charged hydroquinonate ion is also oxidizing, but at a much lower rate than the doubly charged ion.

This assumption gains support from the fact that monomethyl ethers undergo autoxidation, albeit at a very low rate, as exemplified in Table VIII; this is parallel with the autoxidation of benzoin methyl ether.[14]

Table VIII

Autoxidation of Monomethyl Ethers

Monomethyl ethers of	Amount mmol.	1.0 *M* KOH ml.	Rate, ml./min.	Solution
Durohydroquinone	$^1/_8$	2.0	0.003	45 cc. 30% ethanol
Hydroquinone	½	0.4	.002	50 cc. water
Hydroquinone	½	4.0	.002	50 cc. water

The addition of hydrogen peroxide at the start of the oxidation has no measurable effect upon

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(14) James and Weissberger, This Journal, **59**, 2040 (1937).

the initial rate of autoxidation. As the oxidation proceeds, however, the oxidation of the hydroquinone by the peroxide becomes appreciable and the total oxygen uptake decreases. This action of the hydrogen peroxide accounts for the fact that the observed "end" volumes of oxygen absorbed (see page 2089) are somewhat less than 1 mole in the cases of durohydroquinone, ψ-cumohydroquinone, and the xylohydroquinones. With toluhydroquinone and hydroquinone itself, the subsequent reactions prevent the determination of "end" volumes.

An apparent slight induction period was noted in several experiments in the autoxidation of the xylohydroquinones, but in no case was the existence of such an induction period established beyond doubt. *No catalysis was observed when the corresponding quinone was added to the oxidation mixture at the start of the experiments with these compounds.*

Benzoquinone itself autoxidizes at a rate which, at the maximum, is roughly 0.01 of that of hydroquinone under the conditions of our experiments. It therefore can be neglected here.

Effect of Alcohol upon the Rate of Oxidation.—Inasmuch as the low solubility of ψ-cumoquinone and the xylohydroquinones made it necessary to use alcohol–water mixtures as solvent, it was desirable to know to what extent the change of solvent influenced the rate of oxidation. A borate buffer could not be used for this purpose, since the rapid reaction between borate and alcohol affects the hydroxyl-ion concentration of the solution. A phosphate buffer of the following composition was therefore employed: 0.2 M Na_2HPO_4, 10 ml.; 0.067 M NaH_2PO_4, 1 ml.: total volume of solution, 50 ml. The results obtained are recorded in Table IX.

TABLE IX

EFFECT OF ETHANOL ON THE RATE OF OXIDATION OF HYDROQUINONE

Ethanol, %	k_{10}	$k_{10}/[O_2]$
0	0.0172	14.6
1	.0176	14.9
5	.0173	15.0
20	.0162	15.2

In the last column, a correction has been made for the change in solubility of oxygen in the ethanol solution. The variation in the oxidation rate observed scarcely exceeds the limits of experimental error.

Effect of Substitution.—From the data given in Fig. 4, the relative rates of oxidation of hydroquinone and its mono- and dimethyl homologs can be calculated. The figures obtained are given in Table X (aqueous solution, phosphate buffer). In addition, the maximum rate of oxidation of ψ-cumohydroquinone relative to hydroquinone in 20% ethanol solution is added. No corresponding value can be stated, of course, for durohydroquinone, for which the rate of the uncatalyzed reaction is given for comparison.

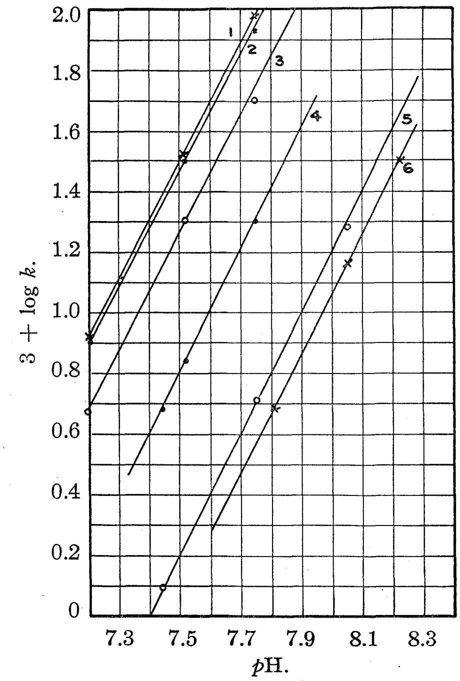

Fig. 4.—pH dependency: 1, m-xylohydroquinone, phosphate buffer, slope 1.95; 2, p-xylohydroquinone, phosphate buffer, slope 1.96; 3, o-xylohydroquinone, phosphate buffer, slope 1.96; 4, toluhydroquinone, phosphate buffer, slope 1.97; 5, hydroquinone, phosphate buffer, slope 1.98; 6, hydroquinone, borate buffer, slope 1.98.

TABLE X

Compound	Relative rate of oxidation
Hydroquinone	1.00
Toluhydroquinone	3.9
o-Xylohydroquinone	10.5
m-Xylohydroquinone	18.2
p-Xylohydroquinone	17.0
ψ-Cumohydroquinone (max. value 20% ethanol)	31.0
Durohydroquinone (uncatalyzed reaction)	1.00

It appears that substitution by methyl groups raises the rate of autoxidation. This can be due to an increase in the dissociation constants, or to other factors. The reaction rate of durohydroquinone may be low by reason of steric hindrance. It might be, however, that the correct value for comparison would be that of a quinone-catalyzed reaction of this compound. This raises the question of whether the values given for hydroquinone, toluhydroquinone, and the xylohydroquinones belong to the uncatalyzed reaction or are maximum values of quinone-catalyzed reactions to be compared with the value given for ψ-cumohydroquinone.

Discussion of Results

The qualitative and quantitative analyses of the *autoxidation products* of hydroquinone, toluhydroquinone, the xylohydroquinones and ψ-cumohydroquinone show that the reaction products are analogous to those of durohydroquinone, *i. e.*, the corresponding quinones and hydrogen peroxide. The *kinetics* of the oxidation are identical with regard to the dependency of the reaction rate on the hydroxyl-ion concentration. This is in the *p*H range 7.2–8.2 very nearly proportional to the square of the hydroxyl-ion concentration. This reveals that the reaction is controlled by the concentration of the doubly charged ion. A slight deviation from the second power may be due to some reactivity of the monovalent ion.

Durohydroquinone, on the one hand, however, and *hydroquinone, toluhydroquinone* and the *xylohydroquinones*, on the other, differ essentially with regard to the directly observed existence of an induction period, and with regard to the catalytic influence of quinones which may be added or formed during the reaction. The autoxidation of *durohydroquinone* is catalyzed by duroquinone, whereas the addition of quinones to *hydroquinone* and its lower homologs is without effect on their autoxidation velocities. The rate of the uncatalyzed oxidation of *durohydroquinone*—under the conditions of our experiments—is proportional to the oxygen concentration, whereas the quinone-catalyzed reaction is unaffected by the latter. The autoxidation rate of *hydroquinone, toluhydroquinone* and the *xylohydroquinones* is proportional to the oxygen concentration.

The autoxidation of *ψ-cumohydroquinone* furnishes the transition between the two types. It shows an induction period and a strong catalysis by small amounts of quinone. (The rate of the uncatalyzed reaction in the absence of quinone could not be determined.) The reaction rate, however, does not increase linearly with the concentration of the quinone, but increases at a slower and slower rate until a further addition of the quinone remains without effect. The oxygen dependency in the region of the strong quinone catalysis resembles that of the quinone-catalyzed autoxidation of *durohydroquinone*. The oxygen dependency in the region where further addition of quinone is without effect corresponds to the behavior of *hydroquinone* and its lower homologs. It may be suggested, therefore, that our observations with durohydroquinone correspond to that autoxidation of ψ-cumoquinone which is represented by the lower portion of the curve in Fig. 3, whereas the autoxidation which we observe with hydroquinone and its lower homologs corresponds to the type of reaction represented by the section of the curve with slope zero. In other words, we suggest that *the autoxidation of the lower members of the series is catalyzed by traces of the quinone too small to be ascertained.* This assumption fits in with the observations recorded in Table X. It offers further an interesting aspect of various photographic problems, of which only the following will be mentioned here.

The catalytic effect of the oxidation products may be significant for the photographic behavior of developers, since this catalysis enhances the differentiation between parts of the emulsion where reaction has started and those which are unattacked.

The quinone catalysis throws new light on the problem of the induction period of hydroquinone developers, since, as far as has been tested, those substances (quinone, phenosafranin, indophenol) which cut down the latter,[15] also remove the induction period in the autoxidation processes.

Sodium sulfite inhibits the autoxidation of hydroquinone and its methyl homologs with the exception of durohydroquinone, *i. e.*, it acts in those cases where it can form hydroquinone sulfonates with the quinone and not in the case where this action is impossible. It may be, therefore, that the inhibiting action of sodium sulfite is due to the removal of the catalyzing quinone.

The probable mechanism of the quinone catalysis of the autoxidation of durohydroquinone has been suggested in the preceding paper. A semiquinone is formed by the interaction of the divalent ion and the quinone, and this semiquinone is oxidized rapidly. If the formation of the semiquinone is the rate-controlling reaction and the subsequent interaction with oxygen proceeds smoothly at a comparatively high rate, the kinet-

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[15] Frötschner, *Phot. Ind.*, **35**, 801 (1937).

ics observed with durohydroquinone are those to be expected.

The fact that, with ψ-cumohydroquinone, the quinone catalysis reaches a saturation value is open to various interpretations and further work must, therefore, be done on the investigation of this problem.

Summary

1. Hydroquinone, toluhydroquinone, the three xylohydroquinones, and ψ-cumohydroquinone are oxidized in alkaline solution by molecular oxygen with the formation of hydrogen peroxide and the corresponding quinones. This is followed by a reaction between the hydrogen peroxide and the quinones.

2. The high rate of the reaction between benzoquinone and hydrogen peroxide made it necessary to use an acceptor (2-methylbenzothiazole-metho-*p*-toluenesulfonate) for the quinone to protect the hydrogen peroxide and to make it available for analysis.

3. The quinones were, in general, identified after isolation. In the case of the autoxidation of hydroquinone, the condensation product with the acceptor was identified spectroscopically and through it the quinone.

4. The formation of hydroxyquinone by reaction of quinone and hydrogen peroxide in the autoxidation of hydroquinone was confirmed by spectroscopic analysis of the condensation products with 2-methylbenzothiazole-metho-*p*-toluenesulfonate.

5. Very close dependency of the autoxidation rate of hydroquinone and its homologs upon the square of the hydroxyl-ion concentration in the *p*H range 7.2 to 8.2 shows that the oxidation involves mainly the doubly charged hydroquinone anion.

6. A slight deviation from the second power may be due to a comparatively slow oxidation of the monovalent ion, suggested by the autoxidation of monomethyl ethers of hydroquinone and of durohydroquinone.

7. The oxidation of ψ-cumohydroquinone is strongly catalyzed by small amounts of quinones. This catalytic action approaches a maximum.

8. In the maximum, the autoxidation rate is proportional to the concentration of the ψ-cumohydroquinone.

9. The rate of reaction of ψ-cumohydroquinone is independent of the oxygen concentration with low amounts of quinone as a catalyst. As the quinone catalysis reaches its maximum, the reaction rate becomes almost proportional to the oxygen concentration.

10. In the presence of small amounts of the quinone, the kinetics of the autoxidation of ψ-cumohydroquinone resemble those of the quinone-catalyzed durohydroquinone reaction; as the quinone concentration increases, the kinetics pass over into those of the autoxidation of the lower members of the hydroquinone series.

11. The rates of oxidation of hydroquinone, toluhydroquinone, and the xylohydroquinones vary directly with the concentrations of oxygen and of the hydroquinones.

12. No quinone catalysis was detected in the autoxidation of hydroquinone, toluhydroquinone, and the xylohydroquinones. However, on the basis of the transition which ψ-cumohydroquinone affords between the kinetics of the oxidation of durohydroquinone and the lower members of the series, it is suggested that quinone catalysis exists for the latter, and that the maximum value is reached at quinone concentrations sufficiently low to escape detection.

13. Sodium sulfite inhibits the autoxidation of hydroquinone, toluhydroquinone, the xylohydroquinones, and ψ-cumohydroquinone.

14. Suggestions are made for the interpretation of the inhibition of the oxidation of hydroquinones by sulfite and of the action and the nature of the induction period of photographic developers.

ROCHESTER, N. Y.

RECEIVED MAY 18, 1938

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE POLYTECHNIC]

The Rate and Mechanism of Hydrolysis of Benzhydryl Chloride in Acetone

BY WILLIAM TAYLOR

Three current mechanisms which have been adopted to interpret the first-order reaction between an alkyl halide and a relatively high concentration of water, alcohol, or acetic acid are those of (a) Hughes and Ingold[1] who assume partially for secondary and completely for tertiary, a slow *unimolecular* ionization of the halide as the rate-determining stage followed by a rapid reaction of the organic cation with a solvent molecule; (b) Taylor,[2] and Olson and Halford,[3] who assume for alkyl halides generally a one-stage *bimolecular* reaction involving the simultaneous addition and dissociation of the reactants, according to the ideas of London,[4] Polanyi,[5] and Olson,[6] and (c) Hammett,[7] who assumes a *polymolecular* reaction, which depends essentially upon the affinity of alcohol or water molecules for halide ion, reaction taking place within something of the nature of a solvation complex.

Taylor[2c] showed that the reaction of *t*-butyl bromide with water of low concentrations in acetone at 50° was kinetically of the second order and that therefore the mechanism of hydrolysis could not be unimolecular but is presumably bimolecular. Olson and Halford,[3] at about the same time, showed that the hydrolysis and alcoholysis of *t*-butyl chloride in aqueous methanol are both second-order reactions, if the fugacities of the reactants (as measured by their vapor pressures) and not their concentrations are employed in calculating the rate constants. These results appear to remove the possibility of mechanism (a). There remain (b) and (c).

Mechanism (c) was based partially on Hammett and co-workers[7] finding that at 25° when benzhydryl chloride (or α-phenylethyl chloride) and small concentrations of water (or of ethyl alcohol) are both dissolved in acetone, the rate of reaction is very low, whereas at the same temperature in dry or wet ethyl alcoholic solution the rate of reaction is high. The purpose of the present investigation was to find whether or not this state of affairs obtains with benzhydryl chloride at 50°. In brief it does not, since there is a measurable rate of hydrolysis of benzhydryl chloride in acetone containing 1, 2, 5 or 10 g. of water per 100 cc. of solution at this temperature. (These solutions are referred to as containing 1, 2%, etc., of water.) Thus, to this extent, the basis of the polymolecular mechanism (c) is weakened. Positive evidence in support of mechanism (b) was sought along the lines of the previous work with *t*-butyl bromide.[2c] Since, when either 2 or 10% aqueous acetone was used, no *s*-tetraphenyldimethyl ether could be detected in the reaction products (compare Ward[8]) but only benzhydrol, the sole reaction between benzhydryl chloride and water which occurs under these conditions can be represented

$$\mathrm{Ph_2CHCl} + \mathrm{H_2O} \underset{k_2}{\overset{k_1}{\rightleftarrows}} \mathrm{Ph_2CHOH} + \mathrm{HCl}$$

and is reversible. Figure 1 shows the dependence of the rate of hydrolysis upon the concentration of water even at the lowest water concentrations.

However, as with the hydrolysis of *t*-butyl bromide in acetone, a slow reaction persisted beyond the equilibrium position due again presumably to the formation of mesityl oxide and other acetone condensation products in the presence of hydrogen chloride. This caused the elimination of water and hence the continued hydrolysis of benzhydryl chloride. The slow increase in acidity thus produced was approximately directly proportional to time for a considerable time interval and thus the equilibrium position for any one system was determined by extrapolation of the straight-line portion of the curve back to the x-axis. From the equilibrium constants $K = k_1/k_2$ the equilibrium positions (n) were calculated,[2c] n being the equilibrium value of x. As in the case of *t*-butyl bromide there is close agreement between the calculated values of n and those observed for the forward reaction (Table I).

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[1] Gleave, Hughes and Ingold, *J. Chem. Soc.*, 236 (1935).

[2] Taylor, *ibid.*, (a) 344, (b) 992, (c) 1853, (d) 1962 (1937).

[3] Olson and Halford, THIS JOURNAL, **59**, 2644 (1937).

[4] London, *Z. Elektrochem.*, **35**, 552 (1929).

[5] Meer and Polanyi, *Z. physik. Chem.*, **B19**, 164 (1932); Bergmann, Polanyi and Szabo, *ibid.*, **B20**, 161 (1933).

[6] Olson, *J. Chem. Phys.*, **1**, 418 (1933); Olson and Voge, THIS JOURNAL, **56**, 1690 (1934).

[7] Steigman and Hammett, *ibid.*, **59**, 2536 (1937); Farinacci and Hammett, *ibid.*, **59**, 2542 (1937).

[8] Ward, *J. Chem. Soc.*, 2285 (1927).

TABLE I

Showing the practical identity of observed and calculated values of n, the equilibrium position, it being assumed that both reactions are kinetically of the same order.

$[H_2O]$	$[Ph_2CHCl]$	2nd order k_1	2nd order k_2	K	n, obsd.	n, calcd.
0.5556	0.0974	0.00230	0.658	0.00350	0.0125	0.0127
1.1111	.1052	.00415	.556	.00746	.0270	.0255
2.7778	.1064	.0171	.127	.134	.0842	.0860
5.5556	.1170	.0636	.0186	3.42	.1140	.1157

The catalytic effect of water on the hydrolysis reaction, as shown by the increase in the values of the second-order coefficient k_1 with a rise in the water concentration, is ascribed[9] to the dissociating effect of water on itself in acetone solution *i. e.*

$$(H_2O)_n \underset{COMe_2}{\overset{H_2O}{\rightleftarrows}} nH_2O$$

the associated form being assumed to be relatively unreactive, compared with the simple form, toward the alkyl halide. Constant values of k_1, therefore, could not be expected since these were calculated using ordinary water concentrations, owing to lack of information regarding the active mass of the simple form.

From the evidence presented, then, the view is taken that the hydrolysis of benzhydryl chloride in acetone is a second-order reaction and that the mechanism is bimolecular.

Experimental

Materials.—"AnalaR" *acetone*, refluxed for ten hours over potassium permanganate and calcium oxide, boiled at 56–56.5°. *Benzhydryl chloride*, prepared by the method of Farinacci and Hammett, had b. p. 190–191° (47 mm.) (Calcd.: Cl, 17.53. Found: Cl, 17.54). *Benzhydrol* (commercial) recrystallized from alcohol melted at 68°.

Rate Measurements.—These were made at 50°. The procedure was identical with that used for *t*-butyl bromide.[2c] As with this compound a dark color developed in the reaction liquids of lower water concentrations. The values of k for the forward reaction were calculated for an irreversible second-order reaction from $k_1 = [2.303/t(a - b)] \log_{10} b(a - x)/a(b - x)$, t being the time in hours, and a and b the concentrations (in g. moles/liter) of water and benzhydryl chloride, respectively.

The value of k_1 employed in the calculation of the equilibrium constant $K = k_1/k_2$, where k_2 is the second-order rate constant for the reverse reaction, was that extrapolated at $t = 0$ from the plot of k_1 against t. Typical data for the forward reaction in 1 and 5% aqueous acetone are given in Table II.

TABLE II

TYPICAL KINETIC DATA OF THE FORWARD REACTION IN ACETONE AT 50°

1%			5%		
$a = 0.5556$		$b = 0.0974$	$a = 2.7778$		$b = 0.1064$
t	x	k_1	t	x	k_1
22.4	0.0030	0.00251	1.65	0.0080	0.0170
70.5	.0072	.00197	3.0	.0140	.0169
100	.0095	.00187	5.35	.0224	.0159
146	.0118	.00161	8.43	.0320	.0154
237	.0170	.00148	11.53	.0420	.0158
334	.0210	.00133	23.5	.0660	.0150
450	.0228	.00102	29.5	.0740	.0147
671	.0250	.00082	48	.0830	..
837	.0266	..	218	.0842	..
1006	.0280	..			

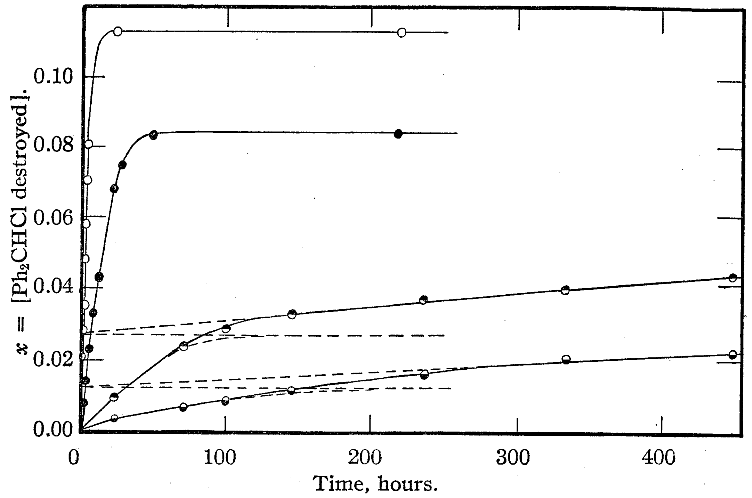

Fig. 1.—Effect of water on the rate of hydrolysis of benzhydryl chloride in acetone. Water "Percentages": ◒, 1; ◓, 2; ●, 5; ○, 10.

The determination of the second-order rate coefficients of the reverse reaction in acetone, containing initially the same concentrations of water as for the forward reaction, was complicated by the rapid removal of hydrogen chloride by the acetone. These constants were therefore calculated from the equation

$$[HCl \text{ removed by } Ph_2CHOH]/t = k_2[Ph_2CHOH][HCl]$$

t being the time in hours, and all concentrations being in g. moles/liter, the two latter being mean concentrations for any one time interval. The amount of water formed by the condensation of acetone under the influence of hydrogen chloride

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(9) Taylor, *J. Chem. Soc.*, 840 (1938).

was so great as not only greatly to retard the formation of benzhydryl chloride in all except the initial stages, but ultimately even to cause the slow hydrolysis of that already formed, as shown by the rapid decrease in acidity giving place to a slow increase and this in spite of the continuous and simultaneous removal of hydrogen chloride by the acetone. Hence the equilibrium positions could not be observed for this reverse reaction. Typical data for the reverse reaction in 1 and 5% aqueous acetone are shown in Table III.

TABLE III

TYPICAL KINETIC DATA OF THE REVERSE REACTION IN ACETONE AT 50°

In column C is shown the rate of removal of hydrogen chloride by 1 and 5% aqueous acetone containing no benzhydrol.

	[HCl]	C [HCl]	[HCl removed by Ph_2CHOH]	k_2
		1%		
$[Ph_2CHOH] = 0.0929$, $[HCl] = 0.1090$, $[H_2O] = 0.5556$				
0	0.1090	0.1090	0.0000	.
0.11	.0860	.0870	.0010	.
0.65	.0816	.0850	.0034	0.685
2.8	.0716	.0840	.0124	.601
3.38	.0682	.0835	.0153	.648
3.8	.0660	.0830	.0170	.697
19.5	.0510	.0780	.0270	..
68.5	.0354	.0635	.0281	..
125	.0340	.0550	.0210	..
332	.0374	..	..	..
		5%		
$[Ph_2CHOH] = 0.0929$, $[HCl] = 0.1160$, $[H_2O] = 2.7778$				
0	0.1160	0.1160	0.0000	..
1.43	.1105	.1125	.0020	0.140
18.3	.0940	.1120	.0180	.114
67	.0920	.1100	.0180	..
163	.0930	.1080	.0150	..
331	.0936	..	..	..

Examination of Reaction Products.—These were examined in 2 and 10% aqueous acetone. Benzhydryl chloride (2.2 g.) in aqueous acetone (100 cc.) was kept at 50° for two hundred and forty and twenty-four hours, respectively; excess anhydrous sodium carbonate was added to remove water and acid. After filtering, and distilling the acetone, approximately 3 cc. of brown oil containing some crystalline solid was obtained; (1) the product had a faint odor of mesityl oxide but no 2,4-dinitrophenylhydrazone could be obtained from it; (2) that from 2% aqueous acetone contained considerable unchanged benzhydryl chloride (Found: Cl, 5.6) whereas that from 10% aqueous acetone contained negligible chlorine; (3) to 2 cc. of the product in each case was added ethyl alcohol (2 cc.) but there was no solid residue and hence no *s*-tetraphenyldimethyl ether had been formed.[8] Addition of water to the alcoholic solution gave benzhydrol only (m. p. and mixed m. p. with authentic specimen).

Summary

The hydrolysis of benzhydryl chloride and the action of hydrogen chloride on benzhydrol have been studied kinetically in acetone containing low concentrations of water. The hydrolysis reaction, under these conditions, yields benzhydrol and hydrogen chloride as the only reaction products. Assuming that both are second-order reactions, there is close agreement between the calculated equilibrium positions and those observed for the hydrolysis reaction, with different initial concentrations of water. This agreement indicates that the assumption is correct; and thus for both reactions a bimolecular mechanism is presumed.

LONDON, ENGLAND RECEIVED MAY 25, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

Methyl Bromide. The Heat Capacity, Vapor Pressure, Heats of Transition, Fusion and Vaporization. Entropy and Density of the Gas

BY CLARK J. EGAN AND J. D. KEMP[1]

Entropies obtained from low temperature calorimetric data with the aid of the third law of thermodynamics recently have been employed to estimate the magnitudes of the potential barriers hindering the free rotation of methyl groups in hydrocarbon molecules.[2-4] In these calculations the height of the barrier has been determined as that necessary to bring the spectroscopic entropy value into agreement with the experimental entropy value. This procedure assumes that the entropies of these molecules containing methyl groups can be obtained correctly from low temperature experimental measurements.

Because the presence of similar barriers in the methyl halides is quite unlikely, the entropies of these compounds may be obtained readily from spectroscopic and molecular structure data. Calorimetric investigations of these halides offer then an opportunity to compare the experimental and spectroscopic entropies in order to confirm further the above assumption.

Purification of Methyl Bromide.—Methyl bromide from a cylinder was condensed in the calorimeter without purification. From the change of the melting point with percentage melted, the amount of impurity was estimated to be 0.1 mole per cent. Another portion of material from the cylinder was distilled twice in a vacuum-jacketed fractionating column, the middle one-third being collected each time. This procedure did not appreciably decrease the amount of impurity. The end portions of the first distillation were then bubbled through 36 N sulfuric acid and passed through a tube containing phosphorus pentoxide. This treatment removed practically all of the impurities and this portion was used for the heat capacity measurements. Additional material purified in the same manner was used in the measurements of the heats of vaporization. From the constancy of the melting point and the course of the premelting heat capacity curve, the amount of liquid-soluble solid-insoluble impurity was estimated to be 0.001 mole per cent.

Apparatus and Measurement of Amount. The Density of Methyl Bromide Gas at 1 Atmosphere and 298.10°K.—The calorimetric apparatus and procedure have been described previously.[5,6] Gold Calorimeter IV was used for the investigation.

After the heat capacity measurements the amount of material in the calorimeter, 2.0610 moles, was condensed and weighed in a previously evacuated bulb. The methyl bromide used for the heats of vaporization was measured volumetrically by means of the 5-liter measuring bulb described by Giauque and Johnston.[7] The gas was then condensed and weighed in order to determine its density under these conditions. At P near 1 atm. and T near 298°K. the molal volume V was found to be

$$V = 82.06T/P - (569 \pm 5) \text{ cc.} \qquad (1)$$

This, combined with the molecular weight of CH_3Br, 94.950,[8] gives 3.9739 ± 0.0009 grams/liter for the density of methyl bromide gas at $P = 1$ atm. and $T = 298.10$°K.

Vapor Pressure.—The procedure used in the measurements of vapor pressure has been described previously.[5] The observations have been represented by the equation

liquid methyl bromide, 203 to 278°K.

$$(0°\text{C.} = 273.10°\text{K.})\ \log_{10} P(\text{Int. cm. Hg}) = -(1541.437/T) + 8.49274 - 0.00424740T + 1.7599 \times 10^{-6}T^2 \qquad (2)$$

A summary of the measurements is presented in Table I. The calculated and observed values are compared in columns 3 and 4. The temperatures have been given to 0.001° because of the high relative accuracy. The absolute temperatures may be in error by several hundredths of a degree. Column 5 contains values of the rate of change of pressure with temperature calculated from equation (2).

The boiling point calculated from equation (2)

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[1] Present address: Standard Oil Company of California, Richmond, Calif.

[2] Kemp and Pitzer, *J. Chem. Phys.*, **4**, 749 (1936); THIS JOURNAL, **59**, 276 (1937).

[3] Pitzer, *J. Chem. Phys.*, **5**, 473 (1937).

[4] Kemp and Egan, THIS JOURNAL, **60**, 1521 (1938).

[5] Kemp and Giauque, *ibid.*, **59**, 79 (1937).

[6] Giauque and Egan, *J. Chem. Phys.*, **5**, 45 (1937).

[7] Giauque and Johnston, THIS JOURNAL, **51**, 2300 (1929).

[8] Int. At. Wt. Committee, *ibid.*, **60**, 737 (1938).

TABLE I

VAPOR PRESSURE OF LIQUID METHYL BROMIDE

0°C. = 273.10°K.

T, °K.	P	$P_{\text{obsd.}} - P_{\text{calcd.}}$	$T_{\text{obsd.}} - T_{\text{calcd.}}$	dP/dT, cm./deg.
203.186	1.298	−0.008	+0.083	0.101
211.245	2.383	.000	.000	.170
220.247	4.418	+ .013	− .045	.288
228.834	7.534	+ .002	− .005	.451
236.484	11.709	− .002	+ .002	.651
243.098	16.739	+ .012	− .014	.875
250.633	24.467	+ .001	.000	1.193
258.008	34.644	− .002	.000	1.581
258.016	34.664	+ .006	− .004	1.582
265.020	47.250	.000	.000	2.027
270.801	60.178	− .003	+ .001	2.456
274.232	69.097	+ .009	− .003	2.739
277.682	79.056	.000	.000	3.044

is 276.66 ± 0.05°K. (3.56 ± 0.05°C.). This is higher than the value 276.33°K. from the vapor pressure equation of Hsia.[9]

Melting Point.—The melting point was observed with various percentages of the methyl bromide melted. The results are summarized in Table II.

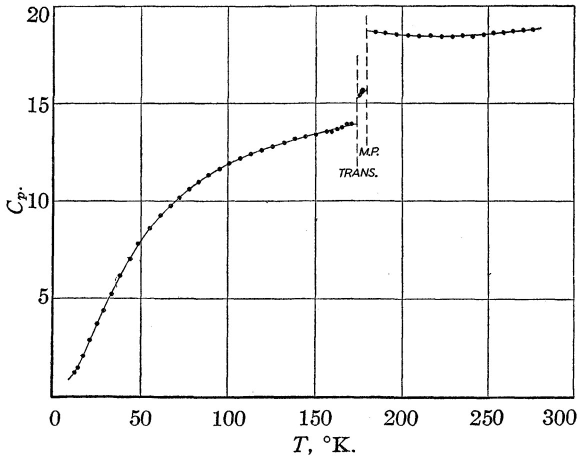

Fig. 1.—Heat capacity of methyl bromide in cal./deg. per mole.

Transition Point.—Methyl bromide undergoes a transition in the solid about 5.7° below the melting point. Determinations of the transition temperature are summarized in Table III. During these observations equilibrium was established very slowly. A region of indifference exists in which the methyl bromide may be superheated or supercooled 0.1–0.2° above or below 173.75°K.

Heat Capacity of Methyl Bromide.—No previous measurements of the heat capacity were found in the literature. The present observations are tabulated in Table IV. One calorie was taken equal to 4.1833 International joules. A graphical representation of the data is shown in Fig. 1. Table V contains values of the heat capacity taken from a smooth curve through the data.

TABLE II

MELTING POINT OF METHYL BROMIDE

0°C. = 273.10°K.

Time	% melted	T, °K. resistance thermometer	T, °K. thermocouple
0:00		Stopped supply of heat	
1:30	10	179.439	179.43
2:00	10	179.440	179.44
2:30	10	179.437	179.44
2:50		Stopped supply of heat	
4:10	20	179.440	179.44
4:50	20	179.447	179.43
5:30	20	179.443	179.43
6:00		Stopped supply of heat	
7:10	40	179.440	179.44
7:45	40	179.439	179.44
8:10		Stopped supply of heat	
10:00	65	179.439	179.44
10:40	65	179.438	179.44

Accepted value 179.44 ± 0.05°K.

TABLE III

TEMPERATURE OF TRANSITION IN SOLID METHYL BROMIDE

Date	Method of approach	Amount of high temp. form present, %	T, °K., from thermocouple	Time in hours after heating or cooling	Drift in degrees per hour
4/30/37	Heating	30	173.84	4	0.011 cooling
	Heating	57	173.86	5	.010 cooling
5/1/37	Cooling	89	173.46	7	.039 warming
6/4/37	Cooling	30	173.67	15	.002 warming
	Heating	40	174.07	1.5	.027 cooling
	Heating	48	174.11	1	
6/5/37	Cooling	36	173.65	18	
	Heating	49	174.10	1	
6/7/37	Heating	15	173.81	4	.010 cooling
	Heating	35	174.01	2	.012 cooling
	Cooling	22	173.71	19	
	Heating	62	174.07	2.75	.010 cooling
	Heating	76	174.10	1.5	

Accepted value 173.75 ± 0.15°K.

Heat of Transition.—The transition in solid methyl bromide has not been reported previously. Six determinations of the heat of transition were made. The results are summarized in Table VI.

The spread of the measured values for the heat of transition is outside of the limits of accuracy of the measurements. However, in determinations 4, 5 and 6 there was evidence that, due to supercooling, some of the high temperature form

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(9) Hsia, *Z. ges. Kälte-Ind. Beihefte*, Series 1, No. 2, 1 (1931).

TABLE IV

HEAT CAPACITY OF METHYL BROMIDE

Molecular weight, 94.950; 2.0610 moles in calorimeter. 0°C. = 273.10°K.

T, °K.	C_p cal./deg. per mole	Approx. ΔT	Series
12.56	1.209	1.8	V
14.62	1.452	2.3	V
17.49	2.046	3.4	V
21.39	2.874	4.4	V
25.45	3.709	3.7	V
29.16	4.394	3.8	V
33.53	5.216	4.4	V
38.27	6.170	5.7	V
44.18	7.047	6.0	V
49.79	7.840	5.2	V
55.19	8.602	5.7	V
61.13	9.278	6.2	V
66.87	9.758	5.6	V
72.21	10.18	5.1	V
77.54	10.62	5.7	V
83.01	10.99	5.3	V
88.60	11.36	5.9	V
94.53	11.65	6.0	V
100.55	11.95	6.1	V
106.72	12.22	6.2	V
112.98	12.44	6.3	V
119.17	12.64	6.0	V
125.46	12.80	6.6	V
131.92	13.01	6.3	V
138.06	13.21	6.1	V
144.01	13.32	5.8	V
150.23	13.42	6.4	V
156.45	13.59	6.1	V
159.28	13.56	6.1	I
162.40	13.69	6.0	V
165.27	13.77	5.9	I
168.21	13.95	5.7	V
170.70	13.97	4.7	I
173.75	Transition temperature		
175.21	15.41	1.0	IV
176.41	15.56	1.3	IV
176.48	15.66	2.6	I
176.88	15.68	2.2	III
177.76	16.41	1.1	IV
179.44	Melting point		
184.46	18.63	3.9	II
190.08	18.62	6.4	II
196.54	18.52	5.9	II
202.92	18.49	6.4	II
209.63	18.45	6.3	II
216.05	18.48	6.1	II
222.40	18.43	6.0	II
228.61	18.42	5.9	II
234.74	18.46	5.7	II
240.60	18.41	5.6	II
247.07	18.53	5.5	II
252.86	18.61	5.4	II
258.47	18.64	5.3	II
264.25	18.69	5.7	II
270.21	18.77	5.5	II
275.59	18.78	4.5	II
276.66	Boiling point		

TABLE V

HEAT CAPACITY OF METHYL BROMIDE

Molecular weight, 94.950; 0°C. = 273.10°K. Values taken from a smooth curve through the observations.

T, °K.	C_p cal./deg. per mole	T, °K.	C_p cal./deg. per mole
15	1.540	140	13.21
20	2.560	150	13.44
25	3.600	160	13.66
30	4.554	170	13.88
35	5.488	173.75	Transition temp.
40	6.366	175	15.36
45	7.170	177	15.53
50	7.925	179	15.70
55	8.594	179.44	Melting point
60	9.155	180	18.70
65	9.600	190	18.59
70	10.02	200	18.51
75	10.42	210	18.45
80	10.79	220	18.43
85	11.12	230	18.44
90	11.42	240	18.48
95	11.68	250	18.56
100	11.92	260	18.65
110	12.34	270	18.74
120	12.67	276.66	Boiling point
130	12.96	280	18.84

TABLE VI

HEAT OF TRANSITION OF METHYL BROMIDE

No.	Temp. interval, °K.	Corrected heat input per mole	$\int C_p dT$	ΔH cal./mole	Series
1	173.010–175.060	155.8	42.5	113.3	I
2	173.333–175.786	166.6	53.8	112.8	III
3	173.247–175.535	164.1	50.0	114.1	V
4	173.271–175.937	164.9	58.4	106.5	
5	171.842–175.190	183.4	71.7	111.7	
6	171.553–175.246	191.9	79.0	112.9	

Accepted value 113.4 ± 1

was already present at the start of the heating period. For this reason these values were given no weight in obtaining the accepted value.

Heat of Fusion.—No measured values of the heat of fusion were found in the literature. The present measurements are summarized in Table VII.

TABLE VII

HEAT OF FUSION OF METHYL BROMIDE

Temp. interval, °K.	Corr. heat input per mole	$\int C_p dT$	ΔH cal./mole
177.826–182.511	1545	115	1430
178.006–181.879	1524	95	1429
175.556–181.742	1574	146	1428

Average value 1429 ± 2

Heat of Vaporization.—The methyl bromide was vaporized from the calorimeter into the 5-liter measuring bulb mentioned previously. A constant pressure regulating device described by Giauque and Johnston[7] was used. Table VIII contains a summary of the individual measurements. The value given by Hsia,[9] and that calculated from equation (2) and Berthelot's equation are also included.

TABLE VIII

HEAT OF VAPORIZATION OF METHYL BROMIDE

Boiling point, 276.66°K.; molecular weight, 94.950.

No. mole vaporized	Time of energy input, min.	ΔH at 760 mm. cal./mole
0.22073	47	5714
.22870	48	5719
.22616	48	5711
	Average value	5715 ± 6
From vapor pressure equation (2). (This includes a Berthelot correction of −189 cal.)		5716
Value of Hsia		5885

Entropy from Calorimetric Data.—The calculation of the entropy of methyl bromide at the boiling point, 276.66°K., from calorimetric data is summarized in Table IX.

TABLE IX

ENTROPY OF METHYL BROMIDE FROM CALORIMETRIC DATA

0–15°K., Debye extrapolation, ($h c \nu / k$ = 91)	0.61
Solid, 15–173.75°K., graphical	19.328
Transition, 113.4/173.75	0.653
Solid, 173.75–179.44°K., graphical	0.489
Fusion, 1429/179.44	7.964
Liquid, 179.44–276.66°K., graphical	8.034
Vaporization, 5715/276.66	20.657
Entropy of actual gas at the boiling point	57.74 ± 0.1
Correction for gas imperfection	0.12
Entropy of ideal gas at 1 atm. and 276.66° K.	57.86 cal./deg. per mole

The correction for gas imperfection was obtained from the expression

$$S_{\text{ideal}} - S_{\text{actual}} = 27RT_c^3P/32T^3P_c$$

Measured values of the critical temperature and critical pressure could not be found in the literature. T_c was estimated to be 475°K. and P_c to be 68 atm.

Entropy from Spectroscopic and Molecular Structure Data.—Stevenson and Beach[10] recently have calculated the entropy of methyl bromide at 298.10°K. The same frequencies and molecular constants were used in the present calculation at the boiling point

C–Br = 1.91 ± 0.06 Å.[11]
C–H = 1.09 Å.
H–C–H = 111°

The values used for the natural constants were those given in the "International Critical Tables." From the above data the moments of inertia times 10^{40} g. cm.^{2} were found to be $I_1 = 5.36$ and $I_2 = I_3 = 85.3$. The symmetry number σ was taken equal to 3.

The following vibration frequencies were used.[12–14]

cm.$^{-1}$	Weight
$\nu_1 = 2900$	1
$\nu_2 = 3061$	2
$\nu_3 = 1305$	1
$\nu_4 = 1450$	2
$\nu_5 = 610$	1
$\nu_6 = 957$	2

Table X contains a summary of the calculation. An uncertainty of ±0.06 Å. in the C–Br distance affects the entropy by ±0.12 cal./deg. per mole. The entropy effect due to the presence of isotopes and of nuclear spin has been neglected.

TABLE X

ENTROPY OF METHYL BROMIDE AT ONE ATMOSPHERE FROM SPECTROSCOPIC AND MOLECULAR STRUCTURE DATA

	T = 276.66°K.	T = 298.10°K.
$S_{\text{trans.}} = 3/2\,R \ln M + 5/2\,R \ln T - R \ln P - 2.300$	39.203	39.572
$S_{\text{rot.}} = R/2 \ln I_1I_2I_3 \times 10^{120} + 3/2\,R \ln T - R \ln 3 - 6.851$	18.226	18.448
$S_{\text{vib.}} = \Sigma_{\nu_1 \text{ to } \nu_6} S_{\text{Einstein}}$	0.563	0.720
Entropy in cal./deg. per mole	57.99	58.74

The good agreement between the experimental entropy at the boiling point, 57.86 ± 0.10 cal./deg. per mole and the spectroscopic value, 57.99, further establishes the validity of using the third law of thermodynamics in conjunction with low temperature calorimetric data to obtain the entropies of compounds containing methyl groups.

The experimental entropy (ideal gas) at 298.10°K. is 58.61 cal./deg. per mole, and the spectroscopic value (ideal gas) is 58.74 cal./deg. per mole.

Summary

The heat capacity of condensed methyl bromide has been measured from 15°K. to the boiling point.

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[10] Stevenson and Beach, *J. Chem. Phys.*, **6**, 25 (1938); **6**, 108 (1938).

[11] Lévy and Brockway, THIS JOURNAL, **59**, 1662 (1937).

[12] Bennett and Myer, *Phys. Rev.*, **32**, 888 (1928).

[13] Barker and Plyler, *J. Chem. Phys.*, **3**, 367 (1935).

[14] Adel and Barker, *ibid.*, **2**, 627 (1934).

This substance has a transition in the solid about 5.7° below the melting point. Equilibrium in the transition was attained very slowly and the methyl bromide could be superheated or supercooled one or two-tenths of a degree above or below the transition point, 173.75 ± 0.15°K.

The melting point was found to be 179.44 ± 0.05°K., the boiling point 276.66 ± 0.05°K., the heat of transition 113.4 ± 1 cal./mole, the heat of fusion 1429 ± 2 cal./mole, and the heat of vaporization 5715 ± 6 cal./mole.

Vapor pressure measurements have been made on liquid methyl bromide and the results have been represented by the following equation

liquid methyl bromide, 203 to 278°K. (0°C. = 273.10°K.)

$$\log_{10}P(\text{Int. cm. Hg}) = -(1541.437/T) + 8.49274 - 0.00424740T + 1.7599 \times 10^{-6}T^2$$

The density of methyl bromide gas at 298.10°K. and one atmosphere was found to be 3.9739 ± 0.0009 grams/liter.

The entropy of methyl bromide (ideal gas) at one atmosphere and at the boiling point, 276.66°K., has been calculated from calorimetric data to be 57.86 ± 0.10 cal./deg. per mole and compared with the value 57.99 obtained from spectroscopic data.

The good agreement indicates that it is correct to use the third law value in thermodynamic calculations. It also gives more experimental substantiation to the assumption made in the calculation of potential barriers in compounds containing methyl groups, namely, that the entropies of these compounds may be obtained correctly from low temperature calorimetric data.

The experimental entropy (ideal gas) at 298.10°K. is 58.61 cal./deg. per mole, and the spectroscopic value (ideal gas) is 58.74 cal./deg. per mole.

BERKELEY, CALIF.

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[CONTRIBUTION FROM THE BURROUGHS WELLCOME & CO. U. S. A. EXPERIMENTAL RESEARCH LABORATORIES]

2-Alkyl-1,2,3,4-tetrahydroisoquinoline Hydrochlorides[1]

BY JOHANNES S. BUCK AND WALTER S. IDE

With a view to carrying out a detailed pharmacological examination of the effects of various 2-alkyl groups on the action of tetrahydroisoquinolines, three series of 2-alkyl-1,2,3,4-tetrahydroisoquinolines were prepared. One series has no nuclear substituents, the second carries 6,7-dimethoxy groups and the third has 6,7-dihydroxy groups. Hydrochlorides were chosen for pharmacological reasons. In no case was a substituent present in the 1-position.

The preparation of the unsubstituted compounds was carried out substantially according to the method of Wedekind, *et al.*[2] and offered no particular difficulties. However, a general method was required for future work, and Wedekind's procedure could not be applied to the substituted derivatives, owing to the relative inaccessibility of substituted isoquinolines. Attempts were made to N-alkylate homoveratrylamine by the Decker[3] method with a view to cyclizing the alkylated amines,[4] but these did not succeed with alkyl groups larger than ethyl, the alkiodides of the Schiff bases being non-crystalline and the homogeneity of the secondary amine being therefore in doubt. However, some 2-ethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline was made by this route, from ethylhomoveratrylamine.

Direct alkylation of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline[5] with ethyl iodide gave considerable amounts of quaternary compound and unchanged material, with some of the desired 2-ethyl derivative.[6] The method, however, was regarded as unsatisfactory. Similar objections apply to the use of toluene sulfonic esters.[7] Attempts to alkylate by means of α-bromo acids[8] gave only the hydrobromide of the starting material.

Finally, 6,7-dimethoxy-3,4-dihydroisoquinoline was investigated. This readily formed crystalline

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[1] This work is part of a joint research being carried out in collaboration with a pharmacological group at the above laboratories. The pharmacological data were contributed by this group.

[2] Wedekind and Oechslen, *Ber.*, **34**, 3986 (1901); Wedekind and Ney, *ibid.*, **42**, 2138 (1909); **45**, 1298 (1912).

[3] Decker and Becker, *Ann.*, **395**, 362 (1913).

[4] *Cf.* Buck, THIS JOURNAL, **56**, 1769 (1934).

[5] Forsyth, Kelly and Pyman, *J. Chem. Soc.*, **127**, 1659 (1925), but prepared from homoveratrylamine by the method of German Patent 257,138 (*cf.* ref. 4.).

[6] *Cf.* German Patent 270,859.

[7] *Cf.* Földi, *Ber.*, **55**, 1535 (1922).

[8] *Cf.* Bischoff and Mintz, *ibid.*, **25**, 2314 (1892).

TABLE I

2-ALKYL-1,2,3,4-TETRAHYDROISOQUINOLINE HYDROCHLORIDES

Alkyl group	Appearance	M. p., °C. (corr.)	Formula	Analyses, % Calcd. C	H	Found C	H
Methyl	Felted tiny prisms	227	$C_{10}H_{14}NCl$	65.37	7.69	65.41	8.06
Ethyl	Felted tiny rectangular prisms	213	$C_{11}H_{16}NCl$	66.81	8.16	67.06	8.28
n-Propyl	Meshed small rectangular prisms	242	$C_{12}H_{18}NCl$	68.06	8.57	68.19	8.67
n-Butyl	Felted tiny prisms	190	$C_{13}H_{20}NCl$	69.14	8.94	69.21	8.96
n-Amyl	Matted tiny obscure crystals	191	$C_{14}H_{22}NCl$	70.11	9.26	70.35	9.45
Isopropyl	Tiny rectangular plates	215	$C_{12}H_{18}NCl$	68.06	8.57	68.35	8.95
Isobutyl	Matted minute obscure crystals	205	$C_{13}H_{20}NCl$	69.14	8.94	69.25	9.12
Isoamyl	Thin flat prisms	229	$C_{14}H_{22}NCl$	70.11	9.26	70.24	9.60

alkiodides which could be reduced to the 2-alkyl-1,2,3,4-tetrahydro derivatives, which, in turn, could be demethylated to give the corresponding dihydroxy compounds. The series of reactions is convenient and the yields are good, and the possibility of the presence of secondary amine and quaternary compound has been eliminated. The substituted hydrochlorides described below were made by the foregoing route.

Experimental

2-Alkyl-1,2,3,4-tetrahydroisoquinoline Hydrochlorides.—This series of compounds was prepared by the reduction of the isoquinoline alkiodides, following the double reduction technique of Wedekind, *et al.*[2] The product was recovered from the steam distillate as hydrochloride and was recrystallized from alcohol–ether until pure. The hydrochlorides all form white crystalline compounds, readily soluble in alcohol (with which they are often solvated) and in water, and insoluble in ether and in ethyl acetate. The three isoalkyl hydrochlorides have a saline taste, the others quinine-like tastes. The *n*-butyl and *n*-amyl compounds have a numbing effect. The properties of the hydrochlorides are described in Table I. The 2-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride was checked against a specimen prepared by sodium–alcohol reduction.[4]

The majority of the isoquinoline alkiodides and reduced bases are described by Wedekind, *et al.*,[2] but hydrochlorides, although sometimes mentioned, are not described. The isobutyl compound, not obtained by the above authors, was prepared in small yield by reaction of equimolecular amounts of isoquinoline and isobutyl iodide, and, after steam distilling, reducing the residual oil in the usual way. The *n*-amyl compounds were not attempted by Wedekind, *et al.* The present authors are indebted to the Ciba Company for the isoquinoline used.

Isoquinoline *n*-amyl iodide, recrystallized from alcohol–ether, forms small, lemon-yellow prisms, soluble in alcohol, methanol and water, insoluble in ether and ethyl acetate, and melting at 139° (corr.).

Anal. Calcd. for $C_{14}H_{18}NI$: C, 51.39; H, 5.55. Found: C, 51.35; H, 5.64.

2 - Alkyl - 6,7 - dimethoxy - 1,2,3,4 - tetrahydroisoquinoline Hydrochlorides.—6,7 - Dimethoxy - 3,4 - dihydroisoquinoline was prepared from formylhomoveratrylamine (homoveratrylamine formate heated for one and one-half hours at 210°) by cyclization with phosphorus oxychloride, the experimental details being practically the same as those used by Haworth[9] for the 5,6-dimethoxy compound. The alkiodides were prepared by dissolving equimolecular amounts of the dihydroisoquinoline and alkyl iodide in twice the volume of benzene and allowing the solution to stand in a warm place until no further reaction was evident. The alkiodides were filtered off and recrystallized from alcohol–ether or alcohol–ethyl acetate. Their properties are described in Table II. The isobutiodide was not obtained, only the hydriodide of the starting material being isolable, and hence 2-isobutyl compounds are missing in Tables II, III and IV.

Reduction of the alkiodides was carried out by means of zinc powder and dilute sulfuric acid on the water-bath.[9] After filtration and cooling the sulfate of the product crystallized out and was filtered off and the base liberated by sodium hydroxide and extracted by ether. Alternatively, the reduction mixture was made strongly alkaline and extracted with ether. After drying the extract over solid potassium hydroxide, the hydrochloride was precipitated by hydrogen chloride, filtered off, dried *in vacuo*, and recrystallized from methanol with ether or ethyl acetate. The hydrochlorides form white, crystalline compounds, moderately to readily soluble in alcohol, more soluble in methanol, readily soluble in water, and insoluble in ether and ethyl acetate. The tastes are not intense or distinctive. The compounds are described in Table III. The 2-methyl compound, prepared by cyclization, has been previously described.[4] Pyman also has prepared this compound, together with the 2-ethyl and 2-*n*-propyl derivatives (the latter as picrate), from laudanosine or papaverine.[10]

2 - Methyl - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydroisoquinoline Hydrochlorides.—The dihydroxy compounds are prepared readily by demethylating the corresponding dimethoxy hydrochlorides with hydrochloric acid (two hours at 165° in a carbon dioxide-filled tube), evaporating the solution to dryness *in vacuo*, and recrystallizing the residue from methanol with ether or ethyl acetate. The solubilities, etc., of the hydrochlorides are practically the same as those of the dimethoxy compounds. The properties are given in Table IV. The corresponding 2-methyl compound has been described previously.[4,11] The hydrochlorides have no distinctive taste.

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[9] Haworth, *J. Chem. Soc.*, 2281 (1927).

[10] Pyman, *ibid.*, **95**, 1266, 1738 (1909).

[11] Pyman, *ibid.*, **97**, 264 (1910).

TABLE II

2-ALKYL-6,7-DIMETHOXY-3,4-DIHYDROISOQUINOLINIUM IODIDES

Alkyl group	Appearance	M. p., °C. (corr.)	Formula	Analyses, % Calcd. C	H	Found C	H
Ethyl	Orange-yellow small glittering prisms	186.5	$C_{13}H_{18}O_2NI$	44.95	5.23	44.84	5.41
n-Propyl	Straw-yellow small glittering plates	158	$C_{14}H_{20}O_2NI$	46.53	5.58	46.72	5.79
n-Butyl	Straw-yellow thin glittering needles	152	$C_{15}H_{22}O_2NI$	47.98	5.91	48.01	5.87
n-Amyl	Lemon-yellow small glittering prisms	123	$C_{16}H_{24}O_2NI$	49.34	6.22	49.40	6.24
Isopropyl	Golden-yellow glittering prisms	201 (gas)	$C_{14}H_{20}O_2NI$	46.53	5.58	46.45	5.76
Isoamyl	Lemon-yellow small glittering prisms	134.5	$C_{16}H_{24}O_2NI$	49.34	6.22	49.43	6.31

TABLE III

2-ALKYL-6,7-DIMETHOXY-1,2,3,4-TETRAHYDROISOQUINOLINE HYDROCHLORIDES

Alkyl group	Appearance	M. p., °C. (corr.)	Formula	Analyses, % Calcd. C	H	Found C	H
Ethyl	Tiny nodules of minute prisms	246	$C_{13}H_{20}O_2NCl$	60.56	7.83	60.49	7.97
n-Propyl	Bulky aggregates of obscure crystals	223	$C_{14}H_{22}O_2NCl$	61.85	8.16	61.93	8.16
n-Butyl	Bulky masses of tiny spherules	224	$C_{15}H_{24}O_2NCl$	63.02	8.47	62.93	8.68
n-Amyl	Chalky masses of obscure flakes	232	$C_{16}H_{26}O_2NCl$	64.07	8.75	64.12	9.05
Isopropyl	Chalky masses of obscure plates	268 (dec.)	$C_{14}H_{22}O_2NCl$	61.85	8.16	61.91	7.98
Isoamyl	Aggregates of flakes	254	$C_{16}H_{26}O_2NCl$	64.07	8.75	64.30	8.94

TABLE IV

2-ALKYL-6,7-DIHYDROXY-1,2,3,4-TETRAHYDROISOQUINOLINE HYDROCHLORIDES

Alkyl group	Appearance	M. p., °C. (corr.)	Formula	Analyses, % Calcd. C	H	Found C	H
Ethyl	Small meshed needle prisms	223	$C_{11}H_{16}O_2NCl$	57.49	7.02	57.38	6.93
n-Propyl	Tiny rosets of prisms	240	$C_{12}H_{18}O_2NCl$	59.11	7.45	58.99	7.47
n-Butyl	Powder of fragmentary prisms	202	$C_{13}H_{20}O_2NCl$	60.56	7.83	60.77	7.83
n-Amyl	Small nodules of flat prisms	187.5	$C_{14}H_{22}O_2NCl$	61.85	8.16	61.79	8.37
Isopropyl	Small stout spindles and clusters	253	$C_{12}H_{18}O_2NCl$	59.11	7.45	59.10	7.35
Isoamyl	Small nodules of minute prisms	208	$C_{14}H_{22}O_2NCl$	61.85	8.16	61.99	8.30

Note on Pharmacology.[12]—Complete results will be published elsewhere, but it can be stated that the nuclear-unsubstituted compounds show a slight depressor effect and that they are relatively strong sympatholytics. The M. E. D. (dogs) ranges from 1 to 10 mg./kg. and L 50 (mice) from 70 to 185 mg./kg.

The first of the series of dimethoxy compounds, 2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, is a rather poor depressor, the M. E. D. (dogs) being 1 to 2 mg./kg. and L 50 (mice), 52 mg./kg.

The corresponding dihydroxy compound, 2-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, is a relatively powerful pressor, the M. E. D. (dogs) being 1 to 2 mg./kg. and L 50 (mice), 280 mg./kg.

Summary

A series of 2-alkyl-1,2,3,4-tetrahydroisoquinoline hydrochlorides is described, together with the corresponding 6,7-dimethoxy and 6,7-dihydroxy derivatives. Some 2-alkyl-6,7-dimethoxy-3,4-dihydroisoquinolinium iodides are included, and preliminary pharmacological data are given.

TUCKAHOE, NEW YORK RECEIVED JUNE 16, 1938

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[12] *Cf.* Laidlaw, *Biochem. J.*, **5**, 243 (1911); Hjort, deBeer and Fassett, *J. Pharmacol.*, **62**, 165 (1938).

[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

Syntheses in the Quinoline Series. I. 2-Hydroxy- and 2-Chloroquinolinearsonic Acids

BY JULIUS D. CAPPS[1] AND CLIFF S. HAMILTON

This investigation deals with the preparation of several quinoline amines and quinoline arsonic acids, most of the amines being produced by the catalytic reduction of certain nitroquinolines and most of the arsonic acids by diazotization of these amines and subsequent treatment with sodium arsenite. 2-Hydroxyquinolinearsonic and 2-chloroquinolinearsonic acids are given extensive consideration.

The 2-hydroxy-4-methyl-7-aminoquinoline used in this investigation was prepared according to the procedure of Besthorn and Byvanck[2] by condensing *m*-phenylenediamine with ethyl acetoacetate. The proof of structure of this product follows from its conversion to 2-chloro-4-methyl-7-methoxyquinoline, which was originally obtained by another method.[3] This structure was further confirmed in our experimental work by its conversion to 2-hydroxy-4-methyl-7-chloroquinoline.[4]

2-Chloroquinolines have been prepared by the replacement of hydroxyl through the use of phosphorus pentachloride and phosphorus oxychloride. Hydrochloric acid was found to hydrolyze 2-chloroquinoline-8-arsonic acid to give 2-hydroxyquinoline-8-arsonic acid.

2-(β-Ethoxyethoxy)-quinoline derivatives were made from 2-chloroquinolines by the use of ethylcellosolve to which had been added metallic sodium.

Experimental

2-Chloro-4-methyl-7-methoxyquinoline was prepared by treating 2-chloro-4-methyl-7-hydroxyquinoline, obtained from 2-hydroxy-4-methyl-7-aminoquinoline according to the method of Besthorn and Byvanck,[2] in 10% by weight sodium hydroxide solution with dimethyl sulfate as well as by refluxing 2-hydroxy-4-methyl-7-methoxyquinoline with phosphorus oxychloride.[3]

Nitroquinolines.—**5-Nitroquinoline** was obtained in a 32% yield by nitrating quinoline sulfate and in a much poorer yield by subjecting *m*-nitroaniline to the conditions of the Skraup reaction. A slight modification of the method of Meigen[5] proved satisfactory for the nitration of quinoline sulfate and for the separation of the isomers formed during the nitration. **6-Nitroquinoline** in a 45% yield and **7-nitroquinoline** in a 5% yield were produced by the method of Knueppel,[6] the procedure of Kochanska and Bobranski[7] being used for the isolation of the 7-nitroquinoline rather than that given by Knueppel.

2-Hydroxyquinolines.—Ten grams of 5-nitroquinoline, dissolved in 50 ml. of water by the addition of sulfuric acid, was poured into 2 liters of water at 60°. Sodium hydroxide solution was added until the *p*H was just sufficient to keep the nitroquinoline in solution. Upon introducing, with stirring, a 5.25% by weight solution of sodium hypochlorite, a solid began to appear. After standing overnight, filtering off the solid, digesting it with 10% by weight sodium hydroxide solution and making acid with sulfuric acid, an 85% yield of **2-hydroxy-5-nitroquinoline** precipitated.[8] When 6-nitroquinolinoline was treated in a similar manner and the resulting product recrystallized from glacial acetic acid, a 46% yield of **2-hydroxy-6-nitroquinoline** was obtained. An 85% yield of **2-hydroxy-7-nitroquinoline** likewise resulted from 7-nitroquinoline.

2-Hydroxyaminoquinolines.—**2-Hydroxy-4-methyl-7-aminoquinoline** in 45 to 60% yields was obtained by heating 30 g. of dry crystalline *m*-phenylenediamine and 37.8 ml. of ethyl acetoacetate in an autoclave at 130° for nineteen hours. Almost quantitative yields of **2-hydroxy-5-aminoquinoline** and **2-hydroxy-7-aminoquinoline** were obtained by the catalytic reduction of 2-hydroxy-5-nitroquinoline in 95% ethanol and 2-hydroxy-7-nitroquinoline in acetone, respectively, using Raney nickel catalyst.

2-Chloroaminoquinolines.—The catalytic reduction of an acetone solution of 2-chloro-5-nitroquinoline at 50° gave an almost quantitative yield of **2-chloro-5-aminoquinoline.** The amine was isolated by partial distillation of the acetone and the addition of water to the concentrated solution resulting. Recrystallization from dilute ethanol–water solution gave long, slender, light green colored needles belonging to the orthorhombic system; soluble in acetone, ethanol, benzene, diethyl ether and acids; m. p. 110–111° (corr.).

Anal. Calcd. for $C_9H_7ClN_2$: N, 15.67; Cl, 19.88. Found: N, 15.60; Cl, 19.72.

Dry 2-chloro-6-nitroquinoline was dissolved in a small quantity of cold hydrochloric acid (sp. gr. 1.19) and the amount of dry powdered stannous chloride calculated for complete reduction added slowly with stirring. The tin double salt, that formed upon standing, was filtered off on a dry filter, dried and dissolved in a small amount of water. After making acid, bringing to the boiling temperature and saturating with hydrogen sulfide, the tin sulfide was removed by filtration. The filtrate was neutralized with ammonium hydroxide, concentrated by evapora-

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[1] Parke, Davis and Company Fellow.

[2] Besthorn and Byvanck, *Ber.*, **31**, 798 (1898).

[3] Späth and Brunner, *ibid.*, **57B**, 1243 (1924).

[4] Soc. Anon. pour l'ind. Chim. à Bâle, German Patent 556,324 (1930); *C. A.*, **26**, 5573 (1932).

[5] Meigen, *J. prakt. Chem.*, [2] **77**, 472 (1908).

[6] Knueppel, *Ber.*, **29**, 703 (1896).

[7] Kochanska and Bobranski, *ibid.*, **69B**, 1809 (1936).

[8] See Claus and Setzer, *J. prakt. Chem.*, [2] **53**, 390 (1896); Einhorn and Lauch, *Ber.*, **19**, 53 (1886); *Ann.*, **243**, 342 (1888).

	Name	Crystalline form	% yield	M. p., °C. (corr.)	Formula	As analyses, %[10] Calcd.	Found
1	2 - Hydroxy - 4 - methylquinoline-7-arsonic acid	Orthorhombic plates	31	...	$C_{10}H_{10}AsNO_4 \cdot H_2O$	24.88	24.83
2	1 Anhydrous	....	..	...	$C_{10}H_{10}AsNO_4$	26.48	26.44
3	Sodium salt of 1	Tetragonal granules	88	...	$C_{10}H_9AsNNaO_4 \cdot 2H_2O$	21.97	22.07
4	3 Anhydrous	....	..	...	$C_{10}H_9AsNNaO_4$	24.56	24.47
5	2 - Hydroxyquinoline - 5 - arsonic acid	Tetragonal plates	23	...	$C_9H_8AsNO_4 \cdot H_2O$	26.11	26.00
6	5 Anhydrous	....	..	...	$C_9H_8AsNO_4$	27.85	27.70
7	2 - Hydroxyquinoline - 7 - arsonic acid	Orthorhombic needles	13	...	$C_9H_8AsNO_4$	27.85	28.00
8	2 - Hydroxyquinoline - 8 - arsonic acid	Orthorhombic needles	Quant.	...	$C_9H_8AsNO_4$	27.85	28.00
9	2 - Chloro - 4 - methylquinoline-7-arsonic acid	Orthorhombic needles	7	192	$C_{10}H_9AsClNO_3$	24.86	24.90
10	2 - Chloroquinoline - 5 - arsonic acid	Orthorhombic needles	24	...	$C_9H_7AsClNO_3$	26.07	26.10
11	2 - Chloroquinoline - 6 - arsonic acid	Orthorhombic needles	18	...	$C_9H_7AsClNO_3$	26.07	26.00
12	2 - Chloroquinoline - 8 - arsonic acid	Orthorhombic needles	11	273–276	$C_9H_7AsClNO_3$	26.07	26.12
13	2-(β-Ethoxyethoxy)-4-methylquinoline-7-arsonic acid	Monoclinic needles	59	183	$C_{14}H_{18}AsNO_5$	21.11	21.20
14	2 - (β - Ethoxyethoxy) - quinoline-5-arsonic acid	Flat prisms	90	172	$C_{13}H_{16}AsNO_5$	21.96	22.00

tion and cooled. **2-Chloro-6-aminoquinoline** precipitated as long, slender, light yellow colored needles belonging to the orthorhombic system; soluble in ethanol, acetone, hot water, warm petroleum ether, diethyl ether and benzene; m. p. 149° (corr.); yield, 67% of the theoretical.

Anal. Calcd. for $C_9H_7ClN_2$: N, 15.67; Cl, 19.88. Found: N, 15.70; Cl, 19.75.

Catalytic reduction of 2-chloro-8-nitroquinoline[9] in absolute ethanol under the same conditions used for reducing 2-chloro-5-nitroquinoline gave **2-chloro-8-aminoquinoline.** After concentrating the alcoholic solution of the amine by distillation and adding water to the resulting concentrated solution, an oil separated; this crystallized upon standing. Recrystallization from dilute ethanol–water solution gave light green colored (almost white) needle-like leaflets, soluble in ethanol, acetone, warm benzene and acids, m. p. 84° (corr.), yield, 98% of the theoretical.

Anal. Calcd. for $C_9H_7ClN_2$: N, 15.67; Cl, 19.88. Found: N, 15.70; Cl, 19.75.

2-Hydroxyquinolinearsonic Acids.—Crushed ice was added to a solution of 0.16 mole of the hydroxyquinoline amine in 2 moles of hydrochloric acid. When a temperature below 5° had been attained, the amine was diazotized with sodium nitrite solution. After making just basic to litmus paper by the careful addition, in the presence of ice with stirring, of 5 *N* sodium hydroxide solution, the diazotized solution was poured slowly with good mechanical mixing into a water solution of 26 g. of sodium metaarsenite to which previously had been added 5–6 ml. of a saturated water solution of copper sulfate. After being stirred for one hour and having stood overnight, the resulting mixture was brought slowly to the boiling temperature and boiled for five minutes. This hot mixture was filtered and the filtrate carefully neutralized with hydrochloric acid. Upon charcoaling this neutral solution, evaporating until a volume of 350 ml. remained, and making acid to Congo red paper with hydrochloric acid, the crude hydroxyquinolinearsonic acid precipitated. When this acid was dissolved in a small quantity of hot dilute sodium hydroxide solution, 3% hydrogen peroxide solution added, the solution boiled for five minutes and made acid to Congo red paper with hydrochloric acid, the pure acid precipitated.

Hydrolysis resulted when 2-chloroquinoline-8-arsonic acid was heated in an autoclave with 12 parts by weight of hydrochloric acid (sp. gr. 1.19) at 125° for one and one-half hours, and 2-hydroxyquinoline-8-arsonic acid was obtained.

When a solution of 2-hydroxy-4-methylquinoline-7-arsonic acid in one equivalent of hot sodium hydroxide solution was added dropwise to cold 95% ethanol in a container fitted with a mechanical stirrer, the monosodium salt of 2-hydroxy-4-methylquinoline-7-arsonic acid precipitated.

2-Chloroquinolinearsonic Acids.—The 2-chloroquinolinearsonic acids were prepared from the corresponding 2-chloroaminoquinolines by a slight modification of the method used for synthesizing the 2-hydroxyquinolinearsonic acids. Instead of neutralizing the diazotized solution of the amine before it was added to the arsenite solution, enough alkali was added to the arsenite solution to neutralize exactly the acid in which the amine was dissolved, and the diazotized amine was added directly.

2 - (β-Ethoxyethoxy) - 4 - methylquinoline - 7 - arsonic Acid.—Five-tenths gram of dry 2-chloro-4-methylquinoline-7-arsonic acid was refluxed with a solution of 0.60 g. of clean dry sodium in 50 ml. of ethylcellosolve for two and one-half hours. After cooling and filtering, the filtrate was made neutral to litmus paper by the careful addition of hydrochloric acid (sp. gr. 1.19). The sodium chloride

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[9] Fischer and Guthmann, *J. prakt. Chem.*, [2] **93**, 378 (1916).

[10] See Cislak and Hamilton, THIS JOURNAL, **52**, 638 (1930).

formed was filtered off and the filtrate diluted with 50 ml. of water. When this was evaporated on a hot-plate until 25 ml. remained and made acid to Congo red paper with hydrochloric acid, 2-(β-ethoxyethoxy)-4-methylquinoline-7-arsonic acid precipitated.

2-(β-Ethoxyethoxy)-quinoline-5-arsonic acid was obtained from 2-chloroquinoline-5-arsonic acid by the same method used in preparing 2-(β-ethoxyethoxy)-4-methylquinoline-7-arsonic acid.

Summary

1. It was proved that 2-hydroxy-4-methyl-7-aminoquinoline rather than 2-hydroxy-4-methyl-5-aminoquinoline resulted when equimolecular quantities of *m*-phenylenediamine and ethyl acetoacetate condensed in an autoclave at 130°.

2. A number of quinoline amines were produced by the reduction of nitroquinolines.

3. Several 2-hydroxyquinoline and 2-chloroquinolinearsonic acids were obtained from the corresponding quinoline amines by diazotization and coupling with sodium arsenite. The monosodium salt of 2-hydroxy-4-methylquinoline-7-arsonic acid was made.

4. The hydrolysis of 2-chloroquinoline-8-arsonic acid resulted in the formation of 2-hydroxyquinoline-8-arsonic acid.

5. 2-Chloro-4-methylquinoline-7-arsonic acid and 2-chloroquinoline-5-arsonic acid reacted with the monosodium salt of ethylcellosolve to give 2-(β-ethoxyethoxy)-4-methylquinoline-7-arsonic acid and 2-(β-ethoxyethoxy)-quinoline-5-arsonic acid, respectively.

LINCOLN, NEBRASKA RECEIVED JUNE 8, 1938

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, SHAWINIGAN CHEMICALS, LTD.]

The Viscosity Function

BY E. P. IRANY

Viscosity is well defined as a physical quantity and accurately measurable. Yet, so far, its relations to temperature, pressure, dilution, chemical constitution, and so forth, are somewhat obscure.

Numerous empirical rules have been proposed but none of them can claim general validity or real physical significance. It may even be questioned whether the task of formulating the exact viscosity laws is not far beyond our present knowledge of the liquid state as such.

It is the main purpose of this paper to offer evidence that such laws exist and can be expressed. Of course, without reliable mathematical assumptions, explicit formulas cannot be derived; the method adopted is one of graphical analysis. It will be shown that, if applied to the large number of measurements and data already available in the literature, this method reveals in them fundamental but so far undiscovered regularities.

Viscosity may be considered a form of friction if the latter is explained in terms of internal forces. Few molecules—probably none—are in so perfect equilibrium that no attractions would be active between them. These forces are chemical by nature though not in intensity, and it is obvious that they are the cause of the mutual interference with motions and mobility of the molecules which is observable as viscosity. The effect may vary between actual chemical union, association, and mere transitory attraction.

For considerations of viscosity the usual distinction between associated and non-associated liquids is only secondary. It is conceivable that a substance may be so perfectly associated that in its larger complexes all residual forces are well compensated; reversely, in a non-associated liquid the identity of the molecules as the structural units may be preserved, but not their independent mobility. Hence, the fundamental distinction should rather be drawn between "ideal" and "non-ideal" conditions, depending not only on existence and magnitude of the intermolecular forces but, primarily, on their constancy. What the mobile entities are—molecules or molecular complexes of some kind—is immaterial as long as problems of internal constitution are not dealt with; for the time being, these must be left outside the scope of this investigation.

The supposed general law of viscosity can only appear in substances of constant structure and force disposition. The question now arises as to where to find and how to recognize "ideal" liquids which may serve as objects of study. Experimental proof of "ideality" such as, *e. g.*, derived from other physical properties, is of doubtful value because it seems that viscosity is still very sensitively affected by intermolecular conditions which would not reveal themselves distinctly enough in calorimetric, gravimetric, or cryoscopic effects.

Recourse must therefore be taken to mere assumption that certain substances are ideal and may be accepted as standards. The best choice are the paraffin hydrocarbons because all that is known about them not only suggests that they are as nearly ideal as possible, but also that this condition is maintained through the whole series which covers the entire range of measurable viscosities.

I. The Viscosity Function of Dilution

Ideal Mixtures.—If two liquids are miscible in such a manner that no specific effects appear between them which depend on and vary with the composition of the mixture, the system can be considered ideal.

For example, the components may be a viscous paraffin oil and a light petroleum fraction with widely differing viscosities at the same temperature. The viscosities fall upon a sharply ascending curve (Fig. 1). This curve represents in graphical form a presumably simple case of the law according to which viscosities should be additive or computable. By selecting any other pair of standard hydrocarbons, a whole series of such curves could be drawn across the diagram.

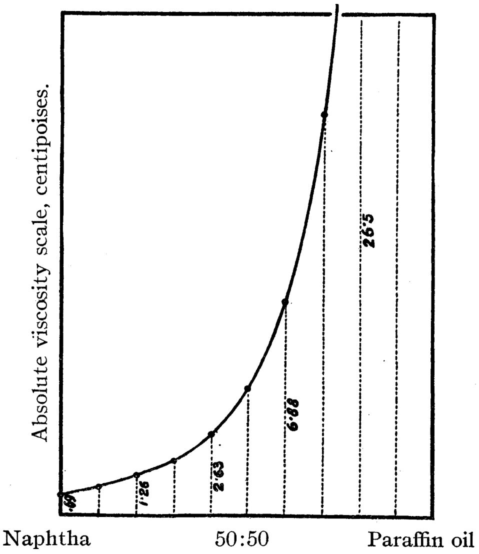

Fig. 1.

If a given system of other components were now to be examined for ideality, one would select two paraffins of the same respective viscosities and construct the ideal curve between them; the mixture under survey would then be recognizable as ideal if its curve coincided with that of the standard.

However, it would be much more convenient to compare in a diagram in which the ideal course would appear as a straight line. For any single standard curve this is easily realized by plotting viscosity not in absolute units, but in a scale which compensates for the curvature in such a manner that a straight line results. This scale would then embody the unknown law according to which viscosities are additive.

There have been numerous attempts to formulate such viscosity functions empirically. For example, the function log (viscosity) has been proposed by Arrhenius.[1] In this case the scale embodying the law of additivity is the logarithm of the natural value of the viscosities, *i. e.*, a semi-log diagram may be used. However, this rule is only a very imperfect approximation, neither accurate nor generally valid. The same applies to other such assumptions, *e. g.*, reciprocal viscosity ("fluidity") by Bingham,[2] or its cube root, by Kendall–Monroe.[3] The true mathematical form of the scale function is unknown, it can only be represented by graphical means.

How the scale function is determined from a number of points fixed by actual viscosity measurements is shown in Fig. 2.

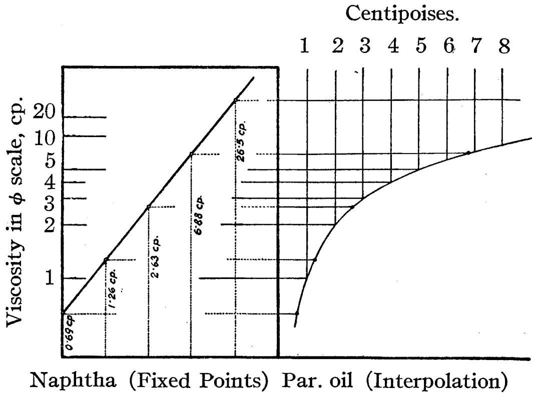

Fig. 2.

A straight line of any convenient position and gradient is assumed to represent the original curve; its intersections at the given mixtures yield the fixed points, and the scale is completed by means of an interpolation curve.

If this is done with other standard curves representing ideal mixtures, a very interesting regularity appears: the resulting scale is always the same, no matter from what particular pair of

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(1) Arrhenius, *Biochem. J.*, **11**, 112 (1917).

(2) Bingham, "Fluidity and Plasticity," McGraw-Hilll Book Co., Inc., New York, 1923.

(3) Kendall and Monroe, THIS JOURNAL, **39**, 1787, 1806 (1917).

components it has been derived. In other words, there is a general function of viscosity according to which it is additive in ideal mixtures. In terms of graphical analysis: *In a diagram in which the scale of viscosity is adjusted so as to make one given ideal mixture appear as a straight line, all other ideal mixtures appear also as straight lines.*

This rule holds with complete accuracy in all ideal mixtures; it is not restricted to those composed of paraffin hydrocarbons, but is independent of the nature of the components. The function expressed in the scale is neither logarithmic, nor otherwise readily representable in mathematical form. It will be referred to as the "Viscosity Function ϕ." This "ϕ-scale," completed over a considerable range of viscosities, appears in Fig. 3.

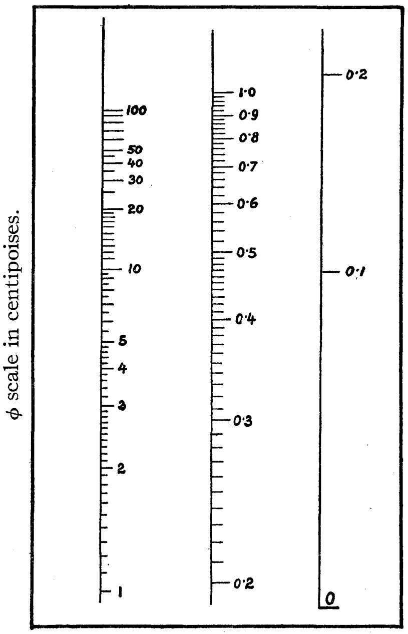

Fig. 3.

The question as to what units should be chosen for the concentrations of the components, *i. e.*, weight, volume, molarity, etc., has been controversial, and each one of the previously proposed empirical rules was based on different terms. It can be shown that the ϕ scale is generally valid if volume concentrations are used, and that all other units of quantity fail to reveal any regularity. Hence, *the unit of quantity with reference to viscosity is volume.*[4]

Various examples of ideal mixtures are shown in Fig. 4. Apart from systems consisting of paraffin hydrocarbons, others of entirely different nature have been described in the literature. Thus, Kendall and Monroe[3] concluded from exact calorimetric, cryoscopic, and density measurements that the following four systems should be ideal:

Benzene–Ethyl benzoate
Benzene–Benzyl benzoate
Toluene–Ethyl benzoate
Toluene–Benzyl benzoate

All these systems appear as straight lines in Fig. 4, including the last-mentioned which failed to satisfy the authors' empirical cube root formula—an exception which they were unable to explain. Actually, there is no exception.

Kendall and Wright[5] investigated other pairs, ethers and esters which should give ideal mixtures. One of these

Phenyl ether–Phenetole

is also shown in Fig. 4.

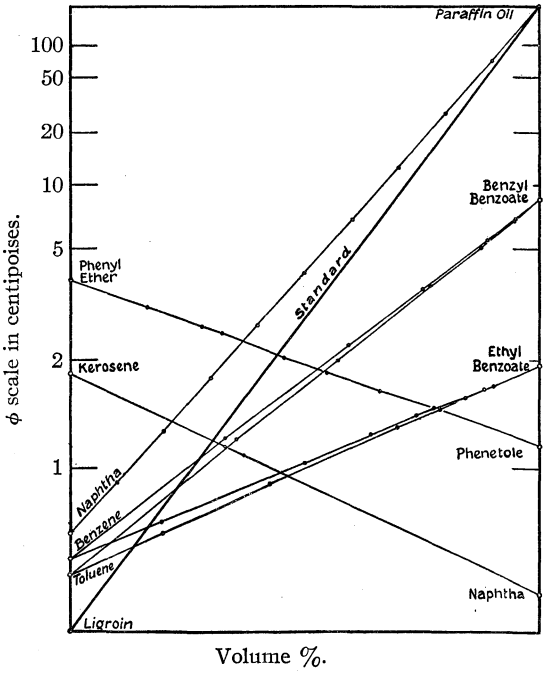

Fig. 4.

Ideal solutions of solid substances can be regarded as ideal mixtures, and they follow the same law. If the viscosities in ϕ scale are plotted against volume concentrations, straight lines result, Fig. 5. Even very complex substances, such as some resins, obey the ϕ function very accurately, also highly concentrated electrolytes, *e. g.*, zinc chloride in water.

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(4) All data used in the diagrams have been recalculated in volume percentages.

(5) Kendall and Wright, This Journal, **42**, 1776 (1920).

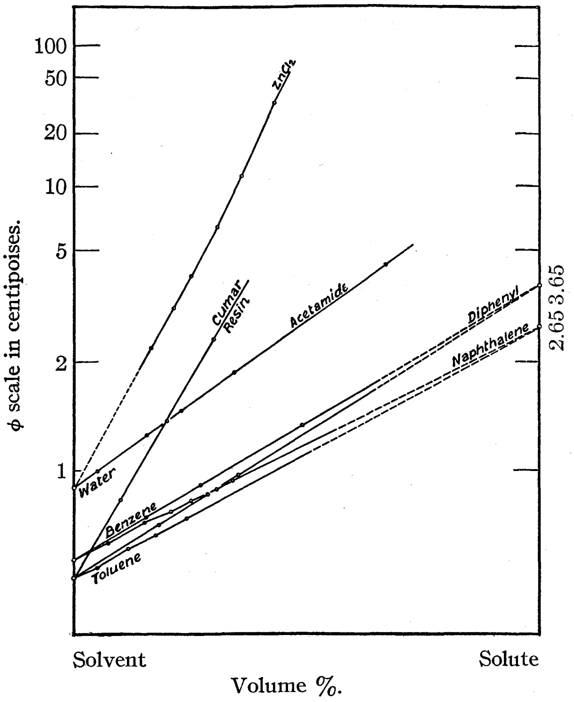

Fig. 5.

Solids in solution are, in fact, components of a liquid system. The straight lines may be extrapolated as far as 100% solute; the viscosity thus intercepted would be that of the solute itself if it could exist in liquid form under the given conditions. It will be seen later that such viscosities, though not readily realizable, have a physical significance; they are the same as those obtained by extrapolating the temperature function below the melting point.

Kendall and Monroe[3] offer evidence for the ideality of

Naphthalene in benzene
Naphthalene in toluene
Diphenyl in benzene
Diphenyl in toluene

In the scale of their assumed cube root formula the extrapolated viscosities of the solutes vary with the solvent: 2.25 and 1.83, respectively, for naphthalene, and 3.44 and 2.82 for diphenyl. In the ϕ scale, however, the lines of each solute converge exactly toward the same point on the 100% axis—2.65 cp. for naphthalene and 3.65 cp. for diphenyl. The temperature function of naphthalene, extrapolated to 25°, gives 2.75 cp., which is in very good agreement with the above value.

Ternary ideal mixtures can be computed in the same manner as binary ones. First, two of the components are combined according to their volume ratios, and the resulting ϕ ordinate is then proportioned against the third component. Examples of this kind are

Benzene–Ethyl ether–Acetone[6]
Allyl phenyl thiourea–Aniline–Toluene[7,8]

The graphical computation of the viscosities of these mixtures agrees perfectly with the measurements.

Some originally binary mixtures may become ternary if a chemical reaction occurs between the components. However, if the reaction is quantitative, and completely consumes one of them, leaving the other in binary mixture with the reaction product, the system may divide itself into two binary parts: A–(AB), and (AB)–B. Many such cases have been plotted and found ideal; *e. g.*

Chloral–(Chloral hydrate)–Water[9]
Stannic chloride–(Mol. compound)–Ethyl benzoate[10]
Allyl thiocyanate–(Subst. thiourea)–Aniline[8]
Allyl thiocyanate–(Subst. thiourea)–Methyl aniline[11]

All these systems give the same kind of diagram; the ascending branches appear as straight lines intersecting at molar ratios of exactly 1:1. Figure 6 shows the last-mentioned system in absolute viscosity and ϕ scale.

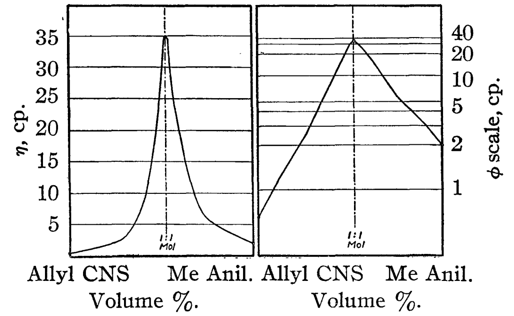

Fig. 6.

Non-ideal Mixtures.—Non-ideal effects occur if either the volume or the force field surrounding the molecules is subject to change. Association generally raises, and dissociation reduces, viscosity from the values it should normally assume. It must be emphasized, however, that these effects need not be real or permanent in order to cause deviations; mere attractions or tendencies in the

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(6) Bingham and Brown, Thesis, Lafayette College, 1921.

(7) Allyl thiocyanate and aniline yield quantitatively allyl phenyl thiourea; the latter forms an ideal binary mixture with excess aniline, and ideal ternary mixtures with toluene.

(8) Kurnakov and Kviat, *Ann. Inst. Polyt. Petrograd,* **20**, 664 (1913).

(9) Dunstan, *J. Chem. Soc.*, **85**, 817 (1904).

(10) Kurnakov, Perelmuter and Kanov, *Ann. Inst. Polyt. Petrograd*, **24**, 399 (1915).

(11) Kurnakov and Zhemchuzhnui, *ibid.*, **18**, 125 (1913).

sense of, *e. g.*, association, would be evident in the viscosity record, without formation of any definite compound.

The difficulty is not in the sensitivity with which viscosity, as a measurable property, responds to these influences; it is mainly in the quantitative evaluation of the results obtained. Empirical formulas are entirely unreliable; they are neither generally valid, nor accurate even within limited ranges. The ϕ scale, however, indicates deviations from the ideal course, no matter how small, or over what range, in the right sense, magnitude and location.

In the following examples the existence of definite association compounds is supported by other evidence, *e. g.*, by maxima in the freezing point curves.

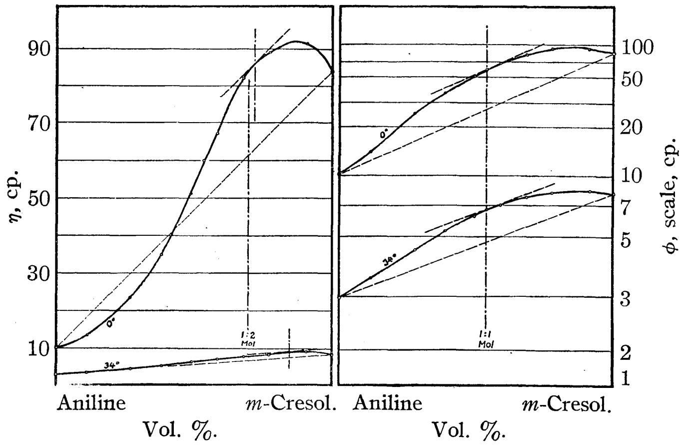

Fig. 7.

Tsakalatos[12] concluded from the absolute viscosities of the systems

m-Cresol–Aniline
m-Cresol–*o*-Toluidine

that compound formation occurred at a ratio of 2:1 moles in both cases. However, Kremann[13] found only 1:1 molar compounds in the freezing point curves. As shown in the diagrams of the first-mentioned system, Fig. 7, the absolute viscosity curves are distorted, and their maxima[14] appear displaced; the ϕ curves deviate steadily toward maxima at exactly equimolar ratios which are not shifted with varying temperature. The second case and many similar systems give analogous figures; among these are, using the data by Bramley[15]

Phenol–Aniline	1:1 mole
Phenol–Dimethylaniline	0.548:0.452 mole
Phenol–Diphenylaniline	No compound

In some cases different compounds seem to occur in the solid and liquid phase. Thus

Phenol–Quinoline[15]

indicate a definite association effect for sharply 1:1 mole. Freezing points show maxima at 2:3 and 2:1 moles, but no singularity at 1:1 mole. The ϕ curve of the system

o-Chlorophenol–Pyridine[15]

has a maximum at 1:1 mole coinciding with the freezing point record; between this mixture and the phenol the ϕ curve, but not the freezing points, shows another sharp maximum.

Where the ϕ curves sag below linearity, dissociation (des-association) either of one or both components must be assumed. Such cases are surprisingly rare; examples are

Phenol–Nitrobenzene[15]
Ethyl alcohol–Benzene[9]

This is interesting, for such "negative" curvatures appear very frequently, not only in absolute viscosity diagrams but also in all empirically assumed scales, particularly where the range of viscosities between the components is considerable. Actually, it seems that associated substances, as a rule, have quite stable constitutional units which do not vary or break down as readily as commonly assumed. This is also evident in their mostly normal response toward temperature changes, as explained in the following.

II. The Viscosity Function of Temperature

Here, again, ideal and non-ideal conditions must be anticipated, depending on the absence or presence of variable individual factors. As in the case of ideal mixtures, the paraffin hydrocarbons may be considered suitable standards.

If the absolute viscosities at different temperatures, *e. g.*, of *n*-octane, are plotted and the resulting curve is straightened into a line by the same method that was used in obtaining the viscosity function ϕ, a scale is obtained which, again, is generally valid. The viscosity–temperature functions of all substances, except those

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(12) Tsakalatos, *Bull. soc. chim.*, **3**, 234 (1908).

(13) Kremann, *Wien. Ber.*, **113**, 878 (1904).

(14) These maxima or minima must be reckoned from the straight line connecting the two terminals and indicating the ideal course. In the points of greatest deviation from this line the tangent to the curve is parallel to it.

(15) Bramley, *J. Chem. Soc.*, **109**, 10, 434 (1916).

of variable nature, appear as straight lines.

There is, moreover, a very significant relation between these two functional scales—the one derived from ideal mixtures, and the other from temperature effects—they are actually identical over their whole extent. *The general law of viscosity relative to temperature is identical with that of viscosity relative to dilution.*

The validity of this postulate has stood the test of all data represented or mentioned in this paper. The complete ϕ scale used in the diagrams and shown in Fig. 3 was assembled from numerous over-lapping sections in which mixture and temperature standards were used indiscriminately. The continuity of the function was found real and precise in all ranges.

Figure 8 shows a selection of liquids, representing various chemical types. The following partial list contains substances which give absolutely straight lines between 0° and their boiling points, using the measurements by Thorpe and Rodger[16] which are recognized as the most accurate on record. Lack of space prevents the reproduction of the diagrams.

Hydrocarbons.—Isoprene, *n*-pentane, isopentane, *n*-hexane, isohexane, diallyl, *n*-heptane, isoheptane, *n*-octane, benzene (0–70°), toluene, *o*-, *m*-, *p*-xylene, ethyl benzene.

Ethers.—Diethyl, methyl propyl, ethyl propyl, dipropyl.

Esters.—Methyl formate, methyl, ethyl and propyl acetates, propionates, *n*- and isobutyrates, valerates.

Ketones.—Acetone, methyl ethyl, diethyl, methyl propyl, methyl butyl.

Halogen Compounds.—Propyl chloride, propyl bromide, propyl iodide, isopropyl chloride, methylene dichloride, chloroform, carbon tetrachloride, ethylene chloride, ethylidene chloride, perchloroethylene, bromine.

Sulfur Compounds.—Methyl sulfide, ethyl sulfide, carbon disulfide, thiophene.

Only very few liquids—the lowest alcohols and fatty acids, for example—show distinct and significant deviations from the straight course, due without doubt to variable association. Even water follows an absolutely straight line with the exception of the well-known anomalous region above its melting point. These examples show very clearly that association in itself does not interfere with normal behavior as long as it remains constant; associated substances may very well conform with ideality.

The almost universal prevalence of ideal conditions in pure substances is important in view of the fact that ideal mixtures are far less common. This suggests that pure substances are in most cases homogeneous, and contain molecular entities of uniform structure. Consequently, the various fractional association factors ascribed to nearly all of them by Ramsay and Shields,[17] Traube,[18] and McLeod,[19] do not seem to have a purely constitutional meaning, *i. e.*, do not correctly represent association.

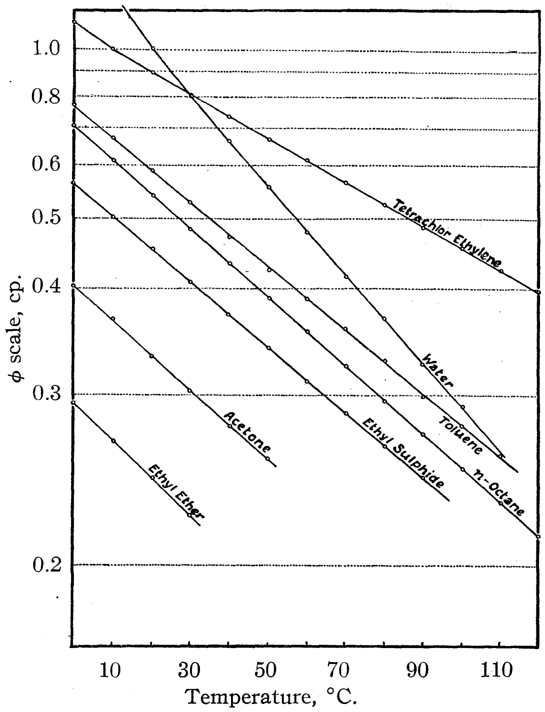

Fig. 8.

The Critical Region.—The present analysis deals with the viscosity of liquids; that of gases is an entirely different phenomenon, and of a negligible order, if expressed in the same measure. The viscosity typical for the liquid state must disappear at the critical temperature; the viscosity of gases is no functional extension of it. One may, therefore, speak of a "zero level of liquid viscosity" at the discontinuity between the gaseous and the liquid states. Since the linearity of the ϕ functions is perfect within the recorded ranges, an extrapolation as far as the critical point may be considered significant.[20]

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(16) Thorpe and Rodger, *Phil. Trans.*, **185**, 397 (1894); *Proc. Roy. Soc.* (London), **60**, 152 (1896).

(17) Ramsay and Shields, *Trans. Chem. Soc.*, **63**, 1089 (1893).

(18) Traube, *Ber.*, **30**, 283 (1897).

(19) McLeod, *Trans. Faraday Soc.*, **19**, 17 (1923).

(20) Data on viscosities above the boiling points of, *e. g.*, benzene, toluene, ether, ethyl and isobutyl acetate, ethyl bromide, carbon tetrachloride, etc., by Heydweiller [*Wied. Ann.*, **59**, 193 (1896)], show that the general straight course continues. Phillips [*Proc. Roy. Soc.* (London), **87**, 48 (1912)] measured viscosities of liquid carbon dioxide within the critical region; these are on a curve which does not merge into that of the gas viscosities, but intersects it.

The linearity of the ϕ function is not affected if, instead of centigrade, reduced absolute temperatures $(1 - T/\Theta)$ are used as abscissas. In such a diagram all lines should converge toward one point, because at the critical temperature Θ, or for $T_r = 0$, all liquid viscosities become equal, *i. e.*, nil. As shown in Fig. 9, many lines are crowded together, and reach the critical temperature at a reasonably well defined level which, therefore, can be taken as that of zero liquid viscosity. However, there are also several whose intercepts indicate viscosities of considerable magnitude at their known critical temperatures.

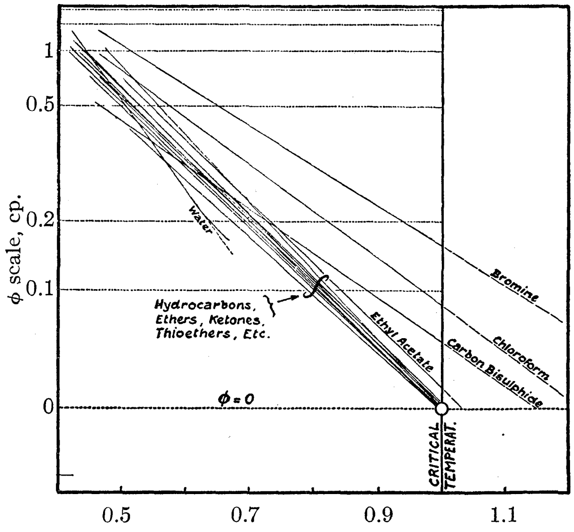

Fig. 9.

This probably means that in these cases the critical temperatures, as of record, are too low, that the observable disappearance of the surface does not mark the end of all liquid structure. That this survival should be most appreciable in substances with strong internal forces, is to be expected and is borne out in Fig. 9.

If then it be justifiable to consider the critical discontinuity expanded over an appreciable temperature interval, this would reach from the conventionally observed critical temperature upward as far as another "limiting" critical temperature which would be defined by the actual and complete disappearance of liquid viscosity.

This critical range can be estimated in Fig. 9; it is represented by the distance from $T_r = 0$ to the intersection of the ϕ line with the zero level.

A peculiar exception is that of water. Its line in Fig. 9 is unusually steep and passes through the zero level at much lower than the critical temperature—the only case of this kind. This is obviously impossible, and it must be assumed that a structural rearrangement occurs at some higher temperature which would cause the curve to reach the critical point. Three viscosity measurements between 100 and 153° seem to indicate this course which is probably due to increasing association.

Table I

Absolute Critical Temperature

	Observed	"Limiting"	Range
n-Pentane	470	464	...
n-Hexane	507	500	...
n-Heptane	540	541	...
n-Octane	569	572	...
Benzene	565	566	...
Toluene	594	597	...
Ethyl ether	466	474	8
Acetone	508	514	6
Ethyl acetate	525	541	16
Thiophene	590	615	25
Carbon disulfide	550	633	83
Methylene chloride	518	594	76
Chloroform	533	649	116
Carbon tetrachloride	557	676	119
Propyl chloride	494	520	26
Ethyl bromide	499	576	77
Ethyl iodide	554	680	126
Bromine	575	810	235

The expansion of the critical discontinuity into a range which, according to the above estimates, may assume the extent of hundreds of centigrade degrees, is of great fundamental importance. Of course, the correctness of the extrapolation of the ϕ lines depends on the absence of discontinuities in the large temperature ranges within which no viscosity data are available. Viscosity measurements over the entire course and up into the critical region, particularly on such substances as, *e. g.*, bromine, would yield very valuable information.

III. The Viscosity Function of Pressure

Moderate variations of pressure hardly affect the viscosity of liquids. It is necessary to employ thousands of atmospheres in order to study the quantitative relation between viscosity and pressure. Such measurements have been carried out by Bridgman[21] in a specially constructed viscometer.

Absolute viscosity, plotted against pressure in atmospheres, yields curves which, after a very

[21] Bridgman, *Proc. Nat. Acad. Am.*, **11**, 603 (1925).

gradual ascent, bend sharply upward. In ϕ scale, these curves are not represented as straight lines, but strongly concave toward the pressure axis, Fig. 10.[22]

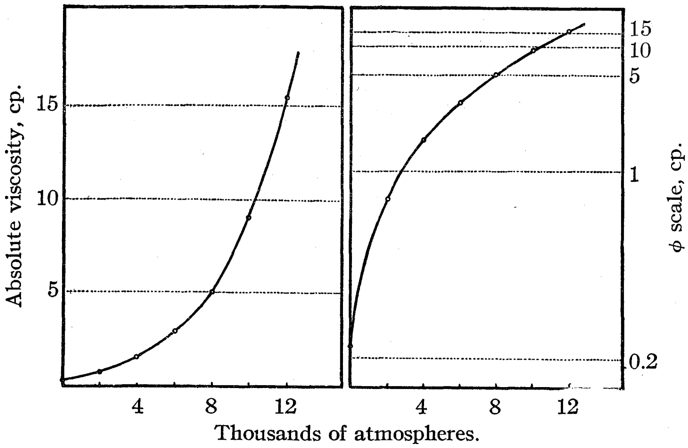

Fig. 10.—Viscosity of *n*-pentane at 30° under high pressures.

The effect of pressure on viscosity, therefore, is not additive in the same function as that of dilution and temperature, but follows a different law.

However, it is possible to rationalize this relation by the same method as was used in the construction of the ϕ scale in Fig. 2. Choosing, *e. g.*, the isotherm of *n*-pentane at 30° as a standard, a functional scale Π can be obtained. This Π scale, shown and applied in Fig. 11, represents the pressure functions of all hydrocarbons, at various temperatures, as well as those of all ideal substances, as straight lines. *All viscosity-pressure functions follow a general law. This law is different from that relating viscosity with dilution and temperature.*

Figure 11 shows Bridgman's data on paraffin hydrocarbons at two different temperatures, and it reveals a very interesting fact: all lines meet in one point.

In this point, viscosity assumes the same value at all temperatures, and for all paraffins. This is conceivable only if the intermolecular forces which control viscosity are counterbalanced by external pressure, so that their effect disappears. Hence, the negative abscissa of the intersection point is the "internal" or cohesional pressure of the liquid, and its level must be that of zero viscosity. That all paraffin hydrocarbons should have the same internal pressure is well in keeping with their known nature and relationship.

The intersections of different isotherms of the same liquid always fall on the zero level of the Π function, except in those cases where association is known to be variable, *e. g.*, water, alcohols, glycerol, etc. The negative pressure intercepts which indicate the internal pressures, are characteristic constants of the normally behaving substances. The values obtained from Π scale diagrams of Bridgman's data agree very well with those deduced by other methods, *e. g.*, from van der Waals' equation or the latent heat of vaporization. It is impossible to reproduce all the diagrams but the resulting internal pressures appear in Table II.

The Π functions of substances of variable association are not linear but they approach the straight course at high pressures, and the negative pressure intercept assumes a definite value.

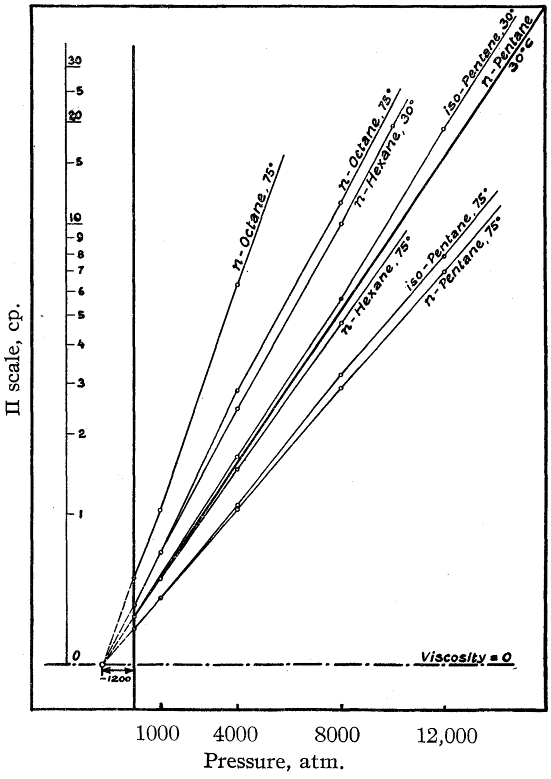

Fig. 11.

In the series of monohydric paraffin alcohols, an interesting regularity is found: the asymptotical intercepts, *i. e.*, the maximum internal pressures

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(22) On the convexity of the curves which Bridgman obtained in absolute viscosity scale, he remarked: "This is unusual; most pressure effects become relatively less high at high pressures by a sort of law of diminishing return." The ϕ scale represents this "diminishing return" without inconsistencies and apparently in its true evaluation.

are identical for all members of the series (Fig. 12). It would seem, therefore, that the internal pressure is characteristic, not only for each liquid, but for whole homologous series.

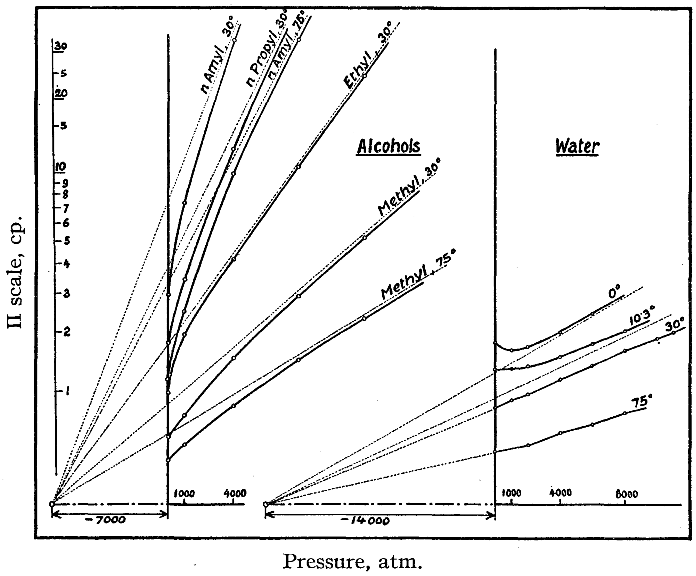

Fig. 12.

The isotherms of water, Fig. 12, run differently; they are convex, but their asymptotes also meet in one point on the pressure axis, with an intercept twice as large as that of the alcohols. Above 30°, the isotherms are straight lines.

TABLE II

		Internal pressures, atm.
All paraffin hydrocarbons		1200
Benzene		1200
Ethyl ether		1400
Chlorobenzene		1400
Alkyl benzenes		1500
Bromobenzene		2000
Chloroform		2300
Aniline		2400
Acetone		2500
Carbon disulfide		2700
Alcohols	(Limit)	7000
Water	(Limit)	14000
Glycerol	(Limit)	14000

IV. The General Viscosity Function; Constitution

The relations of viscosity to volume (dilution), temperature, and pressure must be considered special cases of the equation of state for liquids. The combination of these partial functions into the unknown general law is, of course, beyond the means of the graphical method. Nevertheless, the two functional scales, ϕ and Π, can be used for the computation of all viscosities of normal liquids if three elements are known. These are material factors characteristic for any given substance.

A complete rationalization would have to include that of constitutional additivity of these constants.

Whether the additivity of ϕ in terms of volume, or that of Π in terms of intermolecular attractions, also applies to the constituent parts of the chemical molecule; in other words, whether additive atomic values of ϕ or Π exist, cannot be definitely answered. This depends on precisely what may be understood under comparable conditions, and what kind of unit the "molecule" of a liquid really is.

For the time being, it must be realized that "constitution" to which viscosity phenomena may be related, is not necessarily that accepted in a purely chemical sense. The independently mobile entities whose movements or mobility viscosity records may, but again, may not be the individual chemical molecules.

All available facts point toward the necessity of a finer graduation of intermolecular relationships, apart from, and between complete independence and permanent association. If all these intermediate forms could be included into, and rationalized within a broader concept of constitution, the additive features of viscosity would reveal themselves more clearly.

Summary

Due to our insufficient knowledge of the structure of liquids it is impossible to formulate the basic and generally valid laws which relate liquid viscosity with variables of condition, such as volume (dilution), temperature and pressure. There is no real proof that such laws of broad validity exist, or that they are recognizable.

A method of graphical analysis was used in providing this evidence which may be summarized in three postulates:

1. A function of viscosity exists, $\phi(\eta)$, or the "ϕ scale," which is generally additive in terms of volume, *i. e.*, of dilution in ideal mixtures.

2. A function of viscosity exists which is generally additive in terms of temperature. This function or functional scale is identical with the above, ϕ; temperature and dilution

have the same quantitative effects upon viscosity.

3. Another function of viscosity exists, $\Pi(\eta)$, or the "Π scale," which is generally additive in terms of pressure.

If viscosities are plotted in these functional scales, all normal or "ideal" additivity is represented as a straight line. Deviations from this course are very accurately recognizable and significant.

Thus, the ϕ diagrams reveal "non-ideal" conditions, *i. e.*, associative or dissociative tendencies which could not be detected by other means. Extrapolation into the critical region suggests important conclusions regarding state discontinuity. The Π scale shows the correct magnitude of the internal pressures of liquids which, according to this evidence, are characteristic for whole series of related substances.

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RECEIVED DECEMBER 30, 1937

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF NOTRE DAME]

The Dielectric Properties of Acetylenic Compounds. X. Equipment for Measuring Dielectric Constants of Gases. The Polarity of Gaseous Monoalkyl Acetylenes

BY F. J. KRIEGER AND H. H. WENZKE

In order to determine accurately the low moments of the monoalkyl acetylenes it is necessary to abandon the method of solutions used in the previous papers of this series and employ the temperature variation method on the vapors of the materials to be investigated. This paper describes an apparatus for measuring the dielectric constants of gases and a method for determining their polarizations and gives data obtained for five homologs.

Description of Apparatus

The present apparatus for measuring the dielectric constants of gases was designed with a view to ruggedness and stability in operation. It is essentially a beat-frequency oscillator designed for measuring extremely small capacities with great accuracy. It offers as points of superiority over those described by Groves and Sugden[1] and by Zahn,[2] first, alternating current operation for convenience and maintained foolproof operation; second, excellent stability, combined with the comparison capacity method of eliminating residual drift, as mentioned by Zahn, but not used by Groves and Sugden; and, third, a direct-meter reading of zero beat which, because of precautions taken to eliminate entirely any tendency of the two oscillators in the circuit to "lock in," gives a much higher precision of setting than does either the resonance method of Groves and Sugden or the audible-beat method of Zahn.

Inspection of the circuit diagram, Fig. 1, indicates that the disposition of the circuit capacities, together with the capacity to be measured is similar to that used by Groves and Sugden. However, where they use the amplitude of the voltage developed at a particular point on a steep resonance curve as an indication of resonance, we use the heterodyne note between two oscillators. Frequency drift is eliminated by stabilizing one oscillator with a quartz crystal and furnishing the other oscillator with a suitable reference standard for correcting against the effect of drift should any occur.

Vacuum tube V_1, together with the inductance L_1, the capacity C_1, and the crystal X, form an oscillating circuit at a frequency of 500 kc. per second. The crystal is of the low temperature coefficient type and the oscillator is such that constancy may be assured to a precision of six cycles per degree C.

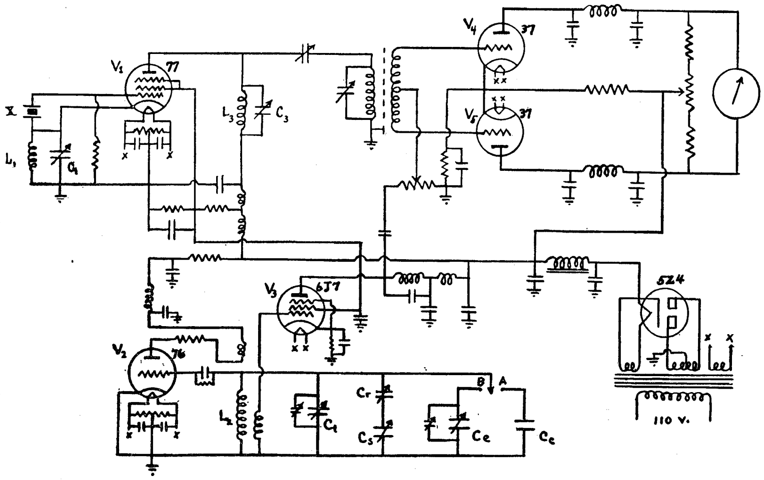

Fig. 1.—Circuit diagram of beat-frequency oscillator used in measuring dielectric constants of gases.

Vacuum tube V_2, the inductance L_2, and the capacities C_t, C_r, C_e and C_s, form the variable oscillator whose frequency is that of the second harmonic of the crystal oscil-

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[1] Groves and Sugden, *J. Chem. Soc.*, 1094 (1934).

[2] Zahn, *Phys. Rev.*, **24**, 400 (1924).

lator. This oscillator is isolated from the crystal-controlled oscillator and from the detector by radio frequency amplifier circuits associated with the buffer tube V_3.

Tubes V_4 and V_5 form a balanced detector system in which the second harmonic of the crystal-controlled oscillator beats with the output of the variable oscillator for the indication of circuit adjustment. This is always done at zero beat, indicated by the meter in the plate circuit of the detector tubes. By this means frequency differences as small as a fraction of a cycle per second may be detected easily.

The variable oscillator contains, as a part of its variable capacity, a General Radio standard condenser, C_s, in series with a small variable capacity, C_r. This arrangement makes possible a maximum sensitivity of 0.000267 mmf. (micromicrofarad) per division, over a total range of 0.56 mmf., while the lowest sensitivity is 0.00186 mmf. per division, over a total range of 3.92 mmf.

Thermal stability is achieved by two general methods. The first of these is the choice of component parts of very low temperature coefficients, and the second is a complete segregation of all tuning elements within a thermally-insulated chamber and thorough ventilation of all heat-producing units. These precautions result in a thermal stability such that the zero-beat adjustment drifted an average of 0.01 mmf. per hour. The effect of even this small drift is, in practice, eliminated by including in the circuit a capacity arrangement which can be set equal to the initial capacity of the circuit under test. By inserting this capacity, the oscillator may be returned to its original adjustment at any time.

The instrument is operated as follows:

(a) The switch is set at A and the gas cell is evacuated.

(b) The standard condenser, C_s, and the range condenser, C_r, are set at values which will accommodate the change in cell capacity that will occur upon the introduction of the gas under test. The dial readings of both condensers are recorded.

(c) The tank condenser, C_t, is tuned until the beat note as indicated in the meter is very low. The auxiliary condenser C_t vernier, is used to bring the beat note to a zero.

(d) The switch is thrown to B.

(e) The equivalent condenser, C_e, is tuned for zero beat. Any slight drift is eliminated by means of the auxiliary condenser C_e vernier.

(f) The switch is reset at A and the gas to be measured is introduced into the cell.

(g) The standard condenser, C_s, is readjusted accurately to zero beat. This value is recorded as C_s'.

(h) Should there be considerable delay between steps (e) and (g), the switch is thrown to B, and if the beat is no longer zero, condenser C_t vernier is readjusted to give exactly zero beat just before step (g) is carried out. Thus, the equivalent capacity, C_e, serves as a standard equal to the evacuated cell in capacity by means of which the oscillator may be readjusted at any time and its residual drift eliminated.

From the capacity values read in steps (b) and (g) the capacity change of the cell due to the introduction of the gas under test may be determined as follows. The total variable capacities must have been equal in the two cases to give the same frequency. Thus

$$C_e + C_t + \frac{C_r C_s}{C_r + C_s} = C_e + C_t + \frac{C_r C_s'}{C_r + C_s} + \Delta C_c$$

where ΔC_c is the change in cell capacity produced by the introduction of the gas. On simplifying the above equation and solving for ΔC_c we obtain

$$\Delta C_c = \frac{C_r^2(C_s - C_s')}{C_r^2 + C_c(C_s + C_s') + C_s C_s'} \qquad \text{(I)}$$

If we make use of the relation

$$\epsilon - 1 = \Delta C_c / C_c$$

where ϵ is the dielectric constant and C_c the replaceable cell capacity, we obtain the expression

$$\epsilon - 1 = \frac{C_r^2}{C_c} \frac{(C_s - C_s')}{C_c^2 + C_r(C_s + C_s') + C_s C_s'} \qquad \text{(II)}$$

This equation is identical in form with that of Groves and Sugden. It is to be noted that in their work these investigators neglect the term C_r^2 in the denominator, stating that C_r as it appears in the denominator need not be known very accurately. This statement is open to question as the capacity, C_r, has some effect on the third figure following the decimal point. It is also to be noted that neither end of the capacity, C_r, is at ground potential, and the determination of the capacity of any condenser when operated under such conditions is an indefinite matter when direct methods are used. The value of the capacity C_r may be obtained indirectly by the use of gases of known dielectric constant.

The dielectric constant gas cell consists of a Pyrex glass-enclosed condenser made of three concentric chromium-plated brass cylinders each 6″ (15.5 cm.) long and 3″ (7.6 cm.), $2^3/_4$″ (7.0 cm.) and $2^1/_2$″ (6.35 cm.) in diameter, respectively, held rigidly in place by means of spring clips pressing against the outer glass wall. The outer and inner cylinders form one plate of the condenser which is maintained at ground potential. The condenser leads are of tungsten and are brought out at the top of the glass container. The top of the cell is furnished with a standard taper silver-clad joint to which is fitted a glass arm leading to a manometer, a vacuum pump and an inlet for the gases to be investigated. This arrangement is similar to that of Schwingel and Williams.(3)

The cell is mounted rigidly in a cottonseed oil-bath, the temperature of which is maintained

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(3) Schwingel and Williams, *Phys. Rev.*, **35**, 855 (1930).

within 0.02° of the desired temperature by means of a mercury thermoregulator and relay-controlled heater system. The cell is connected with the beat-frequency oscillator by means of a special rigid concentric cable whose outer sheath is grounded to prevent capacity losses. In order to prevent condensation of the higher-boiling materials in the glass arm and in the manometer, those parts were wrapped with Chromel-A resistance wire and brought to a suitable temperature by means of an electric current. This precaution permits the measurement of higher pressures of high-boiling materials than would be possible at room temperature.

Calibration of Apparatus

From equation (II) it is seen that, in order to determine the dielectric constant of the cell contents, it is necessary to know the apparatus constants C_r and C_r^2/C_c and the initial and final readings of the standard condenser C_s. The value of cell capacity, C_c, was determined in the following manner. After the gas cell was brought to constant temperature it was evacuated and the oscillator was brought to zero beat. This zero beat was maintained with the equivalent capacity, C_e, in the circuit. Meanwhile the external cell capacity was replaced by a General Radio standard condenser which was tuned to zero beat. The reading of this standard condenser gave the value of the external capacity from which the value of the cell capacity was deduced.

The value of the capacity C_r was determined indirectly by making observations with gases of known dielectric constant. For this purpose the measurements of Bryan and Sanders,[4] Stuart,[5] and Zahn[6] on air and carbon dioxide were employed. The mean polarization of air was taken as 4.368 cm.^{3} and that of carbon dioxide as 7.317 cm.^{3}. Assuming that the polarization of these gases does not change with temperature and that the gas laws hold, the dielectric constants of these gases at a known temperature and pressure may be calculated by means of the relation

$$\epsilon - 1 = 4.810 \times 10^{-5} P_M p/T \qquad \text{(III)}$$

where P_M is the molecular polarization, p the pressure in mm. of mercury, and T the absolute temperature.

The air used in the calibration was passed through a train consisting of bottles containing potassium hydroxide solution, concentrated sulfuric acid, calcium chloride and phosphorus pentoxide in that order. The carbon dioxide used was obtained from a cylinder of the liquefied gas. It was passed through concentrated sulfuric acid and dried over calcium chloride and phosphorus pentoxide.

The values of the dielectric constants of air and carbon dioxide at 25°, obtained by means of equation (III), were substituted into equation (II), which was then solved for the term C_r. The value of the capacity C_r, which was chosen small, was found to be 12.81 mmf. Since the capacity of the gas cell changed with the temperature, it was necessary to determine the apparatus constant, C_r^2/C_c, for each of the temperatures employed. As the value of C_r remained the same throughout, it was necessary only to find the values of C_c.

TABLE I

PRESSURES AND DIELECTRIC CONSTANTS OF CALIBRATING GASES AND CORRESPONDING VALUES OF APPARATUS CONSTANT AT 25°

p, mm.	$(\epsilon - 1) \times 10^4$	C_r, mmf.
	Air	
747.0	5.263	12.74
748.0	5.270	12.80
759.5	5.351	12.87
760.5	5.358	12.80
	Carbon Dioxide	
757.0	8.935	12.83
758.5	8.952	12.82
	Average	12.81

TABLE II

VALUES OF THE CELL CAPACITY AND OF THE APPARATUS CONSTANT AT TEMPERATURES INDICATED

	25°	75°	125°
C_c, mmf.	401.1	405.7	407.3
C_r^2/C_c	0.4089	0.4042	0.4027

Preparation of Materials.—The methyl- and ethylacetylenes were prepared by dropping the corresponding sulfates on sodium acetylide in liquid ammonia. The gas evolved was freed from ammonia by passing it through successive bottles of water and dilute sulfuric acid. The gaseous acetylenes were dried over calcium chloride and condensed by means of a dry ice–acetone bath. The liquid acetylenes were distilled through a Davis column,[7] recondensed, and

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[4] Bryan and Sanders, *Phys. Rev.*, **32**, 202 (1928).

[5] Stuart, *Z. Physik*, **47**, 457 (1928).

[6] Zahn, *Phys. Rev.*, **27**, 455 (1926).

[7] Davis and Daugherty, *Ind. Eng. Chem., Anal. Ed.*, **4**, 193 (1932).

stored in steel cylinders. The propyl-, butyl- and amylacetylenes were prepared by dropping the corresponding bromides on sodium acetylide in liquid ammonia. The acetylenes were distilled through a modified Widmer column.

TABLE III

PHYSICAL CONSTANTS OF ACETYLENES

Acetylene	B. p., °C.	d^{25}	n^{25}_D	MR_D
Methyl	−23			14.04
Ethyl	7.9			18.66
Propyl	39.3	0.6909	1.38270	22.97
Butyl	71.0	.7146	1.39621	27.61
Amyl	98.0	.7297	1.40553	32.31

Technique and Results

The dielectric constants of the gases under consideration were determined by means of equation (II) at pressures, for the most part, above 100 mm. of mercury and at the three temperatures 25, 75, and 125°. In order to avoid the use of an equation of state for each of the gases in measuring its polarization, it was found expedient to plot $(\epsilon-1)/p$ against p and extrapolate to zero pressure. The values of the dielectric constants and of the factors $(\epsilon - 1)/p$ are given in Tables IV, V and VI.

TABLE IV

PRESSURES, DIELECTRIC CONSTANTS AND POLARIZATION FACTORS OF MATERIALS AT 25°

p, mm.	$(\epsilon - 1) \times 10^4$	$((\epsilon - 1)/p) \times 10^6$
	Methylacetylene	
435.5	18.31	4.205
350.5	14.81	4.226
291.5	12.26	4.207
245.5	10.36	4.219
222.5	9.401	4.225
0		4.235
	Ethylacetylene	
480.0	24.70	5.145
391.0	20.10	5.140
287.0	14.77	5.146
269.5	13.93	5.169
180.5	9.339	5.174
0		5.205
	Propylacetylene	
320.0	19.88	6.214
273.5	17.02	6.223
230.5	14.35	6.227
178.0	11.08	6.225
130.5	8.152	6.246
0		6.260
	Butylacetylene	
86.0	6.173	7.178
74.5	5.337	7.164
70.0	4.976	7.110
48.5	3.485	7.185
0		7.153

TABLE V

PRESSURES, DIELECTRIC CONSTANTS AND POLARIZATION FACTORS OF MATERIALS AT 75°

p, mm.	$(\epsilon - 1) \times 10^4$	$((\epsilon - 1)/p) \times 10^6$
	Methylacetylene	
320.0	10.80	3.375
261.0	8.861	3.395
219.5	7.446	3.393
170.0	5.778	3.400
0		3.420
	Ethylacetylene	
486.5	19.47	4.002
411.5	16.51	4.014
327.0	13.23	4.051
227.5	9.229	4.056
144.0	5.865	4.073
0		4.100
	Propylacetylene	
314.0	15.07	4.798
306.5	14.73	4.807
235.0	11.38	4.841
188.0	9.118	4.850
136.5	6.662	4.880
0		4.930
	Butylacetylene	
237.5	13.37	5.632
151.0	8.551	5.663
109.5	6.225	5.685
97.5	5.537	5.679
0		5.725
	Amylacetylene	
209.5	13.15	6.275
152.5	9.60	6.295
104.0	6.578	6.325
0		6.350

The polarization at zero pressure and temperature T was obtained by multiplying the zero intercept, *i. e.*, $(\epsilon - 1)/p$ at $p = 0$, by $RT/3$ in accordance with the relation

$$P = \frac{\epsilon - 1}{\epsilon + 2} V = \frac{\epsilon - 1}{\epsilon + 2} \frac{RT}{p} = \frac{\epsilon - 1}{p} \frac{RT}{3} \qquad \text{(IV)}$$

where P is the polarization at temperature T, V the molar volume, p the pressure, R the gas constant and T the absolute temperature. The use of this perfect gas equation evidently is justified at zero pressure.

The electronic polarizations were obtained by determining experimentally the molar refraction for the sodium D line of propyl-, butyl- and amylacetylenes, and calculating the values for methyl- and ethylacetylenes on the basis of the refractions of their respective electron groups. As the

TABLE VI

PRESSURES, DIELECTRIC CONSTANTS AND POLARIZATION FACTORS OF MATERIALS AT 125°

p, mm.	$(\epsilon - 1) \times 10^4$	$((\epsilon - 1)/p) \times 10^6$
	Ethylacetylene	
351.0	11.55	3.290
263.0	8.918	3.391
201.0	6.982	3.474
195.5	6.501	3.325
164.0	5.736	3.497
0		3.440
	Propylacetylene	
345.5	14.09	4.079
295.0	12.15	4.120
215.5	8.837	4.101
174.0	7.168	4.119
0		4.115
	Butylacetylene	
258.5	12.09	4.677
210.0	9.832	4.682
141.0	6.616	4.692
114.0	5.353	4.696
0		4.712
	Amylacetylene	
173.5	8.955	5.161
149.0	7.710	5.174
120.0	6.219	5.183
0		5.245

TABLE VII

POLARIZATIONS OF MATERIALS AT INDICATED TEMPERATURES

Acetylene	25°	75°	125°
Methyl	26.26	24.76	...
Ethyl	32.27	29.68	28.48
Propyl	38.81	35.69	34.06
Butyl	44.35	41.41	39.01
Amyl	...	45.97	43.42

atomic polarizations could not be accurately determined, they were neglected in the calculations of the electric moments, which were obtained from the relation

$$\mu = 0.01273 \times 10^{-18}\sqrt{(P_{\mathrm{T}} - P_{\mathrm{E}})T} \qquad \text{(V)}$$

where P_{T} is the total polarization, P_{E} is the electronic polarization and T the absolute temperature. The moments at the various temperatures and their mean values are given in Table VIII.

TABLE VIII

ELECTRIC MOMENTS OF ACETYLENES ($\mu \times 10^{18}$)

Acetylene	25°	75°	125°	Mean
Methyl	0.768	0.778	...	0.77
Ethyl	.811	.789	0.799	.80
Propyl	.875	.847	.846	.85
Butyl	.899	.882	.858	.87
Amyl	...	.878	.847	.86

Watson and Ramaswamy,[8] using the temperature variation method, obtained for the moment of methylacetylene the value 0.72, which agrees well with the value obtained by the authors, 0.77, considering that the small atomic polarization was neglected in the calculation of the latter value. The data of Table VIII indicate that the moment induced in the alkyl chain is negligible beyond the third carbon atom from the triple bond.

Summary

1. An apparatus has been constructed for measuring accurately the dielectric constants of gases and vapors at various pressures and temperatures.

2. A method which obviates the necessity of equations of state is used in determining the polarizations of gases and vapors from their dielectric constants.

3. The dielectric constants, polarizations and electric moments have been determined for gaseous methyl-, ethyl-, propyl-, butyl- and amylacetylenes.

NOTRE DAME, INDIANA

RECEIVED APRIL 4, 1938

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[8] Watson and Ramaswamy, *Proc. Roy. Soc.*, **A156**, 130 (1936).

[Contribution from the Chemical Laboratory of the University of Michigan]

Alteration of Adsorption Properties of Charcoal: Activation of Charcoal in Different Gases at Different Temperatures

By F. E. Bartell and Lewis E. Lloyd

Three types of activated charcoal were prepared in this investigation, a "High Temperature Charcoal," activated at 1000° in an oxidizing atmosphere, a "Medium Temperature Charcoal," activated with oxygen at 400°, and a "Low Temperature Charcoal," activated below 250° in a strongly oxidizing gaseous atmosphere. For these charcoals, the following properties were determined: preferential adsorption of benzene–ethanol solutions, acid–base adsorption, and the sign of the particle charge of the charcoals.

Experimental

The ash-free sugar charcoal used in this investigation was prepared by charring recrystallized sucrose. After a preliminary grinding, the charred material was heated in nitrogen for two hours at 950°. It was then purified according to Miller;[1] and after the final heating in nitrogen at 950°, only that portion was used which passed a 300 mesh sieve but did not pass a 350 mesh sieve. The charcoal was stored in a wide-mouthed, screw-cap bottle until used. This charcoal will subsequently be referred to as "stock" charcoal.

The charcoal was activated in a quartz tube which was held in a horizontal position and could be rotated to give more complete mixing of the charcoal and activating gas. The quartz tube was heated by an electric furnace which could be removed from the tube by merely sliding it. This made it possible to cool the charcoal quickly at the end of an activation treatment. In all cases the charcoal was cooled in an atmosphere of the same gas as that used for the activation.

Preferential Adsorption Experiments.—The preferential adsorption which the different types of activated charcoal gave in benzene–ethanol solutions was determined by the interferometric method developed by Bartell and Sloan.[2] The method consists in placing a known amount of the adsorbent in each of several different concentrations of solutions of a pair of suitable liquids, and determining the change in fractional concentration of each solution by means of the interferometer. The data are plotted in terms of the $H\Delta x/m$ value against the mole fractional concentration of ethanol (x), where H is the number of milliequivalents of solution, Δx the change in fractional concentration, and m the weight of adsorbent. The $H\Delta x/m$ value is calculated from the data by the method of Bartell and Sloan.[2]

When the data are plotted in the manner described, an S-shaped curve is obtained. The point at which this S-shaped curve intersects the x-axis will be designated as the X_0 value. The X_0 value gives the maximum concentration at which ethanol is preferentially adsorbed, and since the concentration is given in mole fractions of ethanol, the X_0 value also gives the fraction of the entire concentration range (in molar units) over which ethanol is preferentially adsorbed. Those solids which adsorb polar ethanol over a major portion of the entire concentration range are less organophilic and more hydrophilic than solids which adsorb non-polar benzene over a major portion of the entire range. The X_0 value found by Bartell and Sloan[2] for organophilic charcoal with benzene–ethanol was 0.200. The X_0 value found by Bartell, Sloan, and Scheffler[3] for hydrophilic silica with benzene–ethanol was 0.850. The X_0 value gives, then, a comparative measure of the organophilic or hydrophilic nature of the solid; the higher the X_0 value, the more hydrophilic the solid. As yet no point has been established on the concentration axis dividing organophilic solids from hydrophilic solids. It is possible that such a point may be established by further experimentation.

"High Temperature Charcoal."—In order to make a comparison with the benzene–ethanol preferential adsorption curve of Bartell and Sloan[2] and to make measurements of other properties of a charcoal similar to that which they used, some charcoal was activated at 1000° in a slow stream of oxygen. The oxygen was passed through at the rate of 200 cc. per hour for seven and one-half hours. The S-shaped curve (see Fig. 1) obtained with this charcoal (Charcoal 1) crossed the x-axis at a value of 0.210 mole fraction of ethanol as compared to the 0.200 value obtained by Bartell and Sloan.[2] Their charcoal was activated in a stream of air, but, as was to be expected, air and oxygen gave about the same activation of charcoal at 1000°.

To avoid possible activation effects with oxygen over a temperature range during cooling, carbon dioxide was used as the activating gas in subsequent high temperature treatments. Charcoal 2 was activated for two hours in oxygen at 1000° and then for two hours in carbon dioxide at the same temperature. Charcoals 3 and 4 were activated in carbon dioxide at 1000° for five hours. The S-shaped curves for Charcoals 2, 3, and 4 are given in Fig. 1. The X_0 value for the preferential adsorption was shifted from 0.210 for Charcoal 1, which was cooled in oxygen, to 0.125 for Charcoals 3 and 4, which were cooled in carbon dioxide. The experimental data obtained for Charcoal 4, a typical "High Temperature Charcoal," are given in Table I.

The fact that the charcoals which were activated and cooled in carbon dioxide gave a lower X_0 value than the X_0 value of charcoal which was activated and cooled in air or oxygen indicates that during the process of cooling in oxygen some of the charcoal surface had been changed from the "High Temperature Charcoal" type. The

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[1] E. J. Miller, *J. Phys. Chem.*, **30**, 1031 (1926).

[2] F. E. Bartell and C. K. Sloan, This Journal, **51**, 1637 (1929).

[3] F. E. Bartell, G. Scheffler and C. K. Sloan, *ibid.*, **53**, 2501 (1931).

TABLE I

CHARCOAL No. 4

N = Weight of solution; m = weight of adsorbent; dR = change in scale division on interferometer; c = weight fraction of solute; x = mole fraction of solute; H = total number of millimoles of solution. For method of calculating $H\Delta x/m$, see Bartell and Sloan.[2]

N	m	dR	dc/dR × 10^{-5}	c	x	$H\Delta x/m$
4.3472	0.2387	37.4	1.860	0.012038	0.020235	0.2488
4.3352	.2449	38.1	1.875	.027325	.045452	.2697
4.3255	.2419	20.7	1.900	.051115	.083666	.1475
4.3029	.2388	− 16.9	1.937	.094684	.15057	− .1202
4.2571	.2340	− 77.6	2.020	.18356	.27592	− .5491
4.1702	.2400	−211.7	2.188	.37107	.50000	−1.3688
4.0337	.2402	−345.0	2.420	.60784	.72430	−2.1414
4.0008	.2379	−349.2	2.552	.83565	.84955	−2.1189
3.9556	.2372	−304.5	2.659	.86289	.91429	−1.7766
3.9287	.2382	−240.6	2.720	.92522	.95449	−1.4658
3.9071	.2352	−137.7	2.772	.97915	.98760	−0.8196

"1000° Charcoals" cited in the literature undoubtedly represent various degrees of completeness of 1000° activation, and although their properties are fairly similar, further experiment may show that the term "1000° Charcoal" lacks sufficient specificity to warrant this definite designation.

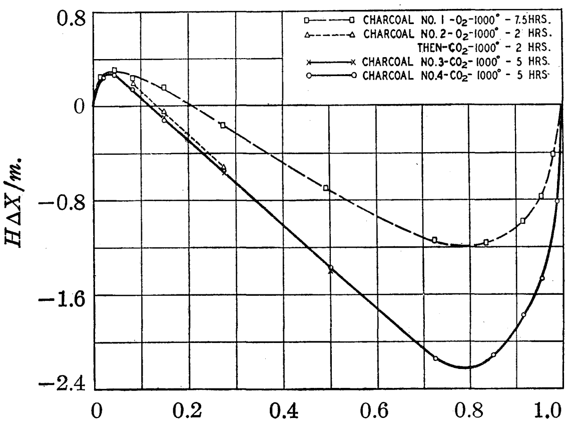

Fig. 1.—Preferential adsorption: Charcoal activated at 1000° in oxidizing atmosphere.

The concept that adsorption occurs at definite activated spots, which are probably unit cells at the crystal surface, has been accepted generally in explaining adsorption phenomena. According to this concept, an adsorbent becomes activated by having each of the spots or units of the surface changed into what constitutes the activated state. Thus, a "High Temperature Charcoal" would be one whose surface had all the unit spaces activated to that type. In actual practice complete activation of one type is probably never attained but may be approached. The exact properties of a given charcoal will depend both on the type of activation and also on the relative proportion of the surface which has the desired activation.

The "High Temperature Charcoal" was found to be quite stable at temperatures up to 150°. Part of the charcoal activated with and cooled in an atmosphere of carbon dioxide, when placed back in the activating tube and treated with dry oxygen for two hours at 150°, showed no change in X_0 value. The curve for the charcoal after this treatment was practically coincident with the one which the 1000° treatment gave.

"Medium Temperature Charcoal."—The first "Medium Temperature Charcoal" prepared during this investigation (Charcoal 5) was taken from the "stock" supply and activated directly at 400° in oxygen for seven and one-half hours without previous activation at 1000°. The preferential adsorption curve for Charcoal 5 is given in Fig. 2.

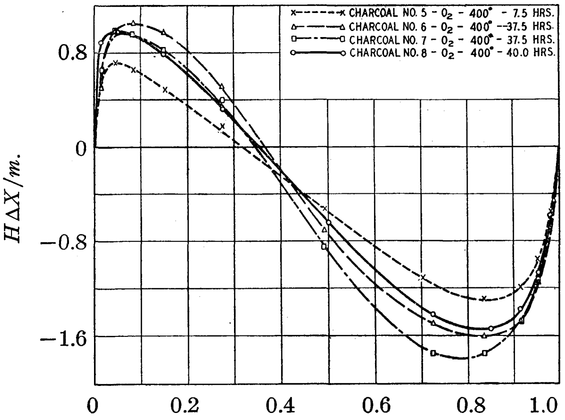

Fig. 2.—Preferential adsorption: Charcoal activated at 400° in oxygen.

This charcoal approached the characteristics which were expected except that the X_0 value, 0.315, was not so high as was expected in view of the fact that it had been predicted by other workers[4] that this charcoal would be hydrophilic. In the next two runs (Charcoals 6 and 7) the charcoal was first activated at 1000° in oxygen for seven and one-half hours and then for thirty-seven and one-half hours at 400° in oxygen. Charcoal 8 was first activated for five hours at 1000° in carbon dioxide and then in oxygen at 400°. The properties of Charcoals 6, 7, and 8 were quite similar to those of Charcoal 5. The preferential adsorption curves for Charcoals 6, 7, and 8 are shown in Fig. 2, and the experimental data for Charcoal 8 are given in Table II. The X_0 values for Charcoals 6, 7, and 8 are

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(4) I. M. Kolthoff, THIS JOURNAL, **54**, 4473 (1932).

TABLE II

CHARCOAL NO. 8

N	m	dR	dc/dR × 10^{-5}	c	x	$H\Delta x/m$
4.3471	0.2455	125.7	1.860	0.012038	0.020235	0.8917
4.3364	.2446	138.1	1.875	.027325	.045452	.9789
4.3236	.2456	135.8	1.900	.051115	.083666	.9532
4.2974	.2487	109.0	1.937	.094684	.15057	.7968
4.2542	.2454	47.6	2.020	.18356	.27592	.3211
4.1740	.2474	− 99.3	2.188	.37107	.50000	− .6327
4.0669	.2460	−232.5	2.420	.60784	.72430	−1.4203
3.9979	.2452	−261.3	2.552	.83565	.84955	−1.5374
3.9550	.2461	−237.6	2.659	.86289	.91429	−1.3783
3.9246	.2471	−187.4	2.720	.92522	.95449	−1.0705
3.9020	.2468	−103.0	2.772	.97915	.97915	−0.5833

very similar, the range being from 0.346 to 0.370. The X_0 value for Charcoal 5 is a little lower, being only 0.315. This difference in X_0 values is probably due to differences in the completeness of the medium temperature activation. As was suggested for the term *1000° Charcoal*, the term *400° Charcoal*, which also appears in the literature, may in the future be shown to lack the previously implied specificity.

A small change in the X_0 value of "Medium Temperature Charcoal" is effected by subsequent low temperature treatment. Some charcoal of this type was heated in oxygen at 125° for forty hours. The X_0 value was found to have been reduced by 0.013 unit. The charcoal was then further treated with oxygen (saturated with water vapor at 25°) at 150° for another forty hours. The X_0 value was reduced by 0.014 unit. The "Medium Temperature Charcoal" was fairly stable, then, since a total low temperature treatment with oxygen for eighty hours changed its X_0 value only by 0.027. At ordinary temperatures "Medium Temperature Charcoal" changes slowly and appears to revert to the "High Temperature Charcoal" type.

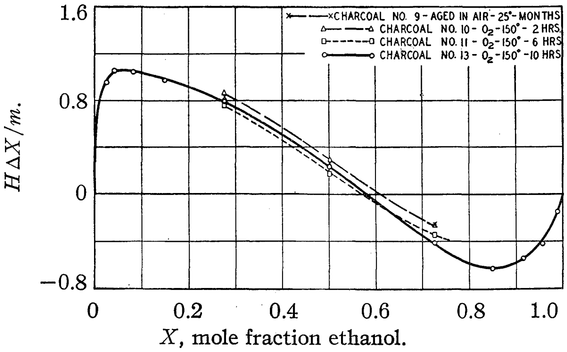

Fig. 3.—Preferential adsorption: Charcoal activated at 150° in oxidizing atmosphere.

"Low-Temperature Charcoal."—Some of our experiments had indicated that the "stock" charcoal had a larger X_0 value, and was more hydrophilic than the "Medium Temperature Charcoal." A special run was made, therefore, to determine the preferential adsorption of the "stock" charcoal. This untreated "stock" charcoal, No. 9, gave an X_0 value of 0.610, which is considerably higher than 0.370, the highest X_0 value for the "Medium Temperature Charcoal." The curve for Charcoal 9 is shown in Fig. 3. The "stock" charcoal was then heated in oxygen at 150° to see if such a low temperature oxidation would produce a more hydrophilic charcoal. Runs at 150° for two hours (Charcoal 10), six hours (Charcoal 11), and for ten hours (Charcoal 12) were made. The curves for these charcoals are given in Fig. 3. A low temperature treatment of the "stock" charcoal in oxygen for ten hours reduced the X_0 value from 0.610 to 0.580, and thus the "stock" charcoal, like the "Medium Temperature Charcoal," is changed slightly by a low temperature oxygen treatment and appears to revert toward a higher temperature type.

Some preliminary preferential adsorption runs on the "stock" charcoal just after it had been prepared and heated at 950° in nitrogen showed that at the time it was prepared the charcoal was organophilic, that is, it preferentially adsorbed benzene over the greater portion of the concentration range. The results on low temperature oxygen treatment of the "stock" charcoal and the "Medium Temperature Charcoal" show that oxygen alone would not be expected to change the "stock" charcoal from its original organophilic to a hydrophilic nature. It appeared that a catalytic effect must have brought about some type of activation during the time that the charcoal stood after its preparation. Oxides of nitrogen are known to be effective catalysts for oxidation reactions. Bartell and Bristol[5] found that traces of nitric oxide added to the oxygen stream greatly increased the oxidizing action on stibnite mirrors even at relatively low temperatures. It seems probable that traces of oxides of nitrogen were formed when the charcoal was heated and cooled in nitrogen during its preparation. Oxygen which is adsorbed on the surface of charcoal is known to be very difficult to remove, its complete removal requiring extreme outgassing.[6,7] Some of the oxygen which was adsorbed on the charcoal before the nitrogen treatment probably reacted with nitrogen during the 950° treatment and formed oxides of nitrogen. It seemed possible that traces of the oxides might have remained on the "stock" charcoal as it cooled, and catalyzed a slow oxidation at 25° as the "stock" charcoal stood in its container.

To test the above theory, some activation treatments were tried using strongly oxidizing gaseous mixtures at low temperatures. These treatments increased the X_0 values of the charcoals. Some "Medium Temperature Char-

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(5) F. E. Bartell and K. E. Bristol, unpublished.

(6) Irving Langmuir, THIS JOURNAL, **37**, 1154 (1915).

(7) A. Frumkin, R. Burstein and P. Lewis, *Z. physik. Chem.*, **157** 445 (1931).

TABLE III

CHARCOAL No. 14

N	m	dR	dc/d$R \times 10^{-5}$	c	x	$H\Delta x/m$
4.2590	0.2317	174.0	2.020	0.18498	0.27781	1.3179
4.1710	.2303	94.1	2.188	.37072	.49963	0.6439
4.0625	.2313	− 8.0	2.420	.60756	.72406	− .0520

coal" (with an X_0 value of approximately 0.370) was treated with a mixture of nitric oxide, oxygen, and water vapor at 150° for ten hours. The resulting product, Charcoal 13, was found to have an X_0 value of 0.545 and had, therefore, been made considerably more hydrophilic.

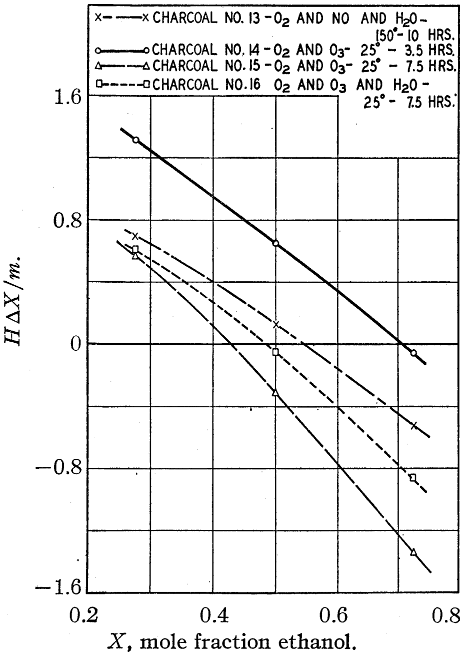

Fig. 4.—Preferential adsorption on charcoal activated at low temperature in oxidizing atmosphere.

Several runs were next made (Charcoals 14, 15, and 16) using ozone as oxidizing gas. Ozone, a fairly strong oxidizing agent, has the advantage that no foreign material other than that already used in the oxygen treatments, is exposed to the charcoal surface. The ozone was generated by a silent discharge apparatus which furnishes from 8 to 10% of ozone. In two of the runs, water vapor was excluded (Charcoals 14 and 15), and in one it was added (Charcoal 16). The starting material for Charcoal 14 was "stock" charcoal, and for Charcoals 15 and 16, it was "Medium Temperature Charcoal." In every case the charcoal thus treated was made more hydrophilic, that is, its X_0 value was increased. In the run in which the "stock" charcoal was treated with ozone (Charcoal 14), its X_0 value was increased from about 0.610 to 0.710. Nitric oxide produced greater effects than ozone, and had "stock" charcoal been activated with nitric oxide and oxygen as was the "Medium Temperature Charcoal" for Charcoal 13, and had the activation been continued for a sufficient period of time, it is possible that a charcoal with preferential adsorption properties approaching those of silica (X_0 = 0.850) might have been prepared. The curves for Charcoals 13, 14, 15, and 16 are given in Fig. 4. Experimental data for Charcoal 14 are given in Table III.

A graph showing the change in the preferential adsorption caused by different activation treatments of charcoal is shown in Fig. 5. (The data for these curves are given in Tables I–III.) On this graph is plotted also the curve for silica as given by Bartell, Sloan, and Scheffler.[3] The X_0 value for the most organophilic charcoal (Charcoal No. 3) is 0.125, while the X_0 value for silica, a very hydrophilic solid, is 0.850. The X_0 value of 0.125, which was found to be quite reproducible for charcoal heated in carbon dioxide at 1000°, appears to be characteristic of the "High Temperature Charcoal." A representative "Medium Temperature Charcoal" curve is given in Fig. 5 and is labeled "M. T. Charcoal." An X_0 value in the range of 0.350 to 0.370 is probably characteristic of the "Medium Temperature Charcoal." This indicates that "Medium Temperature Charcoal" preferentially adsorbs ethanol over a larger

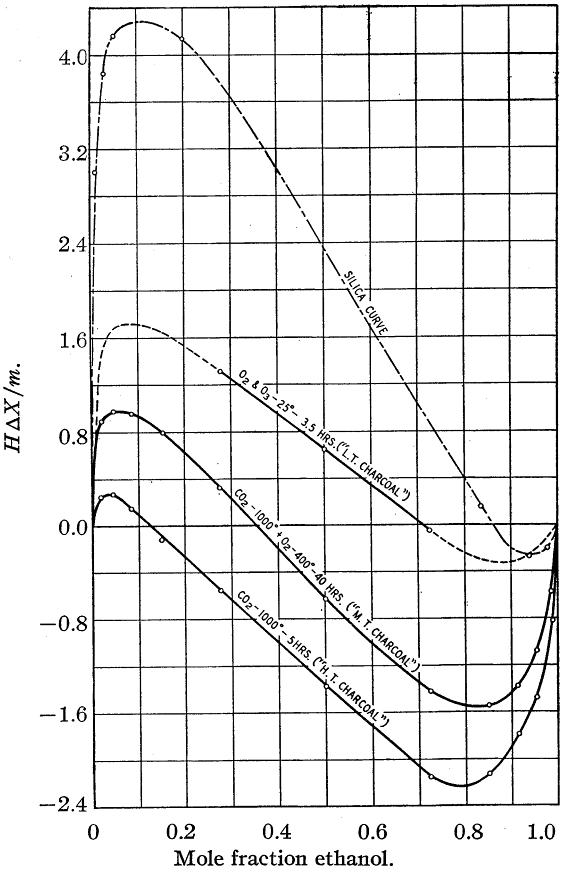

Fig. 5.—Comparison of different charcoals: preferential adsorption of ethanol from benzene.

Table IV

Properties of Different Activated Charcoals

Char-coal	Activation treatment: Pretreatment: Gas	Temp., °C.	Time, hrs.	Final treatment: Gas	Temp., °C.	Time, hrs.	x_0	Charge on particle	Acid–base ads. (50 cc. soln. 1 g. charcoal) milliequiv./g. HCl	NaOH
1				O_2	1000	7.5	0.210	(+) + (−)	0.172	0.000
2				$O_2 + CO_2$	1000	2 ea.	.136	(+) + (−)	.260	.030
3				CO_2	1000	5	.125	(+) + (−)	.281	.000
4				CO_2	1000	5	.125	(+) + (−)	.303	.000
5				O_2	400	7.5	.315	(−)	.029	.395
6	O_2	1000	7.5	O_2	400	37.5	.370	(−)	.000	.468
7	O_2	1000	7.5	O_2	400	37.5	.346	(−)	.002	.462
8	CO_2	1000	5	O_2	400	40	.348	(−)	.000	.462
9	Stock charcoal			Untreated			.610	(−)		
10				O_2	150	2	.615	(−)		
11				O_2	150	6	.575	(−)		
12				O_2	150	10	.580	(−)	.102	.048
13	O_2	400		$O_2 + NO + H_2O$	150	10	.545	(−)		
14	Stock charcoal			$O_2 + O_3$	25	3.5	.710	(−)	.047	.066
15	O_2	400		$O_2 + O_3$	25	7.5	.420	(−)	.030	.889
16	O_2	400		$O_2 + O_3 + H_2O$	25	7.5	.485	(−)	.016	.940

portion of the concentration range than does "High Temperature Charcoal" and is less organophilic, *i. e.*, is more hydrophilic than the latter. A "Low Temperature Charcoal" curve, labeled "L. T. Charcoal," is also given in Fig. 5. A consideration of the curves which were obtained for "Low Temperature Charcoals" leads to the conclusion that none of them are characteristic of charcoal fully activated to the "Low Temperature Charcoal" type. Charcoal completely activated to this type would probably more nearly approach silica ($X_0 = 0.850$) in its preferential adsorption.

The X_0 values were found to be fairly reproducible for a given activation treatment, and, furthermore, the type of charcoal obtained was independent of the treatment given the charcoal before the final activation. This would seem to indicate that some definite surface structure—probably some definite carbon–oxygen complex such as an oxide—is responsible for the different types of activated charcoal.

Acid–Base Adsorption.—In the acid–base adsorption experiments, 0.01 *N* solutions of hydrochloric acid and sodium hydroxide were used. Methyl red was used as indicator. One-gram samples of the activated charcoal were weighed out and placed in dry flasks; to one-half of these flasks was added 50.00 cc. of 0.01 *N* hydrochloric acid, and to the other half, an equal volume of 0.01 *N* sodium hydroxide. Blanks were run with each set of experiments. The solutions stood with intermittent shaking for ten hours. They were then filtered, and 25.00 cc. of the filtrate pipetted off for titration. The blanks were filtered through the same kind of filter paper and titrated in the same manner. To the flasks containing the sodium hydroxide, 25.00 cc. of the 0.01 *N* hydrochloric acid was added directly and the excess back titrated.

The "High Temperature Charcoal," whether activated with oxygen or carbon dioxide, gave acid adsorption but no base adsorption from dilute solutions of strong inorganic acids and bases. A slight base adsorption which was evidenced by Charcoal 2 was undoubtedly due to the fact that there remained some carbon dioxide on the charcoal which was not chemisorbed. Any such carbon dioxide left on the charcoal would form carbonic acid in solution when the charcoal was suspended in water; this carbonic acid would neutralize some of the base during titration. The "Medium Temperature Charcoal" gave base adsorption, and when the activation was quite complete, it gave no evidence of acid adsorption. Several investigators, Bartell and Miller,[8] Schilow and co-workers,[9,10] and Kolthoff,[4] previously have run some experiments on activated charcoal, determining the acid and base adsorption. Their results on acid–base adsorption and those of the present investigation are in full agreement. Since our charcoals were activated to distinct and essentially pure types of charcoal, our data permit the following conclusion: "High Temperature Charcoal" adsorbs strong inorganic acids but not strong inorganic bases from dilute solutions. "Medium Temperature Charcoal" adsorbs strong inorganic bases but not strong inorganic acids from dilute solutions. Charcoal which is not completely activated to either of the above described types of surface would naturally give both acid and base adsorption. The "Low Temperature Charcoal" which we prepared showed some acid adsorption along with considerable base adsorption.

Charge on Particle.—The particle charge of the activated charcoals was determined by direct observation, with a microscope of the direction in which the particles moved when an electrical potential was applied. The apparatus and method is described by Bartell.[11] The "Medium Temperature Charcoal" and "Low Temperature Charcoal" gave only negatively charged particles in suspension. The "High Temperature Charcoal" showed both positive and negative particles when the suspension was first made up. If the observation was made at once, there were more

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[8] F. E. Bartell and E. J. Miller, This Journal, **44**, 1866 (1922).

[9] Nikolai Schilow and Konstantin Tschmutow, *Z. physik. Chem.*, **148**, 233 (1930).

[10] Nikolai Schilow, Helene Schatumowakaja, and Konstantin Tschmutow, *ibid.*, **149**, 211 (1930).

[11] F. E. Bartell, "Laboratory Manual of Colloid and Surface Chemistry," Edwards Brothers, Ann Arbor, Mich., 1936, p. 47.

positive particles than negative ones. In a very short time, less than two minutes, only negative particles remained suspended. The positive particles, which could be seen to settle out very rapidly, apparently had all settled out and left only negatively charged particles. Kruyt and DeKadt[12] reported that charcoal activated at 1000° gave positively charged particles, while charcoal activated at 400° gave negatively charged particles. Kolthoff[4] observed the same relation between particle charge and temperature of activation. Frampton and Gortner[13] attempted to prepare positively charged charcoal but did not succeed in doing so; they reported only negatively charged particles for charcoal activated at 1000°. Wiegand[14] reported that lampblack which was collected by being attracted to a negative plate and, therefore, must have had a positive charge, proved to have a negative charge in an aqueous suspension. Further research regarding the charge of "High Temperature Charcoal" will probably clear up this apparent contradiction in the results on the particle charge for such charcoal.

A summary of the data obtained for all the charcoals is given in Table IV.

Summary

1. Preferential adsorption from benzene–ethanol solutions by charcoals activated at different temperatures and in different gases shows that charcoal can be changed from extremely organophilic charcoal to charcoal approaching in adsorptive properties the hydrophilic adsorbent, silica.

2. The characteristic S-shaped preferential adsorption curves for a series of increasingly hydrophilic charcoals have been plotted, and the points where these curves cross the X-axis, the X_0 values, are shown to be a measure of the relative organophilic or hydrophilic nature of the charcoals.

3. The organophilic "high temperature charcoal" (activated at temperatures near 1000°), when suspended in water, gave both positively and negatively charged particles. This charcoal gave acid adsorption but no base adsorption. The less organophilic "medium temperature charcoal" (activated at temperatures near 400°), when suspended in water, gave only negatively charged particles. This charcoal gave base adsorption. The "low temperature charcoal" (activated in a highly oxidizing atmosphere below 150°), approaching in adsorptive properties hydrophilic silica, when suspended in water, gave only negative particles. This charcoal showed both acid and base adsorption.

ANN ARBOR, MICHIGAN RECEIVED MARCH 17, 1938

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[12] H. R. Kruyt and G. S. DeKadt, *Kolloidchem. Beihefte*, **32**, 349 (1931).

[13] V. L. Frampton and R. A. Gortner, *J. Phys. Chem.*, **41**, 567 (1937).

[14] W. B. Wiegand, *Ind. Eng. Chem.*, **29**, 953 (1937).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF BRITISH COLUMBIA]

Physical Chemical Properties of *cis*- and *trans*-Decahydronaphthalene[1]

BY W. F. SEYER AND R. D. WALKER

Introduction.—Little is known of the chemical and physical properties of the dicyclic naphthalene hydrocarbons. An extensive investigation of these compounds can be undertaken only after a method has been found for obtaining these two compounds in a high state of purity and in suitable quantities. The wide variation in the physical data of the two isomeric forms as given by Hückel[2] in his summary of the literature dealing with this subject would indicate that in some of the methods of synthesis the two forms were produced simultaneously, but in varying amounts.

It was thought, therefore, that the most practical method of obtaining the two forms in sufficient quantity was to fractionate the commercial decalin.

Fractionating Apparatus.—It was discovered in a series of preliminary trials that reduced pressure must be used. Decomposition took place during distillation at atmospheric pressure even with a column length of only 1 meter. The complete apparatus used is shown in Fig. 1. The diagram is self-explanatory; hence only a few remarks are necessary to describe the mode of operation. By utilizing a magnet controlled receiving unit, stopcocks at this point were eliminated. The reflux was controlled by sealing a fine capillary tube to the head of the rectifying column. The lagged column was packed with No. 18 galvanized jack chain. The still had a capacity of 3000 cc. and was electrically heated. Water at 20° was pumped from a constant temperature bath to the condensers.

The reduced pressure of 10 mm. was maintained by a Cenco vacuum pump. At this pressure it was found that no pressure regulation device was required to keep the height of mercury in the manometer constant. A sulfuric acid manometer in connection with the one above showed variations in pressure of less than 1 mm.

Materials.—Decalin from various sources was used. Material from the Eastman Kodak Co. showed a consider-

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[1] Original manuscript received August 20, 1937.

[2] Hückel, *Ann.*, **441**, 1 (1925).

able variation as judged by the density and refractive index. All samples showed some coloration when shaken with concentrated sulfuric acid. However, irrespective of whether or not the decalin had been treated with acid until no further coloration took place, the freezing points of the ultimate products were all the same within the limits of experimental error.

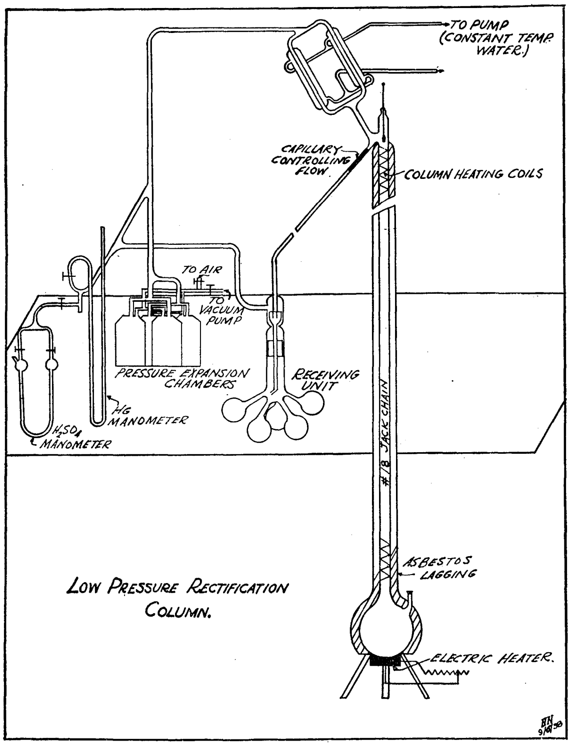

Fig. 1.

Methods of Purification and Procedure.—Two fractional distillations were carried out on each sample of decalin, followed by fractional crystallization until a constant freezing point was obtained. A summary of a typical distillation run is given below.

Table I

Charge, 2065 cc. of decalin about 45% *cis*. Distillation pressure 10 mm. Condenser water at 20°.

Fractions	1	2	3	4	5
Vol., cc.	205	440	483	460	310
Temp. at top of column, °C.	41.0–62.2	62.2–63.7	63.7–67.4	67.4–69.2	69.2–69.9
Time, hrs.	1.67	3.50	4.33	4.83	3.33
Rate, cc./hr.	123	126	112	95	93
$n^{20}\text{D}$	1.47050	1.47093	1.47404	1.47892	1.48082
Total time	17.66 hrs.		Total distillate		1900 cc.
Residue	120 cc.		Loss		45 cc.

Fractions 1 and 2 of this and other runs were then added together and again distilled. Nos. 4 and 5 were treated in a similar manner. The first lot upon the second distillation yielded a fraction of a little over 500 cc. with b. p. 60.3 to 62.7° and refractive index, $n^{20}\text{D}$ 1.46967, corresponding to the value given by Hückel for the *trans* form. A fraction totaling 425 cc. with b. p. 69.5 to 69.7° was selected as the pure *cis* form. The refractive index $n^{20}\text{D}$ was 1.48116 as compared with Hückel's value of 1.48054.

Freezing Point Determination.—The freezing point of the selected fractions was next determined with two Leeds and Northrup quartz encased potential terminal, platinum resistance thermometers of the following characteristics.

	R at ice point	F	δ
Thermometer I	2.5461	0.9941	1.504
Thermometer II	2.5117	.9732	1.502

Thermometer I has shown a change of only 0.0001 ohm in the ice-point over a period of ten years. Thermometer II, on the other hand, had shown a drift, and had therefore been sent to the Bureau of Standards for recalibration shortly before.

The freezing point apparatus consisted of two Dewar tubes. The outer one had a capacity of about 4 liters and was filled with dry ice. The inner tube, having a diameter of about 7 cm. and a depth of 20 cm., had attached to it a stopcock, such that the air pressure inside could be regulated at will, thereby giving any desired rate of cooling.

The change in the freezing point curves with progressive purification is shown in Figs. 2–4.

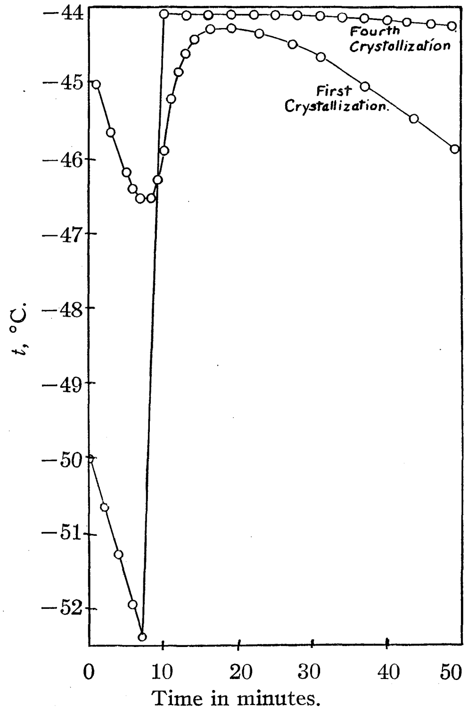

Fig. 2.—Cooling curves (*cis*).

If the slope of the freezing point curve is taken as a criterion of purity, the final (Fig. 4) curves of both the *cis* and the *trans* forms indicate a high state of purity. The final freezing point represents the ninth recrystallization and was taken only after the samples had been in contact with sodium wire for about ten days.

Inasmuch as the liquids were rather viscous at the freezing point it became of interest to find out just how accurately this point could be determined. Hence freezing point

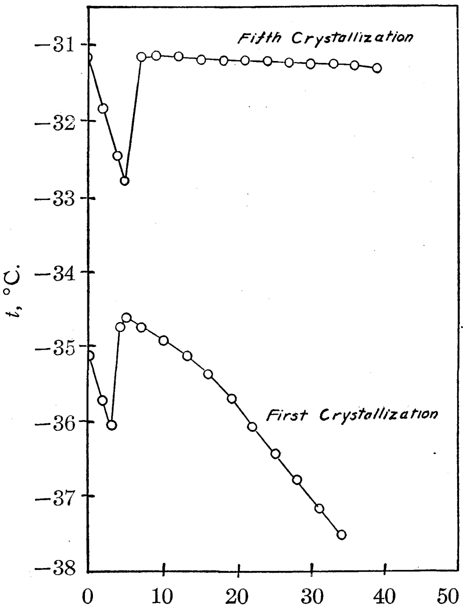

Fig. 3.—Cooling curves (*trans*).

determinations were made first with one thermometer and then with the other, next with constant rotary stirring by means of a propeller driven by a motor, then reciprocatory stirring by hand, and finally no stirring at all during the freezing period. The liquid was seeded with crystals in all cases. The results for the *cis* form were, respectively, −43.25, −43.26, −43.29, −43.23, −43.26°, with a deviation from the mean of 0.03°. The freezing point of the *cis* form is therefore given as −43.26 ± 0.04° and that of the *trans* form as 31.48 ± 0.04°. The last is an average of three determinations, −31.47, −31.46, −31.50°.

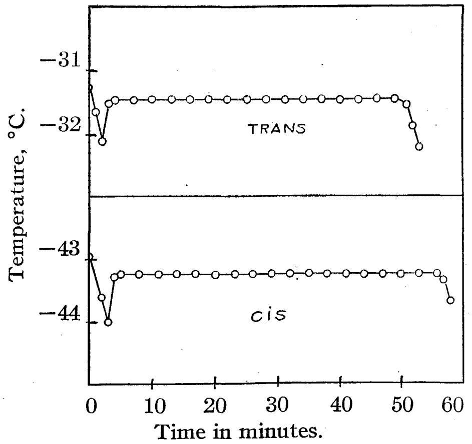

Fig. 4.—Final freezing point curves.

Boiling Point Determinations.—The method outlined in "Laboratory Methods of Organic Chemistry" by Gatterman (Macmillan) was followed closely. The thermometer used was one from an Anschütz set and was calibrated against one of the platinum resistance thermometers used in the previous determination. The boiling points corrected to 760 mm. were as follows; *cis*, 194.6°; *trans*, 185.5°.

Refractive Index.—The refractive indices were measured by a Hilger Pulfrich refractometer. Here two calibrated glass thermometers, graduated in tenths, were used. The one was in a constant temperature bath and the other in the refractometer itself.

Densities.—The densities of the pure compounds as well as the mixtures were measured by means of a modified Perkin pycnometer and are the average of three separate determinations.

Nine solutions of the two isomers were prepared by weight. The densities and refractive indices for D, C, G lines of these solutions were next measured. The results are given in Table II.

TABLE II

Concn. by wt. % *trans.*	d^{20}_4	n^{20}_{D}	n^{20}_{C}	n^{20}_{G}[1]
0	0.8963	1.48113	1.47869	1.49881
10.05	.8934	1.47991	1.47742	1.49762
19.66	.8910	1.47890	1.47632	1.49661
29.69	.8885	1.47770	1.47526	1.49533
39.41	.8858	1.47667	1.47413	1.49429
49.88	.8832	1.47550	1.47292	1.49318
59.84	.8808	1.47437	1.47188	1.49205
69.72	.8779	1.47323	1.47069	1.49098
79.85	.8752	1.47206	1.46956	1.48960
89.77	.8725	1.47092	1.46854	1.48854
100	.8699	1.46968	1.46720	1.48727

Upon examining the properties of these mixtures of known composition, it was found that both density and refractive index were linear functions of the concentrations (Figs. 5, 6). The relationship between the per cent. *trans* form and the density is given by the equation $C = 3395 - 3788d$ when C is per cent. *trans* form and d is the

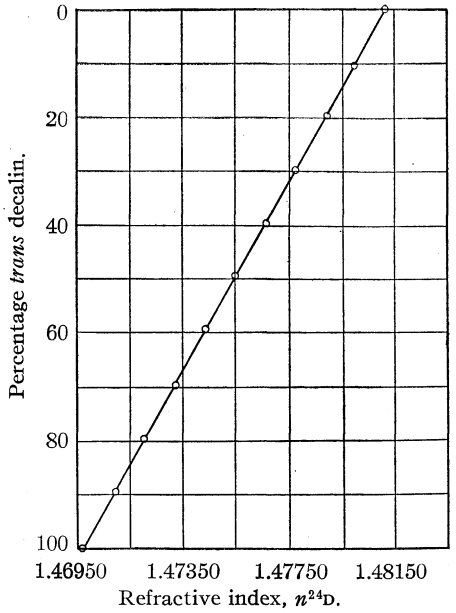

Fig. 5.

density at 20°, also $C = 12936 - 8734n$ when C is the same as above but n is the refractive index for the D line at 20°.

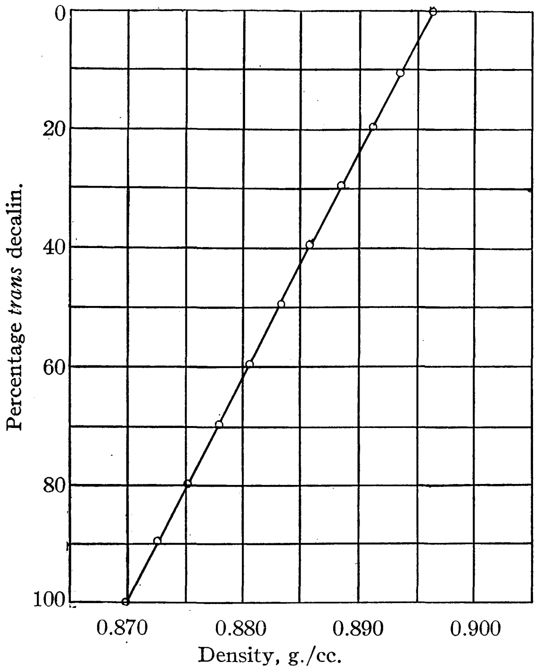

Fig. 6.

Attempts were made to determine the freezing points of the various mixtures by placing them in partially filled bulbs of about 20 cc. capacity. Because of the great amount of supercooling necessary and the low heat conduction of the hydrocarbons the results were only of qualitative significance. They indicated that the eutectic temperature lies between −60 and −70°.

A summary of the physical constants of the *cis* and *trans* forms of decahydronaphthalene is given in the following table.

TABLE III

	d^{20}_4	n^{20}_D	F. p., °C.	B. p. (760 mm.), °C.
cis form	0.8963	1.48113	− 43.26 ± 0.04	194.6
"Int. Crit. Tables"	.898			
Hückel[2]	.8952		− 51	
trans form	.8699	1.46968	− 31.47 ± 0.04	185.5
"Int. Crit. Tables"	.872	1.4701	−125	
Hückel[2]	.8695	1.46958	− 36	

Summary

1. Pure forms of *cis* and *trans* decahydronaphthalene have been prepared and some of their physical properties measured.

2. The freezing points were found to be higher than those so far recorded.

3. The densities and refractive indices of nine mixtures of the two forms were measured and it was shown that both these properties were linear functions of the compositions.

VANCOUVER, B. C. RECEIVED MAY 18, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF YALE UNIVERSITY]

The Thermodynamics of Hydrochloric Acid in Dioxane–Water Mixtures from Electromotive Force Measurements. V. Properties of the 45% Dioxane Mixtures

BY HERBERT S. HARNED AND JOHN G. DONELSON

Measurements of the electromotive forces of the cells

$$H_2 \mid HCl\,(m),\ \text{dioxane}\,(X),\ H_2O\,(Y) \mid AgCl\text{–}Ag$$

in 45% dioxane–water mixtures and at acid concentrations varying from 0.003 to 0.1 M have been reported by Harned and Morrison.[1] These measurements have been extended so as to include concentrations from 0.003 to 3 M. From these results and the standard potential of the cell,[2] the activity coefficient, relative partial molal heat content and specific heat have been computed. Similar results have been obtained by Harned and Ehlers[3] in water and by us[4] in 20% dioxane–water mixtures which in conjunction with present results yield an accurate and very comprehensive study of the thermodynamics of this acid in media of dielectric constants of approximately 80, 60, and 40.

Experimental Results

No further changes in the technique described by Harned and Morrison[5,1] and modified in a few details by us[4] have been made. The present results were obtained with the same care and

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[1] Harned and Morrison, THIS JOURNAL, **58**, 1908 (1936).

[2] Harned, *ibid.*, **60**, 336 (1938).

[3] Harned and Ehlers, *ibid.*, **55**, 2179 (1933).

[4] Harned and Donelson, *ibid.*, **60**, 339 (1938).

[5] Harned and Morrison, *Am. J. Sci.*, **33**, 161 (1937).

accuracy as in the earlier investigations. The cell reproducibility at all concentrations was ±0.05 mv.

Six cells were measured at each concentration, all of which were equilibrated and measured at 25°. Three of these were measured at 5° intervals up to 50° and then brought back to 25°. The other three were measured at 5° intervals until 0° was reached and finally brought back to 25°. All results were finally accepted if and only if all the 25° readings at a given concentration checked to within ±0.05 mv.

The results at eleven temperatures were found to conform to the quadratic equation

$$E = E_{25} + a(t - 25) + b(t - 25)^2 \qquad (1)$$

The constants, a and b, obtained by the method of least squares, and the values of the electromotive forces at 25°, are given in Table I. The fifth column contains the maximum deviations in millivolts between the observed values and those calculated by equation (1). The last column contains the average deviation.

TABLE I

CONSTANTS OF EQUATION (1)

X = 45% by weight of dioxane

m	E_{25}	$-a \times 10^4$	$-b \times 10^6$	Δ(max.)	Δ(max.)
0.10943	0.30896	5.185	2.90	0.05	0.02
.19378	.28371	5.882	2.84	.05	.02
.32247	.26014	6.596	2.72	.05	.03
.52079	.23645	7.065	2.50	.06	.03
.6467	.22500	7.477	2.34	.07	.04
1.0305	.19760	7.892	2.24	.11	.04
1.5496	.16917	8.274	2.28	.07	.04
2.0546	.14575	8.567	2.14	.08	.04
3.1105	.10209	8.850	1.80	.10	.04

Combined with the data of Harned and Morrison[1] suitable observations were available at eighteen concentrations between 0.003 and 3 M. These results were smoothed to round concentrations from suitable large scale plots. The values of a and b also were smoothed and the final values of all these quantities which subsequently were used for the computations are contained in Table II.

In the last row of the table are given the constants of the equation

$$E_0' = E_{0(25)}' + a_0(t - 25) + b_0(t - 25)^2 \qquad (2)$$

in which E_0' is the standard potential at a temperature t, $E_{0(25)}'$ the standard potential at 25°, and a_0 and b_0 empirical constants. These values were obtained from the standard potentials computed by Harned[2] by use of the Gronwall, La Mer, and Sandved extension of the Debye and Hückel theory. The values of $E_{0(25)}'$ and b_0 differ slightly from those obtained by Harned.

TABLE II

ELECTROMOTIVE FORCES AT ROUND CONCENTRATIONS. CONSTANTS OF EQUATION (1)

m	E_{25}	$-a \times 10^4$	$-b \times 10^6$
0.003	0.47082	0.78	3.30
.005	.44670	1.38	3.24
.007	.43108	1.80	3.20
.01	.41470	2.23	3.17
.02	.38343	3.10	3.09
.03	.36549	3.61	3.05
.05	.34316	4.23	2.99
.07	.32848	4.65	2.95
.1	.31290	5.08	2.91
.2	.28236	5.90	2.80
.3	.26358	6.40	2.71
.5	.23855	7.03	2.52
.7	.22061	7.46	2.34
1	.19951	7.91	2.12
1.5	.17162	8.44	1.84
2	.14811	8.82	1.62
3	.10711	9.38	1.29
	$E_{0(25)}'$	$-a_0 \times 10^4$	$-b_0 \times 10^6$
0 (a = 1)	0.16352	11.35	3.70

Activity Coefficients

Values of the activity coefficients γ, computed by means of the equation of the cell

$$-\log \gamma = \frac{(E - E_0')\,F}{4.6052\,RT} + \log m \qquad (3)$$

are given in Table III. Values of the dielectric constant of the solvent[6] at the designated temperatures are given in the last row of the table. Judging from the errors involved in the experiments and the extrapolation, it is estimated that these results possess an accuracy of ±0.001.

TABLE III

ACTIVITY COEFFICIENTS

m	0°	10°	20°	25°	30°	40°	50°
0.003	0.849	0.846	0.844	0.842	0.839	0.834	0.828
.005	.824	.817	.811	.808	.803	.795	.786
.007	.802	.793	.786	.782	.777	.767	.757
.01	.776	.766	.758	.753	.747	.737	.725
.02	.720	.707	.697	.692	.686	.673	.660
.03	.683	.671	.661	.654	.649	.635	.622
.05	.637	.624	.613	.607	.600	.586	.573
.07	.605	.593	.583	.577	.570	.557	.545
.1	.579	.566	.553	.547	.540	.525	.512
.2	.529	.514	.503	.496	.488	.474	.459
.3	.511	.496	.484	.476	.466	.453	.438
.5	.503	.487	.473	.465	.456	.440	.423
.7	.513	.495	.480	.471	.461	.443	.424
1.	.547	.526	.508	.497	.485	.463	.442
1.5	.640	.612	.585	.570	.555	.524	.496
2.	.773	.733	.695	.676	.655	.614	.575
3.	1.191	1.112	1.037	1.001	.962	.887	.818
D	44.3	41.9	39.6	38.5	37.4	35.4	33.4

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[6] Åkerlöf and Short, THIS JOURNAL, **58**, 124 (1936).

TABLE IV

PARAMETERS OF EQUATIONS (4) AND (7). $\overline{L}_2$ AND $(\overline{C}_p - \overline{C}_{p0})$ AT 25°

m	$(-\alpha)$	β	$\overline{L}_{2(25)}$	$(\overline{C}_p - \overline{C}_{p0})_{25}$
0.003	640	0.00923	180	5.5
.005	619	.01061	324	6.3
.007	630	.01154	395	6.9
.01	609	.01223	478	7.3
.02	651	.01408	600	8.4
.03	669	.01500	664	8.9
.05	703	.01638	753	9.8
.07	735	.01730	802	10.2
.1	754	.01823	866	10.9
.2	839	.02077	1007	12.4
.3	934	.02284	1096	13.6
.5	1179	.02723	1241	16.2
.7	1430	.03138	1359	18.7
1	1704	.03646	1536	21.7
1.5	1999	.04292	1815	25.6
2	2169	.04799	2095	28.6
3	2285	.05561	2657	33.1

Relative Partial Molal Heat Content and Heat Capacity.—The heat data have been computed by the method described by Harned and Thomas[7] and mentioned by us.[4] The relative partial molal heat content, $\overline{L}_2$, is expressed by

$$\overline{L}_2 = \alpha + \beta T^2 \qquad (4)$$

α and β are given by

$$\alpha = -23{,}074[(E_{25} - E'_{0(25)}) - 298.1(a - a_0) + 88{,}864(b - b_0)] \qquad (5)$$

$$\beta = 23{,}074(b - b_0) \qquad (6)$$

respectively. $\overline{L}_2$ is in calories. The relative partial molal heat capacity may be computed by the equation

$$(\overline{C}_p - \overline{C}_{p0}) = 2\beta T \qquad (7)$$

Table IV contains the parameters α and β, from which $\overline{L}_2$ may be computed at all temperatures from 0 to 50° with an accuracy of the order of ±30 cal. by equation (4), and $(\overline{C}_p - \overline{C}_{p_0})$ with an accuracy of the order of ±1 cal. by equation (7). Values of $\overline{L}_2$ and $(\overline{C}_p - \overline{C}_{p_0})$ at 25° are given in the fourth and fifth columns of the table, respectively.

Summary

1. The electromotive forces of the cells

H_2 | HCl (m), Dioxane (45%), H_2O (55%) | AgCl–Ag

have been measured at 5° intervals from 0 to 50°, and from 0.1 to 3 M acid concentrations with an accuracy of ±0.05 mv.

2. From these and the results of Harned and Morrison in the dilute concentration range (0.003 to 0.1 M) the activity coefficient, the relative partial molal heat content and the heat capacity of the acid have been computed throughout these ranges of temperature and pressure.

NEW HAVEN, CONN. RECEIVED JUNE 21, 1938

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[7] Harned and Thomas, THIS JOURNAL, 58, 761 (1936).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF YALE UNIVERSITY]

The Thermodynamics of Hydrochloric Acid in Dioxane–Water Mixtures from Electromotive Force Measurements. VI. Extrapolations in the 70% Dioxane Mixtures and Standard Potentials

BY HERBERT S. HARNED AND CALVIN CALMON[1]

In an earlier communication in this series,[2] it was shown that accurate evaluations of the standard potentials of the cell

H_2 | HCl (m), dioxane (X), H_2O (Y) | AgCl–Ag

in mixtures containing 20 and 45% dioxane could be made by employing the Gronwall, La Mer and Sandved extension of the Debye and Hückel theory. At the same time, an extrapolation was made with the results obtained in a mixture of 70% dioxane–30% water at 25°. Since experimental results below 0.003 M were not available, a slight uncertainty in the extrapolation was suspected, and further calculations discontinued for the moment. This communication contains an attempt to obtain results at still lower concentrations, and to determine the lower limit of concentration at which reliable results can be obtained with the technique available.

Experimental Results

The preparation of solutions and the cell technique was carried out with all the precautions and in the same manner as that described by

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[1] This communication contains material from a dissertation presented by Calvin Calmon to the Graduate School of Yale University in partial fulfilment of the requirements for the degree of Doctor of Philosophy, June, 1938.

[2] Harned, THIS JOURNAL, 60, 336 (1938).

Harned and Morrison.[3,4] The only difference which need be mentioned is the preparation and behavior of the silver–silver chloride electrodes. Electrodes of this type prepared electrolytically as described by Harned and Morrison[3] are reproducible to within ±0.1 mv. in solutions containing acid at 0.003 *M* or higher. Below this concentration, they fail to function satisfactorily. After proving this fact, electrodes made by mixing nine parts of silver oxide with one part of silver chlorate were employed. This mixture was spread on a platinum wire spiral and heated at a temperature of 450° for ten minutes as described by Rule and La Mer.[5,6] In solutions containing hydrochloric acid of concentrations 0.002 and 0.003 *M*, these electrodes behaved very satisfactorily. Equilibrium was attained in twelve hours and the electromotive forces agreed very closely at 0.003 *M* with those obtained by the electrolytically prepared electrodes of Harned and Morrison. Further, after measurements at different temperatures, the cells could be brought back to the initial temperature after a period of ten to twenty hours and the original electromotive force reproduced. In more dilute solutions, however, a longer period of time, from forty-eight to sixty hours, was required for equilibration. Also, at concentrations near 0.001 *M*, the reproducibility was found to be considerably less than at 0.002 *M*. Within the limit of ±0.5 mv., these electrodes would operate satisfactorily over periods of forty-eight hours, and after the temperature changes had been made.

Our experience may be summarized by the statement that an accuracy of ±0.1 mv. may be obtained at concentrations of 0.002 *M* and higher; that the reproducibility decreases with concentration decrease, and becomes approximately ±0.5 mv. at 0.001 *M*. These estimates will suffice to show the present experimental status of this subject.

The cells were run in triplicate. For each concentration, two series of measurements were made. Each series was begun at 25° and readings were taken at 5° intervals to 50° and finally at 25° again. The second series was also started at 25°, then readings were taken at 0° and at 5° intervals until 25° was reached. If at the end of each run the difference in readings at 25° was greater than 0.3 mv., the results were discarded. The vapor pressure data of Hovorka, Schaeffer and Dreisbach[7] were employed in making the usual correction for hydrogen pressure. Table I contains the electromotive forces.

TABLE I

ELECTROMOTIVE FORCES OF THE CELLS

H_2 | HCl (m), dioxane (X)–H_2O (Y) | AgCl–Ag

X = 70% by weight

	m				
t	0.003292	0.002366	0.001043	0.001001	0.0008146
0	0.40050	0.41283	0.4463	0.4467	0.4556
5	.39822	.41078	.4430	.4443	.4540
10	.39580	.40860	......	.4427	.4519
15	.39325	.40626	.4395	.4405	.4501
20	.39059	.40376	.4373	.4388	.4480
25	.38780	.40112	.4348	.4364	.4453
30	.38485	.39830	.4321	.4346	.4421
35	.38176	.39535	.4295	.4313	.4402
40	.37855	.39226	.4270	.4286	.4386
45	.37520	.38903	.4245	.4253	.4366
50	.37170	.38568	.4221	.4214	.4319
Reproducibility (mv.)	±0.1	±0.1	±0.5	±0.5	±0.5

Extrapolations and Evaluation of the Standard Electrode Potential.—The extrapolation was carried out in the manner described by Harned[2] by employing the function E', defined by the equation

$$E' = E + 2k \log m - \frac{2ku\sqrt{c}}{1 + A\sqrt{2c}} - 2k \log (1 + 0.002\, G_0 m) = E_0' + f(m) \quad (1)$$

E is the observed potential of the cell, k equals 2.3026 RT/F, u is the universal constant of the Debye and Hückel theory, A is the parameter which involves the mean distance of approach of the ions, a, G_0 is the mean molecular weight of the solvent (ref. 4, eq. (6)), and E_0' is the standard potential of the cell. m is the concentration of the acid in moles per 1000 grams of solvent, and c is its concentration in moles per liter of solution. The use of the Gronwall, La Mer and Sandved extension of the theory makes possible a more certain evaluation of E_0'. Arithmetical approximations showed that a value of "a" of 5.6 Å. at all temperatures gave satisfactory extrapolations. Thus, the values of $E' - E_{\text{Ex}}$, where E_{Ex} represents the contribution of the extended terms to the electromotive force, was very constant at concentrations between 0.002 and 0.02 *M*. At concentrations between 0.0008 and 0.002 *M*, the results are not as consistent, but in general indicate that the method is good.

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[3] Harned and Morrison, *Am. J. Sci.*, **33**, 161 (1937).

[4] THIS JOURNAL, **58**, 1908 (1936).

[5] Rule and La Mer, *ibid.*, **58**, 2339 (1936).

[6] Keston, *ibid.*, **57**, 1671 (1935).

[7] Hovorka, Schaeffer and Dreisbach, *ibid.*, **58**, 2264 (1936).

E_{Ex} is given by

$$E_{\text{Ex}} = 2k\left[C\left(\frac{1}{a}\right)^3\left(10^3\left[\frac{1}{2}X_3(x) - 2\,Y_3(x)\right]\right) + K\left(\frac{1}{a}\right)^5\left(10^5\left[\frac{1}{2}X_5(x) - 4Y_5(x)\right]\right)\right] \quad (2)$$

where

$$C10^3 = \frac{1}{2.3026}\left(\frac{\epsilon^2}{kTD}\right)^3 \quad (3)$$

$$K10^5 = \frac{1}{2.3026}\left(\frac{\epsilon^2}{kTD}\right)^5 \quad (4)$$

and

$$x = \kappa a = A\sqrt{2c} \quad (5)$$

κ is the reciprocal radius of the ionic atmosphere. 4.774×10^{-10}, 1.371×10^{-16}, 6.06×10^{23}, and 273.1 were used for ϵ, k, N and T at 0°, respectively. The values of the dielectric constants of the mixtures were obtained from the data of Åkerlöf and Short[8] and the density data for the computation of c from m were those of Harned and Calmon.[9] Values of the quantities used in the computations are given in Table II. The values of the third and fifth approximations given in parentheses in equation (2) were obtained from Table V in Gronwall, La Mer and Sandved's contribution.

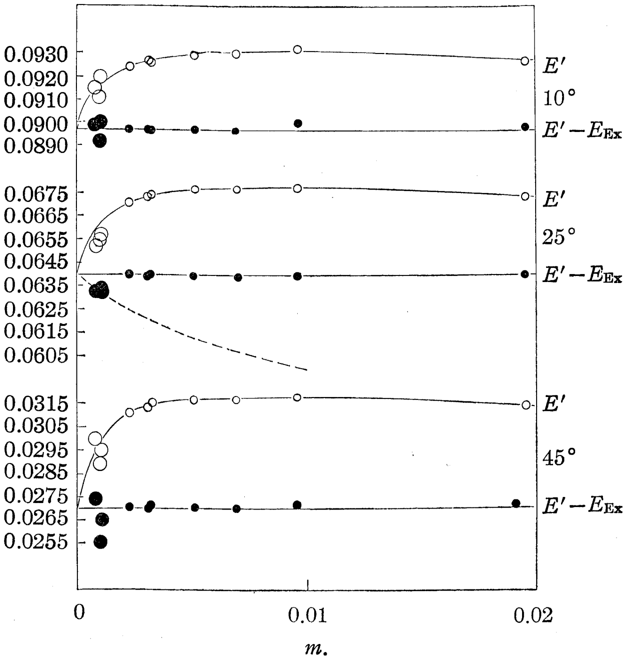

Fig. 1.—Extrapolation at 10, 25 and 45°.

TABLE II

VALUES OF D, u, C/a^3, K/a^5 AND A

$a = 5.6$ Å.

t	D	u	C/a^3	K/a^5	A
0	20.37	1.364	0.06584	0.01872	3.776
5	19.81	1.385	.06778	.01965	3.794
10	19.25	1.406	.07003	.02074	3.815
15	18.72	1.429	.07225	.02186	3.835
20	18.20	1.453	.07467	.02309	3.856
25	17.69	1.477	.07729	.02446	3.878
30	17.20	1.503	.07997	.02546	3.901
35	16.72	1.530	.08295	.02751	3.924
40	16.26	1.557	.08591	.02917	3.947
45	15.80	1.586	.08927	.03109	3.973
50	15.37	1.616	.09255	.03302	3.996

Values of E' and $E' - E_{\text{Ex}}$ are plotted against the molal concentration in Fig. 1. The extrapolations at 10, 25 and 45° are given as typical. The plot at 10° is characteristic of the results at temperatures between 0 and 20°, inclusive, that at 25° is typical also of the results at 30, 35 and 40°, and that at 45° is similar to the result at 50°. The first thing to note is the characteristic "hump" in the plots of the Debye and Hückel function E' and the straight graphs for the functions, $E' - E_{\text{x}}$. $E' - E_{\text{x}}$ remains constant until a concentration of 0.02 M is reached which corresponds to a value of x or κa of the order of 0.7. The final values of E_0' have been computed from the more reproducible results at concentrations of 0.002 M or greater. With very few exceptions, the points computed from the results in the neighborhood of 0.001 M lie below the curves which indicates low values of the cell electromotive forces.

Values of the function $E' - E_{\text{Ex}}$ at the temperatures shown in the graph are given in Table III. The bottom row of the table contains the extrapolated values of E_0'. The consistency of the results between 0.002 to 0.03 M is excellent. The values in parentheses at the lower concentrations indicate a much larger error and were not used in the final evaluation of the standard potential.

A second method of extrapolation which will be described in a future communication dealing with 82% dioxane–water mixtures depends on a previous knowledge of the ionization constant of hydrochloric acid in the mixture. In Fig. 1, the dashed line represents a suitable function computed from the electromotive forces and a value of 0.0077 for the ionization constant of the acid, determined by Owen and Waters in this Laboratory. This extrapolates to the value previously obtained. Our experience indicates that the first method is the more satisfactory in these

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[8] Åkerlöf and Short, THIS JOURNAL, **58**, 1241 (1936).

[9] Harned and Calmon, *ibid.*, **60**, 334 (1938).

TABLE III

VALUES OF THE EXTRAPOLATION FUNCTION, $E' - E_{Ex}$ AT 10, 25, 45°

m	t....10°	25°	45°
0.03203	0.08961	0.06372	0.02720
.01927	.08984	.06400	.02746
.009612	.09003	.06399	.02727
.006950	.08972	.06391	.02704
.005188	.08970	.06389	.02708
.003292	.08965	.06393	.02718
.003164	.08970	.06390	.02699
.002366	.08970	.06400	.02709
.001043	(.0900)	(.0634)	(.0265)
.001001	(.0892)	(.0632)	(.0255)
.000815	(.0899)	(.0632)	(.0274)
E_0' ($m = 0$)	.08970	.06395	.02705

solutions where D equals approximately 20 and where the actual ionization in dilute solutions is high ($\alpha > 0.9$). In media of dielectric constant of 10 (82% dioxane), the second method seems to be more suitable than the one which employs the extended term theory since values of the ionization constant are known, and since the electrolyte is considerably weaker ($K \sim 0.0002$). Also in these solutions values of "a" computed by Bjerrum's theory are more reliable than in those of high dielectric constant.

In Table IV, the standard potentials at all temperatures are given. These results may be expressed by the equation

$$E_0' = 0.06395 - 17.67 \times 10^{-4}(t - 25) - 3.70 \times 10^{-6}(t - 25)^2 \quad (6)$$

The deviations between the observed values and those computed by this equation are given in parentheses immediately following the result. They are in hundredths millivolt and are positive when the calculated is greater than the observed value.

TABLE IV

STANDARD POTENTIAL OF THE CELL

H_2 | HCl (m), DIOXANE (70%), H_2O | AgCl–Ag

t	E_0'	t	E_0'
0	0.10584 (−3)	30	0.05500 (+3)
5	.09784 (−3)	35	.04587 (+4)
10	.08970 (−8)	40	.03661 (+1)
15	.08123 (+2)	45	.02705 (+8)
20	.07267 (+2)	50	.01746 (+1)
25	.06395 (+0)		

Summary

1. Electromotive forces of the cells

H_2 | HCl (m), dioxane (70%), H_2O | AgCl – Ag

have been obtained at 0.0008, 0.001, 0.002 and 0.003 M from 0 to 50° at 5° intervals.

2. From these and Harned and Morrison's results from 0.003 to 0.02 M, the standard potential of the cell has been evaluated.

NEW HAVEN, CONN. RECEIVED JUNE 21, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

The Thermodynamics of Hydrochloric Acid in Dioxane–Water Mixtures from Electromotive Force Measurements. VII. Properties of the 70% Dioxane Mixtures

BY HERBERT S. HARNED, JOHN G. DONELSON AND CALVIN CALMON

Two earlier communications[1,2] contain electromotive forces of the cells

H_2 | HCl (m), dioxane (70%), H_2O | AgCl–Ag

at fourteen concentrations between 0.0008 and 0.2 M, and at temperatures from 0 to 50°. From these, the standard potentials of the cells have been computed throughout this temperature range.[2] To complete this study, measurements have been made at seven concentrations between 0.1 and 1.5 M. From the combined data, the activity coefficient, the relative partial molal heat content, and heat capacity of the acid have been computed. This completes the first comprehensive study of these properties of an electrolyte in a medium of dielectric constant of approximately 20.

Experimental Results

The results obtained from 0 to 50° at 5° intervals have been expressed by the equation

$$E = E_{25} + a(t - 25) + b(t - 25)^2 \quad (1)$$

The values of E_{25}, and the constants a and b are given in Table I. The fifth column of the table gives the maximum deviations in millivolts of the observed results from those calculated, and the last column contains the mean deviations.

These data were combined with those of Harned and Morrison[1] and Harned and Calmon[2] and

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[1] Harned and Morrison, THIS JOURNAL, **58**, 1908 (1936).

[2] Harned and Calmon, *ibid.*, **60**, 2130 (1938).

TABLE I

CONSTANTS OF EQUATION (1)

m	E_{25}	$-a \times 10^4$	$-b \times 10^6$	$\Delta_{max.}$	$\Delta_{av.}$
0.10707	0.25924	8.754	2.28	0.04	0.01
.20852	.23292	9.466	2.12	.05	.02
.31025	.21593	9.798	1.96	.08	.03
.53772	.18864	10.351	1.82	.09	.04
.72377	.17181	10.561	1.62	.10	.06
1.03675	.14754	10.731	1.42	.10	.04
1.55511	.11308	10.778	1.16	.13	.04

smoothed by means of suitable large scale graphs. Values of E_{25}, a, and b, suitable for all subsequent calculations, are given in Table II. At the bottom of the table are given the values of $E_0'_{(25)}$, a_0 and b_0 of the equation for the standard potential E_0', namely

$$E_0' = E_0' + a_0(t - 25) + b_0(t - 25)^2 \qquad (2)$$

TABLE II

CONSTANTS OF EQUATIONS (1) AND (2) AT ROUND CONCENTRATIONS

m	E_{25}	$-a \times 10^4$	$-b \times 10^6$
0.001	0.43716	4.50	3.14
.0015	.42006	4.95	3.02
.002	.40796	5.25	2.92
.003	.39145	5.78	2.85
.005	.37130	6.20	2.71
.007	.35850	6.50	2.65
.01	.34525	6.80	2.60
.02	.32008	7.33	2.48
.03	.30554	7.71	2.42
.05	.28739	8.11	2.33
.07	.27523	8.38	2.28
.1	.26195	8.67	2.22
.2	.23477	9.20	2.09
.3	.21744	9.53	1.98
.5	.19274	9.95	1.80
.7	.17383	10.22	1.64
1	.15010	10.54	1.45
1.50	.11638	10.90	1.19
	$E_0'(25)$	$-a_0 \times 10^4$	$-b_0 \times 10^6$
0(a = 1)	0.06395	17.67	3.70

Activity Coefficients

The activity coefficients, computed by the equation

$$-\log \gamma = \frac{(E - E_0')F}{4.6052\ RT} + \log m \qquad (3)$$

are given in Table III at some of the temperatures. The last row contains the dielectric constants of the solvent at these temperatures.

Relative Partial Molal Heat Content and Heat Capacity.—The relative partial molal heat content, $\overline{L}_2$, and heat capacity are given by the equations

$$\overline{L}_2 = \alpha + \beta T^2 \qquad (4)$$

$$(\overline{C}_p - \overline{C}_{p0}) = 2\beta T \qquad (5)$$

where α and β are defined by equations (6) and (7) of Harned and Donelson's communication.[3] These equations have a range of validity from 0 to 50°, inclusive. The parameters α and β are given in Table IV. Values of $\overline{L}_2$ and $(\overline{C}_p - \overline{C}_{p0})$ at 25° are given in the fourth and fifth columns of this table.

TABLE III

ACTIVITY COEFFICIENTS

m	t....0°	10°	20°	25°	30°	40°	50°
0.001	0.719	0.713	0.705	0.700	0.696	0.686	0.675
.0015	.672	.665	.656	.651	.647	.636	.624
.002	.641	.633	.623	.618	.613	.601	.589
.003	.589	.582	.573	.568	.563	.552	.540
.005	.530	.521	.510	.505	.499	.487	.473
.007	.488	.479	.468	.462	.457	.444	.431
.01	.446	.436	.425	.418	.413	.401	.388
.02	.369	.359	.348	.342	.336	.324	.312
.03	.328	.318	.308	.303	.297	.286	.275
.05	.283	.274	.264	.258	.253	.243	.232
.07	.259	.249	.239	.234	.229	.219	.208
.1	.236	.226	.217	.212	.207	.197	.188
.2	.204	.194	.185	.180	.175	.165	.156
.3	.193	.182	.173	.168	.163	.154	.144
.5	.191	.179	.169	.163	.158	.147	.137
.7	.200	.187	.175	.168	.162	.150	.139
1.0	.227	.211	.195	.187	.179	.165	.151
1.5	.303	.277	.252	.240	.228	.207	.187
D	20.4	19.25	18.2	17.7	17.2	16.3	15.4

TABLE IV

PARAMETERS OF EQUATIONS (4) AND (5), $\overline{L}_2$ AND $(\overline{C}_p - \overline{C}_{p0})$ AT 25°

m	$(-\alpha)$	$(\beta) \times 10^2$	$\overline{L}_{2(25)}$	$(\overline{C}_p - \overline{C}_{p0})_{25}$
0.001	701	1.29	446	7.7
.0015	862	1.57	533	9.4
.002	994	1.80	606	10.7
.003	1121	1.96	621	11.7
.005	1233	2.28	793	13.6
.007	1266	2.42	884	14.4
.01	1270	2.54	987	15.1
.02	1299	2.82	1207	16.8
.03	1348	2.95	1273	17.6
.05	1389	3.16	1419	18.8
.07	1397	3.28	1518	19.6
.1	1413	3.41	1617	20.3
.2	1417	3.71	1880	22.1
.3	1477	3.97	2051	23.7
.5	1558	4.38	2334	26.1
.7	1635	4.75	2586	28.3
1.0	1697	5.19	2915	30.9
1.5	1700	5.79	3445	34.5

Summary

1. Electromotive forces of the cells

H_2 | HCl (m), dioxane (70%), H_2O | AgCl–Ag

have been obtained from 0 to 50° at 5° intervals and at seven concentrations between 0.1 and 1.5 M.

2. These in combination with previous results through a concentration range of 0.0008

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[3] Harned and Donelson, THIS JOURNAL, **60**, 339 (1938).

to 0.1 *M* have been employed to compute the activity coefficient, relative partial molal heat content and heat capacity of the acid in this solvent.

3. The accuracy of the experimental results is of the order of ±0.1 mv., leading to an error of about ±0.001 in the relative activity coefficient and ±30 cal. in the relative heat content. A greater source of error in these values may reside in the uncertainty of the extrapolation. A general discussion of these thermodynamics properties will be reserved until the investigation of the 82% dioxane–water mixtures of dielectric constant of approximately 10 is completed.

NEW HAVEN, CONN. RECEIVED JUNE 21, 1938

[CONTRIBUTION FROM THE DIVISION OF BIOCHEMISTRY, MAYO FOUNDATION, AND THE DEPARTMENT OF PHYSIOLOGY, UNIVERSITY OF MINNESOTA MEDICAL SCHOOL]

The Distribution Coefficients of Porphyrins between Ether and Hydrochloric Acid and Applications to Problems of Quantitative Separation

BY ANCEL KEYS AND JOACHIM BRUGSCH[1]

Differential solubility in various solvents is the basic means of separating porphyrins in mixtures.[2-6] The most useful solvents are ether, chloroform and hydrochloric acid.[7,8] These three reagents have been used to effect separation of biological porphyrins by a procedure involving repeated crystallizations.[9,10] No proof of the quantitative accuracy of this method has been given; in any case it suffers from three limitations: (1) it is very time-consuming; (2) it serves only to isolate the principal porphyrin in the mixture; (3) it is stated that at least 50 micrograms of porphyrin is needed, but the work reported has generally involved much more; these amounts are not always available in biological work.

The porphyrins known or believed to occur in the normal or pathological human metabolism are: protoporphyrin ($C_{32}H_{32}N_4(COOH)_2$), coproporphyrin ($C_{32}H_{34}N_4(COOH)_4$), mesoporphyrin ($C_{32}H_{36}N_4(COOH)_2$) deuteroporphyrin ($C_{28}H_{28}N_4(COOH)_2$), and uroporphyrin ($C_{32}H_{30}N_4(COOH)_8$). All but the last named (uro-) are soluble in ether acidified by glacial acetic acid. Except in extremely rare cases, uroporphyrin occurs naturally only in the most minute amounts. Traces of other unidentified porphyrins have been reported in biological materials but these questionable substances may be neglected for the present.

Most of the natural porphyrins are soluble in chloroform, but repeated trials convinced us that chloroform extraction is not suitable for quantitative separation of porphyrins from natural mixtures unless extraordinary precautions are taken. Traces of impurities, especially colloids, may enable some of the porphyrins to go into colloidal solution in chloroform, prevent their extraction or cause loss by adsorption on the walls of the vessels used.

Willstätter and Stoll[11] made a qualitative separation of the ether-soluble porphyrins by extraction of the ethereal solution with hydrochloric acid. Willstätter[12] has characterized as the "HCl number" that concentration of hydrochloric acid which will extract two-thirds of the porphyrin from an equal volume of porphyrin solution. The available information on hydrochloric acid solubility of the porphyrins is in terms of Willstätter's "HCl number."

Since the naturally occurring porphyrins are reported to differ widely from one another in their hydrochloric acid numbers, a quantitative separation on this basis should be feasible, provided: (1) the hydrochloric acid solubility is a fixed characteristic, (2) the hydrochloric acid solubility for a given porphyrin is independent of

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[1] Fellow in Medicine in the Mayo Foundation.

[2] H. Fischer, *Z. physiol. Chem.*, **132**, 15 (1924); **137**, 228 (1924).

[3] H. Fischer and R. Duesberg, *Arch. exp. Path. Pharm.*, **166**, 95 (1932).

[4] C. J. Watson, *Z. physiol. Chem.*, **204**, 57 (1932).

[5] A. E. Garrod, *J. Physiol.*, **17**, 349 (1894).

[6] A. E. Garrod, "Inborn Errors of Metabolism," 2d ed., London, p. 136.

[7] H. Fischer and A. Treibs, in "Tabulae Biologicae," Vol. III, 1926, pp. 339, et seq.

[8] A. Kirstahler, *ibid.*, Vol. VII, 1931, p. 49, et seq.

[9] K. Dobriner, *J. Biol. Chem.*, **113**, 1 (1936).

[10] K. Dobriner, W. H. Strain and S. A. Localio, *Proc. Soc. Exptl. Biol. Med.*, **36**, 752 (1937).

[11] R. Willstätter and A. Stoll, "Untersuchungen über Chlorophyll," Berlin, 1913.

[12] R. Willstätter, in Abderhalden, "Handbuch der biologischen Arbeitsmethoden," Abt. I, Teil 3, pp. 1–70.

the presence of other porphyrins, (3) suitable hydrochloric acid concentrations are chosen so as to effect the separation in a reasonable number of extractions and (4) a satisfactory means of estimating the amount of porphyrin in the extracts is at hand.

We can begin by stating that the last-named requisite is fulfilled. All the porphyrins with which we are concerned are fluorescent in ultraviolet light and, over a limited range of concentration, the intensity of the fluorescence under standard conditions is directly related to the concentration. The present paper is a study on the partition between ether and various concentrations of hydrochloric acid of the following pure crystalline porphyrins: copro-, hemato-, meso-, deutero-, protoporphyrin and phylloerythrin ($C_{33}H_{34}N_4O_3$).

Preparation of Pure Porphyrins.—Our pure porphyrins were checked by their absorption spectra in ether and in hydrochloric acid solution.[13] In the following paragraphs the wave lengths of the principal bands are given in mμ. The values in parentheses are taken from Kirstahler.[8]

Preparation of Protoporphyrin.—Fresh blood is run into ten times its volume of 0.25% hydrochloric acid, shaken gently and after an hour the brown hydrochloric acid pigment is taken up in glacial acetic acid–ether. The ether is reduced to a small quantity, preferably in a vacuum. With the addition of 4% hydrazine sulfate in strong acetic acid solution the complete conversion to protoporphyrin is brought about when the solution is boiled down to about a fourth the original volume. The protoporphyrin is separated by filtration, and shaken with acetic acid ether in a separatory funnel. By this procedure a part of the protoporphyrin goes over into the ether along with some impurities. From this solution the protoporphyrin is recovered by extraction with 10% hydrochloric acid. The rest is taken up in hydrochloric acid, concentrated and preferably precipitated as the sodium salt by the addition of sodium hydroxide. Purification is readily brought about by washing, re-solution and reprecipitation. Protoporphyrin prepared in this way has the following characteristic absorption bands:

In 5% Hydrochloric Acid
I, 608–594, *602* (601)
II, 575–545, *560* (557)

In Ether Solution
I, 643–629, *636* (633)
II, 594–574, *584* (585)
III, 549–533, *541* (537)
IV, 514–494, *504* (502)

Preparation of Mesoporphyrin.—Crystalline mesoporphyrin was prepared from protoporphyrin by the method of Fischer and Kögl (1924) in which the vinyl groups are reduced by the action of iodic acid. The mesoporphyrin had the following absorption bands:

In 5% Hydrochoric Acid
I, 598–591, *594* (593)
II, 562–544, *553* (549)

In Ether Solution
I, 626–621, *623* (623)
II, 571–567, *569* (577?)
III, 532–523, *528* (529)
IV, 506–489, *496* (495)

Hematoporphyrin.—We used the crystalline preparation made by the Nordmark Company which is known commercially as "Photodyn." This hematoporphyrin had the following bands in the absorption spectrum:

In 5% Hydrochloric Acid
I, 595–588, *592* (596)
II, 559–540, *550* (552)

In Ether Solution
I, 626–623, *625* (625)
II, 599–594, *597* (598)
III, 571–567, *569* (569)
IV, 536–526, *531* (531)
V, 507–487, *497* (497)

Preparation of Coproporphyrin.—We used crystalline synthetic coproporphyrin I supplied by the kindness of Prof. Hans Fischer, as well as a crystalline preparation from human excreta. The latter preparation involved extraction with acetic acid ether, transfer to 5% hydrochloric acid, transfer to ether and repeated fractionation by means of ether and 0.25% HCl. Our preparation had the following absorption bands:

In 5% Hydrochloric Acid
I, 594–578, (594, 575)
II, 553–543, *548* (551)

In Ether Solution
I, 626–621, *624* (624)
II, 598–594, *596* (597)
III, 571–567, *569* (568)
IV, 532–524, *528* (529)
V, 504–486, *495* (498)

Preparation of Phylloerythrin.—We prepared phylloerythrin from ox gallstones in the course of the preparation of bilirubin by the method of H. Fischer (1911). The combined washings were carried over into ether and after purification were taken up by 10% HCl which was then neutralized and the phylloerythrin was carried back to ether, from which typical crystals were obtained. The phylloerythrin had the following absorption spectra:[14]

In 10% Hydrochloric Acid
I, 628–604, *621* (620)
II, 577–565, *571* (568)

In Ether Solutions
I, 638–635, *637* (637)
II, 597–579, *588* (593, 584)
III, 564–554, *559* (561)
IV, 528–513, *521* (521)

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[13] We are indebted to Dr. Charles Sheard for assistance in the determination of the absorption spectra.

[14] Comparison values in parentheses given by H. Fischer, in Oppenheimer, "Handbuch der Biochemie," 1933, 2d ed., Suppl. Vol. I (1), pp. 247, et seq.

Preparation of Deuteroporphyrin.—Deuteroporphyrin was prepared from deuterohemin by the action of hydrazine sulfate. We were unable to obtain sufficient material for recrystallization, but our preparation had the typical absorption spectra of deuteroporphyrin. Through the kindness of Dr. C. J. Watson we were able to check several of the hydrochloric acid solubility points with a solution of pure synthetic deuteroporphyrin from the laboratory of Prof. H. Fischer. However, since our preparation was not recrystallized, we prefer to term it simply "deutero type" porphyrin.

Measurement of Porphyrin Concentration in Hydrochloric Acid Solution

All our measurements of porphyrin concentration have been made in terms of the fluorescence in ultraviolet light. The intensity of fluorescence of a porphyrin solution in hydrochloric acid is stated to be linearly proportional to the porphyrin concentration in extreme dilution but not otherwise.[15—17] We have found this relation to be quantitative over the range 0.05 to 2 micrograms per ml. The fluorescence, however, is markedly affected by *p*H and, to a smaller extent, by temperature.[18] With the exception of phylloerythrin, we have measured the fluorescence of all our porphyrins in 5% HCl. With phylloerythrin we found it necessary to use 10% HCl. We have observed no effect of ordinary variations in room temperature, even in summer when some measurements were made at 30°.

The fluorescence spectra of the porphyrins studied here are not identical,[19] so the relative intensity of the fluorescence of the different porphyrins at equal concentration would be expected to differ slightly according to the system used for measurement. All of our measurements have been made by visual comparison, in some cases with the Zeiss "stufenphotometer."

Fluorescence is excited by the light from a quartz mercury vapor lamp. The ultraviolet light is passed through filters to cut out all radiation of a wave length longer than about 3800 Å. The "uviol" or Wratten No. 18A (ultraviolet) filters are satisfactory, especially when used as the windows of a copper sulfate cell. Wratten Nos. 15G and 18A make an excellent combination but a very powerful ultraviolet lamp must be used. The fluorescence of the porphyrin solutions may be studied in any type of quartz absorption vessels or ordinary glass vessels, provided these latter have relatively thin walls and possess no fluorescence of their own. Lacking more specialized apparatus, satisfactory comparisons can be made with matched test-tubes placed in the path of filtered ultraviolet light from an ordinary clinical ultraviolet lamp.

Standard coproporphyrin solution in 5% HCl was the standard of reference and all results here are expressed in terms of fluorescence equivalent to coproporphyrin. In general, the most useful concentrations for standard solutions are 0.2, 0.1 and 0.05γ of porphyrin per ml.

In the preparation of ethereal porphyrin solutions of known concentration dissolve from 2 to 20 micrograms of the pure crystalline material in about 30 ml. of 5% HCl. The exact concentration of porphyrin in the hydrochloric acid is determined, in terms of intensity of red fluorescence, by comparison with a stock standard solution of coproporphyrin. As soon as this measurement is completed, the acid solution is neutralized with solid sodium acetate and extracted with successive 25-ml. portions of ether until the aqueous phase no longer shows red fluorescence in ultraviolet light. It may be necessary to add a few drops of acetic acid in this process to keep the mixture slightly on the acid side of neutrality. The combined ethereal solution contains all the porphyrin originally dissolved in the 5% HCl.

For the purposes of quantitative analysis it is necessary that the partition between ether and hydrochloric acid be measured under conditions which are reproducible and easily applied. We add the hydrochloric acid to the ethereal solution in a separatory funnel and slowly shake back and forth by hand. Violent or prolonged agitation is unnecessary and may result in loss or oxidation of some of the porphyrin. The partition does not seem to be affected by the ordinary variations in room temperature in the range 20 to 26°. After the extraction, the hydrochloric acid extract was drawn off, the concentration brought up to 5% HCl and the fluorescence intensity measured at once. Finally, the ether was extracted with 5% HCl until all porphyrin had been removed from the ether. The fluorescence intensity was measured in these final extractions so that the total recovery of porphyrin from the ether was measured.

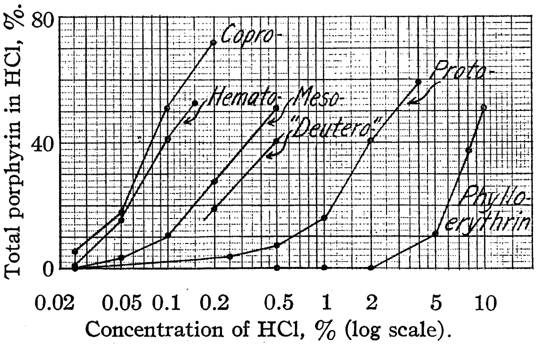

Fig. 1.—Extraction of porphyrins from ethereal solution by various concentrations of hydrochloric acid.

Figure 1 shows the results obtained when the volume relations were 1 part hydrochloric acid solution to 3 parts ethereal solution. Distribution coefficients for the several porphyrins over the useful range of hydrochloric acid concentration are given in Figs. 2 and 3. Most of these values were obtained using the volume relation 1 part hydrochloric acid to 3 parts ether. In a number of cases, however, the constancy of the distribution coefficient was checked by determinations made with the volume relation 1 part hydrochloric acid to 1 part ether.

Included in Fig. 2 are two points from an unknown porphyrin which occurs in very minute amounts in human feces. This porphyrin was soluble in chloroform and

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(15) R. Fikentscher, *Biochem. Z.*, **249**, 257 (1932).

(16) A. A. H. van den Bergh, W. Grotepass and R. E. Revers, *Klin. Wochsch.*, **11**, 1534 (1932).

(17) J. T. Brugsch, *Z. ges. exp. Med.*, **95**, 471 (1935).

(18) H. Fink and W. Hoerburger, *Z. physiol. Chem.*, **202**, 8 (1931).

(19) C. Dhéré, in Abderhalden, "Handbuch der biologischen Arbeitsmethoden," Abt. II, Teil 3, Heft 4, Lieferung 400, pp. 3097, et seq.

was purified so far as possible with repeated fractionation by means of 0.25% HCl, ether, 5% HCl and chloroform. As can be seen from the distribution coefficient this porphyrin appears to be a separate entity. This appearance is fortified by the fact that the distribution coefficient did not change during six successive extractions.

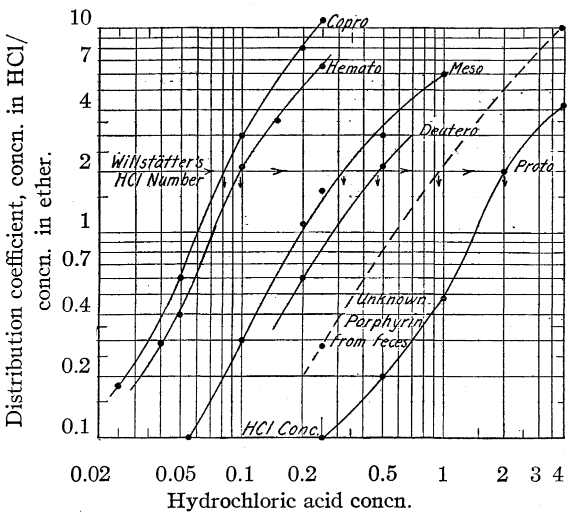

Fig. 2.—Distribution coefficients for the partition of porphyrins between ether and various concentrations of hydrochloric acid.

The distribution coefficient is simply the ratio of the concentration of the solute in the acid phase to that in the ether phase. If we let a = the percentage of the solute in the acid, and v the volume of the acid as percentage of the total volume, the distribution coefficient is

$$K = \frac{a/v}{(100 - a)/(100 - v)} \text{ and}$$

$$a = \frac{100\,Kv}{100 + Kv - v} \qquad \text{(I)}$$

Willstätter's hydrochloric acid number corresponds to a distribution coefficient of 2.0. In Table I we have given the previous values for the HCl number and the values calculated from the present results.

Quantitative analysis using distribution coefficients necessarily must involve successive extractions. It is requisite then that the experimental results with successive extractions conform to theory. General principles applicable to successive extractions were formulated by Herz[21] (1909). Let b_1 = the amount, in percentage terms, unextracted after the first extraction; *i. e.*, $b_1 = 100 - a$. Then

$$b_1 = 100\left(\frac{100 - v}{100 - v + Kv}\right)$$

TABLE I

HYDROCHLORIC ACID NUMBERS OF PORPHYRINS

Concentration of HCl which will extract two-thirds of the porphyrin from ether solution when equal volumes of HCl and ether are used in a single extraction. "Previous Values" taken from A. Treibs,[22] Fischer,[14] Fischer and Treibs[20] and A. Kirstahler.[8]

Porphyrin	Previous values	Present values	Uncertainty
Proto-	2	2.0	±0.1
Deutero-	0.3–0.4	0.47	± .05
Meso-	0.5	.32	± .05
Hemato-	0.1	.098	± .003
Copro-	0.08	.081	± .003
Phylloerythrin	about 9	8.5	± .5
Unknown porphyrin[a] from human feces	...	0.94	...

[a] This porphyrin is recovered in very small amounts from human feces by extraction in the following manner: extract with acetic ether, transfer to 5% HCl, transfer back to ether, extract with 0.25% HCl, neutralize, extract with chloroform, transfer to 5% HCl, carry back to ether, extract with HCl.

After n extractions the amount remaining in the ether (unextracted by the acid) will be

$$b_n = 100\left(\frac{100 - v}{100 - v + Kv}\right)^n \qquad \text{(II)}$$

Figure 4 shows the correspondence between experiment and theory for three successive extractions, using 3 volumes of ether and 1 volume of acid for each extraction. For this case equation II becomes

$$b_3 = 100\left(\frac{3}{3 + K}\right)^3 \quad \text{(IIA)}$$

In Fig. 4 the lines have been calculated from equation IIA and Figs. 2 and 3; the points are experimental observations.

Figure 4 shows that the agreement is good except at the highest hydrochloric acid concentrations where the extraction tends to be more complete than predicted. This is probably due to the fact that a small amount of hydrochloric acid is carried over in the ether to the succeeding extraction so that the hydrochloric acid is somewhat increased. This error is greatest with phylloerythrin and least with coproporphyrin.

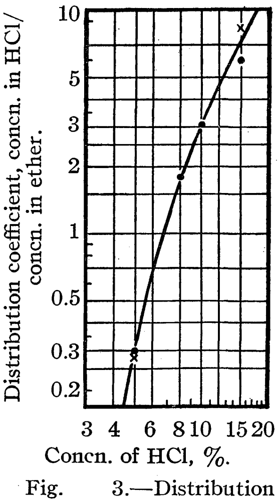

Fig. 3.—Distribution coefficient for the partition of phylloerythrin between ether and hydrochloric acid.

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(20) H. Fischer and A. Treibs, in Oppenheimer, "Handbuch der Biochemie," 2d ed., Suppl. vol. 30, 1930, p. 72.

(21) Herz, "Der Verteilungssatz," Stuttgart, 1909, p. 5.

(22) A. Treibs, in Oppenheimer, "Handbuch der Biochemie," 2d ed., Ergänzungsband, 1930, pp. 104–116.

Accordingly it appears that successive extractions with the lowest effective hydrochloric acid concentration should be satisfactory.

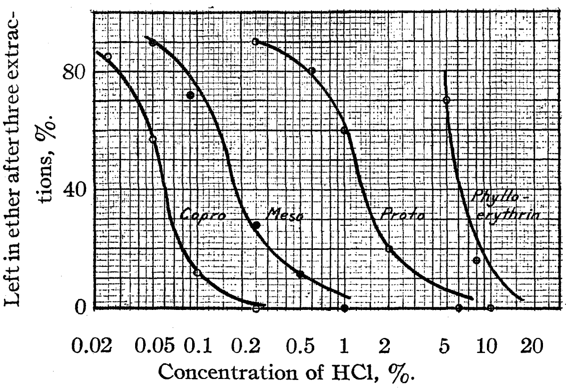


Fig. 4.—Constancy of the distribution coefficient in successive extractions. Lines calculated from distribution coefficients obtained in single extractions, points are experimental results with three successive extractions, using one volume hydrochloric acid to three volumes ether in each.

Finally, it is necessary to know whether the extraction of one porphyrin proceeds in quantitative independence of the presence of a second porphyrin. This question was studied with synthetic mixtures of porphyrins of known composition in terms of fluorescence equivalent to coproporphyrin. The results with two mixtures—copro- and protoporphyrin, and copro- and mesoporphyrin—are given in Fig. 5. In Fig. 5 the circles represent the experimental observations, the heavy lines were calculated from the distribution coefficients. The general agreement is good but there is a tendency to extract less than expected in some of the extractions. In all cases, however, the error is less than 4% of the total porphyrin.

The apparent small discrepancy between theory and observation with mixed porphyrins possibly may mean that the fluorescence intensities per unit concentration for the several porphyrins are not identical. It is generally assumed that the fluorescence intensities of the porphyrins studied here are equivalent per molecule. Our own studies indicate that this is approximately true when measurements are made in 5% HCl, but, owing to the excessively minute amounts of the materials available, an uncertainty of the order of 10% must be admitted.

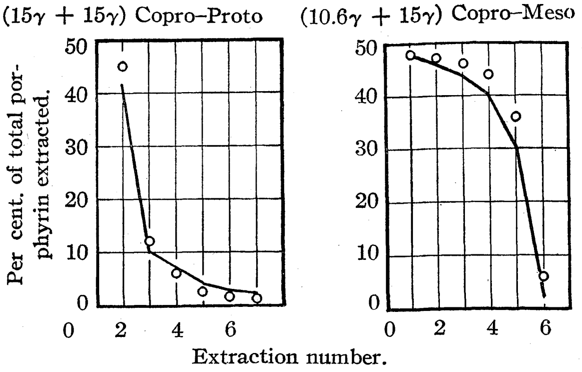

(15γ + 15γ) Copro–Proto (10.6γ + 15γ) Copro–Meso

Fig. 5.—Successive extractions of mixtures of porphyrins. Extraction of ethereal solution by 0.25% HCl, one volume of hydrochloric acid to three volumes ether in each extraction. Points experimentally determined, lines calculated from distribution coefficients (Fig. 2).

Summary

The following pure porphyrins were prepared and studied: copro-, hemato-, meso-, deutero- and protoporphyrin, and phylloerythrin.

Distribution coefficients for the porphyrins between ether and hydrochloric acid were determined by fluorescence measurements, over the range 0.025 to 10% HCl.

For each of the porphyrins the distribution coefficient at a given hydrochloric acid concentration is constant over a range of porphyrin concentration from 0.05 to 2000 micrograms per ml.

The results of successive extractions of ethereal solution by hydrochloric acid are quantitatively predictable from the distribution coefficients, but the error becomes significant when over 85% of the total porphyrin has been extracted.

The results of extractions of mixed porphyrins conform approximately to expectations from the distribution coefficients, but the error in any single extraction may be as great as 5% of the total porphyrin.

The use of successive extractions with appropriate concentrations of hydrochloric acid provides a satisfactory basis for at least semiquantitative separation of the ether-soluble porphyrins when as much as 0.01 mg. of total porphyrin is available.

MINNEAPOLIS, MINN.
ROCHESTER, MINN.

RECEIVED MAY 9, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE WASHINGTON SQUARE COLLEGE OF NEW YORK UNIVERSITY]

o-Methoxyphenylmalonic Acid and its Derivatives

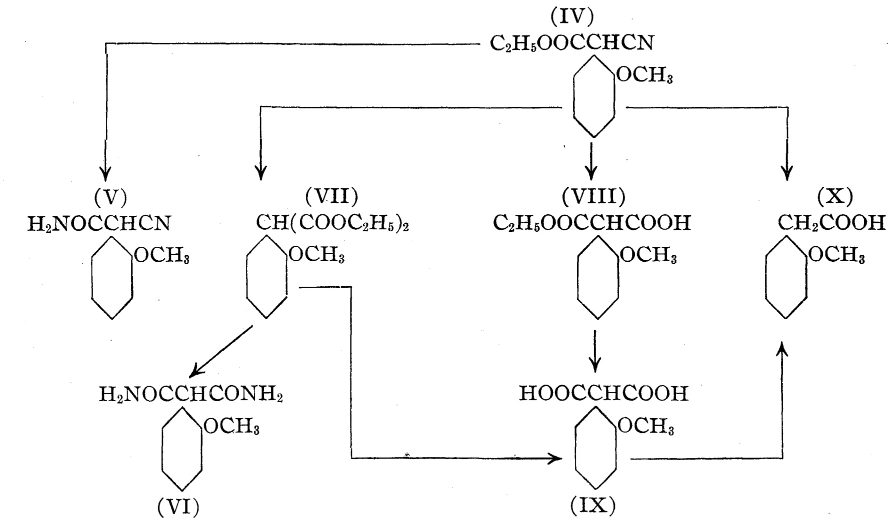
BY JOSEPH B. NIEDERL AND ROSLYN T. ROTH[1]

In a previous report of J. B. Niederl and coworkers,[2] the preparation of *p*-methoxyphenylmalonic acid and its derivatives was described and its general use in organic syntheses demonstrated. It was obvious that the preparation of its ortho isomer should be attempted. Unfortunately, due to the fact that in the diazotization of *o*-aminobenzyl·cyanide not the phenolic product but rather the indazole compound is formed,[3] a similar reaction scheme as for the para acid could not be utilized for the ortho isomer. Instead, the following series of reactions had to be employed

$$o\text{-}CH_3OC_6H_4CH_2OH\ (I) \xrightarrow{+HCl}$$
$$o\text{-}CH_3OC_6H_4CH_2Cl\ (II) \xrightarrow{+KCN}$$
$$o\text{-}CH_3OC_6H_4CH_2CN\ (III) \xrightarrow{+\text{ Claisen cond.}}$$
$$o\text{-}CH_3OC_6H_4CH(CN)COOC_2H_5\ (IV)$$

The ethyl *o*-methoxyphenylcyanoacetate (IV) was converted to the nitrile-amide (V) and the diester (VII). In the preparation of the latter compound, the monoethyl ester (VIII) was obtained as a by-product. On heating and saponification, it was converted into *o*-methoxyphenylacetic acid (X). The diester (VII) was converted into the diamide (VI) and the free dibasic acid (IX), which on heating also yielded *o*-methoxyphenylacetic acid (X). This latter acid was prepared by saponifying the *o*-methoxybenzyl cyanide (II) with alcoholic potassium hydroxide solution.[4]

The structural relationship of these compounds is as shown.



Experimental

***o*-Methoxybenzyl Chloride (II).**—Into a 500-cc. three-necked flask containing 100 g. of *o*-methoxybenzyl alcohol, a vigorous stream of dry hydrogen chloride was introduced. As soon as the temperature began to rise, the mixture was cooled externally with an ice–salt mixture, keeping the reaction temperature below 20°. Introduction of the gas was continued for about two hours, by which time the reaction was practically complete, as recognized by the attainment of constant weight or a fall of the temperature of the reaction mixture to about 2°. To the mixture was added crushed ice and ether. The ether extract was washed with water, 5% sodium carbonate solution and water. The washing was done rapidly to avoid hydrolysis. The ether was removed by distilling under reduced pressure, and the crude chloride was used directly for the preparation of the cyanide.

***o*-Methoxybenzyl Cyanide (III).**—The crude, freshly prepared *o*-methoxybenzyl chloride as prepared above was mixed with 100 cc. of ethyl alcohol and added dropwise over a period of an hour to a gently refluxing mixture of 46 g. of sodium cyanide in 42 cc. of water. Refluxing was continued for one and one-quarter hours (further refluxing decreased the yield due to the formation of high boiling and non-volatile products). The alcohol was removed from the reaction mixture under reduced pressure. The residue was dissolved in ether, the ether extract treated with water, then dried and distilled. The fraction boiling at 100–135° at 4 mm. was allowed to stand on ice for a week. Large prismatic crystals formed from which the oil was separated by placing the crystals on porous tile. The yield of crystals was 38 g.

In this process a large amount of *o*-methoxybenzyl ethyl ether always formed, due to interaction of the chloride with the ethyl alcohol used as solvent. Consequently,

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[1] The material is taken from a portion of the thesis presented by Roslyn T. Roth to the faculty of the Graduate School of New York University in partial fulfilment for the degree of Doctor of Philosophy.

[2] Niederl, Roth and Plentl, THIS JOURNAL, **59**, 1901 (1937).

[3] Pschorr, *Ber.*, **43**, 2543 (1910).

[4] Pschorr, Wolfes and Buckow, *ibid.*, **33**, 166 (1900).

TABLE I

PHYSICAL CONSTANTS AND ANALYSES OF COMPOUNDS

	Compound	M. p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Neut. equiv. Calcd.	Neut. equiv. Found
IV	Et. ester-nitrile	49	$C_{12}H_{13}NO_3$	65.80	66.10	5.94	5.65	6.39	6.40		
V	Nitrile-amide	142–143	$C_{10}H_{10}N_2O_3$	63.16	63.17	5.26	5.04	14.73	14.68		
VI	Diamide	204	$C_{10}H_{12}N_2O_3$	57.69	57.94	5.76	5.49	13.46	13.35		
VII	Diester[a]		$C_{14}H_{18}O_5$	63.16	63.30	6.77	6.64				
VIII	Monoethyl ester	86–87	$C_{12}H_{14}O_5$	60.51	60.66	5.89	5.89			238	235
IX	Free acid	142–143	$C_{10}H_{10}O_5$	57.15	57.30	4.76	4.91			105	106

[a] B. p. 133–135° (2 mm.); sp. gr. at 24°, 1.103; $n^{23°}_{D}$ 1.5020.

substitution of the ethyl alcohol by other organic, water-soluble solvents (acetone, dioxane, etc.) was attempted, leading to the formation of non-volatile high polymeric residues. No cyanide could be obtained under these reaction conditions.

Since the above method would constitute a simplification in the synthesis of alkoxyphenylmalonic acids, this same reaction was applied to *p*-methoxybenzyl alcohol, but in this case no *p*-methoxybenzyl cyanide could be obtained at all, either the *p*-methoxybenzyl ethyl ether (ethyl alcohol as solvent), or the polymer formed (dioxane as solvent), while with acetone as solvent no reaction whatsoever took place.

o-Methoxyphenylmalonic Acid. Ethyl Ester-Nitrile (IV).—A solution of 32 g. of the crystalline *o*-methoxybenzyl cyanide in 150 cc. of anhydrous ether was added dropwise, over a period of two and one-half hours, to a mixture of 5.1 g. of sodium shot, 20 cc. of ether, 26 g. of freshly dried and distilled ethyl carbonate. The mixture was allowed to stand overnight, and then after refluxing for two hours was acidified with ice-cold 25% sulfuric acid and extracted with ether. The ether extract was washed with water, 5% sodium carbonate solution, dried and distilled. The fractions from 150–175° (7 mm.) were collected. After standing, the lower fraction crystallized partly, and the higher fraction completely; yield 10 g. The ester-nitrile crystallized from alcohol in the form of large prisms.

In the preparation of the free *o*-methoxyphenylmalonic acid, 0.2 g. of the ester-nitrile in 10 cc. of ether was shaken for ten minutes with 8 cc. of 2% sodium hydroxide solution. Then the ether layer was removed and the ether allowed to evaporate. The residue thus obtained was unreacted ester-nitrile. Half of the alkaline solution, upon being acidified, yielded a mixture of acidic products. The other half of the alkaline solution, when allowed to stand overnight before being acidified, yielded the water-soluble *o*-methoxyphenylmalonic acid (IX).

o-Methoxyphenylmalonic Acid Amide-Nitrile (V).—Six-tenths of 1 g. of the ester-nitrile (IV) was melted and shaken for five minutes with 20 cc. of concentrated ammonia. Nearly all dissolved, and the rest was removed by filtration immediately. The amide-nitrile crystallized out from the filtrate in long needles; yield 0.3 g. It was recrystallized from hot water; mixed m. p. with the *p*-isomer, 114–126°.

o-Methoxyphenylmalonic Acid Mono and Diethyl Esters (VII and VIII).—A mixture of 4.45 g. of the ester-nitrile (IV), 7 cc. of ethyl alcohol, and 0.2 cc. of water was treated with dry hydrogen chloride, first while cold, then for fifteen minutes while refluxing, and then while being cooled in an ice–salt bath. It was allowed to stand overnight, and then refluxed for one hour, and poured into water. The ether extract of this solution was washed with 5% sodium carbonate solution and water, dried with calcium chloride and distilled, the product being the diethyl ester (VII). Neutralization and extraction with ether of the sodium carbonate washings yielded 0.24 g. of the monoethyl ester (VIII) which crystallized on long standing and was recrystallized from hot water. The monoester was identified by heating to drive off the free carboxyl group and saponification of the ester group by 3% sodium hydroxide. On acidification, the *o*-methoxyphenylacetic acid was obtained, confirmed by a mixed melting point with the same acid prepared from *o*-methoxybenzyl cyanide.

o-Methoxyphenylmalonic Acid Diamide (VI).—Three-tenths of a gram of the diethyl ester (VII) was shaken for several hours with 5 cc. of concentrated ammonia, filtered, and the filtrate allowed to evaporate at room temperature. The residue was recrystallized from absolute alcohol, in the form of flakes.

o-Methoxyphenylmalonic Acid (IX).—An ether solution of 0.24 g. of the diethyl ester (VII) was shaken for three hours with 1 cc. of sodium hydroxide solution. On acidification and extraction with ether, 0.15 g. of the free acid was obtained. It was recrystallized from ether–petroleum ether mixture in the form of prisms. The acid on melting gave off carbon dioxide. The residue when heated to 150° gave *o*-methoxyphenylacetic acid; mixed m. p. with the *p*-isomer, 122°.

The authors desire to express their appreciation to Reed and Carnrick, Jersey City, N. J., for a fellowship grant.

Summary

1. The preparation of *o*- and *p*-methoxybenzyl cyanide was studied.

2. *o*-Methoxyphenylmalonic acid and several of its derivatives were prepared and characterized.

NEW YORK, N. Y. RECEIVED JUNE 10, 1938

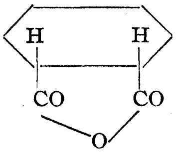
[Contribution from the Chemical Laboratories of Harvard University

The Reactions of Certain Gamma Ketonic Acids. V. Ketonic Beta Lactones and the Walden Inversion[*]

By E. P. Kohler and J. E. Jansen

In a previous paper[1] it was shown that the rates at which two diastereomeric β-bromo acids form β-lactones are dependent on the configurations of the bromo acids. The relations described did not provide a basis for determining whether the closure and opening of the β-lactone ring does or does not involve inversion. That problem is the subject of the present paper.

In order to secure substances of known configuration, it was necessary to resort to cyclic compounds in which the configuration is fixed by the structure and in which it can be determined by the methods that have been evolved for unsaturated ketonic acids.[2] To this end we began with two anhydrides of which the configuration is known, both from the relative ease with which they are formed and from the resolvability of the corresponding *trans* dibasic acid.



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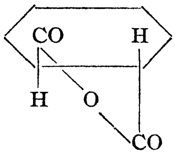
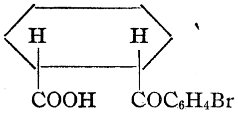
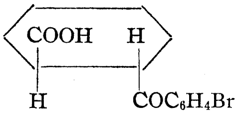


II

Both of these anhydrides were condensed with bromobenzene without difficulty and each gave only one γ-ketonic acid.

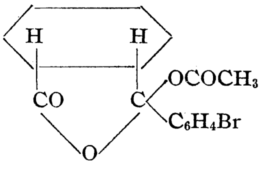


III

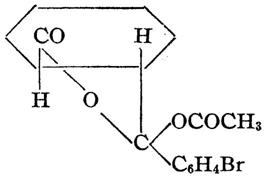


IV

The relative stability of these ketonic acids is the same as that of the corresponding dibasic acids, but, doubtless because of the greater tendency for ketones to enolize, the *cis* acid can be transformed into the *trans* by heating with bases as well as with acids. With the help of these acids of known configuration it was possible to ascertain whether a method which had been found reliable in the case of unsaturated ketonic acids can be employed for determining the configuration of their cyclic analogs. To this end each acid was dissolved in a cooled mixture composed of equal parts of acetic acid and acetic anhydride containing a trace of sulfuric acid, or each acid was dissolved in a warmed mixture of equal parts of acetic acid and acetic anhydride and, in each case, the *cis* acid was converted rapidly and completely into the compound which we assume to be the dicyclic acetate, whereas the *trans* acid was recovered unchanged. In order to convert the *trans* acid into a dicyclic acetate it was necessary to omit the acetic acid and employ only the anhydride. The configuration of these γ-keto acids can be established, therefore, by comparing the relative ease with which they form dicyclic acetates.



V



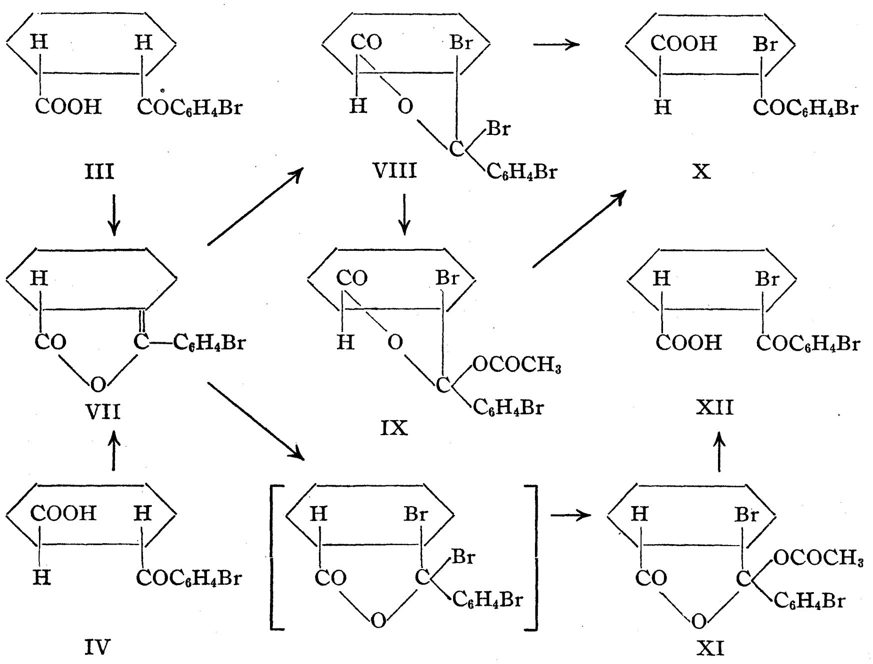
VI

The bromination of the cyclic ketonic acids proved to be unexpectedly troublesome. Neither of the acids could be brominated satisfactorily in non-polar solvents. In direct sunlight bromine reacts slowly with the *cis* acid in boiling chloroform, but the product is a mixture that is extremely difficult to separate. Under the same conditions the *trans* acid reacts still more slowly and forms only oily products. Both acids, however, can be dehydrated to an unsaturated γ-lactone which can be utilized for securing both bromo acids. This unsaturated lactone forms a dibromide which is converted into the dicyclic acetate of the *trans* bromo ketonic acid and when the unsaturated lactone is brominated in a mixture of acetic acid and acetic anhydride, it forms a mixture of the dicyclic acetates of the *cis* and *trans* bromo ketonic acids. The hydrolysis of the acetates to the corresponding bromo ketonic acids presents no difficulties. These relations are shown in the following chart.

(*) This paper was written by Professor Kohler a few months before his death. A few minor additions of experimental work, completed after the paper was written, have been included.—J. E. Jansen.

(1) Kohler, Peterson and Bickel, This Journal, **56**, 2000 (1934).

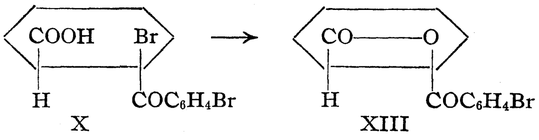
(2) Kohler and Peterson, *ibid.*, **56**, 2192 (1934).



This series of reactions, doubtless, accounts for the fact that both acids can be brominated in acetic anhydride and, also, in a mixture of acetic acid and anhydride. When they are brominated in acetic anhydride the sole product is the same dicyclic bromoacetate (IX) that is formed by the action of the anhydride on the dibromide, and when they are brominated in an acid and anhydride mixture they also form the mixture of bromoacetates that is formed by brominating the unsaturated lactone under the same conditions.

The configurations of the bromo ketonic acids were established without difficulty because they differ even more conspicuously than the unbrominated acids in the ease with which they form dicyclic acetates. The higher-melting bromo acid forms a dicyclic acetate when it is dissolved in cold acetic anhydride, in a warmed mixture of four parts of anhydride and one part acetic acid and when it is warmed with a mixture of equal parts of acetic acid and anhydride. The lower-melting bromo acid is not converted into its acetate in this manner; in order to prepare the dicyclic acetate it is necessary to employ acetic anhydride and sulfuric acid. In the higher-melting bromo acid, therefore, the carbonyl and bromobenzoyl groups are on the same side of the molecule as shown in formula XII. In these experiments two dicyclic acetates of the higher-melting bromo acid are obtained: one from the acetic anhydride solution and the other from the solutions of anhydride containing either acetic acid or sulfuric acid. The formation of two dicyclic acetates is attributable to the generation of a third center of symmetry in the molecule.

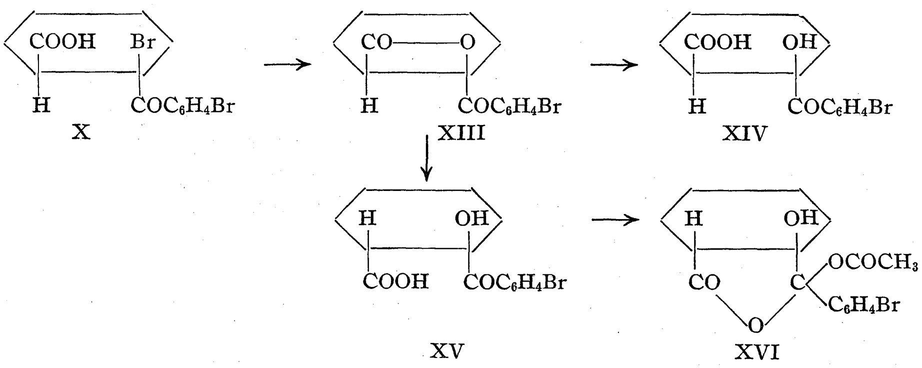
With these two bromo acids of known configuration in hand, it was possible to attack the problem of lactone formation. We found that these acids differ in their behavior toward bases precisely like the corresponding open-chained acids. The bromine derivative of the *trans* ketonic acid is extracted from an ether solution by dilute aqueous sodium bicarbonate, but its salt is converted rapidly and completely into a β-lactone. Under these conditions the bromine derivative of the *cis* ketonic acid is converted into a salt which undergoes no further change. Moreover, unlike the corresponding open chain compound, this bromo compound cannot be converted into a β-lactone by means of caustic alkalies. In this series, therefore, the β-lactone ring can be closed only when the bromine atom and the carboxyl group are on the same side of the molecule.



By analogy to cyclohexene oxide and to the cyclohexane dicarboxylic anhydrides, the β-lactone that is obtained from the bromo ketonic acid has the configuration shown in formula XIII. In view of its relative stability and the rapid cyclization, formation of a β-lactone with a *trans* configuration of the ring appears improbable and is inconsistent with the known properties of these bicyclic compounds. Also, since the isomeric bromo acid, in which the bromine and carboxyl groups are in the *trans* position, fails to form a β-lactone, it is unlikely that the reaction proceeds with inversion. If this were the case, it would be expected that this isomeric bromo acid would more readily form the β-lactone with a *cis* ring.

This β-lactone is exceedingly sensitive to bases. It is rapidly extracted from an ether solution by cold, dilute, aqueous potassium hydroxide, and more slowly by sodium carbonate, to yield, quantitatively, in each case, a salt of a single hydroxy acid. This hydroxy acid is not affected by dilute alkalies—it was recovered quantitatively from a solution of potassium hydroxide which had been boiled for four hours. In methyl alcohol containing a trace of sodium methylate, the β-lactone is opened quantitatively to a methyl ester of this same hydroxy acid. This methyl ester is also obtained from the hydroxy acid with methyl alcohol and sulfuric acid.

The methyl ester of a higher-melting isomeric hydroxy acid is obtained quantitatively when solutions of the β-lactone in methyl alcohol, containing sulfuric acid, are allowed to stand. This higher-melting hydroxy acid is also formed to some extent when the β-lactone is dissolved in methyl alcohol containing an excess of sodium methylate, or when it is boiled for a long time with dilute sulfuric acid. No isomerization of the lower-melting hydroxy acid, obtained from the β-lactone with bases, is observed in acid solutions. Thus, in this manner it was possible to secure the two isomeric hydroxy acids, though it was impossible to prepare more than one β-lactone.



The isomeric hydroxy acids, like all the other pairs of isomers that have been described, differed greatly in the ease with which they formed dicyclic acetates in acetic anhydride, but, unlike the bromo acids, in mixtures of acetic acid and anhydride satisfactory conversion to cyclic acetates could not be achieved. In acetic anhydride, the lower-melting hydroxy acid, which was formed by the action of bases on the β-lactone, failed to form the dicyclic compound, but the higher-melting isomer was converted into a dicyclic acetate without difficulty. On this basis, the latter acid is a derivative of the *cis* ketonic acid and the former is a derivative of the *trans* acid. However, these configurations have not been established with the certainty that was possible with the bromo acids.

The hydroxy groups in both the hydroxy acids were surprisingly resistant to attack. At the ordinary temperatures, with hydrogen bromide in acetic acid, the hydroxyl groups were not replaced with bromine and at elevated temperatures only thick oils resulted. Furthermore, it was not possible to prepare the corresponding methoxy acids by any of the ordinary methods.

With the configurations that are established, it is possible finally to decide whether the β-lactone is closed with or without inversion. Because the ring formation proceeds through closure of two groups in the *cis* position, with formation of a β-lactone of the same configuration, no inversion has occurred. The evidence obtained favors the same *cis* configuration for the hydroxy acid that is obtained from the β-lactone with bases and on this basis the ring opening with bases has also occurred without inversion. These reactions are shown in the chart.

Experimental

A part of the material employed in the investigations was prepared from dimethyl phthalate. The commercial ester was hydrogenated in the presence of Raney catalyst at a temperature of 225° and under a pressure of 2000 lbs. (133 atm.). As it was impossible to attain complete hydrogenation, the product had to be purified by fractional distillation before it was hydrolyzed to the dibasic acid from which the anhydride was made.

The rest of the material was made by adding maleic anhydride to butadiene[3] and hydrogenating the addition product. As the equipment for making butadiene[4] in quantity was available, we found it much more convenient to synthesize the anhydride by this method than to make it from the phthalate.

Tetrahydrophthalic Anhydride.—Diels and Alder operated in sealed tubes, but we found that with our much

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[3] Diels and Alder, *Ann.*, **460**, 113 (1928).

[4] Fieser, *Org. Syntheses*, **17**, 25 (1937).

larger quantities it was quite feasible and much more convenient to operate in strong-walled flasks in the following manner. A suspension of 90 g. of maleic anhydride in 300 cc. of pure benzene was introduced into a suction flask equipped with a delivery tube that dipped under the surface of the liquid, and a Bunsen valve that was constructed out of heavy-walled tubing. The delivery tube was connected with a cooled vessel containing 70 g. of butadiene and the container was allowed to assume the temperature of the room. The gas was absorbed as fast as it was evolved, the temperature of the suspension rose rapidly and the anhydride disappeared before all of the diene had evaporated. The clear solution was allowed to remain under the pressure of butadiene until most of the addition product had separated, then cooled and filtered. The yield was 134 g. or 96%.

Hydrogenation: *cis* Cyclohexane Dicarboxylic Anhydride, I.—A suspension of 40 g. of the anhydride in 40 g. of glacial acetic acid was shaken with hydrogen in the presence of 0.1 g. of Adams catalyst. Hydrogen was absorbed rapidly, the reduction being complete in three to four hours. The catalyst was removed by filtration and the solvent by evaporation under diminished pressure. Nearly all of the residue was pure *cis* anhydride distilling at 161.7–161.9° (25 mm.) and melting at 31°. The yield was 93%.

***trans*-Cyclohexane Dicarboxylic Anhydride, II.**—The *cis* anhydride was heated for three hours at 180° with concentrated hydrochloric acid and the resulting *trans* acid was converted into its anhydride by treatment with acetyl chloride as directed by Baeyer.[5] The anhydride melted at 140–142° and the yield was 70%.

***cis-p*-Bromobenzoyl Cyclohexane Dicarboxylic Acid, III.**—To a solution of 50 g. of the *cis* anhydride in 250 g. of bromobenzene which was cooled to 10° was added, in a single lot, 94 g. of powdered aluminum chloride. The mixture was stirred and the temperature rose to 60–65°. After remaining at room temperature for forty-five minutes it was stirred into a mixture of ice and dilute acid and set aside to allow the acid to solidify. The solid was removed, washed with water and dissolved in sodium carbonate. After removal of the unchanged bromobenzene with ether, the carbonate solution on acidification deposited 98 g. of solid which was recrystallized from 75% acetic acid. It separated in fine needles melting at 169–171°. It is very sparingly soluble in ether, readily soluble in chloroform, benzene and acetone. The yield was 83 g. or 83%.

Anal. Calcd. for $C_{14}H_{15}O_3Br$: C, 54.0; H, 4.8. Found: C, 53.9; H, 4.9.

The methyl ester of the *cis* ketonic acid was prepared by means of diazomethane. It crystallized from ether–petroleum ether in small prisms melting at 60–61°. It also can be obtained by esterifying the acid with methyl alcohol and sulfuric acid but the yield is poor.

Anal. Calcd. for $C_{15}H_{17}O_3Br$: C, 55.4; H, 5.2. Found: C, 55.3; H, 5.2.

The Dicyclic Acetate, V.—(1) To a cooled solution of 1.0 g. of the *cis* ketonic acid in 60 cc. of acetic acid was added 20 cc. of acetic anhydride containing a trace of sulfuric acid (one drop of acid to 50 cc. of anhydride) which had been cooled to 0°. The solution was kept at 10° for half an hour, then stirred into ice water and left to itself for an hour. (2) One gram of the acid was dissolved in 40 cc. of equal parts of acetic acid and acetic anhydride and the solution kept at 60–65° for fifteen minutes. The solution was then treated as above. The resulting solid in each case was recrystallized from ether–petroleum ether. It separated in small prisms melting at 149°. The yields were 0.9 g. The mixed melting point of the two samples was not depressed.

Anal. Calcd. for $C_{16}H_{17}O_4Br$: C, 54.5; H, 4.9. Found: C, 54.5; H, 5.0.

Hydrolysis of the Acetate.—The acetate is hydrolyzed with great rapidity. In boiling moist ether it disappeared within three hours and it was removed from its ethereal solution by dilute sodium bicarbonate. In each case the *cis* ketonic acid was the only product.

***trans-p*-Bromobenzoyl Cyclohexane Carboxylic Acid, IV.**—By the same procedure that was employed for the preparation of the *cis* ketonic acid, the anhydride of *trans* cyclohexane dicarbonic acid was converted into the *trans* ketonic acid. The acid was recrystallized from ether–petroleum ether. It separated in irregular prisms melting at 164°. The yield was 60%.

Anal. Calcd. for $C_{14}H_{15}O_3Br$: C, 54.0; H, 4.8. Found: C, 54.2; H, 5.1.

The Methyl Ester.—The ester was prepared both with diazomethane and with methyl alcohol and sulfuric acid. It crystallized from methyl alcohol in prisms and melted at 98–99°. The yields were quantitative.

Anal. Calcd. for $C_{15}H_{17}O_3Br$: C, 55.4; H, 5.2. Found: C, 55.5; H, 5.4.

The Dicyclic Acetate, VI.—In experiments which were conducted exactly the same as that by which the *cis* ketonic acid was converted into the dicyclic compound, all of the *trans* acid was recovered. The acetic acid was omitted, therefore, and 1.0 g. of the *trans* acid was dissolved in 20 cc. of acetic anhydride containing a trace of sulfuric acid. The solution was kept at the ordinary temperature for fifteen minutes and then manipulated as described under the *cis* acetate. The result was 1.0 g. of the *trans* dicyclic acetate. It crystallized from ether–petroleum ether in small prisms and it melted at 96–97°. The *trans* acetate is more stable than the *cis* isomer in the presence of water but it is rapidly hydrolyzed by dilute acids, regenerating the *trans* acid.

Anal. Calcd. for $C_{16}H_{17}O_4Br$: C, 54.5; H, 4.9. Found: C, 54.6; H, 5.2.

Isomerization of the *cis* into the *trans* Ketonic Acid.—The *cis* ketonic acid, like the dibasic acid, can be isomerized with acids but unlike the dibasic acids it is isomerized much more rapidly with bases. Thus, after a solution of 15 g. of the acid in 400 cc. of 5% aqueous sodium carbonate had been boiled for three hours, it contained only the salt of the *trans* acid. The *trans* acid is, therefore, most easily secured by converting the *cis* anhydride into the corresponding ketonic acid and inverting this acid with sodium carbonate.

The Unsaturated γ-Lactone, VII.—A suspension of 10 g. of the *cis* ketonic acid in 50 cc. of acetic anhydride was cooled to 0°, stirred vigorously and treated with 3 drops of

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[5] Baeyer, *Ann.*, **258**, 217 (1890).

concentrated sulfuric acid. The acid dissolved immediately and in a few moments a new solid appeared. After fifteen minutes the mixture was stirred into ice water where it was left for an hour. The solid was then collected, washed with water, dried and recrystallized from methyl alcohol. It separated in small cubes melting at 95°. The yield was 8 g. In a repetition with the same quantity of the *trans* acid, the same solid was formed in the same quantity and apparently with the same ease.

Anal. Calcd. for $C_{14}H_{13}O_2Br$: C, 57.3; H, 4.5. Found: C, 57.4; H, 4.8.

Hydrolysis.—The unsaturated lactone, like the corresponding monocyclic lactones, reverts to a ketonic acid when it is treated with bases. Thus a solution of 1 g. of the substance in 50 cc. of methyl alcohol containing a gram of potassium hydroxide was boiled for an hour, then diluted with water and acidified. The product was 0.6 g. of the *trans* ketonic acid, the only ketonic acid that is stable in the presence of bases.

Addition of Bromine: the Dibromide, VIII.—To a solution of 4 g. of the unsaturated lactone in 40 cc. of carbon disulfide, which was kept at 0°, was added 2.2 g. of bromine. The bromine disappeared as fast as it was added. After removing a part of the solvent, the residual solution was diluted with petroleum ether. It deposited 5.4 g. of a solid which, after recrystallization from ether–petroleum ether from which it separated in large tables, melted with decomposition at 119–122°.

Anal. Calcd. for $C_{14}H_{13}O_2Br_3$: C, 37.1; H, 2.9; Br, 53.0. Found: C, 37.3; H, 3.2; Br, 52.8.

Hydrolysis.—The dibromide is hydrolyzed slowly in contact with air, more rapidly when shaken with dilute acetic acid. After a suspension of 2 g. of the substance had been shaken with the dilute acid for eight hours it yielded 1.6 g. of pure *trans* bromo ketonic acid X.

Alcoholysis: the Dicyclic Bromomethyl Ether.—A solution of 0.5 g. of the dibromide in 10 cc. of methyl alcohol was kept at the ordinary temperature for three hours and then allowed to evaporate. The resulting oil was dissolved in ether. From the washed and dried ethereal solutions petroleum ether precipitated the solid ether in small hard prisms melting at 93°. The corresponding ethyl ether melts at 115°. These ethers are more stable than the bromide and the acetate but when they are digested with acetic acid and concentrated hydrochloric acid they likewise are hydrolyzed to the *trans* bromo ketonic acid.

Anal. Calcd. for $C_{15}H_{16}O_3Br_2$: C, 44.6; H, 4.0. Found: (93°) C, 44.5; H, 4.2. Calcd. for $C_{16}H_{18}O_3Br_2$: C, 46.0; H, 4.3. Found: (115°) C, 46.1; H, 4.6.

Reaction with Acetic Anhydride: the *trans* Dicyclic Bromoacetate, IX.—A solution of 0.5 g. of the dibromide in acetic anhydride almost immediately deposited 0.4 g. of the solid bromoacetate. It was crystallized from chloroform from which it separated in small, hard prisms melting with decomposition at 174–176°.

Anal. Calcd. for $C_{16}H_{16}O_4Br_2$: C, 44.5; H, 3.7. Found: C, 44.3; H, 3.8.

As this bromo compound can be obtained without difficulty by brominating either the *cis* or the *trans* ketonic acid, it was used as a source for the *trans* bromo ketonic acid. For this purpose it was prepared in the following manner: a solution of 39 g. of bromine in 50 cc. of acetic acid was added slowly to a solution of 75 g. of the *cis* ketonic acid in 200 cc. of acetic anhydride. The reaction started at once and proceeded rapidly. Hydrogen bromide was not evolved. The cyclic acetate began to precipitate before more than a third of the bromine had been added. In order to complete the precipitation the mixture was cooled for several hours in ice water before filtration. The solid was washed with dilute acetic acid, dried and recrystallized from chloroform or benzene. The yield was 94%. When the *trans* ketonic acid was brominated in the same manner the same dicyclic bromoacetate was obtained, the yield being 93%.

Hydrolysis: the *trans* Bromo Ketonic Acid, X.—The bromoacetate is not nearly so sensitive as the corresponding unsubstituted acetate, being unaffected when its ethereal solution is shaken with dilute solutions of bases. For the purpose of hydrolysis a suspension of 98 g. of the compound in 300 cc. of acetic acid and 40 cc. of concentrated hydrochloric acid was heated with constant stirring on a steam-bath for two hours. The clear solution, cooled and diluted with water, deposited a solid which, after recrystallization from ether, from which it separated in hard irregular prisms, melted at 147°. The yield was 94%.

Anal. Calcd. for $C_{14}H_{14}O_3Br_2$: C, 43.1; H, 3.6. Found: C, 43.1; H, 3.9.

The *cis* Dicyclic Bromoacetate, XI.—A solution of 2.6 g. of bromine in 20 cc. of acetic acid was added to a solution of 5.0 g. of the *cis* ketonic acid in 150 cc. of acetic acid and 75 cc. of anhydride. The reaction started slowly and required an hour for completion. When the solution was cooled it deposited 2.5 g. of the *trans* bromoacetate which was removed by filtration. The filtrate, on dilution with water, deposited 2.0 g. of solid that was separated by recrystallization from ether into 0.5 g. of *trans* and 1.5 g. of the *cis* bromoacetate. This *cis* compound crystallized from ether in flat needles melting at 149°.

Anal. Calcd. for $C_{16}H_{16}O_4Br_2$: C, 44.5; H, 3.7. Found: C, 44.3; H, 3.9.

Hydrolysis: the *cis* Bromo Ketonic Acid, XII.—The dicyclic acetate was hydrolyzed in the same manner as the *trans* compound. The product crystallized in fine needles and melted with decomposition at 185–187°.

Anal. Calcd. for $C_{14}H_{14}O_3Br_2$: C, 43.1; H, 3.6. Found: C, 42.8; H, 3.7.

The methyl ester of the *cis* bromo ketonic acid was obtained by means of diazomethane and with methyl alcohol and sulfuric acid. It crystallized from ether in small prisms and melted at 106°.

Anal. Calcd. for $C_{15}H_{16}O_3Br_2$: C, 44.6; H, 4.0. Found: C, 44.3; H, 4.4.

In the bromination of the *cis* ketonic acid the bromo derivatives of the *cis* and *trans* acids were formed in poor yields in the ratio of 30% of the former to 70% of the latter. Under the same conditions bromination of the unsaturated γ-lactone resulted in 25% of *cis* and 75% of *trans* compounds. No *cis* compounds were formed in the bromination of the *trans* ketonic acid but at least 20% of the product formed in the bromination of the methyl ester of the *trans* ketonic acid was the methyl ester of the *cis* bromo ketonic acid. Attempts to isomerize the *cis* bromo acid were unsuccessful.

Configuration of the Bromo Ketonic Acids.—Solutions of 0.5 g. of each bromo acid in 20 cc. of equal parts of acetic acid and acetic anhydride or in 20 cc. of one part acetic acid and four parts acetic anhydride were kept at 80° for forty-five minutes, then poured into ice water. The resulting solutions were stirred for an hour before filtration. The solid in each case from the bromo acid melting at 147° was unchanged bromo acid and the recovery of acid recrystallized from ether–petroleum ether was 80%. The solid from the bromo acid melting at 187° was the dicyclic acetate XI melting at 149° and the yield of pure recrystallized compound was 80%.

In another experiment in which solutions of equal quantities of the two bromo acids in acetic anhydride were kept at the temperature of the room for five hours and then manipulated as in the preceding experiment, the bromo acid melting at 147° was again recovered in an almost quantitative yield. The product from the higher melting bromo acid was a new dicyclic acetate which crystallized from ether–petroleum ether in small prisms which melted at 78°. When this acetate was hydrolyzed with acetic acid and hydrochloric acid it regenerated the bromo acid from which it had been formed.

Anal. Calcd. for $C_{16}H_{16}O_4Br_2$: C, 44.5; H, 3.7. Found: C, 44.5; H, 3.9.

These experiments show quite conclusively that the configuration of the higher-melting bromo acid is represented by XII and that of the lower-melting bromo acid by X.

The β-Lactone, XIII.—A solution of 5 g. of the lower-melting bromo acid in 250 cc. of alcohol-free ether was shaken for two hours with 250 cc. of 1% sodium bicarbonate. The ether layer was washed thoroughly with water, dried over sodium sulfate, concentrated and diluted with low boiling petroleum ether. It deposited a solid which, after recrystallization from methyl alcohol, melted at 83°. The lactone crystallizes in diamond-shaped plates and is soluble in all common solvents except petroleum ether. The yield was 97%.

Anal. Calcd. for $C_{14}H_{13}O_3Br$: C, 54.4; H, 4.3. Found: C, 54.6; H, 4.7.

The β-lactone is stable in methyl alcoholic solutions even with prolonged boiling. With hydrogen bromide in acetone solution the β-lactone was converted completely into the *trans* bromo acid from which it is formed. With ammonia in methyl alcohol only unidentified oily products were obtained.

Action of Bases: the *trans* Hydroxy Acid, XIV.—A solution of 5 g. of the lactone in ether was shaken with 300 cc. of 1% aqueous potassium hydroxide for twenty minutes. The resulting alkaline solution on acidification deposited 4.5 g. of a solid which, after recrystallization from ether–petroleum ether from which it separated in small, hard prisms, melted at 134°. The yield was 90%. As this acid is not affected by aqueous alkalies, it is also the only product that is formed when the bromo acid is shaken with dilute aqueous potassium hydroxide. Isomerization of this acid also was not detected in acid solutions.

Anal. Calcd. for $C_{14}H_{15}O_4Br$: C, 51.4; H, 4.6. Found: C, 51.3; H, 4.6.

The methyl ester, obtained by treating the *trans* hydroxy acid with diazomethane, crystallized from ether–petroleum ether in thick plates melting at 88°.

Anal. Calcd. for $C_{15}H_{17}O_4Br$: C, 52.8; H, 5.0. Found: C, 53.0; H, 5.5.

When a solution containing 2 g. of the β-lactone in 50 cc. of methyl alcohol containing 0.0007 mole of sodium methylate was allowed to stand for fifteen hours there was obtained after the usual manipulations 1.6 g. of a solid methyl ester which, after recrystallization from ether–petroleum ether, from which it separated in small prisms, melted at 142°.

Anal. Calcd. for $C_{15}H_{17}O_4Br$: C, 52.8; H, 5.0. Found: C, 52.6; H, 5.2.

This same 142° methyl ester also was obtained from the *trans* hydroxy acid with methyl alcohol and sulfuric acid in quantitative yields. When the 88° methyl ester is allowed to stand in methyl alcohol solutions containing either sulfuric acid or a trace of sodium methylate, it is converted completely into the 142° methyl ester. Both of these esters are hydrolyzed readily to the *trans* hydroxy acid with bases and less readily with acids. No evidence was obtained to show that one of them is a cyclic ether.

The *cis* Hydroxy Acid, XV.—A solution of 10 g. of the β-lactone in 600 cc. of methyl alcoholic sodium methylate containing 6 g. of sodium was left at room temperature. It deposited 5 g. of the sodium salt of the *trans* hydroxy acid. The filtrate from the salt, diluted with water and acidified, deposited 4 g. of the isomeric acid in nearly pure condition. The acid crystallized from ether in thin plates melting at 187°. The same acid was obtained in a yield of 68% when the lactone was boiled for thirty hours with 5% sulfuric acid. The methyl ester of this same hydroxy acid was also obtained in nearly quantitative yield when methyl alcoholic solutions of the β-lactone containing a few drops of sulfuric acid were allowed to stand at room temperature. This methyl ester was hydrolyzed readily with bases to the hydroxy acid.

Anal. Calcd. for $C_{14}H_{15}O_4Br$: C, 51.4; H, 4.6. Found: C, 51.2; H, 4.6.

The methyl ester obtained by treating the *cis* hydroxy acid either with diazomethane or with methyl alcohol and sulfuric acid, and from the β-lactone with methyl alcohol and sulfuric acid, crystallized from methyl alcohol in hard, irregular prisms, which melted at 54°.

Anal. Calcd. for $C_{15}H_{17}O_4Br$: C, 52.8; H, 5.0. Found: C, 53.1; H, 5.4.

Configuration of the Hydroxy Acids: the Dicyclic Hydroxy Acetate, XVI.—One gram of each of the hydroxy acids was shaken with 40 cc. of pure acetic anhydride until solution was complete—about fifteen minutes. The solutions were kept at the ordinary temperature for forty-five minutes, then poured into ice water. The resulting suspensions were stirred for an hour before the solid products were removed and purified. The solid from the lower-melting acid was unchanged hydroxy acid—the recovery of pure acid after recrystallization from ether–petroleum ether was 70%. The solid from the higher-melting hydroxy acid was a neutral compound which crystallized from ether–petroleum ether in short, stout needles melting at 95°. The yield was 77%.

Anal. Calcd. for $C_{16}H_{17}O_5Br$: C, 52.0; H, 4.6. Found: C, 51.7; H, 4.9.

In ether solution this neutral product was not hydrolyzed with sodium bicarbonate solution but when it was digested with a dilute solution of hydrochloric acid in acetic acid it regenerated the higher-melting hydroxy ketonic acid.

In solutions of acetic anhydride and acetic acid both hydroxy acids failed to react at the ordinary temperature. With heating in such solutions both hydroxy acids gave oils which invariably gave both the hydroxy acids on standing or when their ether solutions were extracted with dilute sodium bicarbonate. On the basis of the experiments with acetic anhydride only the higher-melting acid forms a dicyclic acetate and in this acid the carboxyl and bromobenzoyl groups are on the same side of the ring as shown in formula XV.

Summary

The configurations of two cyclic diastereomeric β-bromo γ-keto acids have been established. The bromo acid in which the bromine and carboxyl groups are in the *cis* position is the only one that will form a β-lactone. Evidence is given to show that this β-lactone formation has occurred without inversion. The β-lactone is opened with bases to give a single hydroxy acid. The evidence indicates that this hydroxy acid has the same configuration as the β-lactone and the bromo acid from which it is prepared.

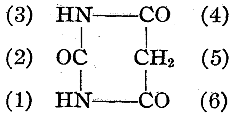
Cambridge, Mass. Received June 27, 1938

[Contribution No. 135 from the Department of Chemistry, the University of Texas]

5,5-Dialkylhydantoins Containing a Dialkylamino Substituent[1,2]

By J. Wm. Magee with Henry R. Henze

Attempts to relate chemical constitution to physiological activity have been of but moderate success and the information thus secured has been used in the development of the barbituric acid series of soporifics.[3,4] Synthesis of additional derivatives in this field has continued with the production of only a few new types. More recently interest has again been centered in the preparation of sedatives through the replacement of the hydrogen attached to the nitrogen of the barbituric acid nucleus by alkyl groups.[5,6] Here, particularly, the substitution of the methyl group for the imidic hydrogen has in certain instances produced compounds of extremely short but intense period of hypnotic activity.[7] A late publication includes evidence of success in the introduction of alkylamino groupings[8] into the alkyl commonly attached to the 5-position of the heterocycle.



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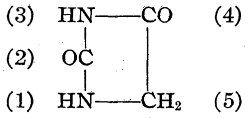

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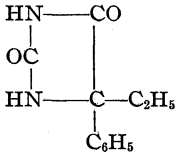

III

A definite similarity exists in the structure of barbituric acid (I) and hydantoin (II), and rather close analogy is evident in the fact of the existence of compounds derived from substitution of identical groupings for the hydrogen atoms in the 5,5-, 1- and 3-positions of both the barbituric acid and hydantoin heterocycles.[4,6,9–11] Although, as yet, but one 5,5-disubstituted hydantoin[12] (III) has found clinical use, the hydantoin nucleus is innocuous and offers hope that additional compounds of value as sedatives may be derived from it by appropriate substitution. In this Laboratory attention has previously been directed to the utilization of alkoxyalkyl[13] and aryloxyalkyl[14] substituents and compounds of definite hypnotic power but unfavorable toxicity have been pro-

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(1) From a portion of a dissertation presented by J. Wm. Magee to the Faculty of the Graduate School of The University of Texas in partial fulfilment of the requirements for the degree of Doctor of Philosophy, June, 1938.

(2) Presented before the Division of Medicinal Chemistry at the 95th meeting of the American Chemical Society, Dallas, Texas, April 18 to 21, 1938.

(3) Shonle, *Ind. Eng. Chem.*, **23**, 1104 (1931).

(4) Shonle, Waldo, Keltch and Coles, This Journal, **58**, 585 (1936).

(5) U. S. Patent 1,073,380 (Sept. 16, 1913); U. S. Patent 1,074,030 (Sept. 30, 1913); German Patent 537,366 (July 9, 1929); British Patent 401,693 (Nov. 17, 1933); U. S. Patent 1,947,944 (Feb. 20, 1934); German Patent 606,499 (Dec. 4, 1934).

(6) Dox and Jones, This Journal, **51**, 316 (1929); Shonle and Doran, *ibid.*, **58**, 1358 (1936); Buck, Hjort, Ide and DeBeer, *ibid.*, **60** 461 (1938).

(7) Tabern and Volwiler, *ibid.*, **58**, 1354 (1936).

(8) Rosenberg, Kneeland and Skinner, *ibid.*, **56**, 1339 (1934).

(9) Fischer and Dilthey, *Ann.*, **335**, 334 (1904).

(10) Bucherer and Lieb, *J. prakt. Chem.*, **141**, 5 (1934).

(11) Biltz and Slotta, *ibid.*, **113**, 245, 255 (1926).

(12) Swiss Patent 72,561 (Sept. 16, 1916).

(13) Rigler with Henze, This Journal, **58**, 474 (1936).

(14) Whitney with Henze, *ibid.*, **60**, 1148 (1938).

duced.[13] These hydantoin derivatives have been obtained from alkoxy- and aryloxy-dialkyl ketones and from alkoxyalkyl aryl ketones by adaptation of Bucherer's method[15] for synthesizing simple hydantoins. This process is much simpler and productive of better yields than is that of Bergs.[16]

The purpose of the present investigation was to obtain 5,5-dialkylhydantoins containing dialkylamino substituents. Although 1-alkyl-5,5-dialkylhydantoins[11] have been prepared, a thorough search of the literature fails to disclose the synthesis of 5-dialkylaminoalkyl-5-alkylhydantoins. In fact, Slotta, Behnisch, and Szyszka[17] reported that they were unable to convert dimethylaminoacetone and *bis*-dimethylaminomethyl ketone into the corresponding hydantoins by means of Bergs' procedure.[16] The former of these ketones, as well as nine other disubstituted aminoacetones, have been prepared in this research and all subsequently converted into 5-dialkyl- or diallyl-aminomethyl-5-methylhydantoins by adaptation of the method of Bucherer.[15]

Five of the dialkylaminoacetones had been synthesized previously but inadequately characterized. Marked discrepancies were found between the melting points of the semicarbazones of three of these ketones as recorded in the literature[18] and as determined in the course of this study.

Experimental

Bromoacetone.—The bromoacetone was prepared by slightly altering Levene's[19] modification of Nef's[20] method. It seemed advantageous to decrease by one-third the volume of water used and to heat on a steam-cone. Using an efficient mechanical stirrer, it was possible to add the required amount of bromine rapidly through a short separatory funnel. Experimental runs using 10 moles of acetone produced 800 g. of bromoacetone in about 55% of the theoretical yield and in sufficient state of purity to use without redistillation.

Preparation of the Disubstituted Aminoacetones.—Two general procedures were used for preparing the dialkylaminoacetones. In one method two moles of a specific secondary aliphatic amine, diluted with 20 volumes of ether, was treated with one mole of bromoacetone diluted with 2 volumes of ether. Usually the hydrobromide of the secondary amine separated as glistening, white leaflets from the reddish-brown colored solution. The ether solution was refluxed until the odor of bromoacetone was no longer evident, chilled in an ice-bath and filtered. The filtrate was fractionated under diminished pressure. In order to avoid the conversion of one-half of the secondary amine into the hydrobromide salt, a second method was developed. To one mole of the secondary amine, suspended in 5 volumes of water containing 2 moles of sodium carbonate, was added one mole of bromoacetone with vigorous stirring during thirty minutes or until the odor of bromoacetone could not be recognized. After filtration from the sodium bicarbonate formed, the filtrate was extracted with ether and the extract dried over anhydrous sodium sulfate before fractionation. Only in the cases of the di-*s*-propyl and di-*s*-butyl compounds was this second method unsuccessful. In these two instances the rate of reaction between the secondary amine and the bromoacetone seemed slower than the rate of decomposition of the bromoacetone by the alkali.

Although the di-*s*-butylaminoacetone was refractionated a number of times, and the analytical results seemed to indicate a state of satisfactory purity, the observed molecular refractivity and parachor did not check the calculated values very closely. Hence the liquid was treated with enough 6 *N* hydrochloric acid to dissolve 90–95% of the material; the acid solution was extracted with ether and then neutralized with sodium hydroxide. The regenerated amino ketone was treated with such a quantity of 6 *N* acid as to dissolve only 5–10% of the material. The residual liquid was washed free of any salt, dried and distilled. The physical properties of the fractionated material were not appreciably altered by this treatment.

All the ketones included in this study are colorless oils when freshly and carefully fractionated, possess a strong basic odor, but darken after standing even for a short time. Only one of the ketones, dimethylaminoacetone, is readily miscible with water but all are soluble in the usual organic solvents such as ether, acetone, alcohol, benzene, and chloroform. The amino ketones are readily dissolved by acids, as hydrochloric, sulfuric, and acetic.

Boiling points were taken with calibrated thermometers and the properly corrected values are reported for the disubstituted aminoacetones. Surface tensions were measured by means of Cassel's[21] precision capillarimeter at 20°. Densities were determined by means of a U-shaped glass tube weighing 1.7231 g. and containing 1.1384 cc. of water at 4°. The data resulting from the determination of physical constants, the values derived from these data by calculation and such information as was obtained through analysis of the substituted aminoacetones have been tabulated in Table I.

Preparation of Semicarbazones from Disubstituted Aminoacetones.—Solid, crystalline semicarbazones were obtained from all of the disubstituted aminoacetones. Those derived from dimethyl- and diethylaminoacetones, whose syntheses have not been reported previously, were so soluble in water as to present difficulty in their isolation. They were obtained best by making a

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[15] Bucherer and Fischbeck, *J. prakt. Chem.*, [2] **140**, 69 (1934); Bucherer and Brandt, *ibid.*, 129; Bucherer and Barsch, *ibid.*, 151; Bucherer and Steiner, *ibid.*, 291; Bucherer and Lieb, *ibid.*, **141**, 5 (1934).

[16] German Patent 566,094 (Dec. 1, 1932).

[17] Slotta, Behnisch and Szyszka, *Ber.*, **67B**, 1529 (1934).

[18] Stoermer and Pogge, *ibid.*, **29**, 866 (1896).

[19] Levene, "Organic Syntheses," John Wiley & Sons, Inc., New York, N. Y., Vol. X, 1930, pp. 12–13.

[20] Nef, *Ann.*, **335**, 259 (1904).

[21] Cassel, *Chem. Ztg.*, **53**, 479 (1929).

TABLE I

DISUBSTITUTED AMINOACETONES, $\mathrm{R_2NCH_2COCH_3}$

	—R	B. p., °C. (corr.)	B. p., Mm.	Density d^{20}_4	Ref. index n^{20}_D	Surface tension γ 20 dynes/cm.	Free surface energy $\gamma(m/d)^{2/3}$	Yield, %
1	—$\mathrm{CH_3}$	31.6[a]	27	0.8688	1.4131	27.77	662.1	36
2	—$\mathrm{CH_2CH_3}$	69.6[a]	32	.8620	1.4249	26.67	752.5	48
3	—$\mathrm{CH_2CH_2CH_3}$	64.6[b]	8	.8520	1.4297	26.69	853.3	72
4	—$\mathrm{CH(CH_3)_2}$	79.7	17	.8593	1.4324	27.37	882.1	69
5	—$\mathrm{CH_2CH_2CH_2CH_3}$	86.7	3	.8505	1.4359	27.20	985.1	71
6	—$\mathrm{CH_2CH(CH_3)_2}$	80.7[b]	9	.8426	1.4315	28.34	1032.5	58
7	—$\mathrm{CH_2CH(CH_3)CH_3}$	104.7	14	.8749	1.4422	28.70	1020.0	64
8	—$\mathrm{CH_2CH_2CH_2CH_2CH_3}$	110.2	7	.8411	1.4382	27.49	1163.7	69
9	—$\mathrm{CH_2CH_2CH(CH_3)_2}$	78.7[b]	2	.8436	1.4379	26.55	1121.3	56
10	—$\mathrm{CH_2CH{:}CH_2}$	80.7	22	.8890	1.4586	28.59	885.5	70

R	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Mol. ref. Calcd.	Mol. ref. Found	ΔMR	Parachor Calcd.	Parachor Found	ΔP
1	59.37	59.18	10.96	10.95	29.24	29.04	−0.20	267.8	265.7	− 2.1
2	65.07	65.02	11.70	11.82	38.48	38.34	− .14	345.8	340.6	− 5.2
3	68.74	68.30	12.18	12.24	47.71	47.64	− .07	423.8	419.5	− 4.3
4	68.74	68.48	12.18	12.25	47.71	47.52	− .19	423.8	418.6	− 5.2
5	71.29	71.18	12.51	12.43	56.95	56.98	+ .03	501.8	497.6	− 4.2
6	71.29	71.16	12.51	12.51	56.95	56.98	+ .03	501.8	507.4	+ 5.6
7	71.29	71.21	12.51	12.37	56.95	56.06	− .89	501.8	490.2	−11.6
8	73.18	73.16	12.76	13.06	66.19	66.46	+ .27	579.8	579.5	− 0.3
9	73.18	73.14	12.76	12.95	66.19	66.29	+ .10	579.8	573.6	− 6.2
10	70.54	70.38	9.87	9.65	46.78	47.10	+ .22	400.8	398.6	− 2.2

[a] Stoermer and Dzimski, *Ber.*, **28**, 2223 (1895), reported only the following boiling points for these ketones: dimethylaminoacetone, 123°; diethylaminoacetone, 155–156° with some decomposition.

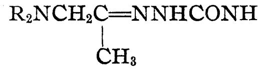
[b] Stoermer and Pogge[18] reported for certain of these dialkylaminoacetones the following data which are noticeably at variance with the data included in Table I.

	B. p., °C.	d 17°
Di-*n*-propylaminoacetone	188	0.8337
Diisobutylaminoacetone	206–207	.8735
Diisoamylaminoacetone	219–220	.8911

concentrated solution of semicarbazide hydrochloride in the amino ketone, adding a slight excess of dilute aqueous solution of sodium hydroxide, and chilling in an ice-bath. Recrystallization of all semicarbazones is accomplished readily by solution in hot benzene and precipitation from the cooled solution by addition of several volumes of petroleum ether. The corrected melting points of, and the analytical constants for, the ten semicarbazones are collected in Table II. It is to be noted that the melting points of three of these semicarbazones, namely, of the di-*n*-propyl, diisobutyl and diisoamyl derivatives differ, as do the densities of the respective amino ketones, from those reported by Stoermer and Pogge.[18] In view of these discrepancies all three of the dialkylaminoacetones were resynthesized and their semicarbazones prepared again and carefully purified and dried. The melting points and analytical data checked closely those of the first preparations.

TABLE II

SEMICARBAZONES OF DISUBSTITUTED AMINOACETONES



$$\mathrm{R_2NCH_2\underset{\displaystyle CH_3}{\underset{|}{C}}{=}NNHCONH_2}$$

	—R	M. p. °C. (corr.)	Nitrogen, % Calcd.	Nitrogen, % Found
1	—$\mathrm{CH_3}$	137	35.42	35.27
2	—$\mathrm{CH_2CH_3}$	143	30.41	30.55
3	—$\mathrm{CH_2CH_2CH_3}$	150[a]	26.14	26.13
4	—$\mathrm{CH(CH_3)_2}$	195	26.14	25.94
5	—$\mathrm{CH_2CH_2CH_2CH_3}$	132	23.12	23.38
6	—$\mathrm{CH_2CH(CH_3)_2}$	175[a]	23.12	23.13
7	—$\mathrm{CH_2CH(CH_3)CH_3}$	196	23.12	23.10
8	—$\mathrm{CH_2CH_2CH_2CH_2CH_3}$	102	20.72	20.62
9	—$\mathrm{CH_2CH_2CH(CH_3)_2}$	124[a]	20.72	20.82
10	—$\mathrm{CH_2CH{=}CH_2}$	105	26.64	26.73

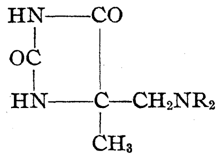
[a] Stoermer and Pogge [*Ber.*, **29**, 866 (1896)] report the following melting points:

	—R	M. p., °C.
3	—$\mathrm{CH_2CH_2CH_3}$	110
6	—$\mathrm{CH_2CH(CH_3)_3}$	132
9	—$\mathrm{CH_2CH_2CH(CH_3)_2}$	166

Formation of the Disubstituted Aminohydantoins.—The hydantoins were easily synthesized directly from the substituted aminoacetones by subjecting the carbonyl compounds to the action

TABLE III

DISUBSTITUTED AMINOHYDANTOINS



	—R	Yield, %	M. p., °C. (corr.)	Nitrogen, % Calcd.	Nitrogen, % Found	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1	$—CH_3$	32	177	24.55	24.64	49.11	49.14	7.65	7.67
2	$—CH_2CH_3$	38	196	21.09	21.32	54.25	54.02	8.60	8.61
3	$—CH_2CH_2CH_3$	84	161	18.49	18.72	58.12	58.23	9.31	9.14
4	$—CH(CH_3)_2$	77	198	18.49	18.31	58.12	58.26	9.31	9.23
5	$—CH_2CH_2CH_2CH_3$	73	173	16.46	16.76	61.14	61.30	9.87	10.03
6	$—CH_2CH(CH_3)_2$	62	222	16.46	16.50	61.14	61.24	9.87	9.79
7	$—CH_2CH(CH_3)CH_3$	68	233	16.46	16.60	61.14	61.20	9.87	9.77
8	$—CH_2CH_2CH_2CH_2CH_3$	92	171	14.83	15.04	63.57	63.74	10.29	10.29
9	$—CH_2CH_2CH(CH_3)_2$	98	204	14.83	14.97	63.57	63.85	10.29	10.39
10	$—CH_2CH{=}CH_2$	91	135	18.82	18.71	59.17	59.50	7.68	7.59

of potassium cyanide and ammonium carbonate in alcoholic solution according to directions of Bucherer.[15] To an Erlenmeyer flask fitted with an air condenser were added 0.10 mole of ketone, 0.30 mole of freshly powdered ammonium carbonate, 0.13 mole of potassium cyanide, and 7–8 volumes of 50% alcohol,[22] and the mixture heated for about eight hours. As the carbonate and cyanide gradually dissolved, gas was evolved and ammonium carbonate formed in the condenser tube. Near the end of the period of heating the condenser tube was removed and the temperature of the bath increased to evaporate the alcohol. Cooling in an ice–salt mixture caused most of the hydantoin to separate and only an additional, small amount was obtained when the solution was neutralized with dilute hydrochloric acid. Because of the dialkylamino substituent, all of the hydantoins are soluble in acid so an excess of the latter was avoided.

The hydantoins are easily recrystallized from dilute alcohol, are soluble in the ordinary organic solvents and, with the exception of the dimethyl homolog, very sparingly soluble in water. Because the compounds are amphoteric they are soluble in both acidic and alkaline solutions from which they are readily precipitated unchanged when such solutions are made exactly neutral. The disubstituted aminohydantoins are stable, white, crystalline solids which melt without decomposition to clear straw colored liquids. The temperatures reported as melting points of the hydantoins in Table III represent corrected values.

Summary

1. The series of 5,5-dialkylhydantoins has been extended by the synthesis of nine examples of dialkylamino derivatives. Likewise the production of 5-diallylaminomethyl-5-methylhydantoin represents the initial preparation of an additional type.

2. Although Slotta, Behnisch and Szyszka were unable to convert dimethylaminoacetone into 5-dimethylaminomethyl-5-methylhydantoin by means of the method of Bergs, this conversion has now been accomplished utilizing the closely related method of Bucherer.

3. Diallylaminoacetone and four new members of the series of dialkylaminoacetones have been prepared and five additional examples of this type have been resynthesized and all adequately characterized. The densities of three of the ketones are in definite disagreement with the data previously reported in the literature.

4. The yield of disubstituted aminoacetones, as based on the weight of the secondary amine used, has been doubled by using dilute alkali to prevent the formation of the secondary amine hydrobromide.

5. Semicarbazones, useful in the identification of the amino ketones, were obtained from each of the ten members of this series. The melting points of the semicarbazones of three of the disubstituted aminoacetones are quite different from those reported in a prior investigation.

6. For diallylaminoacetone and the series of dialkylaminoacetones studied in this investigation, the molecular refraction was found to be more sensitive than the parachor as an index to purity.

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[22] Due to the solubility of the dimethylaminoacetone no alcohol was used in the preparation of 5-dimethylaminomethyl-5-methylhydantoin.

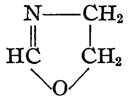
Syntheses from Ethanolamine. V. Synthesis of Δ^2-Oxazoline and of 2,2′-Δ^2-Dioxazoline

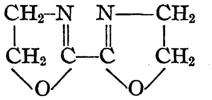
BY HENRY WENKER

As the lowest member of the series, Δ^2-oxazoline (I) is of theoretical interest. The compound has not been described hitherto; earlier attempts[1] to prepare it by dehydration of ethanol formamide resulted invariably in cleavage into carbon monoxide and ethanolamine.

The base has now been obtained by the action of alkali upon β-chloroethyl formamide; the latter was made from ethanol formamide[1,2] and thionyl chloride. Similarly, 2,2′-Δ^2-dioxazoline (II) was prepared from *s*-β,β′-dichlorodiethyl oxamide. The method in itself is not new; Gabriel and Heymann[3] obtained 2-phenyl-Δ^2-oxazoline from β-bromoethyl benzamide and alkali

I





II

Δ^2-Oxazoline is a colorless, mobile liquid which boils at 98° under atmospheric pressure and has a specific gravity of 1.075^{20}_{20}. Its odor is sweetish and somewhat pyridine-like, resembling that of the next higher 2-alkyl homologs. It is miscible with water, ethanol and ether; the aqueous solution reacts alkaline to phenolphthalein. It is less stable than the higher homologs. Boiling water hydrolyzes it to ethanol formamide. Anhydrous hydrogen chloride (in ether) forms an unstable hydrochloride which rearranges quickly to β-chloroethyl formamide, a characteristic reaction which it shares with the higher 2-alkyl homologs. Metallic sodium reacts with formation of sodium cyanide as one of the products. A picrate could not be obtained.

2,2′-Δ^2-Dioxazoline, on the other hand, is a stable, well crystallized compound. It dissolves in water with neutral reaction and forms a stable picrate. With dry hydrogen chloride it regenerates *s*-β,β′-dichlorodiethyl oxamide.

Experimental

β-Chloroethyl Formamide.—Due to its instability, this compound was not obtained in pure form. One hundred twenty-five grams of thionyl chloride was dropped into 89 g. of ethanol formamide with cooling; the charge was then heated on the water-bath for fifteen minutes and subjected to vacuum distillation. Forty-eight grams distilled between 130–155° (20 mm.); the residue then began to decompose. The distillate contained 25.0% of chlorine (theory 32.8%). Slow decomposition took place during the whole operation and made the maintenance of an adequate vacuum difficult. For the same reason, attempts at fractionating the first distillate with the aid of a column were unsuccessful. A second distillation gave 10 g. of material boiling between 137 and 140° (20 mm.) and having 28.5% chlorine; a third distillation gave 6 g. boiling at 137–138° (20 mm.) with 29.4% chlorine. The distillates represented colorless, odorless liquids miscible with water and with ethanol. Experiments in which a larger excess of thionyl chloride was used, gave smaller yields and showed an increased rate of decomposition.

The large amount of non-volatile residue apparently was caused by cleavage of β-chloroethyl formamide into carbon monoxide and β-chloroethylamine; the latter is protected by the dissolved hydrogen chloride from immediate decomposition. This explanation was supported by the following experiments. (a) Sodium hydroxide produced in a concentrated aqueous solution of the residue a liquid base which boiled up and decomposed after short standing; β-chloroethylamine shows the same spontaneous decomposition. (b) In a more dilute solution of the residue alkali produced ethylene-imine: 40 g. of residue was dissolved in a solution of 40 g. of sodium hydroxide in 350 g. of water; the clear solution was distilled, the first 20 cc. of distillate was carefully saturated, and then covered with dry sodium hydroxide, followed by distillation from a boiling water-bath. Two and two-tenths grams of ethylene-imine distilled over and was identified by its boiling point (56°).

Δ^2-Oxazoline.—Fifty-four grams of β-chloroethyl formamide, once distilled, was added to 150 g. of 50% potassium hydroxide contained in a 500-cc. distilling flask over a period of ten minutes. The mixture was shaken frequently and a temperature of 15–18° was maintained by external cooling with ice. Shaking was continued for about five minutes longer; by this time the crude oxazoline base had separated as an oily layer above the alkaline liquid. The flask was now connected with a condenser tube reaching into the bulb of a 250-cc. distilling flask; the latter was surrounded by ice. The base was distilled under a vacuum of 15 mm. from a water-bath heated to 45°. To the distillate, amounting to 25 g., 60 g. of dry potassium hydroxide was added under constant cooling with ice; the first additions had to be made in very small portions, since violent decomposition, due to overheating, occurred during one experiment at this stage. The charge was distilled *in vacuo* as before and the distillate (15 g.), which was already practically anhydrous and gave the correct nitrogen value, was covered again with 60 g. of potassium hydroxide and distilled *in vacuo*, giving 14 g. of the pure base.

Anal. Calcd. for C_3H_5NO: N, 19.7. Found: N, 19.6.

Reactions of Δ^2-Oxazoline. A. Boiling Point.—Two grams of oxazoline, heated in a test-tube over a free flame, boiled without decomposition at 98°. At the end of five minutes, the boiling point was unchanged.

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[1] Wenker, THIS JOURNAL, **57**, 1080 (1935).

[2] French Patent 638,023 (1928).

[3] Gabriel and Heymann, *Ber.*, **23**, 2493 (1890).

B. Hydrolysis with Water.—Three grams of base and 3 g. of water was heated in a test-tube. Boiling began at 94° and continued, after removing the flame, for five minutes, while the temperature rose to 108°. The colorless liquid, which still smelled of oxazoline, was heated for thirty minutes more in the boiling water-bath and then dried *in vacuo* at 100°. A colorless, odorless oil remained which contained 14.9% nitrogen as compared with 15.7% calculated for ethanol formamide. A part of the oil was heated to 100° in oxalic acid solution for one hour; ethanol now precipitated the characteristic alcohol-insoluble ethanolamine oxalate.

C. Reaction with Hydrogen Chloride.—To 3 g. of oxazoline dissolved in 10 g. of ether, 15 g. of a 10% ethereal solution of hydrogen chloride was added with ice cooling. A white crystalline powder separated at once which at room temperature soon melted to a clear colorless liquid. After removing the ether and excess of hydrogen chloride *in vacuo* at 100°, the product contained 32.1% of chlorine; calculated for β-chloroethyl formamide, 32.8%.

D. Reaction with Sodium.—A piece of sodium in 1 g. of oxazoline caused a violent reaction with evolution of gas. The residue, a yellow amorphous mass, gave a precipitate of prussian blue by the usual test for cyanides.

E. Picrate.—The alcoholic solution of the base remained clear with picric acid. Ether precipitated an oil which did not crystallize.

***s*-β,β-Dichlorodiethyl Oxamide.**—Twenty grams of *s*-diethanol oxamide,[4] 100 g. of toluene and 42 g. of thionyl chloride was heated for thirty minutes to 60°, then for ninety minutes in a boiling water-bath. Without first dissolving, the diethanol oxamide changed to a thick white crystal sludge. After cooling, the crystals were filtered, washed subsequently with ethanol, boiling water, ethanol, and crystallized from 200 g. of boiling "cellosolve" (ethylene glycol monoethyl ether). The yield was 19 g. or 78%. The product forms white needles, insoluble in water, sparingly in hot ethanol, which melt at 203°.

Anal. Calcd. for $C_6H_{10}N_2O_2Cl_2$: Cl, 33.3. Found: Cl, 33.1.

2,2′-Δ^2-Dioxazoline.—Ten and six-tenths grams of the preceding compound in 100 cc. of *N* methyl alcoholic potassium hydroxide was boiled for one hour, the clear solution filtered from potassium chloride, evaporated on the water-bath and the crystalline residue recrystallized from 100 g. of toluene. The yield was 5.9 g. or 84%. 2,2′-Δ^2-Dioxazoline crystallizes from toluene in white, fern-like aggregates which melt at 213°. It is very soluble in water and in ethanol, almost insoluble in ether and in cold toluene.

Anal. Calcd. for $C_6H_8N_2O_2$: N, 20.0. Found: N, 19.9.

Reaction with Hydrogen Chloride.—One and four-tenths grams of dioxazoline was dissolved in methanol and 10 g. of a 10% solution of hydrogen chloride in ether was added. White crystals separated and were identified, after crystallization from "cellosolve," by melting point and mixed melting point (203°) as *s*-β,β-dichlorodiethyl oxamide.

Picrate.—Thirty-five hundredths of a gram of dioxazoline and 1.3 g. of picric acid both dissolved in hot ethanol gave a sparingly soluble picrate which crystallized in long needles and melted at 182°.

Summary

Thionyl chloride reacts with ethanol formamide and with *s*-diethanol oxamide with formation of β-chloroethyl formamide and of *s*-β,β-dichlorodiethyl oxamide. With alkali, the latter two compounds yield Δ^2-oxazoline and 2,2′-Δ^2-dioxazoline, respectively. Some characteristic reactions of the two oxazolines are described.

ELIZABETH, N. J.

RECEIVED JUNE 20, 1938

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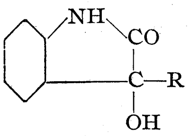
[4] Knorr, *Ber.*, **36**, 1278 (1903).

[CONTRIBUTION FROM THE NICHOLS LABORATORY OF NEW YORK UNIVERSITY]

Reactions of Grignard Reagents with Isatin and N-Alkyl Isatins[1]

BY FREDERICK J. MYERS[2] AND H. G. LINDWALL

The reactions of several Grignard reagents with isatin and N-methylisatin have been reported by Kohn.[3] With isatin the Grignard reagents yield the respective 3-alkyl(or aryl)-3-hydroxy-oxindoles, as would be anticipated. These products have the general formula



I

Kohn prepared the 3-methyl, 3-phenyl and 3-benzyl derivatives of I, but did not investigate the chemical characteristics of these compounds.

Structure I suggested the possibility of the preparation of 3-alkylidene oxindoles through the action of dehydrating agents; using 3-benzyl-3-hydroxyoxindole as the representative of the group, various methods of dehydration were attempted, but without success. In most cases, the compound was recovered unchanged, or, under extremely strenuous conditions, suffered changes more complex than the simple splitting off of a molecule of water.

Kohn[4] also studied the action of phenylmagne-

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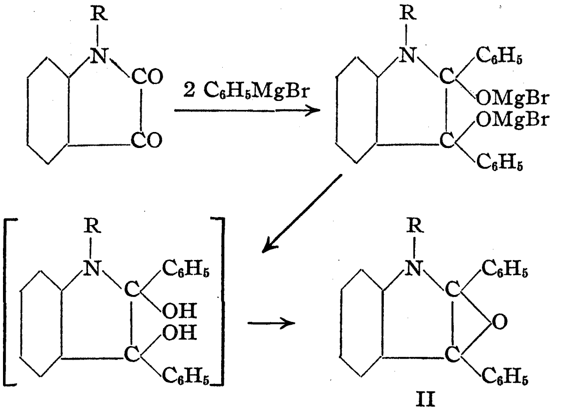
[1] Presented in part at the Rochester meeting of the American Chemical Society, September, 1937.

[2] Present address: c/o Röhm and Haas Co., Bridesburg, Penna.

[3] Kohn and Ostersetzer, *Monatsh.*, **32**, 905 (1911); Kohn, *ibid.*, **31**, 747 (1910).

[4] Kohn and Ostersetzer, *ibid.*, **34**, 789 (1913).

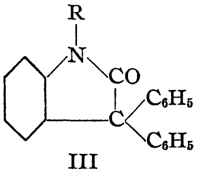
sium bromide upon N-methylisatin, and reported a single compound, 2,3-diphenyl-1-methylindole-oxide-2,3 (II), as the product. He postulated the mechanism



II

The reaction has been repeated; the product isolated was found to melt at 140–143°, which was in close agreement with the melting point (145°) reported for II by Kohn. However, upon repeated recrystallization of the product from dilute ethyl alcohol, it soon became apparent that two compounds were present; one (II) melting at 137.5–138.5°, was yellow and, as reported by Kohn for II, gave a marked fluorescence in solution, and the other (III) was almost white, melted at 171–171.5°, and gave no fluorescent effect in solution. Compound II was obtained as plates, while III was in the form of needles. The longer the period of time of exposure of the original Grignard complex to the hydrolytic agent (sulfuric acid), the larger was the relative amount of III obtained. Analyses showed II and III to be isomeric.

The oxide ring structure assigned by Kohn to II suggested that III might be a rearrangement product of II, and that III was possibly N-methyl-3,3-diphenyloxindole. Synthesis proved this structure for III to be correct. Inagaki's[5] method of preparation of 3,3-diphenyloxindole by the action of benzene upon 3,3-dichlorooöxindole in the presence of aluminum chloride was applied, substituting N-methyl-3,3-dichlorooöxindole. This Friedel–Crafts reaction proceeded smoothly, and yielded III.



III

Furthermore, phenylmagnesium bromide and N-ethylisatin were found to yield two products (IV and V) paralleling II and III. The higher melting compound (V) was shown, by synthesis as above, to be N-ethyl-3,3-diphenyloxindole, and compound IV was similar to II in general characteristics.

Experimental Part

2,3-Diphenyl-1-methylindole-oxide-2,3 (II).—Powdered N-methylisatin (0.05 mole) was added slowly, over the period of one hour, to a boiling solution of phenylmagnesium bromide (0.25 mole) in 150 cc. of ether and 150 cc. of benzene. After addition the mixture was kept at its boiling point with vigorous stirring for one-half hour, and then was poured into an ice and concd. sulfuric acid mixture. After standing overnight, 52% of crude product had separated; the residual liquid mixture was set aside for one week, in the course of which time further solid product appeared (see below).

The crude product, which had separated after overnight standing of the hydrolytic mixture, was obtained as a crystalline mass, green in tint, soluble in dilute ethyl alcohol, dilute methyl alcohol, and dilute acetic acid; thin plates from dilute ethyl alcohol, m. p. 140–143° (Kohn and Ostersetzer report 145°).

Repeated recrystallizations finally yielded II in purer form as thin plates, m. p. 137.5–138.5°, and showing a marked fluorescence in solution. Also (see below), another product (III) was isolated which differed from II in crystal form and did not show fluorescence in solution.

Anal. Calcd. for $C_{21}H_{17}ON$: N, 4.68. Found: N, 4.71, 4.80.

3,3-Diphenyl-1-methyloxindole (III). By the Action of Phenylmagnesium Bromide upon N-Methylisatin.—Repeated recrystallization of II (above) yielded small amounts of III, though not in very pure form (m. p. 167–168°). The residual hydrolytic mixture (see above for II), after removal of crude II and after one week of standing at room temperature, yielded a sample of III, which was easily purified by crystallization from aqueous alcohol; m. p. 171–171.5°; short stubby needles, showing no fluorescence in solution.

Anal. Calcd. for $C_{21}H_{17}ON$: N, 4.68. Found: N, 4.92, 4.52.

Compound III. By the Friedel–Crafts Reaction.—Powdered anhydrous aluminum chloride (0.0125 mole) was added slowly to 3,3-dichloro-1-methyloxindole (0.005 mole) in 20 cc. of absolute benzene, and the mixture was then heated at 50° for four hours. After removing the benzene by distillation under diminished pressure, the residue was treated with ice and dilute hydrochloric acid. A gummy mass resulted which was extracted with dilute methyl alcohol; the extract was decolorized with charcoal and cooled and the product (III) separated as white needles from methyl alcohol, m. p. 171–171.5°. Melting point methods showed samples of III to be identical with that obtained from the Grignard reaction.

2,3-Diphenyl-1-ethylindole-oxide-2,3 (IV).—N-Ethylisatin and phenylmagnesium bromide were allowed to react

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[5] Inagaki, *J. Pharm. Soc. Japan*, **53**, 686 (1933).

following a procedure similar to that shown above for II. After hydrolytic treatment in the usual manner, the crystalline material that had formed in two hours was removed and purified by recrystallization from dilute methyl alcohol to which a little acetic acid had been added. Compound IV was thus obtained as short diamond-shaped crystals, greenish-yellow in color, and showing greenish fluorescence in solution; m. p. 116–117°; yield, 56%. The residual benzene–ether solution, from which the crude IV was obtained originally after the hydrolysis of the Grignard complex, was set aside for ten days, after which time compound V was isolated (see below).

Anal. Calcd. for $C_{22}H_{19}ON$: N, 4.47. Found: N, 4.29.

3,3-Diphenyl-1-ethyloxindole (V). By the Action of Phenylmagnesium Bromide upon N-Ethylisatin.—The residual benzene–ether solution, from which IV had separated (see above), was allowed to stand for ten days and then was concentrated by distillation. Compound V, yield 16%, separated and was purified by crystallization from dilute methyl alcohol; long white needles, m. p. 156–157°, giving no fluorescence in solution.

Anal. Calcd. for $C_{22}H_{19}ON$: N, 4.47. Found: N, 4.40.

Compound V. By the Friedel–Crafts Reaction.—Compound V was prepared by the reaction of benzene with 3,3-dichloro-1-ethyloxindole, as for III. The product was identical with the V obtained from the Grignard reaction in melting point and physical characteristics. A mixture of samples from the two sources showed no depression of the melting point.

Summary

3,3-Diphenyl-1-methyloxindole and 3,3-diphenyl-1-ethyloxindole accompany the respective 2,3-diphenyl-1-alkylindole-oxide-2,3 as products of the reaction of phenylmagnesium bromide with N-methylisatin and N-ethylisatin.

UNIVERSITY HEIGHTS
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[CONTRIBUTION NO. 364 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Friedel–Crafts Reactions on *m*-Diphenylbenzene[1]

BY H. GAINES GOODMAN, JR., AND ALEXANDER LOWY

In the process for the preparation of biphenyl from benzene, considerable amounts of high boiling products are produced. *m*-Diphenylbenzene is one of the constituents of this high boiling material. Wardner and Lowy[2] have reported references to the literature concerned with the preparation of this hydrocarbon and its derivatives up to 1932. Since then the additional articles[3] listed have dealt with the subject.

Because a search of the literature has revealed that no attempt has been made previously to apply the Friedel–Crafts type of reaction to *m*-diphenylbenzene, a study was undertaken, with the object of synthesizing and identifying several new compounds of the ketonic types, prepared by the action of acyl halides and anhydrides on *m*-diphenylbenzene in the presence of anhydrous aluminum chloride.

The Friedel–Crafts reaction needs no discussion here since it is covered admirably by several comprehensive reviews.[4]

The structure of the *m*-diphenylbenzene molecule is such that six theoretical monosubstitution products are possible. It was desirable, therefore, to determine the position of attack in the case of each reactant, and, in order to accomplish this, an oxidation of each acylation product was carried out and a study of the oxidation products made. The oxidation products isolated indicated that, in each reaction, the para position of an end ring had been attacked, except in the case of *m*-diphenylbenzene-phthaloylic acid,[5] the exact structure of which was not determined. This was in agreement with numerous examples contained in the literature, which indicated the para position of a substituted benzene ring to be the one generally attacked in the Friedel–Crafts syntheses.

Experimental

The writers are indebted to Mr. R. E. Bowman, of Wilmington, Delaware, who is investigating the high boiling material furnished by the Monsanto Chemical Co., for a generous supply of *m*-diphenylbenzene. The *m*-diphenylbenzene thus obtained was recrystallized twice from ethyl alcohol, producing white needle-shaped crystals, m. p. 85°. Redissolving these crystals in boiling ethanol, and filtering after cooling to 70°, resulted in the

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(1) Abstracted from a thesis presented by H. Gaines Goodman, Jr., to the Graduate School in partial fulfilment of the requirements for the Ph.D. degree.

(2) Wardner and Lowy, THIS JOURNAL, **54**, 2510 (1932).

(3) Cook and Cook, *ibid.*, **55**, 1212 (1933); Wulff and Roell, U. S. Patent 2,004,546; Busch and Weber, *J. prakt. Chem.*, **146**, 1 (1936).

(4) Kränzlein, "Aluminiumchlorid in der organischen Chemie," Verlag Chemie, G. m. b. H., Berlin, 1932; Calloway, *Chem. Rev.*, **17**, 327 (1935); Groggins, "Unit Processes in Organic Syntheses," McGraw-Hill Book Co., Inc., New York, N. Y., 1935.

(5) *m*-Diphenylbenzene-phthaloylic acid is the term selected for use here, in order to embrace all of the six monosubstitution products which might be obtained theoretically by the action of phthalic anhydride on *m*-diphenylbenzene. Groggins, *Ind. Eng. Chem.*, **22**, 620 (1930), has suggested a better nomenclature in the event that the structures of the acids are definitely known.

Table I

Friedel–Crafts Reactions

m-ϕ_3 = m-Diphenylbenzene. A = Aluminum Chloride. B = Reactant.

	Grams used					
Expt.	m-ϕ_3	A	B	Inert solvent	Conditions (See text)	Product (See Table II)
1	30	20.7	10.2(Acetyl chloride)	Nitrobenzene	28(0.5)–45°(5)	(A)
2	20	25.5	9.1(Acetic anhydride)	Nitrobenzene	28(11)–45°(0.5)	(B)
3	(See text)	21.6	7.9(Acetyl chloride)	Nitrobenzene	30(2)–50°(1)	(C)
4	20	15.4	13.3(Benzoyl chloride)	Nitrobenzene	28°(5)	(D)
5	23	14.6	11.3(Chloroacetyl chloride)	Carbon bisulfide	4°(5)	(E)
6	23	14.6	19.4(Benzenesulfonyl chloride)	None	50(4)–100°(0.5)	(F)
7	23	29.3	14.8(Phthalic anhydride)	*o*-Dichlorobenzene	30(7)–50°(1)	(G)

separation from the cooled filtrate of crystals melting at 87°.

The apparatus described by Riddell and Noller[6] was used throughout the investigation.

In general, the procedures followed throughout the investigation were essentially the same, as is exemplified in the method used in the first experiment, described completely herewith.

Preparation and Identification of *p*-Acetyl-*m*-diphenylbenzene.—To a solution of 30 g. (0.13 mole) of *m*-diphenylbenzene in 100 cc. of nitrobenzene, a solution of 20.7 g. (0.15 mole) of anhydrous aluminum chloride in 100 cc. of nitrobenzene was added and mixed thoroughly. With the above mixture at 28°, 10.2 g. (0.13 mole) of acetyl chloride was added dropwise from the dropping funnel, stirring continuously. A vigorous evolution of hydrochloric acid gas continued for thirty minutes. Then the temperature was raised to 45° and held for five hours. The charge was hydrolyzed by the addition of ice, and the nitrobenzene layer separated and washed thoroughly with water. The nitrobenzene was removed by steam distillation and the resulting crude product dissolved in acetone and filtered. The acetone was then removed by evaporation and the residue subjected to a vacuum distillation. The distillate which passed over from 232 to 246° at 1 mm. pressure was further purified by three recrystallizations from ethanol, whereupon 10 g. of white *p*-acetyl-*m*-diphenylbenzene, melting at 104°, was obtained.

This compound was also produced by the use of acetic anhydride instead of acetyl chloride under the conditions given for experiment 2, Table I. Isolation of the reaction product was accomplished by the method described above.

One gram of *p*-acetyl-*m*-diphenylbenzene was refluxed for five hours with 5 g. of chromic anhydride and 40 cc. of glacial acetic acid. The charge was then poured into ice water, and the precipitated acid filtered and washed thoroughly with distilled water. The free acid was then dissolved in a small amount of 10% sodium hydroxide solution and filtered through asbestos. The filtrate was acidified with concentrated hydrochloric acid to reprecipitate the free acid which was washed thoroughly with distilled water and dried. The acid thus obtained was identified as terephthalic acid by conversion to dimethyl terephthalate, m. p. 140°, thus indicating that acylation had taken place in the para position of *m*-diphenylbenzene.

The essential data concerning each preparation are given in Table I. In this table the conditions are described by giving the initial and final temperatures, followed in parentheses by the duration of each temperature in hours. In each experiment the inert solvent was removed from the crude product by steam distillation. In Experiment 3, *p*-acetyl-*m*-diphenylbenzene, the product of Experiment 1, was used instead of *m*-diphenylbenzene in order to produce *p,p'*-diacetyl-*m*-diphenylbenzene. All efforts to produce this material from *m*-diphenylbenzene failed. After removal of the solvent, the crude product was extracted with ethyl ether and the residue recrystallized. This procedure also was used in working up the crude product of Experiment 4. In Experiment 5, after completion of the reaction, the inert solvent, carbon bisulfide, was decanted from the insoluble complex compound, which was then hydrolyzed, steam distilled to remove any residual carbon bisulfide, and the crude product extracted twice with 100 cc. of boiling ethanol. Upon cooling these extracts, crystals were deposited which were recrystallized from small amounts of ethanol. Benzenesulfonyl chloride was found to react very sluggishly upon *m*-diphenylbenzene if an inert solvent was used. In Experiment 6, therefore, the hydrocarbon and reactant were mixed, raised to 50°, and the aluminum chloride added in small increments. After hydrolysis, the crude product was boiled successively with several large portions of water to remove any remaining benzenesulfonyl chloride. The residue was then recrystallized from large quantities of ethanol. The procedure used in isolating the product of Experiment 7 differed so markedly from the others that it is given in detail, thus. The charge was hydrolyzed by pouring into a mixture of crushed ice containing 10% of concentrated hydrochloric acid. After hydrolysis, the solvent layer was separated and washed thoroughly to remove all the mineral acid, and the *o*-dichlorobenzene removed by steam distillation. The crude product was separated and boiled with 350 cc. of 10% sulfuric acid to remove any residual aluminum salts, and finally with several successive portions of water to remove any residual sulfuric acid and phthalic acid. The remaining solid matter was dissolved in 500 cc. of water containing 50 cc. of concentrated ammonium hydroxide, a small amount of boneblack added, and the solution boiled for one hour. After cooling, the boneblack and any insoluble hydrocarbon or phthalides were filtered off. The carboxylic acid was then reprecipitated by the addition of concentrated hydrochloric acid. After removal by filtration and washing to remove any residual hydrochloric acid or soluble chlorides, this product, 35.5 g., was dried over concentrated sulfuric acid, under reduced pressure. All efforts to purify this product by crystallization were futile. It is very soluble in methanol, ethanol, benzene, toluene,

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[6] Riddell and Noller, This Journal, **52**, 4368 (1930).

TABLE II

CHARACTERISTICS OF PRODUCTS

m-ϕ_3 = *m*-Diphenylbenzene

	Product	Solvent for recrystallization	Yield, g.	M. p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found		Hydrogen, % Calcd.	Hydrogen, % Found	
(A)	*p*-Acetyl-m-ϕ_3	EtOH	10	104	$C_{20}H_{16}O$	88.24	88.09	87.95	5.88	5.74	5.82
(B)	*p*-Acetyl-m-ϕ_3	EtOH	5	104	......	.....	.....	.....	....	....	....
(C)	*p,p'*-Diacetyl-m-ϕ_3	EtOH	1.4	152	$C_{22}H_{18}O_2$	84.08	84.15	83.95	5.73	5.45	5.64
(D)	*p*-Benzoyl-m-ϕ_3	Benzene, EtOH, 1:4	13	117	$C_{25}H_{18}O$	89.82	89.92	89.73	5.39	5.30	5.34
(E)	*p,p'*-Di-(-ω-chloroacetyl)-m-ϕ_3	EtOH	3	150	$C_{22}H_{16}O_2Cl_2$						
					Cl,	18.53	18.23	18.27			
(F)	*p*-Benzenesulfonyl-m-ϕ_3	EtOH	4	119	$C_{24}H_{18}O_2S$ S,	8.64	8.61	8.65			
(G)	m-ϕ_3-Phthaloylic acid[5]	..	35.5	.	$C_{26}H_{18}O_3$	82.54	82.47	82.52	4.76	4.95	4.91
					Neut. eq.	378	385	387			

acetic acid, acetone, and ethyl ether, from any of which it may be recovered by evaporation of the solvent as a glassy, resinous film. The dried product fuses at 90–100° to a straw-colored, opaque, resinous mass.

Table II gives essential data concerning the products obtained.

Table III lists the oxidation products of each of the compounds with the melting points of their derivatives used for identification. These oxidations were all performed in the heretofore described manner, using a mixture of chromic anhydride and acetic acid. All esters were prepared by the method given by Mulliken.[7]

TABLE III

IDENTIFICATION OF PRODUCTS

Compound	Oxidation products	M. p. °C. DME = Dimethyl ester ME = Methyl ester
(A)	Terephthalic acid	DME, 140
(C)	Terephthalic acid	DME, 140
(D)	*p*-Benzoylbenzoic acid	194; ME, 107
(E)	Terephthalic acid	DME, 140
(F)	*p*-Phenylsulfonebenzoic acid	273
(G)	No identifiable products	...

Ring Closure of *m*-Diphenylbenzene-phthaloylic Acid.—Several experiments were performed with the idea of determining the susceptibility of *m*-diphenylbenzene-phthaloylic acid to ring closure, to form a substituted anthraquinone type. Of the five dehydrating agents used, acetic anhydride, anhydrous aluminum chloride, anhydrous ferric chloride, phosphorus pentoxide, and sulfuric acid, positive results were obtained only by the use of the last named reagent, when heated at 136°. Sulfonation, however, was shown to occur simultaneously. The resulting product was water soluble and when treated with zinc dust and 10% sodium hydroxide solution produced a deep red color, which disappeared upon blowing air through the solution.

***m*-Diphenylbenzene-*p*-carboxylic Acid.**—The method of oxidation described below is based upon that described by Bogert and Hasselström[8] for the preparation of retene-α-carboxylic acid from acetylretene.

One gram of *p*-acetyl-*m*-diphenylbenzene was dissolved in 50 cc. of hot methanol and, with stirring, 15 cc. of a strong sodium hypochlorite solution was added drop by drop. Stirring was continued for one hour. The formed suspension of white solid in methanol was poured into ice water and heated until the solid material had dissolved, filtered hot, and allowed to cool. The solid which crystallized was filtered and boiled with water to which sufficient hydrochloric acid had been added to convert the sodium salt to the free acid. This was cooled, filtered, and the residue washed thoroughly with water. The crude product, 0.9 g., was then recrystallized twice from benzene, after which 0.4 g. of white *m*-diphenylbenzene-*p*-carboxylic acid, melting at 221°, was obtained.

Anal. Calcd. for $C_{19}H_{14}O_2$: C, 83.21; H, 5.11; neut. equiv., 274. Found: C, 82.78, 83.03; H, 5.21, 5.26; neut. equiv., 274, 267.

The sodium salt is very insoluble in cold water, soluble in hot water.

Summary

1. The following hitherto undescribed compounds were prepared by means of the Friedel–Crafts synthesis, using *m*-diphenylbenzene as the hydrocarbon: (a) *p*-acetyl-*m*-diphenylbenzene, which was converted to *m*-diphenylbenzene-*p*-carboxylic acid; (b) *p,p'*-diacetyl-*m*-diphenylbenzene; (c) *p*-benzoyl-*m*-diphenylbenzene; (d) *p,p'*-di-(-ω-chloroacetyl)-*m*-diphenylbenzene; (e) *p*-(benzenesulfonyl)-*m*-diphenylbenzene; and (f) *m*-diphenylbenzene-phthaloylic acid.

2. Oxidation experiments upon (a), (b), (c), (d), and (e) yielded products which indicated that, in each case, the substitution had taken place in the para position of an end ring of the *m*-diphenylbenzene molecule. The structure of *m*-diphenylbenzene-*p*-carboxylic acid follows from its synthesis from (a) by oxidation. Most likely (f) is a mixture of two or more isomeric keto acids.

3. Attempts to form a substituted anthraquinone type by ring closure of (f) indicated that, of the five dehydrating agents tried, sulfuric acid alone gave positive results. Sulfonation, however, occurred simultaneously.

PITTSBURGH, PENNA. RECEIVED JULY 14, 1938

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[7] Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1904, Vol. I, p. 85.

[8] Bogert and Hasselström, *Proc. Natl. Acad. Sci.*, **18**, 417 (1932).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Structure of Gossypol. V.[1] Anilino Derivatives

BY ROGER ADAMS, C. C. PRICE AND W. R. DIAL[2]

Gossypol reacts readily with two molecules of aniline;[3] two molecules of water are eliminated and dianilinogossypol is formed. This product is purified easily, and as a consequence aniline has actually been used for the extraction of gossypol.[3]

The formation of this compound has led to the deduction that two keto groups are present in the gossypol structure. However, in a previous paper from this Laboratory it was pointed out that certain vinyl alcohol groups condense equally well with aniline with the elimination of water. There is reason for believing that gossypol contains groupings of this type.

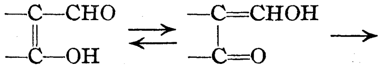
Anhydrogossypol reacts with aniline to give dianilinogossypol quantitatively; moreover, liquid ammonia reacts with gossypol or anhydrogossypol to give diaminogossypol. Both diaminogossypol and dianilinogossypol hydrolyze with unusual ease to give gossypol.

Substituted anilines have now been combined with gossypol. Some of them condense in a manner similar to aniline, β-naphthylamine and *o*-phenylenediamine. The derivative of *o*-phenylenediamine is of particular interest. Karrer and Tobler[4] reported the condensation product of gossypol and *o*-phenylenediamine as consisting of one molecule of gossypol and one of diamine with the loss of two molecules of water. From this they concluded that an *o*-quinone or 1,2-diketone might be present in the parent molecule. All the reliable reactions thus far described and many yet unpublished have conformed to the point of view of a symmetrical molecule for gossypol. An even number of molecules of reagent condense. It is not impossible that two ketone groups are adjacent and are symmetrically located in the molecule but as this seemed unlikely the condensation with *o*-phenylenediamine has been studied again. It has now been established that *o*-phenylenediamine when used in molecular amounts with gossypol gives a non-homogeneous product which agrees in properties with that reported by the above-mentioned authors. On the other hand, if two or more molecules of *o*-phenylenediamine are used, a readily purified, nicely crystalline compound is isolated in quantitative yield which consists of two molecules of *o*-phenylenediamine and one of gossypol with the elimination of two molecules of water. The presence of a 1,2-diketone grouping in gossypol, therefore, appears improbable.

Other substituted anilines condense readily with gossypol. However, in many cases (*o*-, *m*-, and *p*-toluidine, *p*-anisidine, *p*-chloroaniline) the analyses of the products do not conform to a simple derivative similar to the dianilinogossypol. They are more difficult to purify and it appears in some cases that an additional molecule of aniline is present in the product or that an oxygen has entered simultaneously. These compounds, however, all hydrolyze to gossypol. Similarly, the acetates of all but the dianilino compound are difficult to purify and give variable analyses.

Dianilinogossypol acetylates to a hexaacetyl derivative. Pyrolysis of this compound gives acetanilide and as a consequence it seems likely that two acetyls are attached to nitrogen atoms which would be possible only if the dianilinogossypol were so constituted that hydrogens were present on the nitrogen atoms.

Dianilinogossypol also can be methylated. Under certain conditions, a crystalline dimethyldianilinogossypol is sometimes produced. This substance is deep red. It has the methyl groups on the two nitrogens, if the fact that the Zeisel number of the derivatives is almost zero may be used as experimental evidence. Moreover, the compound cannot be hydrolyzed to gossypol under the conditions used for dianilinogossypol. These data and those on the acetylation product make it appear probable that the dianilino compound is tautomeric. The original dianilinogossypol which is yellow possibly may be a Schiff base which upon methylation is converted into a red N-methyl derivative of the hydroxymethylene type. These reactions may be explained by the presence of the following groupings



$$\begin{array}{l}\text{—C—CHO}\\ \ \ \|\\ \text{—C—OH}\end{array} \rightleftarrows \begin{array}{l}\text{—C=CHOH}\\ \ \ |\\ \text{—C=O}\end{array} \longrightarrow$$

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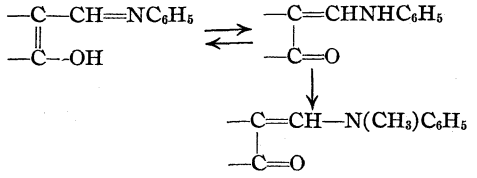
[1] For the previous article in this field see Miller and Adams, THIS JOURNAL, **59**, 1736 (1937).

[2] Dow Chemical Fellow, 1936–38. Portion of a thesis submitted in partial fulfilment for the degree of Doctor of Philosophy.

[3] Clark, *J. Biol. Chem.*, **76**, 229 (1928); Carruth, THIS JOURNAL, **40**, 647 (1918).

[4] Karrer and Tobler, *Helv. Chim. Acta*, **15**, 1204 (1932).



$$\begin{array}{l} —C—CH{=}NC_6H_5 \\ \quad \| \\ —C—OH \end{array} \rightleftarrows \begin{array}{l} —C{=}CHNHC_6H_5 \\ \quad | \\ —C{=}O \end{array} \downarrow \begin{array}{l} —C{=}CH—N(CH_3)C_6H_5 \\ \quad | \\ —C{=}O \end{array}$$

Under slightly modified conditions of methylation, a crystalline dimethyldianilinooxogossypol is readily formed in which it appears that an atom of oxygen has replaced two hydrogens in dimethyldianilinogossypol or possibly merely an atom of oxygen was added. The compound does not hydrolyze to gossypol under the usual conditions. Its structure has not yet been investigated.

Experimental

Dianilinogossypol.—This compound previously described by Carruth[3] and by Clark[5] was prepared by dissolving crude gossypol-acetic acid in ten times its weight of boiling aniline. The orange crystals which separated on cooling were collected and washed thoroughly with ether. It was purified from chloroform–petroleum ether and yielded yellow-orange plates, m. p. 303°, with decomposition.

For hydrolysis, it was dissolved in concentrated sulfuric acid, the solution allowed to heat to 90° on a hot-plate (about two to two and one-half minutes), poured onto ice, filtered, and dried. The product was dissolved in hot glacial acetic acid and water was added dropwise to the boiling solution until crystals started to appear. The solution on cooling deposited gossypol-acetic acid which was usually in practically a pure state as golden platelets.

Dianilinogossypol, when heated on the steam cone for thirty minutes in 40% aqueous alkali, followed by methylation with dimethyl sulfate, gave a 60% yield of apogossypol hexamethyl ether.

By Zeisel methoxyl determination, gossypol is reported to give about 5% methoxyl. A repetition of this determination using a commercial grade of 47% hydriodic acid containing a small amount of preservative (1.5% H_3PO_2) gave less than 0.2% methoxyl. Dianilinogossypol also showed less than 0.2% methoxyl.

Hexaacetyldianilinogossypol.—A solution of 0.5 g. of dianilinogossypol in 10 cc. of pyridine and 5 cc. of acetic anhydride was warmed on a steam-cone for thirty minutes. About 10 cc. of acetic acid was added and the reaction mixture was poured into water. A bright yellow product separated which was purified by crystallization from methanol, m. p. 185°, decomposing vigorously without discoloration at 220°.

Anal. Calcd. for $C_{54}H_{52}N_2O_{12}$: C, 70.40; H, 5.70; N, 3.04; acetyl, 28.0. Found: C, 69.94; H, 5.82; N, 2.89; acetyl, 28.4.

The heat decomposition of this compound led to the isolation of a white crystalline compound, m. p. 112°, which sublimed in the cooler portions of the pyrolysis tube. It proved to be acetanilide. It may thus be deduced that two acetyl groups are probably attached to nitrogens in the starting material.

By hydrolysis with concentrated sulfuric acid, gossypol was recovered. The initial color in the acid is yellow which turns to olive-green in thirty seconds and to scarlet on addition of a drop or two of water.

Di-*o*-phenylenediaminogossypol.—A mixture of 2.5 moles of *o*-phenylenediamine and one of pure gossypol-acetic acid in chloroform solution was refluxed for thirty minutes. On cooling the solution, the product separated as orange crystals. It was recrystallized from chloroform, m. p. 246°.

Anal. Calcd. for $C_{42}H_{42}N_4O_6$: C, 72.13; H, 6.06; N, 8.02. Found: C, 72.01, 71.92; H, 5.84, 6.08; N, 8.18, 7.99.

By the use of one molecule of *o*-phenylenediamine, a non-crystalline substance was obtained which had properties similar to that reported by Karrer and Tobler.[4] An excess of diamine, however, readily converted it to the product reported above.

In the preparation of the di-*o*-phenylenediamine derivative, a product melting at 184° sometimes was obtained. This product, however, on drying and long standing acquires the higher melting point mentioned above.

Di-β-naphthylaminogossypol.—It formed bright orange crystals from chloroform, m. p. 310–313° with decomposition. It hydrolyzed to gossypol with sulfuric acid.

Anal. Calcd. for $C_{50}H_{44}N_2O_6$: C, 78.09; H, 5.97; N, 3.65. Found: C, 77.95; H, 5.78; N, 3.69.

The preparation of similar compounds was attempted from gossypol and *o*-, *m*-, and *p*-toluidine, *p*-chloroaniline and *p*-anisidine. In all these cases, crystalline products were obtained, more difficult to purify than the ones previously described. Analyses did not check the calculated values. In some cases, the analyses indicated that normal condensation took place and an additional molecule of the amine had added. In other cases, addition of one atom of oxygen to the condensation product of two molecules of amine agreed most satisfactorily. All these compounds, however, were hydrolyzed to gossypol. The acetyl derivatives were difficult to purify and did not give the expected values on analysis.

Dimethyldianilinooxogossypol.—To a solution of 1 g. of dianilinogossypol in 100 cc. of chloroform, were added 10 cc. of dimethyl sulfate and 6 cc. of pyridine in portions with shaking. The reaction mixture did not change color but separated into two phases in a few minutes. After standing at room temperature for five days to a week, 15 cc. of pyridine was added to decompose the excess dimethyl sulfate. The chloroform solution was washed twice with water, dried over sodium sulfate, and evaporated. It was purified by recrystallization from benzene as red microcrystals, m. p. 275–280°. It gave a brown color in concentrated sulfuric acid which turned red on standing for five to ten minutes.

Anal. Calcd. for $C_{44}H_{42}N_2O_7$: C, 74.33; H, 5.95; N, 3.94; OCH_3, 8.74. Found: C, 74.22, 74.46; H, 5.96, 5.82; N, 4.00, 3.99; OCH_3, 1.45.

The compound was recovered unchanged after eighteen hours in concentrated sulfuric acid by pouring on ice and recrystallizing from benzene–methanol. The resistance to

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(5) Clark, *J. Biol. Chem.*, **75**, 725 (1927).

hydrolysis, as well as the low Zeisel number, indicates that the methyl groups are probably attached to nitrogens.

Dimethyldianilinogossypol.—By a similar procedure to the preparation of the oxo compound but refluxing overnight rather than allowing the reaction mixture to stand at room temperature resulted in a methylated but unoxidized product. It was purified from benzene and formed red crystals, m. p. 253–258°. It gave a dark red-brown color in sulfuric acid.

Anal. Calcd. for $C_{44}H_{42}N_2O_6$: C, 75.83; H, 6.36; N, 4.02; OCH_3, 8.89. Found: C, 75.70; H, 6.11; N, 4.09; OCH_3, 1.01.

Concentrated sulfuric acid does not hydrolyze this product. This and the low Zeisel number indicate the probability that the methyls are attached to nitrogen.

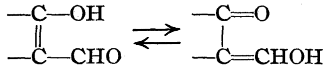
Summary

Gossypol condenses with β-naphthylamine or *o*-phenylenediamine in the same way as with aniline. Two molecules of amine react and two moles of water are eliminated.

Several other aniline derivatives gave products which did not analyze for simple condensation products. All of these hydrolyzed with sulfuric acid to give gossypol.

Dianilinogossypol can be acetylated to a hexaacetate. Two acetyls are attached to nitrogen. Methylation gives sometimes a dimethyldianilinogossypol or more commonly a dimethyldianilinooxogossypol.

It is deduced that there exist in gossypol two of the tautomeric residues



URBANA, ILLINOIS RECEIVED JUNE 27, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

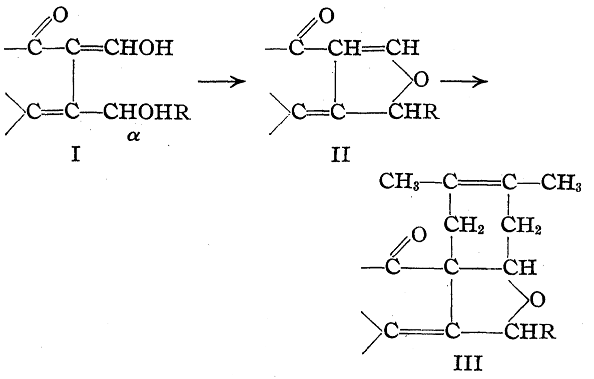
Structure of Gossypol. VI.[1] Addition Products with Butadienes

BY ROGER ADAMS, B. S. FRIEDMAN, C. C. PRICE, R. C. MORRIS AND E. C. KIRKPATRICK[2]

From a study of anhydrogossypol[3] and its reaction products and of the diamino- and dianilinogossypols[1] it was deduced that gossypol contains two similar groupings which are probably vinyl alcohols. Since the most common type of relatively stable vinyl alcohols possesses a carbonyl in place of one of the hydrogens of the methylene group $\left(-\overset{\displaystyle O}{\overset{\|}{C}}-CH=CHOH\right)$, the possibility of two such residues in gossypol has now been studied. The reaction used for this purpose was the Diels–Alder and the reagent, 2,3-dimethylbutadiene.

Gossypol condenses very readily in alcohol solution with the addition of two molecules of dimethylbutadiene and elimination of two molecules of water to give a beautifully crystalline product. In a similar way, anhydrogossypol or diaminogossypol in benzene condenses with two molecules of dimethylbutadiene to give the same derivative.

In the case of gossypol, the reaction involves the elimination of water; in the case of diaminogossypol the loss of ammonia; in the case of anhydrogossypol, however, the same derivative is formed by simple addition. Since anhydrogossypol adds the diene, it is a safe conclusion that the molecule probably contains α,β-unsaturated carbonyl linkages. The addition product, unlike anhydrogossypol itself, is not hydrolyzed. Consequently, the easily-opened oxygen ring which was postulated previously as being present in anhydrogossypol, must have been stabilized. This is no doubt due to the fact that the carbon–carbon double bond to which the diene adds is part of the oxygen-containing ring of the anhydrogossypol. Suggested nuclei which will account for the changes follow: gossypol (I), anhydrogossypol (II), dimethylbutadiene addition product (III).



It is probable that gossypol and diaminogossypol

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(1) For the previous article in this field see Adams, Price and Dial, THIS JOURNAL, **60**, 2158 (1938).

(2) A portion of a thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy by E. C. Kirkpatrick, Solvay Fellow, 1936–1938.

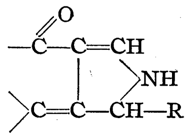
(3) Miller and Adams, THIS JOURNAL, **59**, 1736 (1937).

first lose water and ammonia, respectively, and then the diene adds to the anhydrogossypol formed.

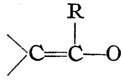
The nucleus II accounts for the ease with which anhydrogossypol is hydrolyzed to gossypol, methylated or acetylated to gossypol hexamethyl ether or gossypol hexaacetate and converted by ammonia or aniline to the corresponding gossypol derivatives. Nucleus III indicates why the addition product is stable to hydrolysis as it no longer contains an easily-opened oxygen ring.

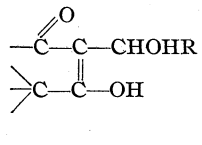
The dimethylbutadiene anhydrogossypol product is soluble in alkali and contains two acidic hydroxyls which are readily acetylated or methylated to form stable crystalline derivatives. It also gives a red color with pyroboroacetate, indicative of a phenol group *ortho* or *peri* to a carbonyl.

Still further deductions concerning the oxygen-containing ring formation when gossypol is converted to anhydrogossypol may be made. Liquid ammonia[3] converts anhydrogossypol to diaminogossypol and not to a molecule containing an imino nitrogen in place of the oxygen of the oxygen-containing ring in anhydrogossypol. It is difficult to believe that the nitrogen compound corresponding to II shown in IV would not be stable if the hydroxyl marked α in formula I were alcoholic in character. On the other hand, if it were phenolic, the non-formation of IV is explicable. For this reason, it is assumed that the oxygen-containing ring in anhydrogossypol is formed by elimination of water between the hydroxyl of an hydroxymethylene group and a phenolic group.

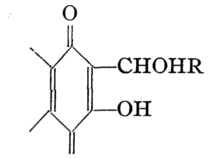


IV

The ease of condensation of anhydrogossypol or gossypol with the diene and the fact that neither gossypol hexamethyl ether nor tetramethyl ether undergoes such a reaction, makes it probable that the hydrogen on the carbon holding the vinyl hydroxyl is unsubstituted. The grouping should therefore be represented preferably by $>C{=}CHOH$ and not by  $>C{=}\overset{R}{\overset{|}{C}}{-}OH$. The ease of the reaction with the diene also tends to nullify the possibility of a structure isomeric with I shown in V and hence eliminates the likelihood of the presence of residues of a quinone-like structure (VI) in the gossypol molecule.



V



VI

The reaction is not limited to dimethylbutadiene. Anhydrogossypol also condenses with 2,3-butadiene to give an analogous product in which two molecules of diene have added, and two acidic hydroxyls remain unaffected. The product apparently is not as stable as the dimethylbutadiene derivative, as it dissociates upon standing in solution. It gives a diacetate similar to the dimethylbutadiene derivative.

From the study of the aniline and ammonia derivatives[1,3] and of the diene addition products, the presence in gossypol of two tautomeric hydroxyaldehyde residues seems fairly well established.

Experimental

The Addition of 2,3-Dimethylbutadiene-1,3 to Gossypol.—To a solution of 1 g. of gossypol in 25 cc. of absolute alcohol was added 1.5 cc. of freshly prepared dimethylbutadiene. The reaction mixture was refluxed for eight hours on the steam-bath, the condenser was then removed and the alcohol allowed to evaporate. After concentrating for a short time, crystals began to separate, the flask was cooled and the precipitate filtered. On further concentration of the mother liquor more product was obtained; yield 0.8 g. The material crystallized from acetone–methanol in bright yellow cubes, m. p. 244–245° with decomposition.

Anal. Calcd. for $C_{42}H_{46}O_6$: C, 78.00; H, 7.12. Found: C, 77.83; H, 7.09.

The crystals gave a bright yellow-brown color in concentrated sulfuric acid. Alcoholic ferric chloride gave a deep red color. Aqueous sodium hydrosulfite solution had no effect on an alcoholic solution of the addition compound. It gave a deep red with pyroboroacetate.

The addition reaction takes place equally well using benzene as the solvent.

The addition product would not condense with aniline. It was unaffected by heating for one-half hour on the steam-bath with 40% aqueous alkali. It decomposed when dissolved in concentrated sulfuric acid and allowed to stand overnight. It did not reduce catalytically with hydrogen and platinum oxide platinum black.

Methylation of the Dimethylbutadiene Addition Product.—To a solution of 0.4 g. of the addition product in 10 cc. of 30% methanolic potassium hydroxide was added an excess of dimethyl sulfate, in portions. When the reaction was complete the solution was made alkaline, diluted with water, and the precipitate filtered and washed. The product was air dried and crystallized from acetone-methanol; bright yellow needles, m. p. 227–229°, yield 0.32 g. It gave a yellow-brown color in concentrated sulfuric acid and gave no color with phenol reagents.

Anal. Calcd. for $C_{44}H_{50}O_6$: C, 78.3; H, 7.42. Found: C, 78.11; H, 7.35.

Acetylation of the Dimethylbutadiene Addition Product.—By heating for a half-hour a mixture of 0.075 g. of addition product, excess of acetic anhydride and sodium acetate, and then pouring into water, 0.065 g. of the acetylated compound was obtained. It crystallized in light yellow plates from acetone–methanol, m. p. 227–229°, and gave a brown color in concentrated sulfuric acid.

Anal. Calcd. for $C_{46}H_{50}O_8$: C, 75.5; H, 6.84. Found: C, 75.22; H, 6.95.

Saponification of this product yielded the original material as shown by melting point and mixed melting point.

The product was not affected by long refluxing (two and one-half hours) with acetic anhydride and sodium acetate.

Condensation of 2,3-Dimethylbutadiene-1,3 with Anhydrogossypol.—To a solution of 0.5 g. of anhydrogossypol in 25 cc. of dry benzene was added 1.5 cc. of freshly prepared dimethylbutadiene. The solution was refluxed overnight on the steam-bath, then evaporated to dryness. The residue was purified by crystallization from acetone–methanol; m. p. 244–245° with decomposition. A mixed melting point with the product from the addition of dimethylbutadiene to gossypol showed no lowering.

Condensation of 2,3-Dimethylbutadiene-1,3 with Diaminogossypol.—A solution of 0.425 g. of diaminogossypol in 25 cc. of dry benzene was refluxed on the steam-bath overnight with 1.5 cc. of freshly distilled dimethylbutadiene.

The material dissolved to give the red solution characteristic of diaminogossypol in benzene. At the end of eight hours the red color had faded to the yellow color common to a solution of gossypol.

The solution was evaporated and the residue crystallized from acetone–methanol, m. p. 244–245° with decomposition. This product was identical with that obtained in the reaction above using gossypol or anhydrogossypol.

Attempted Condensations with 2,3-Dimethylbutadiene-1,3.—Using the same procedure that was employed in the condensation of gossypol with dimethylbutadiene, attempts were made to condense hexaacetylgossypol, the white hexamethyl ethers of gossypol and apogossypol. In every case the starting material was recovered unchanged.

Condensation of Butadiene-1,3 with Anhydrogossypol.—A mixture of 3 cc. of pure butadiene-1,3,5 cc. of pure dry benzene and 0.5 g. of anhydrogossypol was heated in a sealed tube on a steam-bath for twelve hours. After evaporation of the excess butadiene by warming, the red solution was cooled and filtered from the precipitate. The solid thus obtained was purified by rapid crystallization from acetone–methanol; yellow crystals which darkened at 242° and melted with decomposition at 245–246°.

Anal. Calcd. for $C_{38}H_{38}O_6$: C, 77.2; H, 6.43. Found: C, 76.95; H, 6.46.

The product gave an orange color in concentrated sulfuric acid. If the addition compound was allowed to remain standing in solution, there was a reversion with regeneration of anhydrogossypol.

Acetylation of Butadiene Addition Product.—By a procedure similar to that described for the dimethylbutadiene product, a white diacetate was obtained. It was purified from aqueous methanol, m. p. 250–251° with decomposition. It gave a yellow color in concentrated sulfuric acid.

Anal. Calcd. for $C_{38}H_{36}O_4(OCOCH_3)_2$: C, 74.8; H, 6.24. Found: C, 74.91; H, 6.50.

Summary

Gossypol, anhydrogossypol, and diaminogossypol react with dimethylbutadiene to give a product which analyzes for the addition of two moles of diene to one of anhydrogossypol. During the reaction with gossypol or diaminogossypol, two moles of water or two moles of ammonia are eliminated simultaneously. The product contains two hydroxyls which can be methylated or acetylated.

Butadiene gives a similar product with anhydrogossypol though it is less stable than the dimethylbutadiene derivative.

The deduction from these experiments is that two α,β-unsaturated carbonyl groups are present in the anhydrogossypol molecule. Gossypol in forming anhydrogossypol probably loses water between hydroxymethylene groups and phenolic hydroxyls.

Urbana, Illinois Received June 27, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Structure of Gossypol. VII. Gossypol Dimethyl Ether

BY ROGER ADAMS AND T. A. GEISSMAN

Evidence has been presented in previous papers[1] that gossypol is a symmetrical molecule containing six hydroxyl groups and two tautomeric hydroxyaldehydic residues. Of the six hydroxyls, two are much less acidic than the other four. The stability of two of the ether linkages in gossypol hexamethyl ether should be different from that of the other four and this now has been tested experimentally.

The white and red hexamethyl ethers of gossypol are demethylated upon treatment with sulfuric acid in acetic acid with the formation of a dimethyl ether. This new product possesses many of the properties of gossypol. It dissolves in alkali to give solutions which oxidize in the air. It gives a green color with ferric chloride; it forms a compound with one molecule of acetic acid; it gives an orange-red color with pyroboroacetate and an orange-red color with stannic chloride. With concentrated sulfuric acid it gives the orange color characteristic of the hexamethyl ethers of gossypol in contrast to the tetramethyl ether which gives a scarlet color similar to that given by gossypol. This is assumed to mean that the two unmethylated hydroxyl groups in gossypol tetramethyl ether are those which are methylated in the dimethyl ether. This assumption has been supported further by a study of the demethylation of gossypol tetramethyl ether under conditions similar to those used in the demethylation of the hexamethyl ethers. Gossypol is the resulting product.

The hexamethyl and tetramethyl ethers of gossypol do not react with aniline but the new dimethyl ether does react to give a condensation product. Although this derivative appears from analysis to be one of complicated type similar to those obtained from gossypol and certain substituted anilines, it can be hydrolyzed by acids to the original dimethyl ether of gossypol.

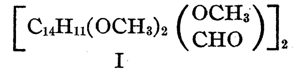
The dimethyl ether does not give an anhydro derivative under the conditions used for preparing anhydrogossypol from gossypol, and could not be converted to the red hexamethyl ether of gossypol either under the conditions used for preparing this compound from gossypol or under conditions which were modifications of these.

Gossypol dimethyl ether undergoes the apo reaction in a manner similar to gossypol, which again is in contrast to the tetra- and hexamethyl ethers which are stable under similar conditions.[2]

Remethylation of the dimethyl ether leads to the lower-melting form of the white hexamethyl ether.

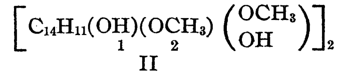
The white hexaethyl ether of gossypol can be deethylated to a gossypol diethyl ether analogous in structure and similar in properties to the dimethyl ether.

If gossypol hexamethyl ether in condensed form is accepted as having the structure indicated in I, and the tetramethyl ether II, then it may be concluded that III would be the structure for the dimethyl ether.



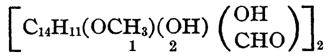
$$\left[C_{14}H_{11}(OCH_3)_2\begin{pmatrix}OCH_3\\CHO\end{pmatrix}\right]_2$$

I



$$\left[C_{14}H_{11}(\underset{1}{OH})(\underset{2}{OCH_3})\begin{pmatrix}OCH_3\\OH\end{pmatrix}\right]_2$$

II



$$\left[C_{14}H_{11}(\underset{1}{OCH_3})(\underset{2}{OH})\begin{pmatrix}OH\\CHO\end{pmatrix}\right]_2$$

III

The methylation of gossypol was reported to give a tetramethyl ether, two white hexamethyl ethers which were dimorphic and a red hexamethyl ether. It has now been found that the methylation conditions must be controlled very carefully in order to obtain the tetramethyl ether in a pure state. Moreover, it is possible to methylate gossypol-acetic acid to yield either the tetramethyl ether or the two white hexamethyl ethers.

Three different white gossypol hexamethyl ethers have now been isolated, m. p. 188, 225, 238–240°. The first two are apparently dimorphs but the highest melting appears to be diastereoisomeric or isomeric with the other two, if the depressed mixed melting point of the 225 and 240° forms is considered a proper criter-

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[1] (a) Campbell, Morris and Adams, THIS JOURNAL, **59**, 1723 (1937); (b) Miller and Adams, *ibid.*, **59**, 1729 (1937); (c) Morris and Adams, *ibid.*, **59**, 1731 (1937); (d) Miller and Adams, *ibid.*, **59**, 1736 (1937); (e) Adams, Price and Dial, *ibid.*, **60**, 2158 (1938); (f) Adams, Friedman, Price, Morris and Kirkpatrick, *ibid.*, **60**, 2160 (1938).

[2] The apogossypol dimethyl ether could not be isolated in a pure state but upon methylation yielded apogossypol hexamethyl ether. This work will be reported in a subsequent paper.

ion. Fortunately, the chemical reactions of all these forms lead to the same products, so that their exact character is less significant.

The gossypol dimethyl ether can be oxidized in alkaline or acid medium. A solution in aqueous alkali when treated with air gives a deeply colored crystalline compound. This substance forms a violet salt the solution of which is decolorized by sodium hydrosulfite. The properties of this product indicate it to be a quinone. The dimethyl ether is also oxidized by ferric chloride in acetic acid or by dilute nitric acid to a deep orange crystalline compound. The mechanism by which these substances are produced has not yet been determined.

Experimental

Gossypol Dimethyl Ether.—To 1 g. of gossypol hexamethyl ether (m. p. 238–240°) dissolved in 40 cc. of hot acetic acid was added a solution of 10 drops of concentrated sulfuric acid in 10 cc. of acetic acid. The solution turned a deep red. After heating for thirty minutes on the steam-bath, 23 cc. of water was added carefully, with stirring and scratching of the walls of the flask. The initially flocculent precipitate soon became crystalline. It was filtered, washed with acetic acid and water and dried. The product was a yellow-green crystalline material and weighed 0.82 g. This crude product melted at about 155–165° with decomposition and obviously contained acetic acid. It was difficult to purify directly by further crystallization from acetic acid. By the action of aqueous alkali, a product was obtained which crystallizes from benzene–petroleum ether (b. p. 30–60°) as soft yellow needles, m. p. 191–193° (corr.), with decomposition. This is acetic acid free. The acetic acid also may be removed from the crude product merely by crystallization from benzene–petroleum ether without previous treatment with alkali. Recrystallization of this yellow crystalline form, m. p. 191–193° (corr.), from dilute acetic acid, results in the formation of a pure acetic acid derivative of gossypol dimethyl ether, m. p. 230–232° (corr.), with decomposition. The melting point varies considerably with the rate of heating.

Anal. Calcd. for $C_{30}H_{28}O_6(OCH_3)_2$: C, 70.33; H, 6.23. Found: (benzene–petroleum ether) C, 69.96; H, 6.01. (Removal of acetic acid by alkali) C, 70.48; H, 6.22. Calcd. for $C_{30}H_{28}O_6(OCH_3)_2 \cdot CH_3COOH$: C, 67.33; H, 6.26; OCH_3, 10.20. Found: C, 67.56; H, 5.99, 6.30; OCH_3, 14.2, 12.4, 13.5, 14.4.[3]

Aniline Derivative of Gossypol Dimethyl Ether.—A solution of 0.1 g. of the dimethyl ether of gossypol and 0.25 cc. of aniline in 4 cc. of benzene, was refluxed for thirty minutes. On dilution with petroleum ether (b. p. 30–60°), the aniline compound separated as orange prisms weighing 95 mg. Recrystallized from chloroform–petroleum ether (b. p. 30–60°), it formed bright orange prisms which melted at 268–270° (corr.) with decomposition.

Anal. Calcd. for $C_{44}H_{44}N_2O_6$: C, 75.86; H, 6.3; N, 4.0. Found: C, 74.92, 74.78; H, 6.30, 6.22; N, 5.20.

Deanilination of the Gossypol Dimethyl Ether–Aniline Compound.—To about 50 mg. of the aniline compound dissolved in 2 cc. of hot acetic acid was added one drop of concentrated hydrochloric acid. The clear orange solution was diluted drop by drop with water until crystallization started. The product was recrystallized from benzene–petroleum ether (b. p. 30–60°) (soft yellow needles, m. p. 187–189° (corr.) with decomposition), and then from dilute acetic acid (shining yellow leaflets, m. p. 229–230° (corr.) with decomposition). The latter sample showed no depression in melting point when mixed with a sample of dimethyl ether–acetic acid compound, m. p. 230–232° (corr.) with decomposition.

Gossypol Diethyl Ether.—To 0.1 g. of hexaethyl ether of gossypol in 4 cc. of hot acetic acid was added 1 cc. of acetic acid containing one drop of concentrated sulfuric acid. After heating on the steam-bath for fifteen minutes the solution was diluted with 2 cc. of water and cooled. The crude product was a yellow crystalline powder which weighed 95 mg. After one recrystallization from dilute acetic acid and a second from benzene–petroleum ether (b. p. 30–60°), it formed bright yellow needles, m. p. 193–195° (corr.) with decomposition.

Anal. Calcd. for $C_{34}H_{38}O_8$: C, 71.08; H, 6.62. Found: C, 71.17; H, 6.36.

The compound dissolves in alkali to give a yellow solution which slowly turns violet on standing in air. It gives a bright orange color with concentrated sulfuric acid and a brownish-green color with ferric chloride.

The fact that the material after a crystallization from dilute acetic acid melted at the same point as that from benzene–petroleum ether, indicates that an acetic acid compound analogous to the gossypol dimethyl ether derivative may not form.

Methylation of Gossypol Dimethyl Ether.—To a solution of 1.49 g. of the dimethyl ether in a mixture of 20 cc. of methanol and 20 cc. of dimethyl sulfate, 30 cc. of 10% methanolic potassium hydroxide was added slowly with cooling and the mixture was allowed to stand for forty-eight hours. The excess dimethyl sulfate was decomposed with 10% aqueous sodium hydroxide and the product collected. It formed white needles, weighing 1.5 g. Recrystallization from methanol gave white prisms, m. p. 209–211° (corr.).

Recrystallization from acetone–methanol gave small prisms which could be obtained melting as high as 221–223° (corr.), although it usually was possible to raise the melting point over 219° only by numerous recrystallizations. Recrystallization from ligroin (b. p. 90–110°) or from acetone–water gave long, crisp white needles which melted at 173° when heated quickly to this temperature, or at 223° when heated slowly (with shrinking at about 173°).

Anal. Calcd. for $C_{30}H_{26}O_2(OCH_3)_6$: C, 71.76; H, 6.97; OCH_3, 30.9; mol. wt., 602. Found: (prism form) C, 71.85; H, 6.93; OCH_3, 31.9, 33.3; (needle form) C, 71.78; H, 6.71; mol. wt. (Rast), 620.

This compound was proved by mixed melting point to be identical with the hexamethyl ether, m. p. 225°, obtained by methylating gossypol–acetic acid under suitable condi-

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(3) Gossypol and most of its derivatives invariably give results from one to five per cent. high in the Zeisel determination. Compare Clark, THIS JOURNAL, **51**, 1479 (1929).

tions, and different from the hexamethyl ether, m. p. 240°, obtained by the methylation of the tetramethyl ether of gossypol (mixed m. p. 210–218° (corr.)).

Methylation of Gossypol–acetic Acid. (a) Gossypol Hexamethyl Ether (240° form).[4]—A solution of 10 g. of pure gossypol–acetic acid in a mixture of 50 cc. of dimethyl sulfate and 50 cc. of methanol was treated with 75 cc. of 10% methanolic potassium hydroxide with efficient cooling in an ice-bath. The solution was allowed to stand at 10–15° for about thirty-six hours and the excess dimethyl sulfate decomposed by the addition of 10% aqueous sodium hydroxide with ice cooling. The precipitate was washed well with water and with methanol, and consisted of buff needles weighing 5.95 g. and melting at 162–164°. It gave a scarlet color with concentrated sulfuric acid, indicating it to be crude tetramethyl ether.

This was remethylated to the hexamethyl ether according to the previously described procedure.[1c] It was recrystallized from acetone–methanol, when it formed colorless prisms, m. p. 238–240° (corr.). A sample recrystallized from ligroin (b. p. 90–110°) also formed prisms, m. p. 239–241° (corr.).

(b) Gossypol Hexamethyl Ether (225° form).—The proportions were the same as those just described for the first methylation, but the reaction mixture was cooled under the tap (*ca.* 20–25°) during the first addition of alkali and the final decomposition with 10% aqueous sodium hydroxide, and was allowed to stand for thirty-six hours at room temperature. The first product, methanol washed, weighed about 7.5 g., gave a deep orange color with concentrated sulfuric acid and melted at about 213°. Remethylated in the usual way,[1] it gave a product which melted (crude) at 211–213°, after one recrystallization from acetone–methanol at 216–218°, and after a second crystallization at 224–225° (corr.). A mixture of this with the product melting at 238–240° (corr.) melted at 212–217°.

This compound crystallized from ligroin (b. p. 90–110°) in clusters of white needles which sintered at about 179° and melted to a clear liquid at 221–224°. Plunged into a preheated bath at various temperatures it sintered at 185° and melted at 188°. At 198° it melted instantly, then resolidified, and remelted at 223–225° (corr.). The melted and resolidified samples of the *needle* form were found to have been converted to the *prism* form.

Both forms (m. p. 240° and 225°) were identical in their reactions.

Oxidation Products of Gossypol Dimethyl Ether. (a) Air Oxidation in Alkaline Solution.—Air was bubbled through a warm solution of 0.1 g. of the dimethyl ether in 25 cc. of 4% aqueous sodium hydroxide. After about five minutes the color became red and sodium hydrosulfite caused the reappearance of the initial yellow color. Continued treatment with air caused the solution finally to turn a deep violet and a purple sodium salt separated. The solution was acidified with sulfuric acid, extracted with ether, the ether solution dried and concentrated. The addition of petroleum ether caused the separation of 60 mg. of a compound crystallizing in tiny rosets. Recrystallized from ether–petroleum ether (b. p. 30–60°), the compound formed rosets of maroon prisms, m. p. 246° (corr.) with decomposition.

Anal. Calcd. for $C_{30}H_{30}O_8$: C, 69.50; H, 5.79. Found: C, 69.46, 69.51; H, 6.02, 6.10.

The compound gives a deep purple solution in sulfuric acid which changes through red to orange to yellow on dilution. The purple-red solution of the compound in dilute aqueous alcoholic alkali is changed to a yellow color by sodium hydrosulfite. Air reoxidizes the solution rapidly.

(b) Oxidation with Ferric Chloride.—To 0.8 g. of the dimethyl ether of gossypol dissolved in 80 cc. of hot glacial acetic acid was added 60 cc. of a 10% aqueous solution of ferric chloride. The solution turned deep greenish-brown and a small amount of tarry substance separated and was removed. The solution was heated on the steam-bath for a few moments and scratching of the walls of the flask caused orange crystals to form. These were collected and washed with acetic acid. They weighed 0.52 g. Recrystallized from acetic acid or dilute acetone the compound formed shining orange leaflets, m. p. 215–216° (corr.).

Anal. Calcd. for $C_{32}H_{30}O_{10}$: C, 66.90; H, 5.23. Found (acetone): C, 66.56; H, 5.19; (acetic acid): C, 67.02; H, 5.12.

The compound gives a red-brown color with ferric chloride and a red-brown color with concentrated sulfuric acid. It is soluble in dilute alkali, giving a red-violet solution which is unaffected by sodium hydrosulfite. It leaves no residue on ignition (not a Fe^{+++} salt).

(c) Oxidation with Nitric Acid.—Two attempts to isolate crystalline products after prolonged heating of the dimethyl ether with dilute nitric acid (1:4) were unsuccessful.

In another experiment 0.5 g. of the compound was dissolved in 10 cc. of benzene and 50 cc. of nitric acid (1:4) was added. The mixture was heated until the benzene had distilled off, the solid remaining suspended in the aqueous layer as a reddish, spongy mass. The heating was continued (gentle boiling) until this solid had turned a brick-red color. It was collected and washed free of nitric acid and crystallized three times from slightly diluted acetic acid; orange leaflets, m. p. 213–214° (corr.). Mixed with a sample of the ferric chloride oxidation product (m. p. 212–213°) it melted at 212–214°. Its color reactions with ferric chloride, concentrated sulfuric acid, and alkali were also identical.

Anal. Calcd. for $C_{32}H_{30}O_{10}$: C, 66.90; H, 5.23. Found: C, 66.70; H, 5.22.

Summary

Gossypol hexamethyl ethers are demethylated to gossypol dimethyl ether by the action of a drop of sulfuric acid in glacial acetic acid. Gossypol tetramethyl ether under similar conditions gives gossypol, which leads to the deduction that the two methoxyls in the dimethyl ether correspond to the two hydroxyls in the tetramethyl ether.

This dimethyl ether, in contrast to the tetra- and hexamethyl ethers, reacts with aniline or

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[4] This product was reported in a previous paper to melt at 235°.

with alkali, and in general shows many of the reactions of gossypol. It may be remethylated to gossypol hexamethyl ether.

The color reactions and oxidation products of the dimethyl ether are described.

URBANA, ILLINOIS RECEIVED JUNE 27, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Structure of Gossypol. VIII.[1] Derivatives of the Ethers of Gossypol

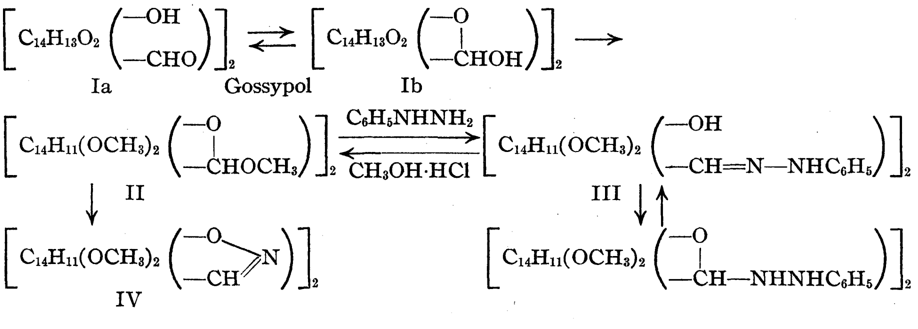
BY ROGER ADAMS AND T. A. GEISSMAN

The non-reactivity of gossypol tetra- and hexamethyl ethers with many carbonyl reagents leaves doubt concerning the presence of aldehyde groups in these molecules in spite of the fact that experiments indicate that six hydroxyls and two aldehyde groups are present in gossypol. This paper presents evidence which points to the belief that in the tetra- and hexaalkyl ethers of gossypol the systems involving the two aldehyde groups and two of the six hydroxyls may be stabilized in the lactol form by alkylation with the formation of two acetal (or lactol ether) linkages (formulas Ia, Ib, II).

Although gossypol (Ia and Ib) and its dimethyl ether form derivatives with aniline and with substituted anilines,[1,2] neither the hexamethyl ethers nor the tetramethyl ether of gossypol have been found previously to form any derivatives which showed unequivocally the presence in the molecule of a carbonyl group. In fact, all attempts to form such a derivative in alkaline or neutral solution have yielded negative results.[3] The white hexamethyl ether (either form) shows a remarkable stability in neutral or alkaline solution, being unattacked by permanganate in acetone or pyridine solution. In the latter case fairly vigorous treatment results in the complete degradation of a small percentage of the starting material with the recovery of the remainder unchanged.

Gossypol hexamethyl ether does not react with malonic acid in alcohol in the presence of piperidine or in pyridine solution.[4] With methylmagnesium iodide in benzene–ether solution some reaction seemed to occur, but a large proportion of starting material was recovered along with a small amount of an uncrystallizable oily product.

In acetic acid solution, however, the hexamethyl ether (II) behaves quite differently. It is attacked instantly by potassium permanganate (no crystalline products isolated), and it forms readily a crystalline condensation product with two molecules of phenylhydrazine (III) or with two molecules of hydroxylamine (IV). These latter condensation products appear to be formed by loss of two methylene groups due to hydrolysis of two methoxyls to hydroxyls followed by the loss of water between the resulting aldehyde groups and the reagents. The dihydroxylamine derivative was found by analysis to have lost an additional two molecules of water, probably through the formation of two orthoxazine rings. The unusual ease with which the methyl groups of two of the methoxyls in gossypol tetramethyl and hexamethyl ethers are eliminated in mildly acid solution leads to the deduction that acetal methoxyls are probably present. The chemical changes just described may be formulated structurally:



The phenylhydrazone can be reconverted to the hexamethyl ether by treatment with methanolic hydrogen chloride, and converted by treatment with ethanolic hydrogen chloride to a diethyl tetramethyl ether which presumably has

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(1) For previous paper see Adams and Geissman, THIS JOURNAL, **60**, 2163 (1938).

(2) Adams, Price and Dial, *ibid.*, **60**, 2158 (1938).

(3) Morris and Adams, *ibid.*, **59**, 1731 (1937).

(4) Kuhn, *Ber.*, **63**, 2164 (1930).

two ethoxy groups of the acetal type. Attempts to convert it to a tetramethyl ether by hydrolysis in aqueous or non-alcoholic media were unsuccessful; treatment of the compound with dry hydrogen chloride in acetic acid led to a compound containing chlorine whose constitution has not yet been investigated.

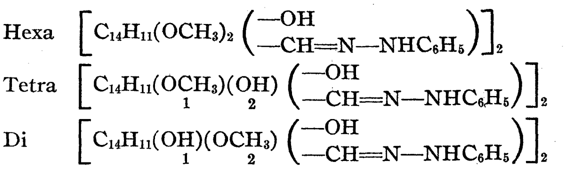
The tetramethyl ether of gossypol reacts with phenylhydrazine under conditions similar to those used for the hexamethyl ether and forms an analogous product, the diphenylhydrazone of a gossypol dimethyl ether. It can be reconverted into the gossypol tetramethyl ether or converted into a gossypol diethyldimethyl ether. The gossypol tetramethyl ether also reacts with two molecules of hydroxylamine. Two methoxyl groups are hydrolyzed and two molecules of water are lost followed by the elimination of two more molecules of water just as occurred in the gossypol hexamethyl ether derivative.

The facts presented in this paper favor the structures written for these compounds; the acetal structure for gossypol hexa- and tetramethyl ethers adequately explains the stability of these compounds toward alkaline reagents, their ready reaction in acid solution *with the hydrolysis of methyl groups from two of the ether linkages*, and the hydrolysis of the hexamethyl ether to the dimethyl ether by sulfuric acid in acetic acid solution.

The dimethyl ether of gossypol also forms a diphenylhydrazone and a dioxime, but as is to be expected no methyl groups are lost in the process. The dioxime, moreover, does not lose water. That acetic acid is not necessary in these condensations is indicated by the ready condensation of the dimethyl ether with aniline in benzene or chloroform solution.

It is significant that the diphenylhydrazone of the dimethyl ether of gossypol is isomeric with the diphenylhydrazone obtained from the tetramethyl ether. As was previously mentioned, two methyl groups are lost in the synthesis of the latter compound. That the two substances are not identical is to be expected from the fact that the two methoxyl groups in gossypol dimethyl ether are the ethers of the two free hydroxyl groups in gossypol tetramethyl ether, as was shown in a previous communication.[1]

The relationship between the phenylhydrazine derivatives of gossypol di-, tetra- and hexamethyl ethers may be formulated as follows

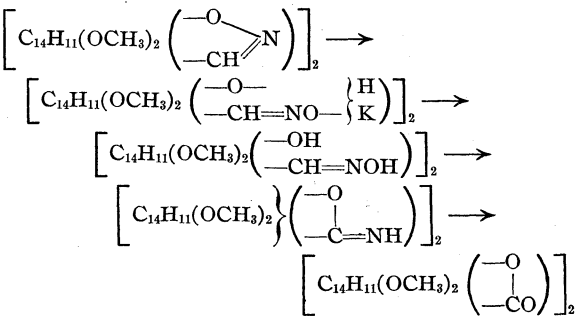


$$\text{Hexa}\quad\left[C_{14}H_{11}(OCH_3)_2\begin{pmatrix}-OH\\-CH{=}N-NHC_6H_5\end{pmatrix}\right]_2$$

$$\text{Tetra}\quad\left[C_{14}H_{11}(\underset{1}{OCH_3})(\underset{2}{OH})\begin{pmatrix}-OH\\-CH{=}N-NHC_6H_5\end{pmatrix}\right]_2$$

$$\text{Di}\quad\left[C_{14}H_{11}(\underset{1}{OH})(\underset{2}{OCH_3})\begin{pmatrix}-OH\\-CH{=}N-NHC_6H_5\end{pmatrix}\right]_2$$

The dehydro dioxime or orthoxazine derived from the hexamethyl ether and hydroxylamine forms a crystalline potassium salt when treated with alcoholic potassium hydroxide. This salt on treatment with acetic acid undergoes a change resulting in the formation of a compound which no longer contains nitrogen, formulated as a lactone



$$\left[C_{14}H_{11}(OCH_3)_2\begin{pmatrix}-O-\\-CH{=}\end{pmatrix}N\right]_2\longrightarrow\left[C_{14}H_{11}(OCH_3)_2\begin{pmatrix}-O-&\\-CH{=}NO-&\left\{\begin{matrix}H\\K\end{matrix}\right.\end{pmatrix}\right]_2\longrightarrow\left[C_{14}H_{11}(OCH_3)_2\begin{pmatrix}-OH\\-CH{=}NOH\end{pmatrix}\right]_2\longrightarrow\left[C_{14}H_{11}(OCH_3)_2\left\}\begin{pmatrix}-O\\ |\\-C{=}NH\end{pmatrix}\right.\right]_2\longrightarrow\left[C_{14}H_{11}(OCH_3)_2\begin{pmatrix}-O\\ |\\-CO\end{pmatrix}\right]_2$$

The reactions of this compound, which corresponds to the dilactone of a gossypol tetramethyl ether in which the two aldehyde groups are converted into carboxyls and then dehydrated with two hydroxyl groups to lactone residues, will be the subject of a later paper. It is proposed to call the molecule theoretically obtained by oxidizing the two aldehyde groups in gossypol to carboxyls, gossylic acid. This new compound would then be a gossylic acid lactone tetramethyl ether.

The fact that in this molecule there are only eight oxygens, the same number as in gossypol, lends additional weight to the conclusion that the oxygens in gossypol are present in the form of six hydroxyls and two aldehyde groups.

Speculation concerning the structure of the $(C_{14}H_{11})_2$ residue in gossypol may be made. On the basis of the available knowledge, the presence of two naphthyl or analogous residues directly or indirectly linked is indicated. This assumption is founded partly on the work of Schmid[5] and partly on absorption spectra data and on chemical data not yet published which have been accumulated in this Laboratory. Assuming the molecule to be symmetrical and that six hydroxyls and two aldehyde groups may replace eight hy-

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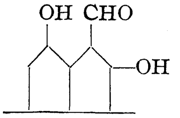
(5) Schmid and Margulies, *Monatsh.*, **65**, 391 (1934).

drogens in the naphthalene nuclei, the residue becomes $(C_4H_9)C_{10}H_2–C_{10}H_2(C_4H_9)$ or an isomer of it, in which each of the C_4H_9 radicals represents more than one group. The two naphthyl groups, however, may be attached through an alkylene residue, thus $C_{10}H_3–(C_8H_{16})–C_{10}H_3$. Still another possible combination is that in which one or more alkyl groups are present in each of the naphthalene nuclei and the two naphthalene residues are connected by one or more methylene groups.

One type of hydroxyaldehyde which may explain many of the reactions of gossypol and its ethers is represented by the partial nucleus.



. A study of a naphthalene derivative with substituents of this type is now being made. An attempt to give a complete formula for gossypol is not yet justified as certain conflicting experimental facts must first be clarified.

Experimental

Condensation of Phenylhydrazine and Gossypol Hexamethyl Ether (a).—To a solution of 0.27 g. of pure gossypol hexamethyl ether (m. p. 239–241°) in 20 cc. of glacial acetic acid was added 1.5 cc. of phenylhydrazine. After heating for several minutes on the steam-bath bright yellow needles began to separate. After thirty minutes the solution was filtered hot and the product washed with acetic acid. It formed bright yellow needles, m. p. 266–267° (corr.) with decomposition, and weighed 0.25 g. No satisfactory method was found for recrystallization of this product.

(b). A solution of 0.25 g. of gossypol hexamethyl ether (m. p. 223–225°) was treated as in (a). The product weighed 0.28 g. In larger runs the yield was nearly quantitative.

Anal. Calcd. for $C_{46}H_{50}O_6N_4$: C, 73.22; H, 6.63; N, 7.43. Found: C, 72.78, 73.09; H, 6.59, 6.58; N, 7.40.

The compound is insoluble in alkali (aqueous or alcoholic) and gives no ferric chloride color. It gives an orange color with concentrated sulfuric acid.

To a suspension of 0.5 g. of the phenylhydrazone in 10 cc. of glacial acetic acid was added 5 drops of concentrated hydrochloric acid. The yellow-brown solution which rapidly formed, began to deposit clusters of yellow needles after standing for an hour at room temperature. The product was collected and washed with acetic acid and water. It could not be recrystallized successfully. It was insoluble in alkali and in ether, acetone and benzene. It was soluble in methanol and slightly so in acetic acid. It contained halogen (Beilstein test) and nitrogen. The compound melted at 257–262° (corr.) with decomposition.

When the solution of this material in methanol was saturated with dry hydrogen chloride a thick mass of short white needles separated. This compound is nicely crystalline, contains halogen and nitrogen, gives a yellow color with concentrated sulfuric acid, dissolves in warm alcoholic alkali to a bluish-red solution, and melts at 274–276° (corr.) with decomposition. It turns brown on standing in air and no method has yet been found for its purification.

Conversion of the Phenylhydrazine Derivatives of Gossypol Hexamethyl Ether to Gossypol Hexaalkyl Ethers

(a) With CH_3OH–HCl: Formation of Gossypol Hexamethyl Ether.—A suspension of 0.5 g. of the phenylhydrazone in 20 cc. of absolute methanol was treated with dry hydrogen chloride until the compound had gone into solution. The solution was allowed to stand overnight at room temperature. A crystalline product separated in clusters of stout prisms. It weighed 0.32 g. After recrystallization from ligroin, then from methanol it formed tiny white prisms, m. p. 219–221° (corr.), and mixed with gossypol hexamethyl ether (m. p. 221–223°), it melted at 221–223°.

(b) C_2H_5OH–HCl: Formation of Gossypol Tetramethyl Diethyl Ether.—A solution of 0.5 g. of the phenylhydrazone in 20 cc. of absolute ethanolic hydrogen chloride (prepared as in the case of the methanol) was allowed to stand at room temperature. Within two hours white needles began to separate from the solution. The crude product weighed 0.35 g. Recrystallized from ethanol–acetone, it formed white prisms, m. p. 229–230° (corr.).

Anal. Calcd. for $C_{30}H_{24}O_2(OCH_3)_4(OC_2H_5)_2$: C, 72.38; H, 7.30. Found: C, 72.19; H, 7.49.

A mixture of this compound (m. p. 229–230°) with the hexamethyl ether (m. p. 221–223°) melted at 203–208°. The compound gave the usual (for hexaalkylated gossypol) orange color with sulfuric acid.

Condensation of Hydroxylamine with Gossypol Hexamethyl Ether.—To 2.0 g. of gossypol hexamethyl ether dissolved in 30 cc. of hot acetic acid was added a solution of 1.0 g. of hydroxylamine hydrochloride in a very small quantity of water. The solution was heated on the steam-bath (five to ten minutes) until scratching of the walls of the flask caused crystallization to start. After allowing the mixture to stand until cool (overnight is preferable) the product was collected and washed with acetic acid and water. It formed greenish-yellow leaflets weighing 1.5 g.

Recrystallized from dilute acetic acid it forms flat buff needles and from benzene–petroleum ether it forms tiny buff platelets. Both forms when heated rapidly melt with decomposition at 192–204° but when heated slowly merely sinter at this temperature and do not melt below 280°.

Anal. Calcd. for (dioxime) $C_{34}H_{40}O_8N_2$: C, 67.5; H, 6.63; N, 4.64. Calcd. for (dioxime less $2H_2O$) $C_{34}H_{36}O_6N_2$: C, 71.82; H, 6.34; N, 4.92. Found (acetic acid): C, 71.83; H, 6.44. Found (benzene–petroleum ether): C, 72.05; H, 6.51; N, 4.83.

The oxime gives an orange color with concentrated sulfuric acid and no ferric chloride color. It is soluble in hot 10% methanolic potassium hydroxide, and the potassium salt crystallizes from the hot solution in clusters of bright yellow needles.

Degradation of the Hydroxylamine Derivative of Gossypol Hexamethyl Ether to a Lactone.—A suspension of 4.69

g. of the crude hydroxylamine derivative of gossypol hexamethyl ether in 60 cc. of 10% methanolic potassium hydroxide was heated to boiling with stirring. The compound gradually went into solution, then the potassium salt rapidly crystallized as a thick sludge of yellow needles. After being heated for a short time just below the boiling point to complete the reaction the mixture was allowed to cool and the product collected and washed with a small amount of alcoholic potassium hydroxide and with ether. The salt weighed 5.15 g. Purified hydroxylamine derivative gives a better yield but no over-all advantage is gained by such a procedure.

Analysis of the crude product for potassium indicated that it is a dipotassium salt.

Anal. Calcd. for $(C_{17}H_{19}O_4NK)_2$: K, 11.5. Calcd. for $(C_{17}H_{18}O_4NK_2)_2$: K, 20.6. Found: K, 10.8, 10.2.

A solution of 5.15 g. of crude potassium salt in 50 cc. of boiling glacial acetic acid was diluted carefully with water until crystallization started. It was then diluted with several times its volume of water and allowed to cool. The crude, crystalline product was collected and dried. It was found most convenient to recrystallize it from glacial acetic acid in the following way. The crude product was dissolved in 46 cc. (0.5 mole) of boiling acetic anhydride and the acetic anhydride carefully decomposed by the addition of 9 cc. of water dissolved in 10 cc. of acetic acid. As soon as the acetic anhydride had been hydrolyzed the product crystallized in shining leaflets. It weighed 4.05 g. and after recrystallization from acetic acid (in which it is difficultly soluble) or acetic anhydride it melted at 327–328° (corr.).

Anal. Calcd. for $C_{17}H_{17}O_4$: C, 71.58; H, 5.96; 2-OCH_3, 21.75. Found: C, 71.17; H, 6.11; OCH_3, 21.40.

The lactone is difficultly soluble in cold alcoholic alkali but dissolves readily on warming. It gives a yellow color with concentrated sulfuric acid and no ferric chloride color.

Condensation of Phenylhydrazine with Gossypol Tetramethyl Ether.—To a solution of 0.5 g. of gossypol tetramethyl ether in 20 cc. of hot glacial acetic acid was added 1 cc. of phenylhydrazine. On standing overnight the solution deposited 0.61 g. of a bright yellow crystalline product. Recrystallized from acetic acid it forms canary-yellow platelets, from benzene a bright yellow crystalline powder, and from benzene–petroleum ether bright yellow rosets of scale-like crystals which effloresce on drying at 100° to a yellow powder, m. p. 246–248° (corr.) with decomposition.

Anal. Calcd. for $C_{44}H_{46}O_6N_4$: C, 72.73; H, 6.34. Found (acetic acid): C, 73.07; H, 6.29. Found (benzene): C, 72.76; H, 6.52. Found (benzene–petroleum ether): C, 72.32; H, 6.53.

The compound gives a scarlet color with concentrated sulfuric acid, no ferric chloride color, and is soluble in alcoholic alkali with a reddish-yellow color.

Conversion of the Phenylhydrazine of Gossypol Tetramethyl Ether to Tetraalkyl Ethers

(a) **Gossypol Tetramethyl Ether.**—A solution of 0.5 g. of the phenylhydrazone from gossypol tetramethyl ether in 20 cc. of absolute methanolic hydrogen chloride was allowed to stand at room temperature overnight. A crystalline deposit weighing 0.30 g. was obtained and purified by recrystallization from acetone, m. p. 186–189° (corr.). It gave no depression in melting point when mixed with an authentic sample of gossypol tetramethyl ether.

(b) **Gossypol Dimethyl Diethyl Ether.**—A solution of 0.5 g. of the phenylhydrazone from gossypol tetramethyl ether in 15 cc. of absolute ethanolic hydrogen chloride began to deposit white needles after several hours at room temperature. The product was collected after diluting the solution and weighed 0.32 g. Recrystallized from dilute acetone it formed slender white needles, m. p. 160–162° (corr.).

Anal. Calcd. for $C_{30}H_{26}O_4(OCH_3)_2(OC_2H_5)_2$: C, 71.76; H, 6.98. Found: C, 71.49; H, 6.89.

The compound gives a scarlet color with concentrated sulfuric acid.

Condensation of Hydroxylamine with Gossypol Tetramethyl Ether.—To a solution of 0.5 g. of gossypol tetramethyl ether in 5 cc. of glacial acetic acid was added a solution of 0.25 g. of hydroxylamine hydrochloride in 0.5 cc. of water. After heating on the steam-cone for fifteen minutes, the solution was filtered and cooled. On scratching the walls of the flask the product separated as a yellow powder weighing 0.33 g. It can be recrystallized from benzene or benzene–petroleum ether from which it is obtained as fine canary-yellow platelets or prisms which melted poorly from 140–190° (with decomposition). Analysis indicated that it contained combined solvent. Recrystallized from ligroin (b. p. 90–110°) it formed short yellow needles which melted at 281–283° (corr.) with decomposition.

Anal. Calcd. for (dioxime less $2H_2O$) $C_{32}H_{32}O_6N_2$: C, 71.11; H, 5.92; N, 5.18. Calcd. for $C_{32}H_{32}O_6N_2 \cdot {}^1/_2C_6H_6$: C, 73.78; H, 6.15; N, 4.63. Found (ligroin): C, 70.93; H, 5.97. Found (benzene–petroleum ether): C, 73.56; H, 6.28; N, 4.79.

The compound dissolves in concentrated sulfuric acid to give an orange solution which turns deep wine-red on standing. It gives no color with ferric chloride. It dissolves readily in cold, dilute alcoholic potassium hydroxide to give a yellow solution which quickly turns wine-red. This red color is discharged by sodium hydrosulfite, giving the original yellow color.

Condensation of Phenylhydrazine with Gossypol Dimethyl Ether.—To a solution of 1.9 g. of the dimethyl ether in 20 cc. of glacial acetic acid was added 3 cc. of phenylhydrazine, and the mixture was warmed for fifteen minutes on the steam-bath. The solution was diluted carefully with water, with scratching, until crystallization began. The crude product weighed 2.0 g. Recrystallized from benzene, the compound formed rosets of yellow needles, m. p. 248–249° (corr.) with decomposition. From dilute acetic acid it forms yellow platelets, m. p. 246–248° (corr.) with decomposition. The melting point varies with the heating rate.

Anal. Calcd. for $C_{44}H_{46}O_6N_4$: C, 72.73; H, 6.34; N, 7.72. Found (benzene): C, 72.89; H, 6.58; N, 7.17.

The compound depressed the melting point of the isomeric phenylhydrazone from gossypol tetramethyl ether (mixed m. p. 232–234° corr.) with decomposition. It gives an orange-yellow color with concentrated sulfuric acid, and with ferric chloride a cherry-red which changes immediately to orange. It is soluble in cold alcoholic alkali.

Attempts to hydrolyze the compound by the procedure described for the phenylhydrazones did not yield a tetramethyl ether.

Condensation of Hydroxylamine with Gossypol Dimethyl Ether.—The product was prepared by treatment of an acetic acid solution of gossypol dimethyl ether with a neutralized solution of hydroxylamine hydrochloride in water, heating for thirty minutes on the steam-bath and diluting and scratching the hot solution. The hydroxylamine derivative was recrystallized from dilute acetic acid, from which it formed buff platelets, m. p. 229–232° (corr.) with decomposition.

Anal. Calcd. for $C_{32}H_{36}O_8N_2$: C, 66.66; H, 6.25; N, 4.85. Found: C, 66.33; H, 6.45; N, 4.38.

In contrast to the hydroxylamine derivative prepared from the hexamethyl ether, this substance has not lost the elements of water to form an orthoxazine.

The compound gives a yellow-orange solution in concentrated sulfuric acid, a green color with ferric chloride, and its yellow solution in aqueous alkali turns red on standing in the air.

Zeisel Determinations

The Zeisel numbers on gossypol and many of its derivatives appear to have very little significance, for the values found are usually too high. They are given in the table.

ZEISEL DETERMINATIONS ON GOSSYPOL ETHER DERIVATIVES

		Found	Calcd.
1	Phenylhydrazone from hexamethyl ether	17.8	16.4 (4-OCH_3)
2	Phenylhydrazone from tetramethyl ether	11.8 12.3	8.5 (2-OCH_3)
3	Phenylhydrazone from dimethyl ether	13.0 11.3	8.5 (2-OCH_3)

Although the found and calculated values are discordant, it is noteworthy that essentially the same values were obtained for the phenylhydrazones of the tetra- and dimethyl ethers and the compounds therefore are isomeric. This coincides with the other analytical data.

Summary

Gossypol hexamethyl ether and tetramethyl ether react with phenylhydrazine in acetic acid solution to give derivatives in which two molecules of water and methyl groups have been eliminated. Treatment of the products with ethanolic or methanolic hydrogen chloride results in the reconversion to hexa- or tetraalkyl ethers of gossypol.

The hexa and tetra ethers also react with hydroxylamine with elimination of four molecules of water and hydrolysis of two methoxyl groups. Apparently the two oxime groups initially formed lose water with formation of orthoxazine rings.

The phenylhydrazine derivatives of gossypol tetramethyl ether and of gossypol dimethyl ether are isomeric, as would be anticipated from the fact that the two methoxyls in gossypol dimethyl ether correspond to the two hydroxyls in gossypol tetramethyl ether.

The hydroxylamine derivative of gossypol hexamethyl ether by treatment with alkali, then with a mixture of acetic acid and acetic anhydride, gives a compound which appears to be a lactone and corresponds to a gossypol derivative in which the aldehyde groups have been converted to carboxylic acid groups.

URBANA, ILLINOIS RECEIVED JUNE 27, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Structure of Gossypol. IX.[1] Oxidation and Degradation of Gossypol Hexamethyl Ether; Gossic Acid

BY ROGER ADAMS, R. C. MORRIS AND E. C. KIRKPATRICK[2]

The experimental evidence previously published on the structure of gossypol has given much information concerning the functional groupings present in the molecule and some knowledge concerning the relative arrangement of these groups. On the other hand, it has not been demonstrated that the molecule contains two naphthyl residues or a binaphthyl residue as has been tentatively assumed.

It is only by obtaining degradation products and by identifying them that it may be hoped to clarify the complete structure of gossypol. The search for a convenient degradation reaction has, up to this time, been fruitless. Now, however, a most promising reaction has been discovered by which a smaller molecule can be isolated in a pure state and in reasonable yields.

The white gossypol hexamethyl ether (I) or gos-

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[1] For previous paper in this field see Adams and Geissman, THIS JOURNAL, **60**, 2166 (1938).

[2] Abstract of a portion of a thesis submitted in partial fulfilment for the degree of Doctor of Philosophy by E. C. Kirkpatrick, Solvay Fellow 1936–1938.

sypol tetramethyl diethyl ether[1] can be oxidized with chromic acid, periodic acid or dilute nitric acid. By very short treatment with chromic acid, oxidation occurs to give chiefly a yellow crystalline compound (II) which for convenience may be looked upon as being formed by the hydrolysis of two methoxyl groups followed by replacement of four hydrogen atoms by two oxygens. This product will be called gossypolone tetramethyl ether since it is analogous to the compound described by Clark,[3] designated by him as tetraacetylgossypolone and obtained by the oxidation of gossypol hexaacetate; thus $C_{30}H_{24}O_2(OCOCH_3)_6$ to $C_{30}H_{22}O_6(OCOCH_3)_4$.

Along with the gossypolone tetramethyl ether was invariably found a very small amount of a second oxidation product $C_{30}H_{22}O_4(OCH_3)_4$, III, which proved to be a lactone and identical with the gossylic acid lactone tetramethyl ether described in a previous paper.[1]

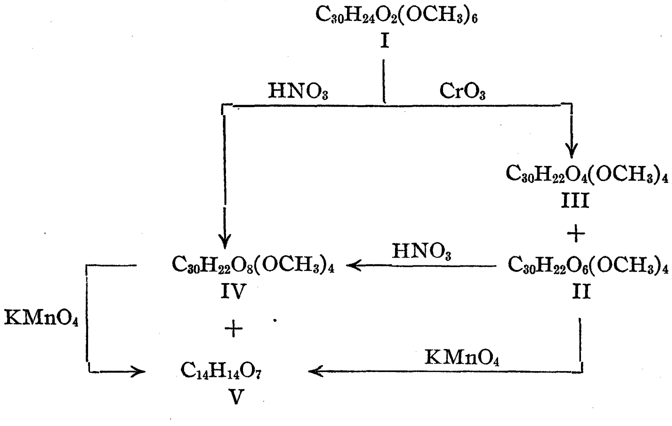
Gossypolone tetramethyl ether probably contains aldehydic carbonyls as shown by the condensation with two molecules of aniline. Preliminary tests indicate that it may also contain quinone groupings. It does not contain carboxyl groups, for the product could not be titrated electrometrically. If gossypol hexamethyl ether is accepted as containing two aldehyde and six methoxyl groups, there may have occurred in this oxidation the hydrolysis of two methoxyls to hydroxyls and the conversion of two phenolic residues to quinones. The product may well be a gossypoloquinone tetramethyl ether.

Gossypolone tetramethyl ether also could be obtained from gossypol hexamethyl ether by the action of periodic acid but this reaction was not nearly as satisfactory as the oxidation with chromic acid.

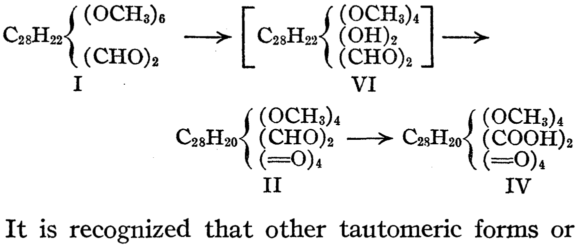
The oxidation of gossypol hexamethyl ether with dilute nitric acid is more deep-seated than with chromic or periodic acid. By this procedure, two products which account for essentially all of the starting material are formed, a yellow crystalline water-insoluble compound (IV), and a white crystalline water-soluble product (V). Approximately equal amounts of each are obtained.

The water-insoluble substance (IV) has a molecular weight comparable with that of the starting material and has two more oxygens than gossypolone tetramethyl ether (II). It is an acid and a tetramethyl ether and some indications are that it is a quinone. It will be called gossypolonic acid tetramethyl ether. Although stable to dilute nitric acid, it is readily oxidized with permanganate to give the same water-soluble compound (V), $C_{14}H_{14}O_7$, which results by the direct dilute nitric acid oxidation of gossypol hexamethyl ether. It is thus obvious that a close relationship in structure between these compounds exists. The oxidation of gossypol hexamethyl ether apparently takes place in two directions, one without degradation and the other with a cleavage to approximately a half molecule.

Moreover, these substances and gossypolone tetramethyl ether (II) are related as shown by the fact that the latter upon treatment with dilute nitric acid readily oxidizes to the water-insoluble product, gossypolonic acid tetramethyl ether (IV), obtained by direct nitric acid oxidation of gossypol hexamethyl ether. By treatment with permanganate gossypolone tetramethyl ether gives the water-soluble product (V) obtained either by the nitric acid oxidation of gossypol hexamethyl ether or by the permanganate oxidation of gossypolonic acid tetramethyl ether. These conversions are shown in the chart



A possible breakdown of these molecules with a postulated intermediate VI may be suggested



$$\underset{\text{I}}{C_{28}H_{22}\begin{cases}(OCH_3)_6\\(CHO)_2\end{cases}} \longrightarrow \underset{\text{VI}}{\left[C_{28}H_{22}\begin{cases}(OCH_3)_4\\(OH)_2\\(CHO)_2\end{cases}\right]} \longrightarrow$$

$$\underset{\text{II}}{C_{28}H_{20}\begin{cases}(OCH_3)_4\\(CHO)_2\\(=O)_4\end{cases}} \longrightarrow \underset{\text{IV}}{C_{28}H_{20}\begin{cases}(OCH_3)_4\\(COOH)_2\\(=O)_4\end{cases}}$$

It is recognized that other tautomeric forms or perhaps closely related isomeric forms of these structures may be the more nearly correct con-

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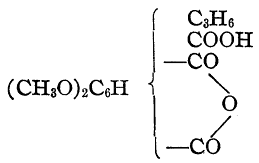
(3) Clark, THIS JOURNAL, **51**, 1475 (1929).

figurations but this will have to be determined after further experimentation.

The water-soluble product, because of its ease of preparation and of its molecular size of about 300, is a most promising derivative for immediate study to obtain a further insight into the gossypol structure. It will be called *gossic acid.* This product is a dimethyl ether and is acid in character as shown by its decomposition of aqueous sodium carbonate. It forms a monomethyl ester with diazomethane but titrates in aqueous solution approximately for a tribasic acid. Consequently a dibasic acid anhydride linkage in addition to a carboxyl group may be present. In all respects the compound acts like a substituted benzene. It gives none of the unusual color reactions of the higher molecular weight gossypol derivatives and has entirely normal solubility and crystallizing characteristics. From these meager results a partial breakdown of the gossic acid molecule may be postulated as follows



but the exact constitution must await further investigation.

It is significant that, under similar conditions, gossypol tetramethyl ether is oxidized by dilute nitric acid only to water-soluble acids which have not been obtained in a crystalline state. Neither could crystalline derivatives be obtained by the oxidation with chromic or periodic acid.

Experimental

Chromic Acid Oxidation of Gossypol Hexamethyl Ether or Gossypol Tetramethyl Diethyl Ether: Gossypolone Tetramethyl Ether (II).—To a solution of 2 g. of white gossypol hexamethyl ether in 50 cc. of boiling glacial acetic acid, was added rapidly with vigorous stirring 10 cc. of a 10% aqueous solution of chromic oxide and the mixture was allowed to boil for one minute. It was then poured onto a mixture of 100 g. of ice and 75 cc. of water. The product was filtered with suction and the yellow residue was washed with water until the washings were neutral. The air-dried residue was added to 40 cc. of boiling methanol. The material at first became gummy and then went gradually into solution, but, before solution was complete, a yellow material began to crystallize. By keeping warm on a steam-bath and breaking up the lumps with a stirring rod, all non-crystalline material went into solution. After standing for two hours at room temperature, the yellow crystalline product was filtered; yield 1.5 g. To purify, it was heated with 120 cc. of boiling methanol and filtered hot. The insoluble residue is described below. After cooling and allowing the filtrate to stand for two hours in an ice box, the yellow crystalline plates of gossypolone tetramethyl ether were filtered and washed with 20 cc. of petroleum ether (b. p. 30–60°). After two more crystallizations, the melting point was constant at 156–157°.

Anal. Calcd. for $C_{30}H_{22}O_6(OCH_3)_4$: C, 67.77; H, 5.64; $4CH_3O$, 20.59; mol. wt., 602. Found: C, 67.69, 67.42; H, 5.83, 6.06; CH_3O, 21.0, 20.8; mol. wt. (b. p. acetone), 664, 616.

Exactly the same substance was formed by a similar oxidation of gossypol tetramethyl diethyl ether.

The product gave a dark brown color in concentrated sulfuric acid which changed to a light orange on standing for a half hour. It gave no color with ferric chloride and a deep red with pyroboroacetate.

It was insoluble in 10% aqueous sodium hydroxide but was soluble in a 10% methanolic potassium hydroxide solution with decomposition.

This same product may also be made, though less conveniently, by the oxidation of gossypol hexamethyl ether with periodic acid.

By-Product from Oxidation with Chromic Acid: Gossylic Acid Lactone Tetramethyl Ether (III).—The material insoluble in the 120 cc. of boiling methanol was dissolved in 4 cc. of boiling acetone and the solution filtered. Upon standing, a yellow product separated. By crystallization from 4 cc. of acetone it formed yellow needles. A second crystallization this time from 15 cc. of boiling glacial acetic acid gave light yellow needles, m. p. 315–317°.

Anal. Calcd. for $C_{30}H_{22}O_4(OCH_3)_4$: C, 71.58; H, 5.96; CH_3O, 21.75. Found: C, 70.82; H, 5.84; CH_3O, 21.2.

It proved to be identical by mixed melting point determination with the lactone obtained by treating gossypol hexamethyl ether with hydroxylamine followed by alkali and acetic anhydride.

Oxidation of Gossypol Hexamethyl Ether with Dilute Nitric Acid

Water-Insoluble Oxidation Product: Gossypolonic Acid Tetramethyl Ether (IV).—A suspension of 0.40 g. of white gossypol hexamethyl ether in a mixture of 10 cc. of concentrated nitric acid (sp. gr. 1.42) and 40 cc. of water was refluxed for twelve hours. At the start of the reaction the material was a flocculent suspension, in about two hours it became a reddish-brown gummy mass which floated on the acid. Toward the end of the reaction, the mass had become hard. After cooling, the solid was filtered and the filtrate set aside for isolation of the water-soluble product.

The solid was dissolved in ether and the solution shaken repeatedly with sodium bicarbonate solution until all the alkali-soluble material was extracted. The bicarbonate extract was acidified, the yellow precipitate filtered, washed and dried. On crystallization from benzene, it formed small yellow plates, m. p. 249–251° with decomposition, yield 0.14 g. The product is essentially insoluble in methanol.

Anal. Calcd. for $C_{34}H_{34}O_{12}$: C, 64.4; H, 5.36; $(4OCH_3)$, 21.2; mol. wt., 634. Found: C, 64.33; H, 5.32; OCH_3, 20.9; mol. wt. (acetone), 644.

In concentrated sulfuric acid, the compound gave a deep red color, which rapidly faded to a yellow-brown. An alcohol solution gave no color with aqueous ferric chloride. It was not decolorized with sulfur dioxide or aqueous sodium hydrosulfite.

Although stable when dissolved in aqueous sodium bicarbonate, it was unstable in aqueous sodium hydroxide with the appearance of a green color and precipitation of a gummy mass.

It was unchanged by further refluxing (fifteen hours) with dilute nitric acid and was only very slowly affected by chromic acid in acetic acid solution.

When dissolved in concentrated sulfuric acid and the solution allowed to stand for one-half hour and then diluted with water, there was obtained only a brown amorphous powder which could not be made to crystallize.

Demethylation with constant boiling hydrobromic acid yielded no definite product.

The product can be nitrated with cold 100% nitric acid to give a crystalline nitro derivative which obviously has been oxidized also. Its chemical reactions will be reported later.

Water-Soluble Oxidation Product: Gossic Acid.—The dilute nitric acid filtrate from the oxidation reaction was neutralized with sodium carbonate, then acidified to Congo red with sulfuric acid, saturated with sodium chloride and extracted several times with ether. The crude brown product was crystallized twice from toluene from which it separates slowly in the form of long colorless needles, m. p. 184–186°. It may also be crystallized from petroleum ether (b. p. 60–110°), yield 0.16 g. A preferable method of purification for analysis is one crystallization from toluene, followed by sublimation at 15 mm. and then a second crystallization from toluene or petroleum ether (b. p. 60–110°).

Anal. Calcd. for $C_{14}H_{14}O_7$: C, 57.2; H, 4.76; $2OCH_3$, 21.0; neut. equiv., 98; mol. wt., 294. Found: C, 57.18; H, 4.95; OCH_3, 21.0, 20.6; neut. equiv., 104; mol. wt. (camphor), 316.

When larger amounts of gossypol hexamethyl ether were oxidized it was found an advantage to heat the sodium carbonate solution with potassium permanganate until the purple color had become permanent. The precipitate of manganese dioxide was destroyed with sulfur dioxide, the solution acidified with sulfuric acid and saturated with sodium chloride. Extraction in the way previously described gave a product very easily purified. The yields were equivalent to those obtained without the use of potassium permanganate.

The compound gave no color when dissolved in concentrated sulfuric acid. Such a solution after standing one-half hour gave unchanged product on dilution with water. It gave no color with aqueous ferric chloride solution.

Attempts to nitrate the compound with cold 100% nitric acid were unsuccessful and the product was recovered unchanged. The compound was very stable to chromic acid in acetic acid.

An aqueous solution was not oxidized by periodic acid. Refluxing for eight hours in nitric acid (1:1) did not affect the compound.

Permanganate Oxidation of Gossypolonic Acid Tetramethyl Ether: Gossic Acid.—To a suspension of 0.35 g. of gossypolonic acid tetramethyl ether in 200 cc. of water was added, in portions, 1.5 g. of solid potassium permanganate. The reaction mixture was heated on the steam-bath for five hours, at the end of which time there was still excess permanganate present. The flask was cooled, acidified with dilute sulfuric acid and sulfur dioxide was passed through until the excess permanganate and precipitate of manganese dioxide was destroyed. The solution was filtered, saturated with sodium chloride and extracted with ether. The ether extract was evaporated and the gummy residue crystallized from toluene. It formed long, colorless needles that became opaque on drying, m. p. 184–186°, yield 0.15 g. It proved to be gossic acid.

Oxidation of Gossypol Tetramethyl Ether.—Dilute nitric acid oxidation of gossypol tetramethyl ether, according to the directions used for the hexamethyl ether, gave only a nitric acid soluble product. Upon neutralizing and extracting with ether, an oily product, acidic in nature, was obtained. No crystalline substance was separated.

Methyl Ester of Gossic Acid.—To a solution of 0.10 g. of the acid in 5 cc. of ether was added an ether solution of diazomethane from 0.15 g. of nitrosomethyl urea. The reaction mixture was allowed to stand overnight at room temperature, then evaporated to dryness. The residue was purified by sublimation at 20 mm. and crystallized from petroleum ether (b. p. 30–60°) in long colorless needles, m. p. 106°.

Anal. Calcd. for $C_{15}H_{16}O_7$: C, 58.5; H, 5.19; $3OCH_3$, 30.2; mol. wt., 308. Found: C, 58.86; H, 5.25; OCH_3, 31.2; mol. wt. (Rast), 316.

The ester was saponified back to gossic acid by the following procedure. A suspension of 0.10 g. of the ester was refluxed gently with 5 cc. of 10% aqueous sodium hydroxide. The material was insoluble but gradually went into solution on heating. When solution was complete the reaction mixture was acidified, saturated with sodium chloride and extracted with ether. The ether was evaporated and the residue crystallized from petroleum ether (b. p. 60–110°), m. p. 184–186°.

Nitric Acid Oxidation of Gossypolone Tetramethyl Ether.—A suspension of 0.2 g. of gossypolone tetramethyl ether in 25 cc. of water and 8 cc. of concentrated nitric acid was refluxed for six and one-half hours. The insoluble product was worked up as described in the nitric acid oxidation of gossypol hexamethyl ether; yield 0.15 g. Recrystallized from benzene, it formed yellow needles, m. p. 237–238°. A mixed melting point showed it to be identical with gossypolonic acid tetramethyl ether.

Permanganate Oxidation of Gossypolone Tetramethyl Ether.—To a suspension of 0.1 g. of gossypolone tetramethyl ether in 20 cc. of water was added over a period of thirty minutes, 0.4 g. of potassium permanganate crystals. The mixture was heated under reflux for seven hours. Sulfur dioxide was then bubbled in till the manganese dioxide had dissolved and the solution was colorless. Unchanged gossypolone tetramethyl ether was filtered and 1 cc. of concentrated hydrochloric acid added to the filtrate. The filtrate was then extracted several times with ether, the ether extract dried with sodium sulfate, filtered and evaporated to remove the solvent. The gum obtained was dissolved in 10 cc. of boiling acetone, 10 cc. of petroleum ether (b. p. 60–110°) was added, and the mixture evaporated to 9 cc. The product was obtained as described previously and purified in a similar way: yield 0.045 g. of white needles; m. p. 183–184.5°. This product was gossic acid.

Anal. Calcd. for $C_{14}H_{14}O_7$: C, 57.1; H, 4.76. Found: C, 56.52; H, 4.85.

Concentrated aqueous ammonia converted gossypolone tetramethyl ether dissolved in a mixture of 5 cc. of acetone and 5 cc. of ethanol to a yellow crystalline material which separated from solution. It could not be recrystallized and was insoluble in all common organic solvents. It melted above 300°. It gave a deep yellow solution in concentrated sulfuric acid.

Reaction of Aniline with Gossypolone Tetramethyl Ether.—A solution of 0.5 g. of gossypolone tetramethyl ether in 100 cc. of methanol and 0.2 cc. of aniline was boiled gently on a steam-bath for about an hour. The solution was concentrated to 50 cc. and allowed to stand. The crude product which separated was crystallized from 20 cc. of acetone: yellow plates; m. p. 213–215°.

Anal. Calcd. for $C_{34}H_{32}O_8(NHC_6H_5)_2$: C, 73.37; H, 5.84; N, 3.72; $4CH_3O$, 16.45. Found: C, 73.54; H, 5.86; N, 3.70; CH_3O, 16.8.

The product was stable when dry. A solution, however, when exposed to air discolored.

It gave a light yellow color in concentrated sulfuric acid.

Action of Concentrated Nitric Acid on Gossypol Hexamethyl Ether.—By the action of cold 100% nitric acid, gossypol hexamethyl ether is nitrated and oxidized to a crystalline product, the nature of which will be reported later.

Summary

Gossypol hexamethyl ether has been oxidized by chromic acid, periodic acid and by dilute nitric acid. By the action of chromic acid or periodic acid a yellow crystalline product, gossypolone tetramethyl ether, is obtained which is formed by hydrolysis of two methoxyls followed by replacement of four hydrogens by two oxygens. Dilute nitric acid, however, gives two products, one which is water insoluble of a molecular weight comparable with the starting material, named gossypolonic acid tetramethyl ether and the other water-soluble, called gossic acid, of only about half the size. The former can be oxidized with permanganate to the latter. Gossypolone tetramethyl ether is oxidized with dilute nitric acid to gossypolonic acid tetramethyl ether and with permanganate to gossic acid. A discussion of the relationship of these compounds is given.

Gossic acid, $C_{14}H_{14}O_7$, appears to be a benzene derivative and contains a carboxyl, a dibasic acid anhydride linkage, and two methoxyls.

URBANA, ILLINOIS RECEIVED JUNE 27, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Structure of Gossypol. X.[1] Apogossypol and its Degradation Products

BY ROGER ADAMS AND D. J. BUTTERBAUGH[2]

Clark[3] discovered that by the action of hot concentrated alkali, gossypol, $C_{30}H_{30}O_8$, loses two carbon and two oxygen atoms with the formation of two moles of alkali formate and one mole of a white unstable compound, $C_{28}H_{30}O_6$, which he designated as apogossypol. He demonstrated by methylation and acetylation that this substance contained six hydroxyl groups, for the stable hexaacetyl and hexamethyl derivatives were prepared readily.

Clark did not attempt to speculate as to what occurred in the gossypol molecule by the action of alkali but it is quite obvious from the results published in papers V–IX of this series. The evidence is convincing that gossypol is a hexahydroxy dialdehyde and consequently the ready removal of the aldehyde groups by the action of alkali might be anticipated. Examples of the elimination of aldehyde groups from hydroxy aldehydes in this way are well-known. This is especially true also of easily tautomerized hydroxyaldehydes such as the conversion of hydroxymethylene camphor to camphor by alkali.[4]

It has been shown that two of the six hydroxyls in gossypol are more difficult to methylate than the other four. Moreover, two of the acetyls in gossypol hexaacetate are more difficult to saponify than the other four. Attempts to methylate or acetylate apogossypol to a tetramethyl ether or tetraacetate were unsuccessful but it was found by us that benzoylation yielded merely a tetrabenzoate.

Both apogossypol hexamethyl ether and hexa-

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(1) For previous paper see Adams, Morris and Kirkpatrick, THIS JOURNAL, **60**, 2170 (1938).

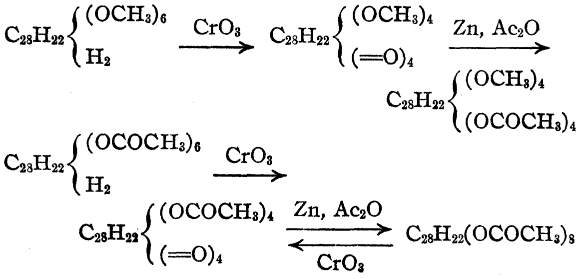
(2) Abstract of a thesis submitted in partial fulfilment for the degree of Doctor of Philosophy in chemistry; Chemical Foundation Fellow, 1936–1938.

(3) Clark, *J. Biol. Chem.*, **78**, 159 (1928).

(4) Bishop, Claisen and Sinclair, *Ann.*, **281**, 314 (1894).

acetate may be oxidized by chromic acid. Clark designated the oxidation product from the hexaacetate as tetraacetylapogossypolone and assigned it the structure $C_{22}H_{16}O_2(OCOCH_3)_4$. To the product from the oxidation of the hexamethyl ether he gave the formula $C_{28}H_{22}O_4(OCH_3)_4$ and named it tetramethoxypseudogossypolone. Our results have demonstrated that these two compounds are analogous and the proper formula for Clark's tetraacetylapogossypolone is actually $C_{28}H_{22}O_4(OCOCH_3)_4$. It is proposed to avoid further confusion by naming both these compounds as apogossypolone derivatives, apogossypolone tetramethyl ether and apogossypolone tetraacetate. The analytical data on the oxidation product of the hexaacetate are equally satisfactory for Clark's assumed compound and the structure assigned it in this Laboratory.

These oxidation products were considered by Clark to be quinones but he offered no experimental evidence for this assumption. It has now been found that they are quinones, since both apogossypolone tetramethyl ether and tetraacetate may be reductively acetylated and the reduction product of the tetraacetate may be reoxidized to the quinone. The formulas, therefore, may be written as follows



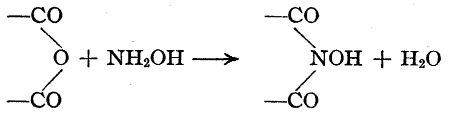
$$C_{28}H_{22}\begin{cases}(OCH_3)_6\\ H_2\end{cases}\xrightarrow{CrO_3}C_{28}H_{22}\begin{cases}(OCH_3)_4\\ (=O)_4\end{cases}\xrightarrow{Zn,\ Ac_2O}C_{28}H_{22}\begin{cases}(OCH_3)_4\\ (OCOCH_3)_4\end{cases}$$

$$C_{28}H_{22}\begin{cases}(OCOCH_3)_6\\ H_2\end{cases}\xrightarrow{CrO_3}C_{28}H_{22}\begin{cases}(OCOCH_3)_4\\ (=O)_4\end{cases}\underset{CrO_3}{\overset{Zn,\ Ac_2O}{\rightleftarrows}}C_{28}H_{22}(OCOCH_3)_8$$

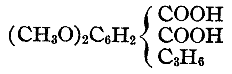
It is obvious that two methoxyl or two acetoxy groups are replaced by oxygens and two additional hydrogens are replaced by oxygens; or, interpreted in another way, two methoxyphenyl or acetoxyphenyl residues in the molecules are converted to quinones. Moreover, it is significant that these molecules differ from the corresponding gossypolone tetramethyl ether or tetraacetate by two carbon and two oxygen atoms. Since the apogossypolone derivatives are unquestionably quinones, this is indirect evidence for the assumed quinone structures of gossypolone derivatives. The analysis of the reductively acetylated apogossypolone tetraacetate does not agree with a formula derived from Clark's postulated structure of apogossypolone tetraacetate.

The apogossypolone tetraacetate is much more sensitive to reagents than the tetramethyl ether and consequently only the latter has been given an exhaustive investigation. Clark[5] oxidized apogossypolone tetramethyl ether with cold permanganate to a white acidic substance which he called apogossypolic acid. He believed this to have the formula $C_{20}H_{24}O_9$ and to be the trimethyl ether of a tricarboxylic acid, which on heating above its melting point lost one molecule of water to produce a trimethyl ether of a ketonic dibasic acid. The latter compound formed a hydrazone and a semicarbazone and hence the presence of a ketonic group was deduced.

A careful study of apogossypolic acid has led us to different conclusions concerning its structure. It proved by titration in aqueous solution to be a dibasic acid. Upon sublimation it lost water to give an anhydride and upon treatment with diazomethane it gave a dimethyl ester. Moreover, the molecular weight of the anhydride gave values which indicated the molecule to be most probably a simple benzene derivative. The molecular formula may be written as $C_{13}H_{16}O_6$ or $C_9H_8(OCH_3)_2(COOH)_2$. The formation of a semicarbazone of the anhydro product with the loss of a molecule of water does not necessarily imply the presence of a ketone group. It readily can be explained by analogy to other dibasic acid anhydrides which react with ketone reagents. Phthalic anhydride, for example, with hydroxylamine gives hydroxyphthalimide[6]



Apogossypolic acid therefore may be given the structural formula



$$(CH_3O)_2C_6H_2\begin{cases}COOH\\ COOH\\ C_3H_6\end{cases}$$

The problem is to determine the disposition of the C_3H_6 residue. It is obvious that in order to explain the facile formation of an anhydride, the two carboxyls must either both be in the *ortho* positions to each other in the ring or one may be in the ring *ortho* to a side-chain holding the carboxyl on the first carbon atom. This limits the structure to (1) a *n*-propyl or isopropyl group in the ring, (2) an ethyl and a methyl group in the ring, (3) a side-chain of the type —$CH(C_2H_5)$-

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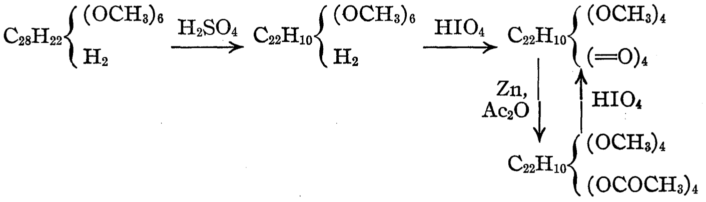
(5) Clark, *Oil and Fat Industries*, **6**, July (1929).

(6) Orndorff and Pratt, *Am. Chem. J.*, **47**, 88 (1912).

COOH or —$C(CH_3)_2COOH$, (4) a side-chain —$CH(CH_3)COOH$ with a methyl group in the ring, (5) a side-chain —CH_2COOH with one ethyl or two methyl groups in the ring. The determination of its exact structure will be the subject of a subsequent communication.

Apogossypol hexamethyl ether undergoes a very unusual reaction under the influence of concentrated sulfuric acid at room temperature. A white stable crystalline substance is formed containing no sulfur and still retaining the six methoxyl groups. This substance will be designated as desapogossypol hexamethyl ether. The molecular weight and analyses agree unusually well for the loss of the residue C_6H_{12} from the starting material and this assumption was confirmed by a study of its oxidation products which apparently are analogous to those of apogossypol hexamethyl ether. Desapogossypolone tetramethyl ether is obtained by a periodic acid oxidation and this product may be reductively acetylated. This latter substance may be reoxidized to the quinone. Both the quinone and its reduction product have C_6H_{12} less than the corresponding apogossypol hexamethyl ether derivatives, and the reaction thus may be formulated as follows



$$\begin{tikzcd}
C_{28}H_{22}\begin{cases}(OCH_3)_6\\ H_2\end{cases} \arrow[r, "H_2SO_4"] & C_{22}H_{10}\begin{cases}(OCH_3)_6\\ H_2\end{cases} \arrow[r, "HIO_4"] & C_{22}H_{10}\begin{cases}(OCH_3)_4\\ (=O)_4\end{cases} \arrow[d, shift right, "{Zn,\ Ac_2O}"'] \\
 & & C_{22}H_{10}\begin{cases}(OCH_3)_4\\ (OCOCH_3)_4\end{cases} \arrow[u, shift right, "HIO_4"']
\end{tikzcd}$$

Assuming that apogossypol is a symmetrical molecule just like gossypol, the elimination of C_3H_6 from each half of the molecule has taken place. Since the reagent for this degradation is cold sulfuric acid, it appeared likely that propyl or isopropyl acid sulfate might be the by-product. The diluted sulfuric acid reaction mixture therefore was distilled and the distillate treated with potassium dichromate and mercuric sulfate. After boiling for one to two minutes, an orange precipitate separated similar to that obtained by the use of acetone. Moreover, the iodoform test of the original distillate is positive. The quantities of material available were so small as to lack the desired convincing proof, but tentatively it has been postulated that two isopropyl groups have been removed from the original molecule. No exact parallel for such a reaction has been found but it is interesting to note that isopropylnaphthalene can be dealkylated by means of hydriodic acid.[7]

The orange quinone, desapogossypolone tetramethyl ether, undergoes oxidation by means of cold permanganate to give a water-soluble dibasic acid which was identified as *m*-hemipinic acid, 1,2-$(CH_3O)_2C_6H_2(COOH)_2$-4,5, by comparison of it, its anhydride and its N-ethylimide with synthetic samples.

The isolation of *m*-hemipinic acid proves definitely that apogossypol hexamethyl ether and therefore gossypol hexamethyl ether contain two pairs of *ortho* methoxyl groups.

Since both *m*-hemipinic acid and apogossypolic acids are formed by permanganate oxidation of quinones, it may be inferred that the *o*-methoxyl groups are not in the quinone rings of the apogossypolone or desapogossypolone tetramethyl ethers since the quinone portions of the molecules probably account for two carboxyl groups found in the oxidation products.

The analogy between the degradation reactions of apogossypol and desapogossypol and the possible identification of acetone in the formation of desapogossypol hexamethyl ether make the assumption inviting that two isopropyl groups have been removed and, hence, that apogossypolic acid and *m*-hemipinic acid differ only by an isopropyl residue.

Apogossypol hexaethyl ether can be prepared readily, but it did not undergo the transformation to the desapogossypol hexaethyl derivative under the conditions used. The discussion of the reagents and conditions employed for preparing these different compounds is given in the experimental part. Suffice it to say here that the yields in the degradation reactions are usually not good and only if the conditions are carefully controlled can crystalline, easily purified compounds be obtained.

Experimental

Apogossypol.—The method employed for the preparation of apogossypol was that described by Clark[3] except for minor modifications. In place of pure gossypol as a raw material, it was found possible to use crude gossypol-acetic acid. To the alkaline solution sodium hydrosulfite, to the extent of about one-fifth the weight of the gossypol-acetic acid, was added to inhibit air oxidation. The apogossypol is unstable and turns dark on standing even in a nitrogen atmosphere in a desiccator. It must be converted immediately after preparation to a hexamethyl ether or a hexaacetate.

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[7] Meyer and Bernhauer, *Monatsh.*, **54**, 721 (1929).

Freshly prepared apogossypol gives a yellow color in concentrated sulfuric acid, a dark green with ferric chloride and an orange-red with pyroboroacetate. The nickel acetate, diethyl malonate, thiophene-sulfuric acid and stannic chloride tests were all negative. Attempts to prepare an anhydro compound by the method employed for preparing anhydrogossypol were unsuccessful.

Apogossypol Hexamethyl Ether.—The apogossypol was converted to its hexamethyl ether by the method of Clark.[8] A 40% yield of crystalline apogossypol hexamethyl ether or a 60% yield of methanol-insoluble material suitable for oxidation purposes could be obtained from crude gossypol-acetic acid. Pure apogossypol hexamethyl ether was purified by dissolving in the smallest possible volume of benzene, concentrating to one-half the volume and adding three volumes of methanol, m. p. 259°. Clark also reports 259°.

Apogossypolone Tetramethyl Ether.—This product was prepared from crude gossypol hexamethyl ether by oxidation with Kiliani's reagent according to the directions of Clark[8] (called by him tetramethoxy pseudogossypolone).

It could also be obtained by the oxidation with periodic acid. To a solution of 2.0 g. of (methanol-insoluble) apogossypol hexamethyl ether in 90 cc. of dioxane was added 30 g. of periodic acid in 20 cc. of water. The mixture was refluxed for four hours. During this period a 5-g. portion of periodic acid was added at the end of two hours and another at the end of three hours. The bright red solution changed to light yellow. After cooling, the solution was poured into 300 to 400 cc. of water and part of the dioxane removed by a current of air. The orange solid separating during this concentration was collected on a filter, dried and treated with just enough methanol to cover the solid. A bright orange solution resulted from which apogossypolone tetramethyl ether precipitated as a bright yellow solid. For further purification the material was recrystallized from a small volume of methanol in preference to an ether–acetic acid mixture recommended by Clark: m. p. 212–214°; yield 0.37 g.

Anal. Calcd. for $C_{28}H_{22}O_4(OCH_3)_4$: C, 70.3; H, 6.23; mol. wt., 546. Found: C, 70.30, 70.20; H, 6.27, 6.27; mol. wt., 538.

No crystalline products could be obtained by the action of *o*-phenylenediamine or by demethylation with hydrobromic acid in acetic acid.

It gave in concentrated sulfuric acid a dark orange color changing rapidly to bright purple. With the diethyl malonate–ammonia reagent it gave a blue-green.

Reductive Acetylation of Apogossypolone Tetramethyl Ether; Hydroapogossypolone Tetramethyl Ether Tetraacetate.—A mixture of 0.02 g. of pure apogossypolone tetramethyl ether, 0.02 g. of anhydrous sodium acetate, 1.0 g. of zinc dust and 2.0 cc. of acetic anhydride was refluxed for twenty-five minutes. Small additions of zinc dust were made intermittently during this time. The mixture was filtered hot, the residue washed twice with small portions of acetone and the filtrate poured into water to decompose the acetic anhydride. A few drops of glacial acetic acid aided materially in this decomposition. The white hydroapogossypolone tetramethyl ether tetraacetate was purified by crystallization from anhydrous ethanol, m. p. 229–230.5°, yield 0.015 g.

Anal. Calcd. for $C_{28}H_{22}(OCOCH_3)_4(OCH_3)_4$: C, 66.85; H, 6.41. Found: C, 66.93; H, 6.44.

Apogossypolic Acid.—This product was prepared according to unpublished directions of Clark.[9] A solution of 1.0 g. of crude apogossypolone tetramethyl ether (methanol-insoluble material) in 100 cc. of acetone distilled from potassium permanganate was cooled to 0° in an ice-bath. To this was added with stirring in three portions one hour apart 1.7 g. of potassium permanganate. The mixture was stirred, kept cold for twenty-four to thirty hours, after which time the manganese dioxide was collected on a gravity filter and washed free of any excess permanganate with acetone. After *thorough* air drying of the manganese dioxide precipitate, it was covered with water to which two or three drops of ethanol were added to decompose any permanganate that might not have been removed. It was then heated on a steam-bath for fifteen minutes. The manganese dioxide was removed by filtration and the alkaline solution acidified with dilute sulfuric acid. The yellow semi-solid material which separated was extracted with ether. The ether solution was dried and then concentrated to a few cubic centimeters. After addition of 15 cc. of dry benzene and concentration until the product started to separate (about 5–8 cc.), the solution was allowed to stand a day for crystallization. The apogossypolic acid obtained is essentially pure but may be purified further by dissolving in dry ether, pouring into benzene and concentrating till crystallization begins: white crystals, m. p. 162–165°, but the value obtained is very dependent on the rate of heating.

Anal. Calcd. for $C_{13}H_{16}O_6$: C, 58.2; H, 5.97; neut. equiv., 2COOH, 134. Found: C, 58.10, 58.00; H, 5.89, 5.90; neut. equiv., 134.

Dimethyl Ester of Apogossypolic Acid.—To an ether solution of 0.07 g. of apogossypolic acid was added an ether solution of diazomethane prepared from nitrosomethyl urea. At the end of twenty-four hours at room temperature, the solution was filtered and concentrated by evaporation. The oil obtained required about twenty days in an ice box before it became crystalline. For purification, it was twice sublimed at 25 mm.: white crystals; m. p. 45–46.5°.

Anal. Calcd. for $C_{15}H_{20}O_6$: C, 60.8; H, 6.76. Found: C, 60.49; H, 6.77.

Apogossypolic Acid Anhydride.—Sublimation of apogossypolic acid at 25 mm. with a bath temperature of 170–180° gave the anhydride in quantitative yields. After a second sublimation at 90–100°, a white product, m. p. 93–94° (Clark, 95°), resulted.

Anal. Calcd. for $C_{13}H_{14}O_5$: C, 62.40; H, 5.60; neut. equiv., 2COOH, 125; $2OCH_3$, 24.8. Found: C, 62.10; H, 5.39; neut. equiv., in H_2O, 123; OCH_3, 23.6.

The Action of Semicarbazide Hydrochloride on Apogossypolic Acid Anhydride.—A mixture of 0.075 g. of apogossypolic acid anhydride, 0.075 g. of semicarbazide hydrochloride, 0.112 g. of sodium acetate and 1.2 cc. of 95% ethanol was immersed in a bath of hot water and left while

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(8) Clark, THIS JOURNAL, **51**, 1475 (1929).

(9) Private communication from E. P. Clark.

the bath cooled. After standing for five hours, a few drops of water was added and the sides of the container scratched. The product crystallized and was purified by dissolving in a little methanol and adding an equal volume of water. Fine white crystals separated in the course of a few hours, m. p. 221–223°, yield 0.055 g. Clark reported 233°.

Anal. Calcd. for $C_{14}H_{17}O_5N_3$: C, 54.8; H, 5.54; N, 13.68. Found: C, 54.91; H, 5.60; N, 13.58.

Action of Concentrated Sulfuric Acid on Apogossypol Hexamethyl Ether; Desapogossypol Hexamethyl Ether.—To 80 cc. of concentrated sulfuric acid was added with vigorous stirring to aid solution, 4.0 g. of apogossypol hexamethyl ether. The mixture was allowed to stand for thirty minutes at room temperature and then poured onto ice. A fine purple-tinted amorphous material precipitated which was extremely difficult to filter. The dilute sulfuric acid suspension was therefore shaken with 25 to 50 cc. of ether, the two layers separated and the ether suspension poured into water. As the ether was evaporated on the steam-bath, a gray-white granular precipitate was obtained; yield 3.3 g. The product was purified by dissolving it in the smallest possible volume of boiling benzene, concentrating to about 40% of its original volume and adding two volumes of methanol. Crystallization was complete in about three hours; yield 1.6 g. An additional treatment in benzene with Norite followed by concentration and addition of methanol as previously described gave a white crystalline product, m. p. 295–296°.

Anal. Calcd. for $C_{28}H_{30}O_6$: C, 72.70; H, 6.50; mol. wt., 462; OCH_3, 40.2. Found: C, 72.62, 72.73, 72.68; H, 6.79, 6.56, 6.56; mol. wt., 425; OCH_3, 36.1, 35.8, 36.3, 37.8, 37.7, 35.8, 36.7.

In preparing the above compound in larger quantities, crude (methanol-insoluble) apogossypol hexamethyl ether proved satisfactory. Once recrystallized sulfuric acid compound was satisfactory for degradation purposes.

The product gave an orange-yellow color in concentrated sulfuric acid.

Periodic Acid Oxidation of Desapogossypol Hexamethyl Ether; Desapogossypolone Tetramethyl Ether.—A solution of 2.0 g. of desapogossypol hexamethyl ether in 140 cc. of dioxane was prepared by heating to boiling. After cooling to 40–50°, a saturated aqueous solution of 30 g. of periodic acid was added. The mixture was heated gently for a half hour during which time the solution refluxed vigorously and turned a dark red-brown color. The solution was then heated till it refluxed and after another thirty minutes a second 30-g. portion of periodic acid was added. After two more hours of refluxing, during which period the solution generally changed to orange in color, the solution was cooled to 60–70° and poured into 400 cc. of water. An orange flocculent precipitate formed. The major portion of the dioxane was removed by a current of air and the orange powder filtered; yield 1.5 g. This crude product was digested with 10 cc. of warm methanol for thirty minutes during which time all the lumps were crushed thoroughly with a glass rod. After standing for one hour, an orange powder weighing 0.53 g. was obtained. This was further purified by dissolving in a small volume of acetone, adding two volumes of methanol and concentrating till crystals appeared. The product formed orange spikes, softening at 199° and melting at 236–238° with decomposition. This product retained a small amount of solvent which was very difficult to remove; consequently, it was dissolved in benzene and concentrated to one-half volume, diluted with benzene and again concentrated. Petroleum ether (b. p. 60–110°) was then added, the mixture concentrated to one-half and this procedure repeated till practically all the benzene was removed. On cooling, an orange microcrystalline product separated, m. p. 245–248° with decomposition. This was used for analysis.

Chromic acid and Kiliani's reagent could not be substituted for periodic acid. With these reagents an orange product resulted but could not be obtained crystalline.

Anal. Calcd. for $C_{26}H_{22}O_8$: C, 67.5; H, 4.76; $4OCH_3$, 26.8. Found: C, 67.20; H, 4.98; OCH_3, 23.5, 23.3.

It gave a permanent dirty brown color in concentrated sulfuric acid. The *o*-quinone test with thiophene-sulfuric acid was negative.

Reductive Acetylation of Desapogossypolone Tetramethyl Ether; Hydrodesapogossypolone Tetramethyl Ether Tetraacetate.—A mixture of 0.4 g. of *pure* desapogossypolone tetramethyl ether, 5 cc. of acetic anhydride, 0.4 g. of fused sodium acetate and 2 g. of zinc dust was refluxed gently for twelve minutes. Small additions of zinc dust were made from time to time during this period. The solution was then filtered, the zinc washed with acetone and the filtrates poured into water. The fine white crystalline powder was purified by crystallization from methanol, m. p. 264–266°, yield 0.36 g.

Anal. Calcd. for $C_{34}H_{34}O_{12}$: C, 64.40; H, 5.37; $4CH_3CO$, 27.1. Found: C, 64.03, 64.28; H, 5.50, 5.18; CH_3CO, 25.8, 25.8.

Periodic Acid Oxidation of Hydrodesapogossypolone Tetramethyl Ether Tetraacetate.—Excess (2 to 3 g. in 2 cc. of water) periodic acid was added to a dioxane solution of 0.030 g. of hydrodesapogossypolone tetramethyl ether tetraacetate and the solution warmed gently on a steam-bath for fifteen to twenty minutes. During this time a colorless to yellow to orange-red change was observed. The orange product, precipitated by the addition of water to the dioxane solution, was collected on a filter, dried, digested with a small volume of methanol and crystallized from a hot mixture of benzene and methanol. The orange crystals so obtained proved to be identical with desapogossypolone tetramethyl ether obtained by the periodic acid oxidation of desapogossypol hexamethyl ether.

Permanganate Oxidation of Desapogossypolone Tetramethyl Ether; *m*-Hemipinic Acid.—To a cold (0°) solution of 0.5 g. of desapogossypolone tetramethyl ether in 130 cc. of acetone (distilled from permanganate) was added portionwise over a period of five hours, 1 g. of potassium permanganate. The solution was stirred and maintained at 0° for forty-eight hours. The manganese dioxide was filtered and washed to remove excess permanganate. The manganese dioxide precipitate was air-dried, then covered with water to which two to three drops of ethanol and 0.5–1 cc. of 10% aqueous sodium bicarbonate had been added. After heating on a steam-bath for fifteen minutes, the manganese dioxide was filtered and a dark orange solution remained. Dilute sulfuric acid precipitated a tan flocculent material which was extracted with ether. After drying the ether solution with sodium sulfate, a little benzene was added and the mixture concentrated. After the ether was removed, a light colored crystalline product began to separate. After standing for several hours, it was filtered and purified by a Norite treatment in acetone solution, followed by concentration after the addition of benzene, m. p. 191°, yield 0.13 g.

To complete the purification of this slightly colored material, it was sublimed at 60 mm. in a bath at 195°. A perfectly white crystalline product resulted, m. p. 179–181°, which apparently was the anhydride of the unsublimed material. This substance proved to be *m*-hemipinic acid anhydride. Carr and Pyman[10] report m. p. 176° for this substance.

Anal. Calcd. for $C_{10}H_8O_5$: C, 57.70; H, 3.85; mol. wt., 208. Found: C, 57.82; H, 4.14; mol. wt. (Rast), 215.

This anhydride was dissolved in 5% aqueous sodium hydroxide and the solution acidified with acid, keeping the mixture below 20°. The white insoluble *m*-hemipinic acid was extracted with ether, the ether solution dried and mixed with an equal volume of petroleum ether (b. p. 30–60°). Upon evaporation at room temperature long white needles of *m*-hemipinic acid separated, m. p. 191°. Carr and Pyman report a melting point of 192°.

Anal. Calcd. for $C_{10}H_{10}O_6$: C, 53.20; H, 4.43; neut. equiv., 113; mol. wt., 226. Found: C, 53.29; H, 4.65; neut. equiv., 115; mol. wt. (Rast), 224.

N-Ethylimide.—The acid just described was dissolved in an excess of ethanolic ethylamine containing 30–40% water. The product obtained by evaporating the solution to dryness on a steam-bath was sublimed at 60 mm. and a bath temperature of 235–240°. The fine white needles were then recrystallized from methanol, m. p. 229–231°. Carr and Pyman report a variety of melting points of the N-ethylimide of *m*-hemipinic acid ranging from 228–234°.

Anal. Calcd. for $C_{12}H_{13}O_4N$: C, 61.35; H, 5.54; N, 5.96. Found: C, 61.49; H, 5.68; N, 5.92.

m-Hemipinic acid, its anhydride and N-ethylimide were synthesized from veratric aldehyde[11] by Perkin's[12] method. The melting points are recorded in Table I.

TABLE I

COMPARISON OF *m*-HEMIPINIC ACID FROM APOGOSSYPOL AND BY SYNTHESIS

	Acid	Anhydride	N-Ethylimide
Synthetic	190–191	176–177	228–231
Mixture	190–191	176–178	229–231
From apogossypol	190–191	179–181	229–231

Apogossypol Dimethyl Ether.—To a small pressure bottle filled with nitrogen was added 12 cc. of 30% methanolic potassium hydroxide and 0.5 g. of gossypol dimethyl ether.[13] The flask was closed and heated at 100° for four hours after which period it was cooled and the contents poured into 8 cc. of water and acidified immediately with concentrated sulfuric acid. A light cream colored precipitate formed which could not be separated by filtration. The suspension was extracted with ether, dried and evaporated to yield a light brown amorphous solid. No method of purification was discovered. Methylation of this product in 20% aqueous alkali gave apogossypol hexamethyl ether, m. p. 259°.

Apogossypol Hexaethyl Ether.—To a solution of 2.0 g. of freshly prepared dry apogossypol in 10 cc. of methanol was added 12 cc. of pure diethyl sulfate and then dropwise with stirring a saturated methanolic solution of potassium hydroxide until the mixture was alkaline to moist litmus. After standing for several hours, the mixture was poured into water and the brown powder filtered. It was purified by dissolving in the smallest possible amount of benzene followed by addition of four volumes of methanol. This was repeated several times until the melting point was constant, 176–180°; yield 0.8 g.

Anal. Calcd. for $C_{28}H_{24}(OC_2H_5)_6$: C, 76.15; H, 8.57. Found: C, 75.82; H, 8.36.

Apogossypol Hexaacetate.—This product was prepared by the method of Clark[3] in yields of 62% of crystalline material, using crude gossypol-acetic acid for the conversion to apogossypol.

Apogossypolone Tetraacetate.—Clark's[3] procedure was used in this preparation. It was found that crude apogossypol hexaacetate gave satisfactory results. The product was purified from methanol, m. p. 230–232°. Clark reports 230°.

It gave in concentrated sulfuric acid a dark orange color changing rapidly to bright purple; with diethyl malonate–ammonia reagent, it gave a reddish-purple.

Reductive Acetylation of Apogossypolone Tetraacetate; Hydroapogossypolone Octaacetate.—A mixture of 0.62 g. of apogossypolone tetraacetate, 10 cc. of acetic anhydride, 0.3 g. of fused sodium acetate and 2 g. of zinc dust was refluxed gently for twelve minutes. The product was isolated as described for hydroapogossypolone tetramethyl ether tetraacetate; yield quantitative. After crystallization from ethanol it formed white crystals, m. p. 225–229°.

Anal. Calcd. for $C_{44}H_{46}O_{16}$: C, 63.8; H, 5.32. Found: C, 63.74; H, 5.33.

Oxidation of hydroapogossypolone octaacetate gave apogossypolone tetraacetate. To a hot solution of 0.2 g. of octaacetyl product in 10 cc. of glacial acetic acid was added 1 cc. of 10% aqueous chromic acid. The mixture was heated for one minute and poured onto ice. The bright orange apogossypolone tetraacetate melted at 230–232°.

Apogossypol Tetrabenzoate.—To 45 cc. of a cooled 20% aqueous sodium hydroxide solution of 2.5 g. of apogossypol was added in portions with stirring and cooling 18 cc. of benzoyl chloride. A light yellow product separated and was purified by dissolving in a small volume of hot benzene, concentrating one-half, adding an equal volume of methanol and allowing to stand. The benzoate crystallizes as white crystals with a faint pinkish tint: m. p. 314–316°; yield 1.9 g.

Anal. Calcd. for $C_{28}H_{24}(OCOC_6H_5)_4$: C, 76.55; H, 5.24. Found: C, 76.42; H, 4.89.

Gossypol Tetrabenzoate.—In a previous article[14] gossypol hexabenzoate was described. The analysis of this sub-

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(10) Carr and Pyman, *J. Chem. Soc.*, **105**, 1630 (1914).

(11) The preparation of veratric aldehyde was best accomplished by adding simultaneously concentrated aqueous sodium hydroxide and dimethyl sulfate to fused vanillin, *Org. Syn.*, **16**, 91 (1936).

(12) Perkin and Robinson, *J. Chem. Soc.*, **91**, 1073 (1907).

(13) Adams and Geissman, THIS JOURNAL, **60**, 2163 (1938).

(14) Miller, Butterbaugh and Adams, *ibid.*, **59**, 1729 (1937).

stance was poor for the hexa but it conforms satisfactorily to a tetrabenzoate which we now believe it to be. This opportunity is therefore taken to correct the error appearing in the earlier paper.

Summary

Apogossypol formed by the action of concentrated aqueous sodium hydroxide on gossypol yields a stable hexaacetate and a stable hexamethyl ether.

Both these products are oxidized to quinones, apogossypolone tetraacetate and apogossypolone tetramethyl ether. During this reaction, two acetoxy groups in the acetate and two methoxyl groups in the ether have been eliminated.

The presence of two quinone nuclei in each was proven by reductive acetylation. Hydroapogossypolone octaacetate and hydroapogossypolone tetramethyl ether tetraacetate are thus produced and the former could be reoxidized readily to apogossypolone tetraacetate.

The apogossypolone tetramethyl ether is oxidized with permanganate to a water-soluble acid, called apogossypolic acid, $C_{13}H_{13}O_6$. It contains two methoxyls and two carboxyl groups.

Apogossypol hexamethyl ether by the action of cold concentrated sulfuric acid loses the residue C_6H_{12} with the formation of a product called desapogossypol hexamethyl ether. This product is oxidized with periodic acid to desapogossypolone tetramethyl ether which corresponds to apogossypolone tetramethyl ether in being a quinone but with C_6H_{12} lost. Reductive acetylation gives hydrodesapogossypolone tetramethyl ether tetraacetate which can be reoxidized to desapogossypolone tetramethyl ether. This reductively acetylated product also analyzes for C_6H_{12} less than hydroapogossypolone tetramethyl ether.

When apogossypolone tetramethyl ether is oxidized with permanganate, *m*-hemipinic acid is formed as proved by a comparison with an authentic sample. It is thus demonstrated that two methoxyls are adjacent and since gossypol or apogossypol are symmetrical molecules, two pairs of *o*-methoxyls must be present.

Since apogossypolic acid and *m*-hemipinic acid differ by a C_3H_6 or half the C_6H_{12} lost in conversion of apogossypol tetramethyl ether to desapogossypol tetramethyl ether, it is a reasonable assumption that the difference is merely an isopropyl or propyl residue. The difference between the apo and desapo series would then be two isopropyl or propyl residues. Evidence is presented to indicate these groups to be isopropyl.

URBANA, ILLINOIS RECEIVED JUNE 27, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Structure of Gossypol. XI.[1] Absorption Spectra of Gossypol, its Derivatives and of Certain Dinaphthalene Compounds

BY ROGER ADAMS AND E. C. KIRKPATRICK[2]

Previous work on the structure of gossypol has involved the preparation of derivatives and degradation products. While much information has thus been obtained concerning the functional groups present, little evidence is available as yet to indicate the nature of the basic nucleus of gossypol. Ultraviolet absorption offers a method of procuring such knowledge.

An examination of the spectra of gossypol[3] and many of its derivatives shows them all to be characterized by an absorption maximum at approximately 2500 Å. with the logarithm of the molal extinction coefficient close to 5 and a maximum or point of inflection near 3000 Å. with a log *e* of 4. Thus, gossypol is a very intense absorbent which can be explained only by assuming the presence of aromatic rings.

A comparison of the absorption spectrum of gossypol with those of substituted naphthalenes indicates that it is of the same general shape but with subdued detail.[4] The peaks of the gossypol curve are regularly more intense. If this intensity were due merely to auxochromes or other

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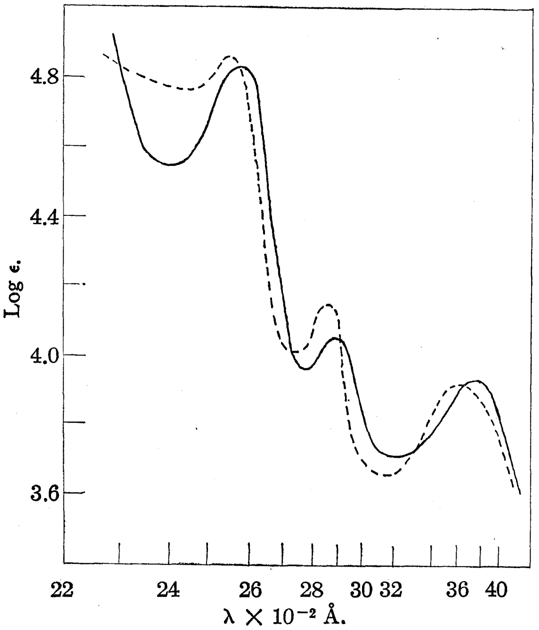
(1) For previous paper, see Adams and Butterbaugh, THIS JOURNAL, **60**, 2174 (1938).

(2) Portion of a thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry by E. C. Kirkpatrick, Solvay Fellow, 1936–1938.

(3) Grünbaumowna and Marchlewski, *Biochem. Z.*, **286**, 295 (1936); see also Marchlewski, *J. prakt. Chem.*, **60**, 84 (1899); Tobler, Dissertation "Arbeiten über Gossypol," Zürich, 1932; Podolskaja, *Biochem. Z.*, **284**, 401 (1936); Zamyshlyaeva and Krivich, *J. Gen. Chem.* (U. S. S. R.), **7**, 1936 (1937).

(4) De Laszlo, *Z. physik. Chem.*, **118**, 369 (1925); *Proc. Roy. Soc.* (London), **111**, 355 (1926); Henri and de Laszlo, *ibid.*, **A105**, 355 (1936); Ley, *Handbuch der Physik*, **21**, 176 (1929).

chromophores in the molecule, the peaks of the curves of the various derivatives of gossypol in which the functional groups have been modified or eliminated, should vary considerably from those of gossypol and in general should be less intense. This has been found not to be the case. Thus, for example, the absorption spectrum of apogossypol hexamethyl ether (Figs. 1 and 4) which has two aldehyde groups less than gossypol shows only minor differences in the two main peaks from that of gossypol, instead of approaching in resemblance more closely that of naphthalene.

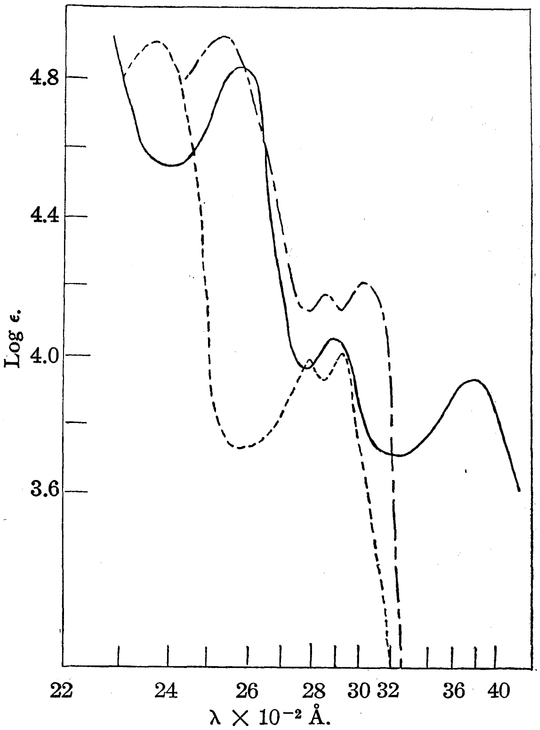


(1) —, Gossypol; (2) - - -, gossypol dimethyl ether.

Fig. 1.

The spectra of compounds with more complex condensed ring systems such as phenanthrene, anthracene, chrysene, naphthacene, benzanthracene, etc., are quite different from those of naphthalene derivatives or of gossypol. Both absorption regions, log e = 4 and log e = 5, become much broader, contain many more peaks shifted toward the visible and in general show no sharp distinction between the two regions. Closely-packed ring systems such as pyrene and perylene enhance this effect so that they both have strong absorption in the visible. Fluorene, as illustrative of a molecule containing separated benzene rings, has much less intensity of absorption than gossypol. Oxygen-containing rings and quinones also have distinctly different spectra.[5]

The difference between the two principal peaks in gossypol and in naphthalene derivatives is one of intensity. The enhancement of the intensity in the gossypol spectrum is by an amount which could be satisfactorily explained by assuming double the number of naphthalene rings per mole.



(1) —, Gossypol; (2) — -, β,β-binaphthyl; (3) - - -, α,α-binaphthyl.

Fig. 2.

Consequently, the absorption spectra have been determined of four dinaphthalene compounds: α,α-binaphthyl, β,β-binaphthyl, *sym*-di-α-naphthylethane, and *sym*-di-β-naphthylethane (Figs. 2 and 3). These all have absorption regions of the same character and intensity as gossypol but nearer the ultraviolet. Because of the many substituents in gossypol, it is impossible to identify its absorption spectrum with any one of the four. However, the log e = 5 absorption region is closer to the visible in the two binaphthyls than in the two dinaphthylethanes and consequently the position and character of the peaks

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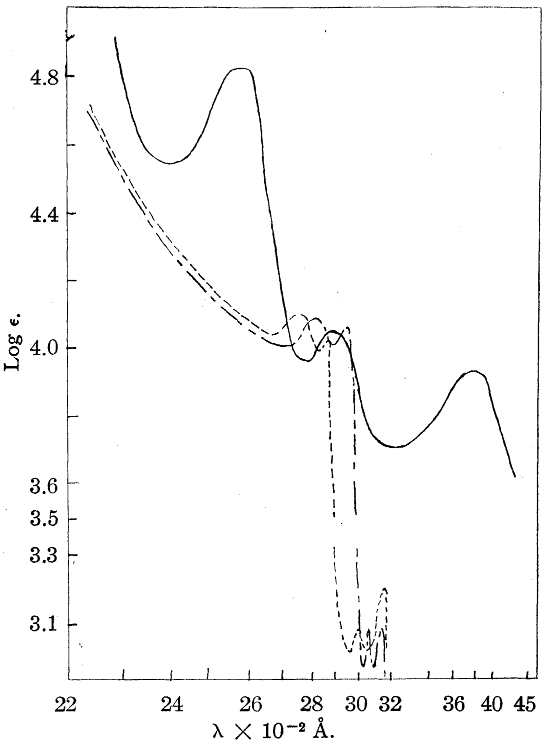
(5) (a) Dadieu, *Z. physik. Chem.*, **135**, 347 (1928); (b) Mayneord and Roe, *Proc. Roy. Soc.* (London), **152**, 299 (1935); **158**, 634 (1937); (c) Seshan, *Proc. Ind. Acad. Sci.*, **3A**, 148, 191 (1936); (d) Conrad-Billroth, *Z. physik. Chem.*, **B15**, 1 (1932); (e) Macbeth, Price and Winzor, *J. Chem. Soc.*, 325 (1935); (f) Shibata and Kimatsuki *J. Tokyo Chem. Soc.*, **39**, 771 (1918); Shibata and Nagai, *J. Chem. Soc. Japan*, **43**, 101 (1922); Tasaki, *Acta Phytochim.*, **2**, 119 (1925).

in the curves of the former two resemble more closely those of gossypol. The conclusion is that either an α,α-binaphthyl or a β,β-binaphthyl is probably the basic nucleus of gossypol.

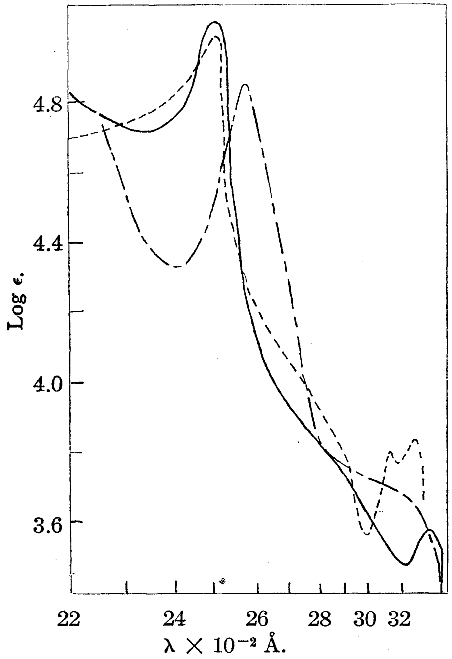


(1) —, Gossypol; (2) - - -, *sym*-di-β-naphthylethane; (3) — -, *sym*-di-α-naphthylethane.

Fig. 3.

Gossypol and gossypol dimethyl ether, which resemble each other chemically, have very similar absorption spectra, Fig. 1, with an absorption maximum at 3600 Å. This maximum was not found in the spectra of gossypol tetramethyl ether, hexamethyl ether or hexaacetate. All of these gossypol derivatives show none of the characteristic aldehyde reactions of gossypol and are in general less reactive. The fact that the region of strong absorption in or near the visible is a low energy excitation coupled with its complete disappearance in the more highly methylated or the acetylated derivatives points strongly to a tautomeric structure in gossypol and gossypol dimethyl ether. Tautomerism is also to be inferred from the fact that ordinary analogous hydroxy and methoxy compounds differ from each other in absorption spectra only slightly whereas a marked change occurs in these gossypol derivatives when methylation or acetylation has been effected.

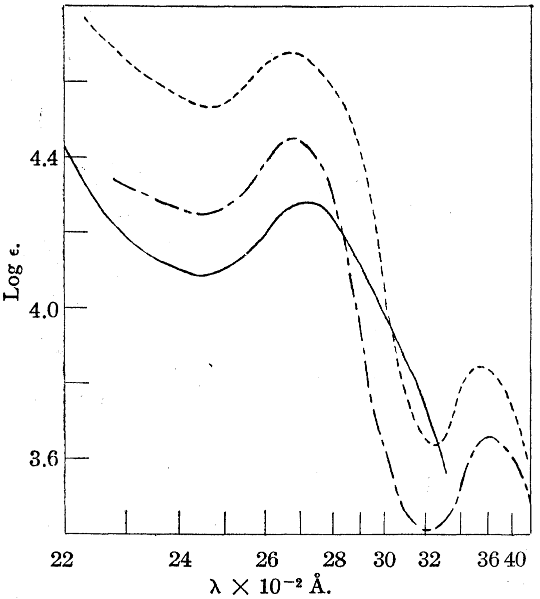
The absorption spectra of gossypol hexamethyl ether, apogossypol hexamethyl ether and desapogossypol hexamethyl ether are shown in Fig. 4. The basic nuclei must be very similar or identical in all of these. Apogossypol hexamethyl ether is converted into desapogossypol hexamethyl ether by the action of cold sulfuric acid. The alteration which takes place in this transformation as deduced from absorption spectra comparisons must be in the substituents and not in the nucleus. This is confirmatory of the deductions from chemical information.



(1) —, Apogossypol hexamethylether; (2) - - -, desapogossypol hexamethyl ether; (3) — -, gossypol hexamethyl ether.

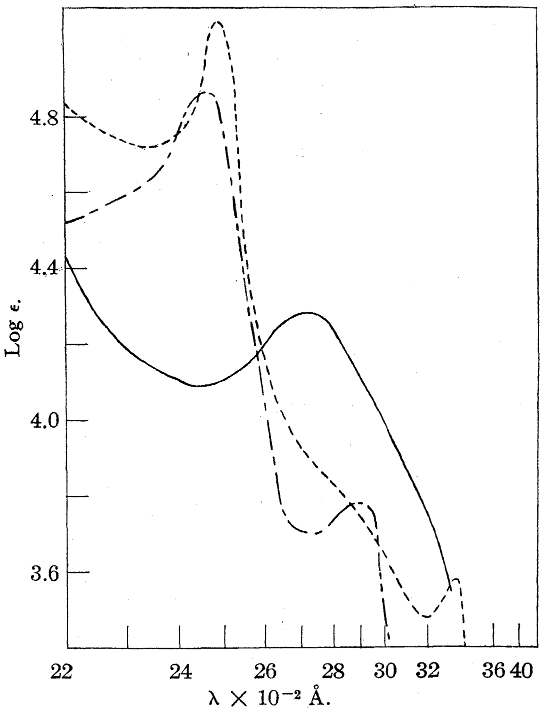
Fig. 4.

Gossypol hexamethyl ether is oxidized first to gossypolone tetramethyl ether, then to gossypolonic acid tetramethyl ether. Apogossypol hexamethyl ether is oxidized to apogossypolone tetramethyl ether. The molecular weights of all these oxidation products are not far different from the parent compounds. The absorption spectra, however, are materially different. In place of the sharp peak near 2500 Å. in the unoxidized substances, these products have less intense broad bands at a position nearer the visible, (Fig. 5). Solubility difficulties prevented the study of apogossypolone tetramethyl ether at higher concentrations which would allow observation of the second less intense maximum. The curve obtained, however, is less intense though very similar to that of the gossypolone tetramethyl ether or gossypolonic acid tetramethyl ether. The difference in the absorption spectra between the unoxidized and oxidized products resembles the difference between the absorption spectrum of naphthalene and 1,4-naphthoquinone. Broad bands appear with decrease in intensity indicating a change in ring structure.[5c,d] These facts substantiate the chemical experiments which gave evidence of quinone nuclei.



(1) —, Apogossypolone tetramethyl ether; (2) - - -, gossypolone tetramethyl ether; (3) — -, gossypolonic acid tetramethyl ether.

Fig. 5.

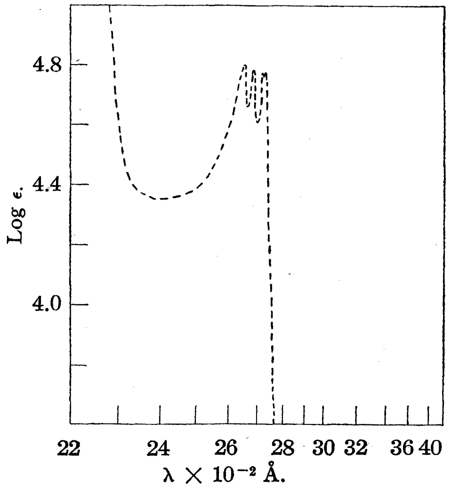


(1) - - -, Apogossypol hexamethyl ether; (2) —, apogossypolone tetramethyl ether; (3) — -, hydroapogossypolone octaacetate.

Fig. 6.

Reductive acetylation of apogossypolone tetramethyl ether results in hydroapogossypolone tetramethyl ether tetraacetate and the latter product[6] has a spectrum resembling that of apogossypol tetramethyl ether, thus suggesting a return to the original ring structure. These changes are shown in Fig. 6. Conversion of a naphthalene to a naphthoquinone then reconversion to a naphthalene may be inferred from the absorption spectra of this series of compounds.

Anhydrogossypol (Fig. 7) has a spectrum entirely different from those of other gossypol derivatives tested. It may be concluded that loss of water when gossypol is converted to anhydrogossypol involves a deep-seated change such as the formation of a new ring containing unsaturation and the alteration of the electronic configuration of the basic ring structure.



Anhydrogossypol.

Fig. 7.

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[6] In taking the absorption spectra, hydroapogossypolone octaacetate was the substance actually used. Since, however, the acetates and the ethers in the apogossypol series resemble each other very closely, the curve given in Fig. 6 must be essentially the same as that of the tetramethyl ether tetraacetate.

Experimental

The absorption spectra were taken on a Bausch and Lomb ultraviolet spectroscope using a hydrogen discharge tube operating under 15,000 volts as a light source. The calibration of wave length was made from the lines Hα, Hβ and Hγ from this source. A quartz cell exactly 1 cm. thick was used throughout with a slit width of 60 μ and appropriate exposure. Stock solutions 5×10^{-4} molar were diluted to yield a series of seven concentrations between this and 5×10^{-6} molar. These concentrations covered the critical concentrations in all cases.

Gossypol and all its derivatives except anhydrogossypol were dissolved in alcohol for these determinations. Anhydrogossypol was dissolved in absolute alcohol and the absorption spectrum taken immediately. Of the α,α-binaphthyl, β,β-binaphthyl, *sym*-di-α-naphthylethane and *sym*-di-β-naphthylethane only the first two were sufficiently soluble in alcohol; as a consequence purified dioxane[7] was used as a solvent for all four. That dioxane gives absorption spectra comparable to those taken in alcohol was shown by the fact that α,α-binaphthyl gave identical curves in both solvents.

Summary

On the basis of the comparison of the ultraviolet absorption spectra of gossypol and its derivatives with known spectra of aromatic ring systems and with four dinaphthalene compounds, α,α-binaphthyl, β,β-binaphthyl, *sym*-di-α-naphthylethane, *sym*-di-β-naphthylethane, it was concluded that gossypol probably contains a binaphthyl nucleus.

The following deductions were drawn from a study of the absorption spectra of gossypol derivatives. (a) Gossypol and gossypol dimethyl ether have a third absorption maximum not found in gossypol tetramethyl ether, hexamethyl ether or hexaacetate. (b) The difference between the absorption spectra of the oxidation products of gossypol hexamethyl ether or apogossypol hexamethyl ether resembles the difference between the naphthalene and 1,4-naphthoquinone. Quinone structures for the oxidation products were thus deduced.

URBANA, ILLINOIS RECEIVED JUNE 27, 1938

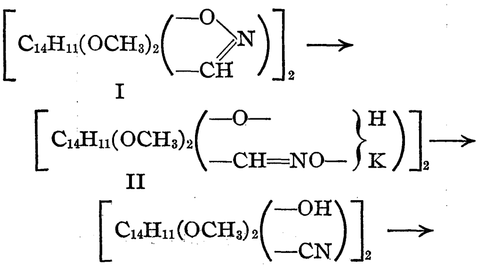
[7] Oxford, *Biochem. J.*, **28**, 1325 (1934).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

The Structure of Gossypol. XII.[1] Gossylic Acid Lactone Tetramethyl Ether

BY ROGER ADAMS AND T. A. GEISSMAN

When the compound (I) obtained by treatment of gossypol hexamethyl ether with hydroxylamine hydrochloride in acetic acid is dissolved in methanolic potassium hydroxide, a crystalline potassium salt (II) is obtained. This salt when heated in acetic acid solution undergoes a change which is assumed to follow the course formulated below, resulting in the formation of a lactone (III)[2]



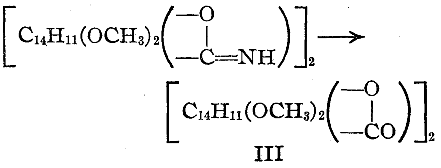
$$\left[C_{14}H_{11}(OCH_3)_2\left(\begin{matrix}-O-\\ -CH=\end{matrix}N\right)\right]_2 \longrightarrow$$

I

$$\left[C_{14}H_{11}(OCH_3)_2\left(\left.\begin{matrix}-O-\\ -CH=NO-\end{matrix}\right\}\begin{matrix}H\\ K\end{matrix}\right)\right]_2 \longrightarrow$$

II

$$\left[C_{14}H_{11}(OCH_3)_2\left(\begin{matrix}-OH\\ -CN\end{matrix}\right)\right]_2 \longrightarrow$$



$$\left[C_{14}H_{11}(OCH_3)_2\left(\begin{matrix}-O\\ |\\ -C=NH\end{matrix}\right)\right]_2 \longrightarrow$$

$$\left[C_{14}H_{11}(OCH_3)_2\left(\begin{matrix}-O\\ |\\ -CO\end{matrix}\right)\right]_2$$

III

The same compound is obtained in small yields as a by-product in the oxidation of gossypol hexamethyl ether with chromic acid in acetic acid.[3]

In this communication evidence is presented that this substance not only is a lactone but that it is formed from a carboxyl and a *phenolic* hydroxyl group. This information along with the results reported in previous papers and additional evidence since accumulated in this Laboratory leads to the conclusion that a lactone structure between the *peri* positions of a naphthalene nucleus (IV) is actually in hand.

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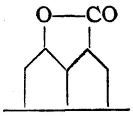
[1] For previous paper see Adams and Kirkpatrick, THIS JOURNAL, **60**, 2180 (1938).

[2] Adams and Geissman, *ibid.*, **60**, 2166 (1938).

[3] Adams, Morris and Kirkpatrick, *ibid.*, **60**, 2170 (1938).



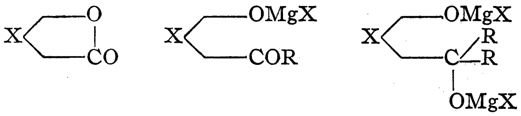
IV

The lactone ring can be opened by warming the compound in 10% methanolic potassium hydroxide solution; acidification of the alkaline solution gives the hydroxy acid (V). It can be converted into the lactone merely by warming in acetic anhydride.

By treatment of the hydroxy acid in methanolic alkali with dimethyl sulfate, the hydroxyl and carboxyl groups are methylated leading to the dimethyl ester of gossylic acid hexamethyl ether (VI). Moreover, the hydroxy acid may be methylated in ether solution with diazomethane to give the same compound (VI). This latter reaction is significant in that alcohols do not ordinarily methylate with this reagent and, hence, it may be inferred that the hydroxyls are phenolic groups. Attempts to hydrolyze the ester (VI) to the corresponding acid were unsuccessful, lending support to the conclusion that ortho substituents to the carbomethoxy groups are present, which hinder saponification. Added confirmation of this is found in the fact that attempts to esterify the hydroxy acid (V) in methanol–sulfuric acid or methanol–hydrochloric acid were equally unsuccessful. Attempted esterification by the methanol–mineral acid procedure resulted in the formation of the lactone.

Methylmagnesium iodide reacts with the lactone to give a compound in which each lactone residue has added one mole of reagent (VII); this substance will be called homogossypol tetramethyl ether since it is homologous with a tautomeric form of one of the possible gossypol tetramethyl ethers. The product is soluble in methanolic alkali and can be methylated in two ways with the formation of isomeric methyl ethers. Upon treatment of an alkaline solution of homogossypol tetramethyl ether (VII) with dimethyl sulfate, the ether produced is formulated as a methoxy methyl ketone (VIII), while treatment with methanol containing a few drops of sulfuric acid gives an isomeric ether probably of the acetal type (IX).

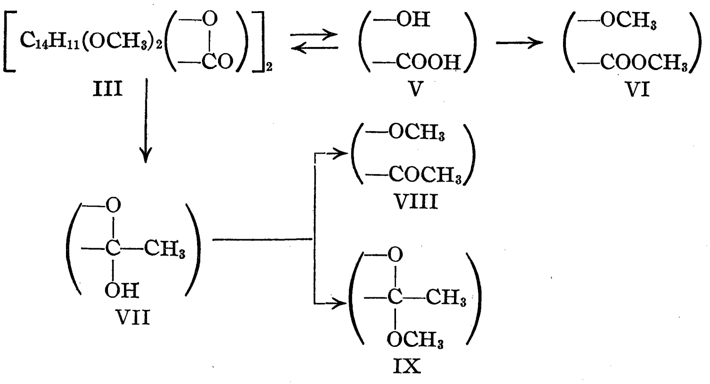
Considerable significance can be attached to the fact that a large excess of Grignard reagent did not bring about the addition of more than one mole to each of the two lactone linkages. The usual course of the reaction between a lactone and a Grignard reagent is as follows



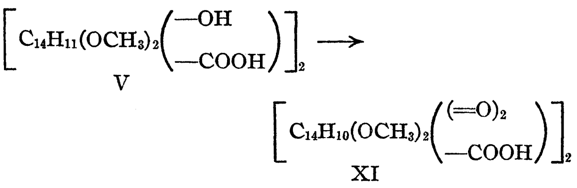
Xa Xb

Since in the present case the keto group represented by step Xa does not undergo further addition (Xb), a reasonable assumption is that it is present in the molecule with ortho substituents on each side as in a 2-substituted 1-naphthyl methyl ketone. The same explanation accounts for the resistance of the ester (VI) to saponification.

The lactone (III) was surprisingly stable to oxidizing agents; it was unattacked by potassium permanganate under most conditions, severe treatment resulting in complete destruction of the molecule. Chromic acid did not oxidize the molecule, which indicates that in the chromic acid oxidation of gossypol hexamethyl ether,[3] the lactone is formed as a by-product and not as an intermediate. The lactone was not affected by dilute nitric acid of a strength which readily oxidized gossypol hexamethyl ether. It was found impossible also to reduce the lactone although a variety of reagents was employed.



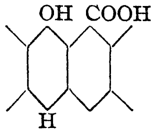
The hydroxy acid (V) differs from the lactone in that it can be oxidized by dilute nitric acid ($1HNO_3{:}4H_2O$) and the product (XI) is gossypolonic acid tetramethyl ether, the water-insoluble compound obtained by a similar oxidation of gossypol hexamethyl ether. It is probable that the ring containing the *peri* hydroxyl is converted to a quinone and since only two hydrogens for each quinone ring formed are lost in the process, a hydrogen in the



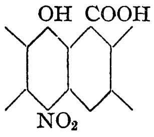
$$\left[C_{14}H_{11}(OCH_3)_2\left(\begin{matrix}-OH\\-COOH\end{matrix}\right)\right]_2 \longrightarrow \left[C_{14}H_{10}(OCH_3)_2\left(\begin{matrix}(=O)_2\\-COOH\end{matrix}\right)\right]_2$$

V XI

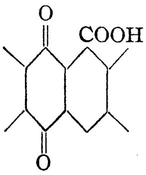
ortho position or more probably in the para position to the hydroxyl in the original ring must be unsubstituted (XII). The para hydrogen seems the more likely since the series of quinones in the gossypol and apogossypol series are all yellow in color while the vast majority of *o*-quinones are red or at least not yellow. The quinone produced by this oxidation may be assumed to have the structure shown in XIII.



XII



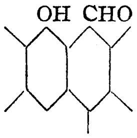
XIV



XIII

The lactone, however, when treated with the proper concentration of nitric acid was readily nitrated and two nitro groups were introduced (XIV). The corresponding diamine was formed by reduction and this was characterized through the acetyl derivative. The nitro group generally enters a 1-naphthol in the 4-position, if unoccupied, and this is in agreement with the results of the oxidation of the hydroxy acid.

Since the carboxyl group in the lactone which has been studied unquestionably has been formed from the corresponding aldehyde, three positions in each of the naphthalene rings in gossypol can be considered as definitely established (XV): 1-aldehydo, 5-hydrogen, 8-hydroxyl.



XV

Experimental

Gossylic Acid Lactone Tetramethyl Ether.—This was prepared by the method previously described.[3]

Gossylic Acid Tetramethyl Ether (V).—To a solution of 1.10 g. of gossylic acid lactone tetramethyl ether in 30 cc. of 10% methanolic potassium hydroxide was added about a gram of zinc dust and 10 cc. of water. The solution (deep red at first) was boiled until the color had faded to yellow and filtered into dilute sulfuric acid. The hydroxy acid was extracted with ether, the ether solution dried over anhydrous sodium sulfate and concentrated. Dilution with petroleum ether (b. p. 30–60°) caused the compound to crystallize in soft white needles weighing 0.85 g. Recrystallized from ether–petroleum ether, the compound formed soft white needles which, when heated slowly, melted at the melting point of the lactone, but when plunged into a bath preheated to 290° melted with vigorous decomposition, resolidified and then remelted at the melting point of the lactone.

Anal. Calcd. for $C_{28}H_{22}(OCH_3)_4(OH)_2(COOH)_2$: C, 67.33; H, 6.27. Found: C, 67.34; H, 6.20.

Dimethyl Gossylate Tetramethyl Ether (VI)

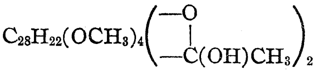
(1) With Dimethyl Sulfate.—To a hot solution of 0.5 g. of gossylic acid lactone tetramethyl ether in 10 cc. of 10% methanolic potassium hydroxide was added slowly 1.65 cc. of redistilled dimethyl sulfate. Then 15 cc. of potassium hydroxide and 1.7 cc. of dimethyl sulfate were added in that order and the mixture heated on the steam-bath for five minutes longer. After dilution with water, the mixture was allowed to stand for an hour and filtered. The air-dried solid obtained was recrystallized twice from dilute acetic acid, yielding 0.46 g. of white plates, m. p. 215–216.5°, to a yellow liquid which did not decompose when heated to 300°.

Anal. Calcd. for $C_{28}H_{22}(OCH_3)_6(COOCH_3)_2$: C, 68.89; H, 6.94; OCH_3, 37.5. Found: C, 69.18; H, 6.80; OCH_3, 35.6, 35.4.

The compound gives a pale yellow color in concentrated sulfuric acid. It is insoluble in alkali.

(2) With Diazomethane.—A solution of 0.18 g. of gossylic acid lactone tetramethyl ether in 10 cc. of 10% methanolic potassium hydroxide was diluted with 80 cc. of water and acidified with hydrochloric acid. The precipitated hydroxy acid was taken up in ether, extracted from the ether solution with sodium carbonate solution, and after acidification of the sodium carbonate solution extracted with 10 cc. of ether. The ether solution was added to 10 cc. of a solution of diazomethane in ether prepared from 0.2 g. of nitrosomethyl urea. Nitrogen was evolved for about ten minutes. The solution was allowed to stand overnight and then evaporated on the steam-bath. The yellow gum remaining was crystallized from dilute acetic acid by careful dilution of an acetic acid solution held at the boiling point. Recrystallized from 62% acetic acid, the compound formed colorless crystals which gave no depression in melting point when mixed with the compound obtained by methylating the lactone with dimethyl sulfate.

Homogossypol Tetramethyl Ether (VII).—To a solution of methylmagnesium iodide prepared from 10 g. of methyl iodide and 1.7 g. of magnesium in 50 cc. of dry ether was added a suspension of 3.5 g. of gossylic acid lactone tetramethyl ether in 40 cc. of dry ether. Reaction took place immediately with moderate refluxing of the solution, which acquired an orange color. Refluxing was continued for thirty minutes, at the end of which time the lactone had all dissolved. The solution was poured into an iced solution of ammonium chloride, and the ether layer was separated and concentrated. The product separated as a white crystalline powder as the ether evaporated. After washing with fresh ether the product weighed 3.07 g. Recrystallized from chloroform–petroleum ether (b. p. 90–110°) it formed a white crystalline powder, and from dilute pyridine it formed rosets of pinkish-white prisms, m. p. 308–309° (corr.), with decomposition.



Anal. Calcd. for $C_{28}H_{22}(OCH_3)_4\left(\begin{array}{l}—O\\ \ \ |\\ —C(OH)CH_3\end{array}\right)_2$: C, 71.76; H, 6.98. Found: C, 71.97; H, 7.10.

It gives a deep yellow color with concentrated sulfuric acid and no ferric chloride color. It is readily soluble in alcoholic alkali to a rose-pink solution which is decolorized by sodium hydrosulfite. The compound is insoluble in sodium carbonate solution.

Phenylmagnesium bromide and gossylic acid lactone tetramethyl ether gave only oily products.

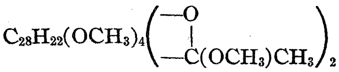
Methylation of Homogossypol Tetramethyl Ether

(1) Dimethyl Sulfate and Alkali (VIII).—To a solution of 0.5 g. of homogossypol tetramethyl ether in 5 cc. of 30% ethanolic potassium hydroxide, dimethyl sulfate was added until the solution was no longer alkaline. Alcoholic alkali and dimethyl sulfate were each added in slight excess several times; the solution was finally made alkaline, diluted and filtered. The crude product was white and crystalline and weighed 0.5 g. After two recrystallizations from methanol and two from dilute dioxane the compound was obtained as tiny clusters of white needles, m. p. 242–243° (corr.), to a colorless liquid which was stable up to 270°.

Anal. Calcd. for $C_{28}H_{22}(OCH_3)_6(COCH_3)_2$: C, 72.38; H, 7.30. Found: C, 72.61; H, 7.58.

The compound is insoluble in alcoholic alkali and gives a yellow color with concentrated sulfuric acid.

(2) Methanol–Sulfuric Acid (IX).—To a suspension of 0.2 g. of homogossypol tetramethyl ether in 10 cc. of methanol was added 8 drops of concentrated sulfuric acid. On warming, the compound dissolved with the formation of an emerald green solution and after a few moments' refluxing, colorless prisms began to separate from the solution. After cooling, the product was collected. It was obtained as colorless flat prisms and weighed 0.2 g. After several recrystallizations from dilute acetone it was obtained as flat white prisms, m. p. 255–256° (corr.), to a pink liquid. The same product was obtained by methylation in methanol with dimethyl sulfate and alkali but with an excess of dimethyl sulfate. In this case to a solution of 0.5 g. of homogossypol tetramethyl ether in 4 cc. of methanol and 4 cc. of dimethyl sulfate was added 6 cc. of 10% methanolic potassium hydroxide and the mixture was allowed to stand overnight. The solid (product and methyl potassium sulfate) was collected on a filter, the potassium salt washed out with water, and the water-insoluble portion recrystallized from dilute acetone. It formed flat white prisms, m. p. 255–256°, and gave no depression in melting point when mixed with the product obtained by the use of methanol–sulfuric acid.



Anal. Calcd. for $C_{28}H_{22}(OCH_3)_4\left(\begin{array}{l}—O\\ \ \ |\\ —C(OCH_3)CH_3\end{array}\right)_2$: C, 72.38; H, 7.30. Found: C, 72.52; H, 7.23.

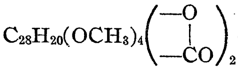
A mixture of IX (m. p. 255–256°) and VIII (m. p. 242–243°) melted at 221–236°.

The compound is insoluble in alcoholic alkali and gives a deep yellow color with concentrated sulfuric acid.

Oxidation of Gossylic Acid Tetramethyl Ether.—The directions followed for this oxidation were those previously described for the oxidation of gossypol hexamethyl ether. One gram of the lactone was converted to the hydroxy acid as described above, and the latter compound was refluxed for four hours with a mixture of 10 cc. of concentrated nitric acid and 40 cc. of water. The solid first became gummy, then gradually formed a hard pale yellow mass (with spots of red-brown gum). After cooling, the solution was neutralized and extracted with ether, the solid dissolved in this ether solution and the solvent removed and replaced with methanol. On standing, 0.48 g. of bright yellow needles separated. Recrystallized from benzene–ligroin (b. p. 60–110°), the compound formed soft yellow needles which gave no depression in melting point when mixed with the product obtained in a similar oxidation of gossypol hexamethyl ether, and gave identical color reactions in sulfuric acid (brownish-red) and methanolic alkali (blue-green).

Dinitrogossylic Acid Lactone Tetramethyl Ether (XIV).—A suspension of 0.95 g. of the lactone in a mixture of 20 cc. of glacial acetic acid and 3 cc. of concentrated nitric acid was heated to boiling on a hot-plate. The lactone dissolved in the course of several minutes to a clear brownish-yellow solution. Water was added carefully. The solution was kept at the boiling point until crystallization started, and the mixture was allowed to cool. The product separated in pale yellow, flat needles melting at 246–248°, and weighed 0.87 g.

Recrystallized from acetone–methanol, ether–petroleum ether or ethyl acetate–petroleum ether, the compound formed pale yellow prisms which melted at 238–239° (corr.), resolidified, and then remelted at 247–248° (corr.). Recrystallized from dilute acetic acid the compound formed flat, slender, pale yellow needles which melted sharply at 247–248°.



Anal. Calcd. for $C_{28}H_{20}(OCH_3)_4\left(\begin{array}{l}—O\\ \ \ |\\ —CO\end{array}\right)_2(NO_2)_2$: C, 61.82; H, 4.85; N, 4.25. Found (methanol–acetone): C, 61.97; H, 5.03; N, 4.43. Found (dilute acetic acid): C, 62.16; H, 5.06; N, 4.48.

The compound gives a yellow color with concentrated sulfuric acid and no ferric chloride color. It is insoluble in aqueous alkali, but dissolves readily in cold methanolic alkali to a deep orange-red solution.

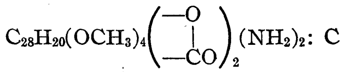
Diaminogossylic Acid Lactone Tetramethyl Ether.—Reduction of the nitro compound with zinc dust in acetic acid, sodium hydrosulfite in alkali or iron in acetic acid yields the same compound.

To a hot solution of 0.5 g. of the nitro compound (XIV) in 5 cc. of acetic acid was added 0.5 g. of iron powder. The pale yellow color of the solution changed quickly to a deep orange. After the addition of a drop of hydrochloric acid the solution was heated for thirty minutes on the steam bath. A heavy precipitate of orange needles formed after a few minutes.

At the end of thirty minutes some acetic acid was added to dissolve the product which had separated and the solution was filtered, several small portions of boiling acetic acid being used to extract the product which was admixed with the iron. The hot solution was diluted carefully until crystallization started. On cooling, there was obtained

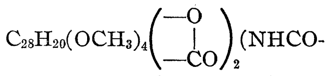
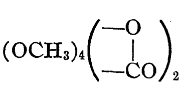
0.38 g. of bright orange platelets, and on dilution of the mother liquors there was obtained an additional 80 mg. of what was largely unreduced nitro compound.

Recrystallization of the main portion several times from slightly diluted acetic acid (with the addition of a small amount of iron) resulted in the formation of bright orange platelets, m. p. 293–294° (corr.), with decomposition.

Anal. Calcd. for  $C_{28}H_{20}(OCH_3)_4\left(\begin{array}{c}\text{—O}\\ |\\ \text{—CO}\end{array}\right)_2(NH_2)_2$: C, 68.00; H, 6.00; N, 4.67. Found: C, 67.52; H, 6.09; N, 4.54.

The compound gives a pale yellow color with concentrated sulfuric acid and is readily soluble in methanolic hydrochloric acid (but not in methanol) or in a mixture of acetic acid and hydrochloric acid. Upon the addition of hydrochloric acid to the orange solution of the compound in acetic acid the color fades to pale yellow. It dissolves with some difficulty in warm alcoholic alkali with the formation of a yellow solution which rapidly turns deep blue in air.

Acetylation of Amino Derivative.—A solution of 0.27 g. of the diamine and 0.1 g. of anhydrous sodium acetate in 5 cc. of acetic anhydride was refluxed for one hour. The initially deep orange solution soon became a pale yellow. The excess acetic anhydride was decomposed with water and the product, which weighed 0.29 g., was recrystallized twice from methanol, from which it formed pearly-white leaflets, m. p. 252–253° (corr.).

Anal. Calcd. for  $C_{28}H_{20}(OCH_3)_4\left(\begin{array}{c}\text{—O}\\ |\\ \text{—CO}\end{array}\right)_2(NHCOCH_3)_2$: C, 66.66; H, 5.85; N, 4.10. Calcd. for  $C_{28}H_{20}(OCH_3)_4\left(\begin{array}{c}\text{—O}\\ |\\ \text{—CO}\end{array}\right)_2[N(COCH_3)_2]_2$: C, 65.63; H, 5.73; N, 3.65. Found: C, 66.03; H, 5.71; N, 3.71.

The compound is insoluble in alcoholic hydrochloric acid.

Summary

Gossylic acid lactone tetramethyl ether has been shown to be a *peri*-naphthalene lactone. It can be hydrolyzed to the corresponding hydroxy acid which can be methylated with diazomethane or alkali and dimethyl sulfate to the ether ester. The hydroxy acid is oxidized with dilute nitric acid to gossypolonic acid tetramethyl ether, the same water-insoluble quinone obtained by the oxidation of gossypol hexamethyl ether with nitric acid. The color indicates a *p*-quinone which demonstrates the probability of unsubstituted hydrogens para to the hydroxyls in the hydroxy acid.

The lactone is resistant to oxidation but is nitrated to a dinitro derivative. The nitro groups presumably occupy the unsubstituted positions para to the hydroxyls.

Gossypol can be considered as having two naphthalene nuclei each containing the following substitutions: 1-aldehydo, 5-hydrogen, 8-hydroxyl.

URBANA, ILLINOIS RECEIVED JUNE 27, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Structure of Gossypol. XIII.[1] Conversion of Gossic Acid to Apogossypolic Acid

BY ROGER ADAMS AND R. C. MORRIS

Two products are obtained by oxidation of gossypol hexamethyl ether with nitric acid, a water-insoluble, gossypolonic acid tetramethyl ether, and a water-soluble, gossic acid. The former is converted into the latter by the action of potassium permanganate.[2] Gossic acid has approximately half the molecular weight of the original compound and consequently knowledge of its structure would be of unusual value in clarifying the structure of gossypol.

It was shown previously that gossic acid contains two methoxyls, one carboxyl, and one dibasic acid anhydride linkage formulated as I. These facts were deduced from a Zeisel determination, titration for a tribasic acid in aqueous solution, formation of a monomethyl ester (II) by the action of diazomethane and a molecular weight determination. Various derivatives and degradation products now have been prepared. Gossic acid is hydrolyzed by alkali to a tribasic acid (III) which could not be isolated in a pure state due to its tendency to revert to gossic acid. However, an ether solution of the hydrolyzed gossic acid was methylated with diazomethane and a stable crystalline trimethyl ester (IV) obtained. This confirms the presence of a carboxyl and a dibasic acid anhydride residue in gossic acid. By demethylation of gossic acid, the corresponding dihydroxy acid (V) was isolated readily. That no rearrangement was involved was indicated by the action of diazomethane on the demethylated product. The methyl ester

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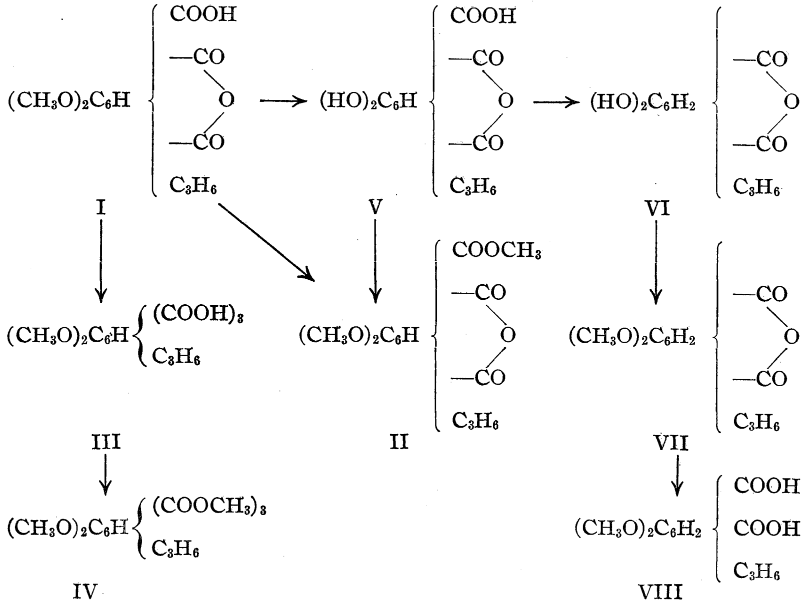
[1] For previous paper in this series see Adams and Geissman, THIS JOURNAL, **60**, 2184 (1938).

[2] Adams, Morris and Kirkpatrick, *ibid.*, **60**, 2170 (1938).

of gossic acid (II) previously prepared from gossic acid resulted. The demethylated gossic acid, when heated with quinoline and copper bronze, lost carbon dioxide to give a dihydroxy dibasic acid anhydride, $C_{11}H_{10}O_5$ (VI). This in turn, upon methylation with diazomethane, gave a dimethoxy dibasic acid anhydride (VII), which proved to be identical with apogossypolic acid anhydride and which hydrolyzed to apogossypolic acid (VIII).[3] This series of reactions is shown as



There are several interesting deductions which may be drawn from these experiments. Gossic acid is derived from gossypol hexamethyl ether, and apogossypolic acid from apogossypol hexamethyl ether. The difference between gossic and apogossypolic acids is merely a single carboxyl group. Since gossypol has two aldehyde groups and apogossypol none, and since the oxidation products are obtained by not dissimilar reactions, it is a reasonable speculation that one of the aldehyde groups in the gossypol hexamethyl ether accounts for the carboxyl group which is present in gossic acid and which is not found in apogossypolic acid anhydride.

The dihydroxy compounds (V and VI) both give a green color with ferric chloride indicative of two ortho hydroxyls. These compounds are oxidized by blowing air through the alkaline solutions. Upon acidification of the oxidized solutions they both yield the same red crystalline compound, which has the formula $C_9H_{10}O_4$, and which appears to be a quinone, since it can be reduced with sodium hydrosulfite and the colorless solution thus obtained can be reoxidized by shaking in air.

Experimental

Trimethyl Ester of Hydrolyzed Gossic Acid.—A solution of 0.100 g. of gossic acid in 5 cc. of 10% aqueous sodium hydroxide was prepared by warming for a few minutes on the steam-bath and then cooling in an ice–salt mixture. The cooled solution was acidified carefully with dilute hydrochloric acid and extracted a number of times with ether. The ether extracts were combined and washed with cold water. To this solution was added an ether solution of diazomethane from 0.5 g. of nitrosomethyl urea. The reaction mixture was allowed to stand overnight at room temperature, then washed with dilute sodium hydroxide. The ether was evaporated and the residue purified by crystallization from petroleum ether (30–60°), m. p. 70–71°.

Anal. Calcd. for $C_{17}H_{22}O_8$: C, 57.6; H, 6.21. Found: C, 57.56; H, 5.92.

Demethylation of Gossic Acid.—A suspension of 0.15 g. of gossic acid was refluxed very gently with 5 cc. of constant boiling hydrobromic acid for twenty to twenty-five minutes. The material dissolved in a short time and at the end of the reaction the solution had only a light yellow color. The reaction mixture was diluted with water, neutralized with sodium carbonate, acidified to congo red with dilute sulfuric acid, and extracted with ether. The ether was evaporated and the residue crystallized from acetone–petroleum ether (b. p. 60–110°). Long colorless needles formed, m. p. 140–141°.

Anal. Calcd. for $C_{12}H_{10}O_7$: C, 54.2; H, 3.76; mol. wt., 266. Found: C, 54.43; H, 3.80; mol. wt. (Rast), 280.

This product gave a green color with alcoholic ferric chloride, and a very light yellow color when dissolved in cold concentrated sulfuric acid. The material dissolved easily in 10% aqueous sodium hydroxide to give a light yellow solution, which became bright red upon shaking with air.

Action of Diazomethane on Demethylated Gossic Acid.—To an ether solution of 0.10 g. of the demethylated gossic acid was added an ether solution of diazomethane from 0.15 g. of nitrosomethyl urea. The reaction mixture was allowed to stand overnight at room temperature, then the ether was evaporated and the residue purified by sublimation at 15 mm., followed by crystallization from petroleum ether (b. p. 30–60°); white needles, m. p. 106°. The mixed melting point gave no lowering with the ester of gossic acid previously described.

Oxidation of Demethylated Gossic Acid.—A solution of 0.10 g. of the demethylated gossic acid in 5 cc. of 10%

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(3) Adams and Butterbaugh, THIS JOURNAL, **60**, 2174 (1938).

aqueous sodium hydroxide was oxidized by blowing a stream of air through it. The alkaline solution was at first a bright yellow, changing to a deep orange, and finally to a bright red. After nine hours the solution was acidified with dilute sulfuric acid and the flocculent precipitate filtered, washed, and dried. The residue was purified by sublimation at 15 mm., and subsequent crystallization from benzene; large red plates, m. p. 179–181°.

Anal. Calcd. for $C_9H_{10}O_4$: C, 59.5; H, 5.49. Found: C, 59.56; H, 5.55.

Sodium hydrosulfite causes the red color to disappear from an aqueous alkaline solution of the compound; on shaking in the air the red color reappears immediately.

Decarboxylation of Demethylated Gossic Acid.—To a solution of 0.20 g. of demethylated gossic acid in 0.8 cc. of dry quinoline was added 0.1 g. of copper bronze. The reaction mixture was heated in a Wood's metal bath at 160–165°. At this temperature there was a vigorous evolution of gas.

When the evolution of gas ceased, the tube was cooled and the reaction mixture diluted with ether. The ether solution was filtered and washed a number of times with dilute hydrochloric acid. The ether was evaporated and the residue purified by sublimation at 15 mm. It crystallized from ether–petroleum ether (b. p. 60–110°) in white plates, m. p. 165–166°.

Anal. Calcd. for $C_{11}H_{10}O_5$: C, 59.5; H, 4.52. Found: C, 59.62; H, 4.40.

The compound gave a green color with alcoholic ferric chloride. It dissolved in aqueous alkali to a yellow solution which changed to red on standing. It was soluble in water and a spontaneous evaporation formed long needles.

Oxidation of Demethylated Decarboxylated Gossic Acid.—Air was blown through a solution of 0.10 g. of demethylated decarboxylated gossic acid in 5 cc. of 10% aqueous sodium hydroxide for nine hours. The material dissolved to give a yellow solution which quickly turned to a bright red on passing through the air.

The solution was acidified with dilute sulfuric acid and extracted with ether. The ether was evaporated and the residue purified by sublimation and crystallization from benzene, m. p. 179–181°. It was shown by mixed melting point to be identical with the product obtained by the alkaline–air oxidation of the demethylated gossic acid.

Diazomethane on Demethylated Decarboxylated Gossic Acid; Apogossypolic Acid Anhydride.—To a solution of 0.10 g. of the demethylated decarboxylated gossic acid in 10 cc. of ether was added an ether solution of diazomethane from 0.15 g. of nitrosomethyl urea. The reaction mixture was allowed to stand at room temperature overnight.

The ether was evaporated and the residue purified by sublimation at 15 mm., followed by crystallization from petroleum ether (b. p. 30–60°); white needles, m. p. 93–94°. The compound gave no depression in melting point when mixed with apogossypolic acid anhydride.

Anal. Calcd. for $C_{13}H_{14}O_5$: C, 62.4; H, 5.60; $2OCH_3$, 24.8. Found: C, 62.1; H, 5.39; OCH_3, 23.6.

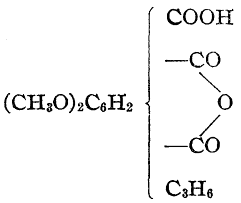
A solution of 0.050 g. of this product in 10% aqueous sodium hydroxide was cooled in an ice-bath and carefully acidified with dilute sulfuric acid. The suspension that formed was extracted with ether, the ether extract dried and evaporated. The residue was crystallized from petroleum ether (b. p. 30–60°), m. p. 170–171° with decomposition. This compound gave no depression in melting point when mixed with *apogossypolic* acid.

Anal. Calcd. for $C_{13}H_{16}O_6$: C, 58.3; H, 5.97; neut. equiv., 134. Found: C, 58.31; H, 6.24; neut. equiv., 134.

On sublimation at 15 mm. dehydration takes place with formation of apogossypolic acid anhydride as shown by melting point and mixed melting point.

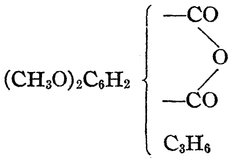
Apogossypolic acid was very stable to alkaline permanganate and was recovered unchanged even on long refluxing.

Summary

Gossic acid, 

$$(CH_3O)_2C_6H_2\left\{\begin{array}{l} COOH \\ -CO \\ \qquad \diagdown \\ \qquad\quad O \\ \qquad \diagup \\ -CO \\ C_3H_6 \end{array}\right.$$

, obtained by oxidation of gossypol hexamethyl ether has been degraded through (1) demethylation with hydrobromic acid followed by (2) heating with quinoline and copper bronze and subsequent (3) methylation with diazomethane. The final product proved to be apogossypolic anhydride,



$$(CH_3O)_2C_6H_2\left\{\begin{array}{l} -CO \\ \qquad \diagdown \\ \qquad\quad O \\ \qquad \diagup \\ -CO \\ C_3H_6 \end{array}\right.$$

, the product obtained by oxidation of apogossypol hexamethyl ether. It appears likely that the carboxyl group in gossic acid is produced from an aldehyde group in gossypol.

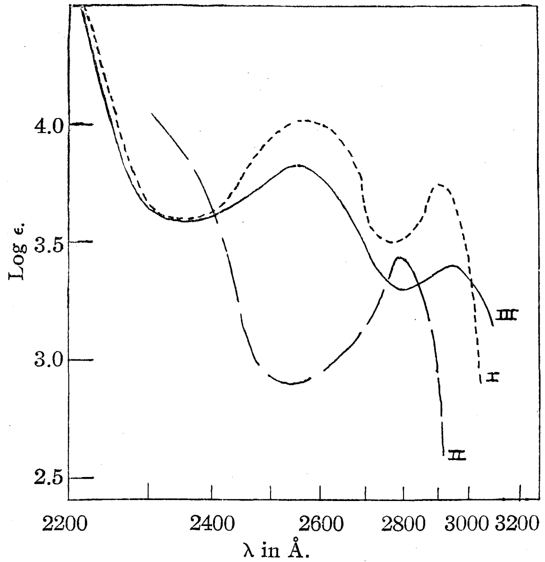
URBANA, ILLINOIS RECEIVED JUNE 27, 1938

[Contribution from the Chemical Laboratory of the University of Illinois]

Structure of Gossypol.[1] XIV. Apogossypolic Acid

By Roger Adams, R. C. Morris, D. J. Butterbaugh[2] and E. C. Kirkpatrick[2]

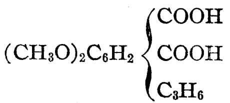
Apogossypolic acid[1,3] which can be obtained from gossypol hexamethyl ether by oxidative and degradation reactions and from apogossypol hexamethyl ether by oxidation has the formula shown in I. The possible position or positions for the C_3H_6 residue have been discussed previously.[3]



I, Veratric acid; II, homoveratric acid; III, decarboxylated apogossypolic acid.

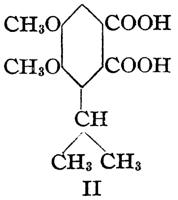
Fig. 1.

The two most likely structural formulas are assumed to be II and III.

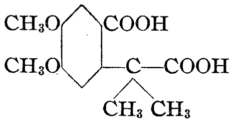


$$(CH_3O)_2C_6H_2\left\{\begin{array}{l}COOH\\COOH\\C_3H_6\end{array}\right.$$

I

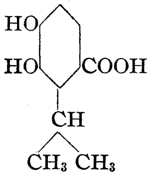


II

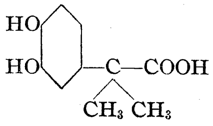


III

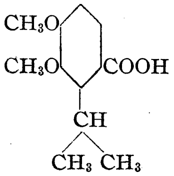
By extended boiling with hydrobromic acid, two methoxyls are converted to hydroxyls and one molecule of carbon dioxide is lost. The compound thus produced is postulated as IV or V. Upon treatment of this substance with diazomethane, methylation of the hydroxyl and carboxyl groups occurs and upon saponification the dimethoxy acid (VI or VII) results. The fact that the ester saponifies with reasonable ease is in favor of structure VI, for esters of the type of the acid shown in VII saponify only with great difficulty. This monobasic acid (VI or VII) is surprisingly resistant to oxidation and no satisfactory results were obtained after repeated experiments. Moreover, the carboxyl from compound IV or V could not be eliminated by any of the usual procedures which decarboxylate 1,2-dihydroxy-4-benzoic acid.



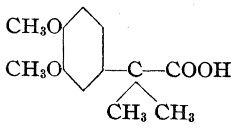
IV



V

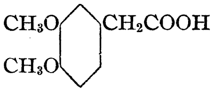


VI

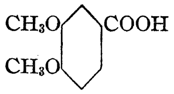


VII

The absorption spectra of homoveratric acid (VIII) and of veratric acid (IX) were compared with that of compound VI or VII. The results are shown in Fig. 1. It is clearly apparent that the absorption spectra of veratric acid and the acid from gossypol resemble each other closely and differ from that of homoveratric acid. Formula V, therefore, was assumed to be that of decarboxylated apogossypolic acid. The presence of the isopropyl group ortho to the carboxyl may account for the difficulty in eliminating the carboxyl in compound IV. The difficulty with which the compound apparently is



VIII



IX

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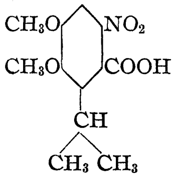
[1] For previous paper in this field see Adams and Morris, This Journal, **60**, 2188 (1938).

[2] Portions of theses submitted in partial fulfilment of the degree of Doctor of Philosophy by D. J. Butterbaugh, Chemical Foundation Fellow 1935–1938, and E. C. Kirkpatrick, Solvay Process Fellow, 1936–1938.

[3] Adams and Butterbaugh, This Journal, **60**, 2174 (1938).

oxidized may be explained by the hindrance of the isopropyl group by ortho substitutents.

Apogossypolic acid reacts with nitric acid and a carboxyl group is replaced by a nitro. Two alternative structures, based on formula V, are possible but compound X is the more likely because oxidation of the nitro compound failed and oxidation might have been expected if the nitro were ortho to the isopropyl group. This replacement is analogous to that reported for the substitution of the carboxyl group in veratric acid by a nitro group.[4] Upon reduction of the mononitromonocarboxylic acid (X), an amino compound was formed which was purified by sublimation. The product proved to be not the expected amino acid but an amine (XI) due to loss of carbon dioxide. A lactam (XII) undoubtedly would have resulted if the structure of the apogossypolic acid was III. The decarboxylation of the amino compound upon sublimation resembles the reaction of *o*-aminobenzoic acid under similar conditions. These facts leave little doubt that the C_3H_6 is present in the molecule as a propyl or isopropyl substituent in the benzene ring. It cannot be present as two groups, an ethyl and methyl, because apogossypolic acid may be formed from gossic acid which contains in the ring two methoxyls and three carboxyls and hence only a single position for the C_3H_6 residue is available. The group is probably isopropyl since experimental evidence indicated that isopropyl alcohol was lost in the conversion of apogossypol hexamethyl ether to desapogossypol hexamethyl ether.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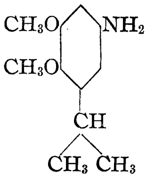
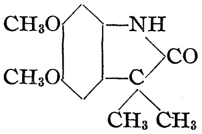
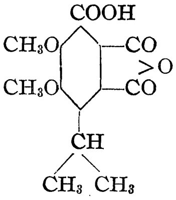
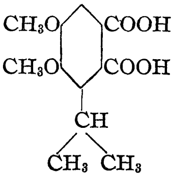
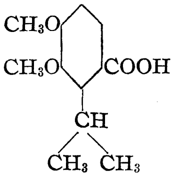

XI


XII

It is true that the experimental facts available do not allow a conclusive deduction concerning the relative positions of the methoxyl, isopropyl, and carboxyl groups in apogossypolic acid. However, indirect evidence adduced from the study of the various degradation products of gossypol and apogossypol is very helpful[5] and practically limits the structures of gossic acid to XIII, apogossypolic acid to XIV and decarboxylated apogossypolic acid to XV. The absolute proof of these must await synthesis.


XIII


XIV


XV

Experimental

Action of Hydrobromic Acid on Gossic Acid, Apogossypolic Acid or Apogossypolic Acid Anhydride.—The same product was obtained by the action of constant boiling hydrobromic acid on gossic acid, apogossypolic acid or its anhydride. Since from a preparative standpoint gossic acid is the most convenient raw material, the detailed directions below involve this product. The procedure for the other compounds is exactly the same except that only two hours of boiling with hydrobromic acid instead of four is necessary.

A suspension of 0.10 g. of gossic acid was refluxed for four hours with 5 cc. of constant boiling hydrobromic acid. At the end of this time the reaction mixture was poured into a beaker. On cooling there separated a precipitate of light pink crystals. The product was filtered and purified by sublimation and crystallization from benzene or toluene. It formed colorless plates, m. p. 216–217°. The product may be heated until it distils and is recovered unchanged.

Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.2; H, 6.12. Found: C, 61.21; H, 6.55.

The compound gave a green color with alcoholic ferric chloride. A solution of the compound in dilute aqueous sodium hydroxide rapidly becomes yellow and on standing longer changes to deep orange.

Diazomethane on Demethylated Decarboxylated Apogossypolic Acid.—To a solution of 0.02 g. of the demethylated decarboxylated apogossypolic acid in ether was added an ether solution of diazomethane. The reaction was allowed to stand overnight at room temperature. The ether solution was then washed with cold 2% aqueous sodium hydroxide and evaporated. The residue was purified by sublimation and then crystallization from petroleum ether (b. p. 30–60°); colorless prisms, m. p. 106–107°.

Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.6; H, 7.56. Found: C, 65.42; H, 7.20.

Saponification of the Methyl Ester of Decarboxylated Apogossypolic Acid.—A suspension of 0.10 g. of the ether was refluxed with 10% aqueous sodium hydroxide until solution was complete. The reaction mixture was then cooled, acidified with dilute sulfuric acid, and extracted with ether. The ether was evaporated and the residue

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[4] Zincke and Franke, *Ann.*, **293**, 177 (1896). See also Wegscheider and Klemenc, *Monatsh.*, **31**, 740 (1910); Rossin, *ibid.*, **12**, 493 (1891).

[5] See papers VII–XIII of this series.

purified by sublimation followed by crystallization from benzene; colorless plates, m. p. 167–169°.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.4; H, 7.15. Found: C, 64.85; H, 7.42.

Action of Dilute Nitric Acid on Apogossypolic Acid.—A mixture of 0.15 g. of apogossypolic acid, 3 cc. of concentrated nitric acid and 9 cc. of water was refluxed for two hours. Upon cooling, fine white crystals separated. These were purified by crystallization from cyclohexane, m. p. 155–158°; yield 0.105 g.

Anal. Calcd. for $C_{12}H_{15}O_6N$: C, 53.55; H, 5.58; N, 5.21; neut. equiv., 269. Found: C, 53.79; H, 5.75; N, 5.19; neut. equiv., 268.

Reduction of the Nitric Acid Product of Apogossypolic Acid.—The product just described was reduced with Raney nickel and hydrogen under 2.5 atm. pressure in ethanol solution. The product was purified by twice subliming at 25 mm.; white crystals, m. p. 74–76°, that turn dark after standing a few hours in air.

Anal. Calcd. for $C_{11}H_{17}O_2N$: C, 67.7; H, 8.72; N, 7.18. Found: C, 67.84; H, 8.62; N, 6.96.

This material was insoluble in dilute aqueous sodium hydroxide but soluble in 5% aqueous hydrochloric acid. It diazotized with nitrous acid and the solution gave a red color on treatment with a solution of β-naphthol.

Acetylation of the Amine.—A mixture of 30 mg. of the amine just described, 2 cc. of acetic anhydride and 50 mg. of fused sodium acetate was refluxed gently for thirty minutes. After cooling, the excess acetic anhydride was decomposed by the addition of three to four volumes of water. The solution was evaporated to dryness under a stream of air and the amine acetate extracted from the sodium acetate by means of ether. From this extract a colorless oil was obtained which crystallized after standing for two to three hours. Purification of this crystalline material was accomplished by two sublimations at a bath temperature of 100–125° (18 mm.). This was followed by a dilute acid wash and by a third sublimation; white crystals, m. p. 85–86°.

Anal. Calcd. for diacetate, $C_{15}H_{21}O_4N$: C, 64.52; H, 7.53; N, 5.02. Found: C, 64.73; H, 7.49; N, 5.11.

Summary

Apogossypolic acid is decarboxylated and demethylated by the action of hydrobromic acid. The product, upon methylation with diazomethane and subsequent saponification gives a monobasic acid, decarboxylated apogossypolic acid. A discussion of the structure of this latter product is given.

Apogossypolic acid is converted to a mononitro monocarboxylic acid by the action of nitric acid. The nitro compound upon reduction followed by sublimation gives an aromatic amine containing no carboxyl group. This must be a dimethoxy *n*- or isopropyl aminobenzene. Its structure and the analogous compounds from gossypol are discussed.

The absorption spectrum of decarboxylated apogossypolic acid is similar to that of veratric and dissimilar to homoveratric acid.

URBANA, ILLINOIS RECEIVED JUNE 27, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Structure of Gossypol. XV.[1] An Interpretation of its Reactions

BY ROGER ADAMS, R. C. MORRIS, T. A. GEISSMAN, D. J. BUTTERBAUGH AND E. C. KIRKPATRICK

A large number of reactions of gossypol and of its degradation products have been studied. As the result of this accumulation of experimental evidence, it is now possible to formulate deductively a reasonable structure for the gossypol molecule. The purpose of this communication is to correlate and interpret the physical and chemical properties of gossypol in terms of this structure.

The absorption spectra of gossypol[2] and its derivatives and the formation of many of its degradation products are indicative of a molecule containing two naphthalene nuclei connected either directly or through an alkylene chain. The formula for gossypol must be essentially symmetrical and probably completely so, for an even number of moles of reagent reacts in every instance. The diverse and unusual reactions of gossypol as well as the absorption spectra show every indication that the molecule is tautomeric.

The postulated structure of gossypol is represented by Ia with Ib and Ic representing two possible tautomeric forms.

The structural configuration of gossypol will be discussed and formulas will be assigned for all the significant derivatives and degradation products.

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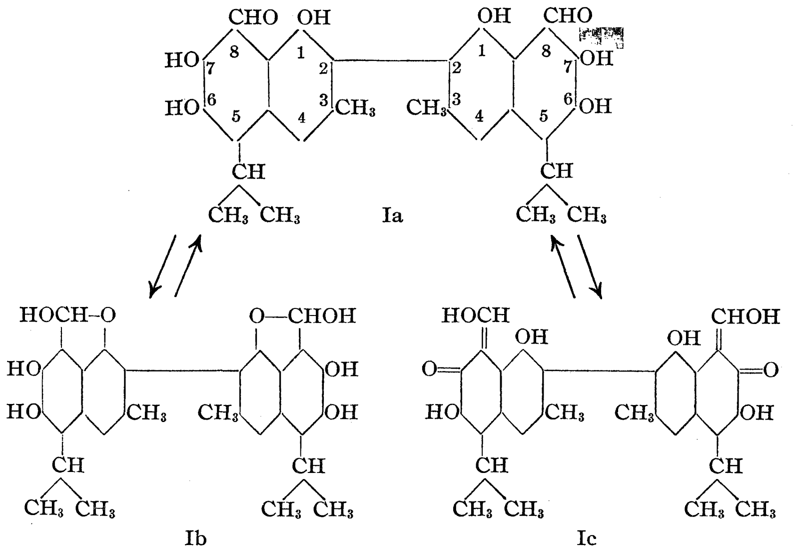
(1) For previous paper in this series, see Adams, Morris, Butterbaugh and Kirkpatrick, THIS JOURNAL, **60**, 2191 (1938).

(2) Adams and Kirkpatrick, *ibid.*, **60**, 2180 (1938); Marchlewski, *J. prakt. Chem.*, **60**, 84 (1899); Grünbaumowna and Marchlewski, *Biochem. Z.*, **286**, 295 (1936); Zamyshlyaeva and Krivich, *J. Gen. Chem.*, (U. S. S. R.), **7**, 1969 (1937).


Ia

Ib

Ic

Wherever structural formulas are used, only half the molecule will be written in order to conserve space. It must be remembered, however, that in all cases double the number of moles of reagents react than is indicated by the half molecules and double the number of groups are introduced.

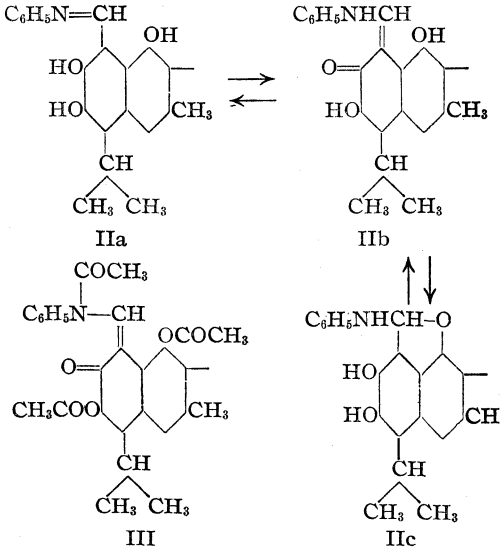
Color Reactions and Salts.[3]—Gossypol gives (1) a green color with ferric chloride, (2) a deep red with pyroboroacetate and (3) a purple red with stannic chloride. These colors have been shown previously to be rather characteristic, particularly in the naphthalene series, (1) of two phenolic hydroxyls ortho to each other, (2) and (3) of a hydroxyl peri or ortho to a carbonyl. These colors may be expected of a molecule with formula Ia. Gossypol forms a stable compound with stannic chloride which was isolated and analyzed. It has a Sn:Cl ratio of 1:2. Naphthalene molecules with two peri hydroxyls and a ketone or aldehyde group form similar compounds. It is not unreasonable to believe that an arrangement of hydroxyls and aldehyde groups as shown in formula Ia would give the same result though no simple naphthalene derivatives with hydroxyls and aldehyde thus placed have been tested.

Gossypol titrates dibasic and forms a dipyridyl salt. Many hydroxyaldehydes show a similar acidity for the phenol group possibly due to the vinylogous relationship of an *o*- or *p*-hydroxyaldehyde to a carboxylic acid.

Aniline and Ammonia Derivatives.[4]—Gossypol condenses readily with two moles of aniline with the elimination of two moles of water. Several substituted anilines, including *o*-phenylenediamine, also condense in the same ratio; others give products which do not analyze for simple derivatives. All these products, however, are readily hydrolyzed by acid to gossypol.

Liquid ammonia reacts similarly to give an easily hydrolyzed diaminogossypol.

Of importance from the structural standpoint are the methylation and acetylation of the yellow dianilinogossypol.[4] Under proper conditions a red dimethylated compound is isolated which has the methyl groups attached to nitrogens since they cannot be removed by hydriodic acid; the methylated compound cannot be hydrolyzed to gossypol. The hexaacetyldianilinogossypol has two acetyls attached to nitrogens since acetanilide is obtained by pyrolysis. These experiments establish the probability of the dianilino compound existing not as a simple Schiff base but as a tautomeric structure such as might be formed from an hydroxymethylene compound, the tautomeric form of an *o*-hydroxy aldehyde. The anilino compound of gossypol therefore is formulated as IIa, IIb, IIc and the hexaacetate possibly as III though it could be based on structure IIc.


IIa

IIb

III

IIc

The amino derivatives produced by the action

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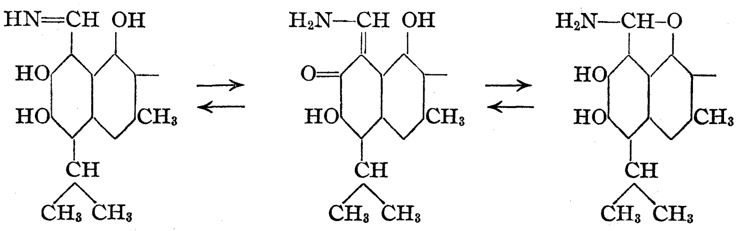
(3) Campbell, Morris and Adams, This Journal, **59**, 1723 (1937).

(4) Adams, Price and Dial, *ibid.*, **60**, 2158 (1938).

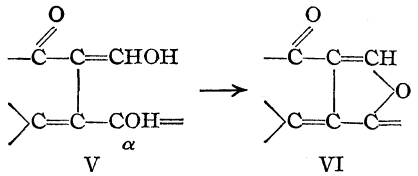
of liquid ammonia probably have analogous formulas, IVa, IVb, IVc.



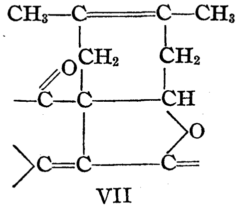
IVa IVb IVc

Anhydrogossypol.[5]—Anhydrogossypol is produced by heating gossypol above its melting point or by the use of a mild dehydrating agent in an inert solvent. It is very sensitive to hydrolysis, regenerating gossypol. The reactions which were attempted such as methylation, acetylation or treatment with liquid ammonia or amines even under strictly anhydrous conditions result not in anhydrogossypol derivatives but in derivatives of gossypol. In the case of anhydrogossypol, the reactions always involve simple addition; in the case of gossypol, the same derivatives are obtained by elimination of water, acetic acid or analogous molecules but never by simple addition. A very easily opened oxygen-containing ring must therefore be present in anhydrogossypol.

The anhydro compound reacts with both butadiene and dimethylbutadiene[6] to give addition products. This indicates the probability of the presence of an α,β-unsaturated carbonyl grouping. The stability of the diene addition compounds to hydrolysis leads to the conclusion that the unstable oxygen-containing ring of anhydrogossypol has been modified and stabilized. It is probable, therefore, that the carbon–carbon double bond of the α,β-unsaturated carbonyl grouping is part of the oxygen-containing ring of anhydrogossypol. Nuclei postulated to account for these transformations are shown in V (gossypol), VI (anhydrogossypol), and VII (diene addition product).



V VI

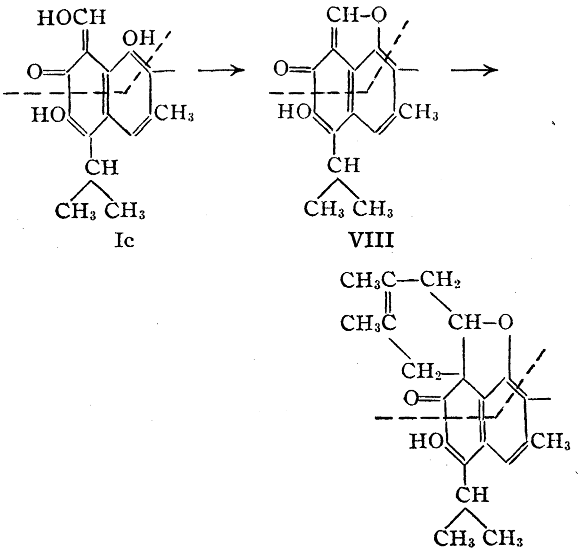


VII

Gossypol also adds dienes but with the simultaneous loss of water to give the same compound obtained from anhydrogossypol.

The α-hydroxyl in formula V must be phenolic since otherwise a nitrogen-containing ring[4] analogous to VI should be produced upon treatment with anhydrous ammonia.

The tautomeric formula of gossypol (Ic) contains just such a nucleus as is shown in V and the formula of anhydrogossypol may thus be VIII and the dimethylbutadiene addition product IX. The portions of the molecules above the dotted lines in Ic, VIII and IX are identical with the corresponding nuclei V, VI and VII.



Ic VIII IX

The oxygen-containing ring structure in VIII probably would hydrolyze readily and that in IX would undoubtedly be stable.

The diene addition products also contain two phenolic hydroxyls which are readily methylated or acetylated. These are shown in IX. The red color which the addition products give with pyroboroacetate is found in molecules with an hydroxyl ortho or peri to a carbonyl.

From a survey of the literature of hydroxy aldehydes of the benzene and naphthalene series, it was impossible to find any record of a derivative

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[5] Miller and Adams, This Journal, **59**, 1736 (1937).

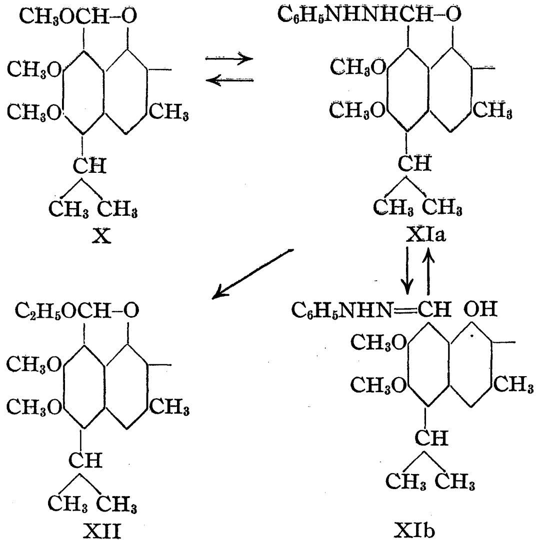
[6] Adams, Friedman, Price, Morris and Kirkpatrick, *ibid.*, **60**, 2160 (1938).

of the tautomeric forms of the hydroxymethylene type. On the other hand, it seems likely they should exist, especially in certain types of polyhydroxy naphthaldehydes and an attempt is now being made to prepare such derivatives. It is worthy of note that Windaus[7] on the basis of sound experimental evidence postulated the hydroxymethylene form of an aromatic hydroxy aldehyde for the structure of colchicine.

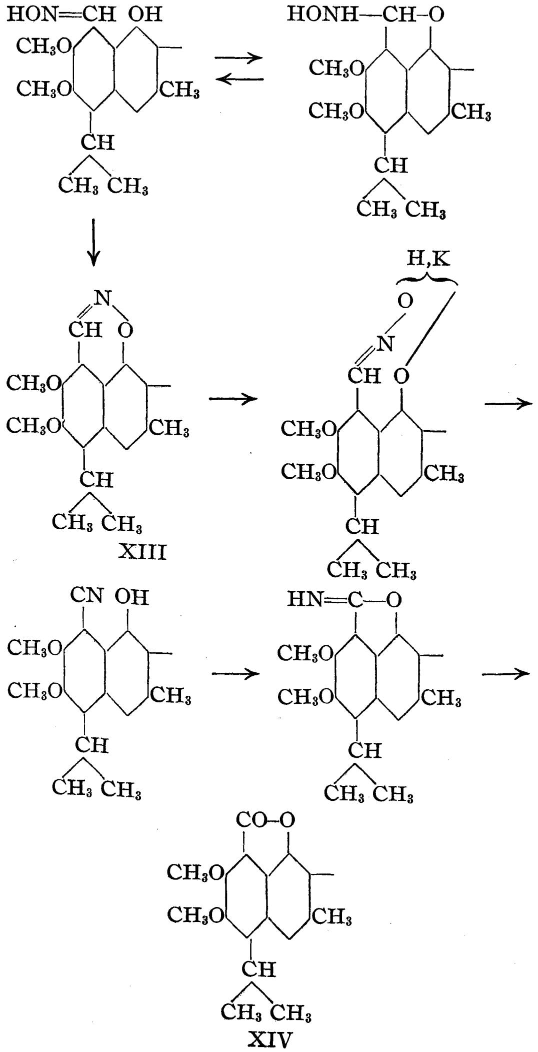
Ethers of Gossypol.[8]—A white tetramethyl ether of gossypol is obtained by the action of dimethyl sulfate on gossypol under conditions which exclude degradation due to the presence of alkali. Further methylation of this compound gives a white or a red hexamethyl ether, depending on the experimental conditions. Moreover, it acetylates to a gossypol tetramethyl ether diacetate.

The tetramethyl ether and the white hexamethyl ether are very stable to alkali or alkaline oxidizing agents in contrast to gossypol. They do not react with aldehyde reagents in neutral solvents. In the presence of acetic acid, however, condensation reactions with aldehyde reagents take place.[9] The substances produced no longer contain six methoxyls. Two apparently are hydrolyzed to hydroxyls and then two moles of reagent react in the normal way with the aldehyde groups. The phenylhydrazine derivative of gossypol hexamethyl ether is a diphenylhydrazone of a gossypol tetramethyl ether; of gossypol tetramethyl ether a diphenylhydrazone of a gossypol dimethyl ether. By means of methanolic hydrochloric acid, the diphenylhydrazone of gossypol tetramethyl ether is reconverted to gossypol hexamethyl ether or by ethanolic hydrochloric acid to gossypol tetramethyl diethyl ether.

It is thus obvious that two of the methoxyls in gossypol hexamethyl ether differ from the other four and their reactivity suggests they are of an acetal type. A lactol structure of a *peri*-hydroxynaphthaldehyde is written to account for these results. Gossypol hexamethyl ether (X) is thus based on structure Ib. The phenylhydrazine derivative is represented by XIa and XIb and the gossypol tetramethyl diethyl ether by XII.



The reaction of hydroxylamine[9] in acetic acid solution with gossypol tetramethyl and hexamethyl ethers also involves the hydrolysis of two methoxyl groups. Two moles of reagent then condense in the usual way, followed however by loss of two more molecules of water. These



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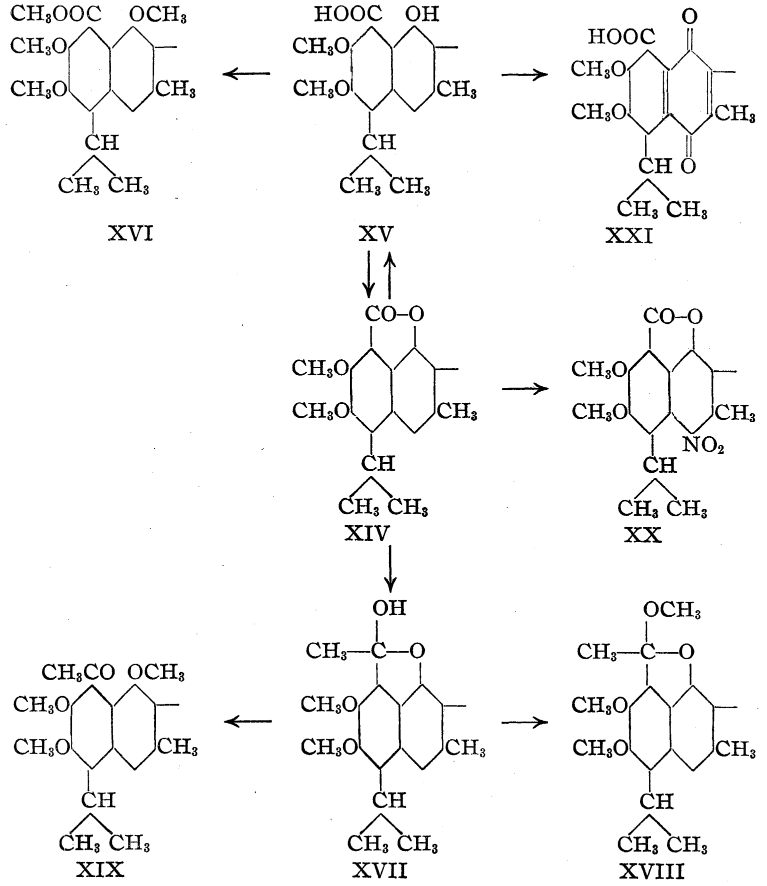
[7] Windaus, *Ann.*, **439**, 59 (1924).

[8] Morris and Adams, This Journal, **59**, 1931 (1937).

[9] Adams and Geissman, *ibid.*, **60**, 2166 (1938).

reactions may best be interpreted by the assumption that orthoxazine rings have formed XIII.

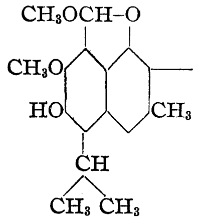


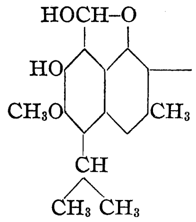
Hydrolysis of the orthoxazine (XIII) followed by treatment with acetic acid results in a lactone, gossylic acid lactone tetramethyl ether (XIV). The hypothetical intermediates in this transformation, the structures of which are given but not numbered, were not isolated.

The lactone[10] (XIV) is hydrolyzed to the hydroxy acid (XV), which can be methylated by treatment either with diazomethane, thus indicating that a phenolic hydroxyl is involved in the lactone, or by dimethyl sulfate and alkali, to give dimethyl gossylate hexamethyl ether (XVI). The fact that XVI could not be hydrolyzed under any usual conditions constitutes evidence for the presence of orthosubstituted groups.

Additional reactions of the lactone (XIV) were also carried out. It reacts with one molecule of methylmagnesium iodide instead of two, as is common to ordinary lactones which are not hindered, and gives homogossypol tetramethyl ether (XVII). Upon methylation with methanolic sulfuric acid, this yields the ether (XVIII) whereas dimethyl sulfate and alkali gives the isomeric ether (XIX). Nitration of the lactone (XIV) results in a dinitro compound (XX). The action of dilute nitric acid upon the hydroxy acid (XV), however, oxidizes it to the quinone, gossypolonic acid tetramethyl ether, shown in XXI.

Gossypol hexamethyl ether[11] can be demethylated partially by means of a drop of sulfuric acid in acetic acid. A dimethyl ether is formed which, unlike the tetra- and hexamethyl ethers, shows many of the characteristic reactions of gossypol. It condenses readily with aniline in neutral solution and undergoes loss of two carbons and two oxygen atoms by treatment with concentrated aqueous sodium hydroxide. Gossypol tetramethyl ether, when demethylated in a similar way, is converted to gossypol. This shows conclusively that the two hydroxyls in gossypol tetramethyl ether are those which are methylated in gossypol dimethyl ether. In view of these facts the formula for the tetramethyl ether is XXII and of the dimethyl ether XXIII.


XXII


XXIII

It becomes obvious why the phenylhydrazine derivatives of gossypol tetramethyl ether (XXIV) and of the dimethyl ether (XXV) are isomeric and not identical.[9]

The structure assigned the hexamethyl ether (X) accounts satisfactorily for the existence of two stereoisomeric forms.[11] The two lactol carbon atoms are asymmetric and, therefore, allow two stereoisomers. Stereoisomers could

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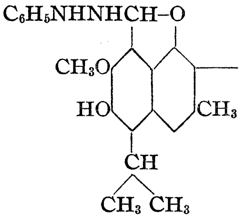
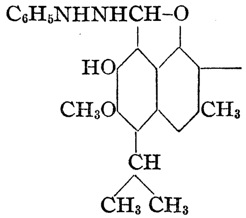
[10] Adams and Geissman, THIS JOURNAL, **60**, 2184 (1938).

[11] Adams and Geissman, *ibid.*, **60**, 2163 (1938).



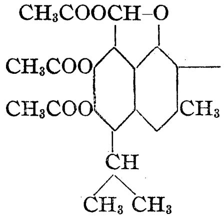
XXIV



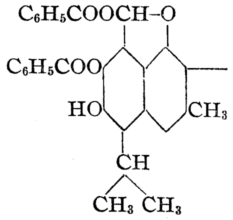
XXV

also be explained on the basis of formula Ia due to restricted rotation between the naphthalene nuclei. Since, however, stereoisomers were isolated only in the case of gossypol hexamethyl ether, the first explanation seems preferable. The formula (X) also explains why its absorption spectra[2] and that of the tetramethyl ether (XXII) differ from those of gossypol and the dimethyl ether (XXIII). The third peak in the spectra of the latter two compounds is missing in the first two. This peak is presumably due to the tautomeric *o*-hydroxyaldehyde nucleus and confirms the structures written for those molecules.

Esters of Gossypol.—Gossypol hexaacetate[12] is formed from gossypol, acetic anhydride and sodium acetate under very mild conditions. In addition to the white hexaacetate, a yellow product is obtained. This latter product is also formed upon heating the white hexaacetate with acetic anhydride. The yellow substance has not been obtained in an analytically pure state so that its character is undetermined. It is natural to assume that the white gossypol hexaacetate has a structure analogous to the hexamethyl ether and is, therefore, XXVI, though other formulas may be written based on the other tautomeric forms of gossypol. Benzoylation of gossypol[13] results merely in a tetrabenzoate and is represented by XXVII.

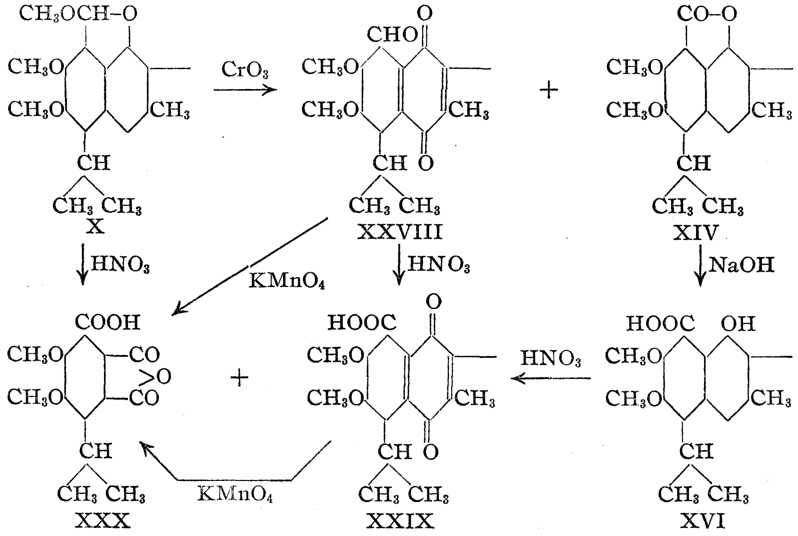


XXVI



XXVII

Oxidation Reactions of Gossypol Hexamethyl Ether.[14]—Gossypol hexamethyl ether (X) upon oxidation with chromic acid yields primarily a compound, gossypolone tetramethyl ether (XXVIII), in which two methoxyls have been hydrolyzed and two hydrogens have been replaced by an oxygen. As a minor by-product the lactone (XIV) is formed. Oxidation of X by dilute nitric acid yields two products in about equal amounts, the first, the water-insoluble gossypolonic acid tetramethyl ether (XXIX) of molecular size about that of the starting material, the second the water-soluble gossic acid (XXX) of about half the molecular size. Gossypolonic acid tetramethyl ether (XXIX) by the action of permanganate gives gossic acid (XXX). Moreover, gossypolone tetramethyl ether (XXVIII) is oxidized by nitric acid to gossypolonic acid tetramethyl ether (XXIX) and by permanganate to gossic acid (XXX). The lactone (XIV) is stable to nitric acid but the corresponding acid (XVI) is oxidized with nitric acid to gossypolonic acid tetramethyl ether (XXIX).



It is obvious how gossic acid (XXX) is produced. The quinone rings of gossypolonic acid tetramethyl ether (XXIX) are oxidized to two *o*-carboxyls which form the anhydride linkage. On the other hand, it is not so clear why gossypolonic acid tetramethyl ether (XXIX) cannot be oxidized with nitric acid to gossic acid (XXX) and still gossic acid is formed directly and simultaneously along with (XXIX) by the nitric acid oxidation of gossypol hexamethyl ether (X). An oxidation with degradation of the naphthalene

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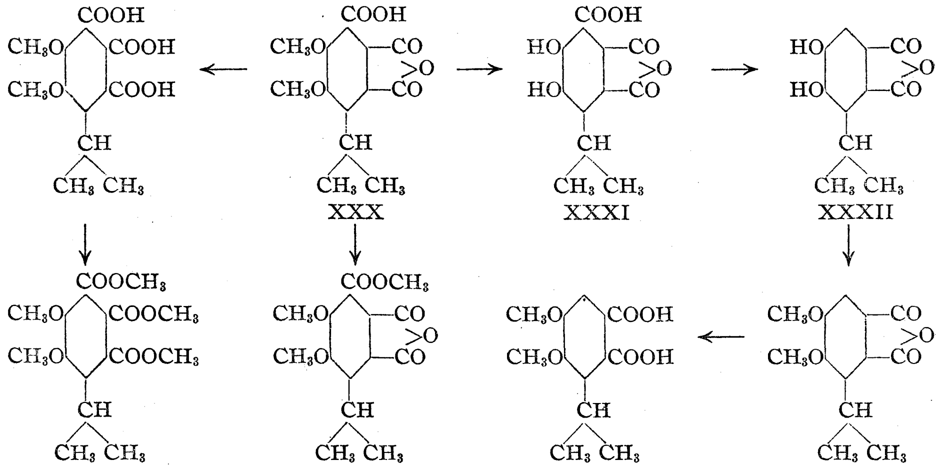
[12] Miller, Butterbaugh and Adams, This Journal, 59, 1729 (1937).

[13] Adams and Butterbaugh, *ibid.*, 60, 2174 (1938).

[14] Adams, Morris and Kirkpatrick, *ibid.*, 60, 2170 (1938).



XXX XXXI XXXII

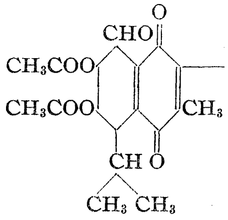
XXXVI XXXV XXXIV XXXIII

nucleus can take place apparently without quinone formation as an intermediate.

An extended study of the reactions of gossypolone tetramethyl ether (XXVIII) or of gossypolonic acid tetramethyl ether (XXIX) has not yet been completed. It has been shown, however, that the former contains no carboxyl groups while the latter contains two. Evidence yet unpublished is that they are quinones. Gossic acid (XXX), on the other hand, by degradation studies has been shown to be a benzene derivative with two methoxyls, a carboxyl, a dibasic acid anhydride and an isopropyl group. The evidence for this last group will be discussed under the heading "Desapogossypol."

Gossic acid[15] (XXX) is converted to apogossypolic acid (XXXIV) through the following intermediates, all of which can be isolated in a pure state, (1) demethylated gossic acid (XXXI), (2) demethylated decarboxylated gossic acid (XXXII), (3) decarboxylated gossic acid or apogossypolic acid anhydride (XXXIII), (4) apogossypolic acid (XXXIV). Other derivatives of gossic acid are also shown, methyl gossate (XXXV) by the action of diazomethane on gossic acid and the trimethyl ester (XXXVI) of hydrolyzed gossic acid by treatment of gossic acid with alkali, followed by acidification and methylation.

Gossypol hexaacetate[16] acts similarly to gossypol hexamethyl ether and undergoes oxidation with chromic acid to gossypolone tetraacetate (XXXVII). Further degradations of this molecule are not feasible because of the tendency for the acetyls to hydrolyze and thus to give products which are unstable and which rapidly decompose.



XXXVII

Apogossypol and its Derivatives.—Gossypol (Ia or Ic) loses two carbons and two oxygens by the action of concentrated aqueous sodium hydroxide.[5,13] The unstable compound produced, apogossypol (XXXVIII), is undoubtedly formed by the loss of the two aldehyde groups. Such a reaction is common to many hydroxyaldehydes of the benzene and naphthalene series. The instability of the product is explicable if compared with many polyhydroxynaphthalenes. The hexaacetate (XXXIX) and hexamethyl ether (XLII) of apogossypol, however, are stable compounds. Both of these derivatives oxidize, the first to apogossypolone tetraacetate (XL) and the second to apogossypolone tetramethyl ether (XLIII). Two methoxyls or two acetoxyls are lost during these reactions and the products are quinones as shown by reductive acetylation to hydroapogossypolone octaacetate (XLI) and hydroapogossypolone tetramethyl ether tetraacetate (XLIV). In the case of the hydroapogossypolone octaacetate (XLI) reoxidation to the quinone takes place readily. It is important to note that parallel series of derivatives are formed from the hexaacetate and hexamethyl ether.

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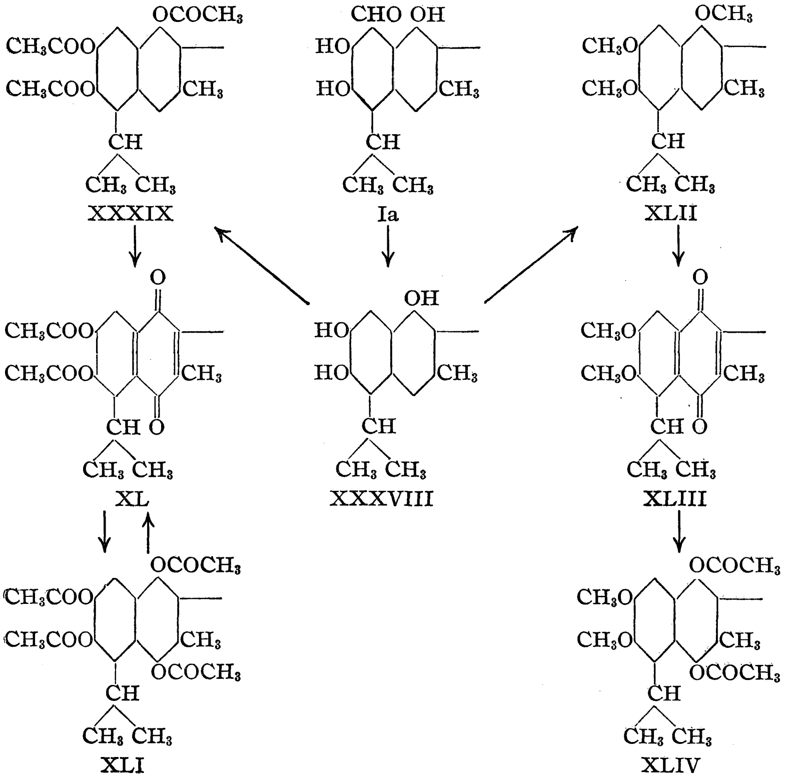
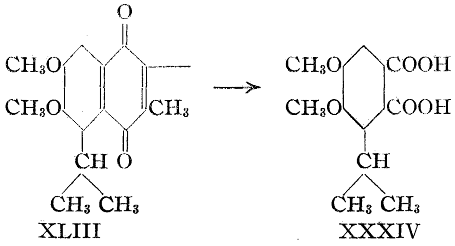
[15] Adams and Morris, THIS JOURNAL, 60, 2188 (1938).

[16] Clark, *ibid.*, 51, 1475 (1929).



The quinone,[13,17] apogossypolone tetramethyl ether (XLIII), upon oxidation with permanganate gives the water-soluble apogossypolic acid (XXXIV) described in connection with the degradation reactions of gossic acid (XXX). This transformation is shown below, the quinone ring oxidizing to two carboxyl groups.



It is significant that apogossypol (XXXVIII), apogossypol hexamethyl ether (XLII) and apogossypolone tetramethyl ether (XLIII) correspond exactly to gossypol Ia, gossypol hexamethyl ether (X), and gossypolone tetramethyl ether (XXVIII). There are two aldehyde groups less in each of the members of the former series, and consequently no condensation with aniline occurs. With the latter series aniline derivatives are formed. Apogossypolic acid (XXXIV) from the first series and gossic acid (XXX) from the second series differ merely by a carboxyl group[18] which presumably has formed from the aldehyde group by oxidation. Observation of this parallelism in the gossypol and apogossypol series leads to the conclusion that gossypolone tetramethyl ether and apogossypolone tetramethyl ether must have analogous structures. Since the latter has been shown unquestionably to be a quinone, the former is almost certain to be one also. This is confirmed by comparison of their absorption spectra.

Apogossypolic acid (XXXIV) has been degraded in a number of ways.[1] Methylation gives a dimethyl ester (XLV), and sublimation, the anhydride (XXXIII). Hydrobromic acid hydrolyzes the methoxyl groups and at the same time a carboxyl group is eliminated as carbon dioxide giving compound (XLVI). Methylation of (XLVI) gives the dimethoxy ester (XLVII) and saponification of the latter the acid (XLVIII).

Apogossypolic acid upon treatment with nitric acid is converted to a compound in which one carboxyl has been replaced by a nitro group, postulated as XLIX. Reduction of this substance gives the amino acid (L) which was not isolated as such, for attempted purification by sublimation results in the loss of carbon dioxide with the formation of the amine (LI). This series of reactions has eliminated both of the carboxyl groups in apogossypolic acid and has thus demonstrated that they must be directly attached to the benzene nucleus.

The structures of these substances are assigned on the basis of indirect evidence or by analogies and not upon experimental data. Further study may necessitate changes in them. Thus, the nitro derivative (XLIX) of apogossypolic acid may have the nitro group in place of one or the other of the two carboxyls. Moreover, by hydrobromic acid treatment of apogossypolic acid,

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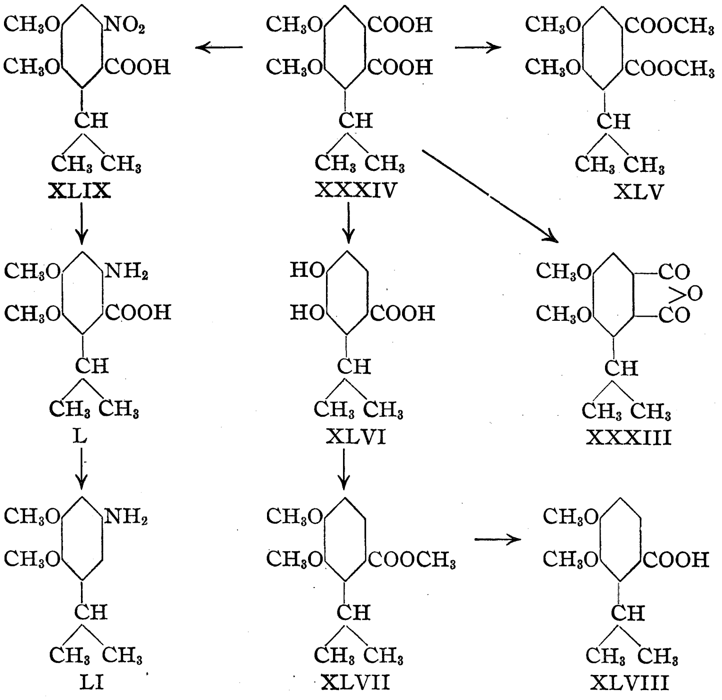
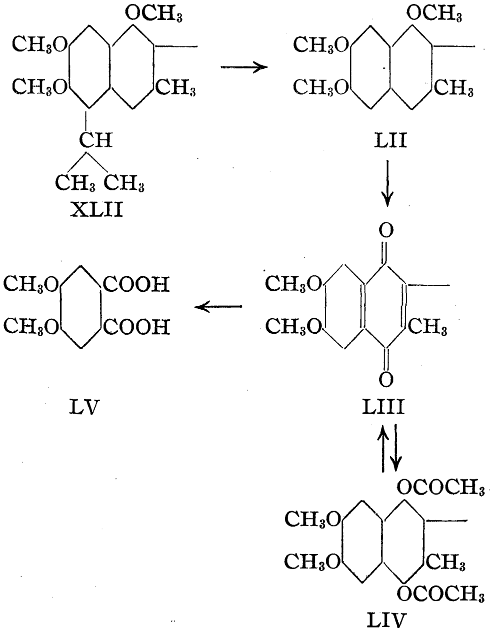
(17) Clark, *Oil & Fat Industries*, **6**, 7, 15 (1929).

(18) The fact that two carboxyls stabilize themselves as an anhydride linkage in gossic acid is of secondary importance.



the resulting molecule will be different depending upon which carboxyl is lost. The relative positions of the methoxyls and isopropyl group from indirect evidence appear indisputable and are the important factor in these molecules. The position of the other groups is less significant.

Desapogossypol and its Derivatives.[13]—Apogossypol hexamethyl ether (XLII) reacts with cold concentrated sulfuric acid and a loss of C_6H_{12} occurs. The product, which still contains six methoxyl groups, is desapogossypol hexamethyl ether (LII). It is not unlike the corresponding apo compound in its reactions for it oxidizes to a quinone, desapogossypolone tetramethyl ether (LIII), with loss of two methoxyls. Moreover, the quinone is reductively acetylated to hydrodesapogossypolone tetramethyl ether tetraacetate (LIV) which in turn can be reoxidized to the quinone (LIII).



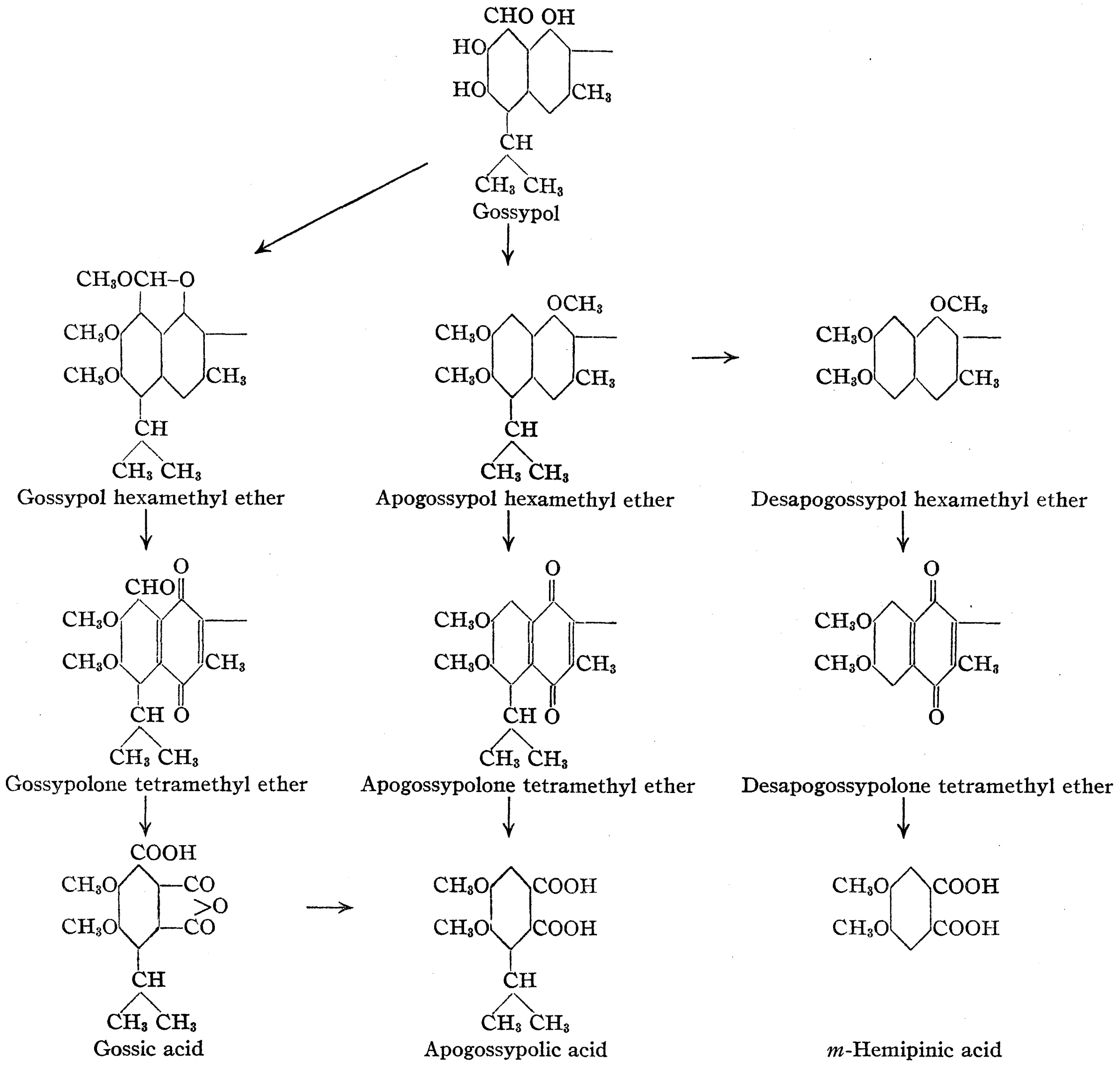
Desapogossypolone tetramethyl ether oxidizes with permanganate to *m*-hemipinic acid (LV), the only known product from gossypol which has yet been isolated. The difference between the molecular formula of *m*-hemipinic acid and apogossypolic acid (XXXIV) is a C_3H_6 residue. Between the corresponding but less degraded compounds of the desapogossypol and the apogossypol series, there is a difference of C_6H_{12} and between those of the desapogossypol and gossypol series C_6H_{12} and 2CO. It is, therefore, reasonably certain that the C_6H_{12} residue merely corresponds to two C_3H_7 groups, one in each naphthalene nucleus. By distilling the dilute sulfuric acid filtrate from the preparation of desapogossypol, a distillate is obtained which on oxidation gives a test for acetone. This demonstrates that the groups are isopropyls and are being removed directly from the naphthalene nuclei by hydrolysis.

The deductive evidence that has just been submitted for assuming gossypol to contain two naphthalene nuclei and that the functional groups present are of the kind and in the location shown in Ia, can best be summarized by a table of formulas (Table I) in which the relationships between the most important derivatives of gossypol are clearly apparent. All intermediates are omitted.

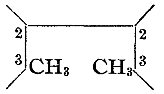
The experimental facts discussed in this communication have established without much question the functional groups in the 1, 5, 6, 7 and 8-positions of the two naphthalene nuclei. There is reasonable certainty of a hydrogen in the 4-position as deduced by the yellow color of the quinones; the possibility that the hydrogen may be in the 2-position is not absolutely excluded. No direct evidence is yet in hand from which the linkages and groups in the 2,3-positions may be

TABLE I

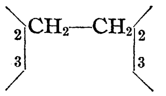
CORRELATION OF GOSSYPOL, APOGOSSYPOL AND DESAPOGOSSYPOL DERIVATIVES



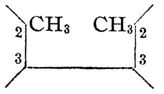
assigned. Alternative isomeric structures for that portion of the molecule associated with the linkage of the two naphthalene rings are shown in LVIa, LVIb, LVIc, LVId.



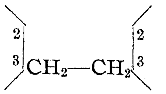
LVIa



LVIb



LVIc



LVId

All four of these structures could be formed from isoprene units of which so many natural products appear to be built. Thus, two examples are given in formulas LVII and LVIII.

Numerous naturally-occurring compounds contain methyl and isopropyl groups in the relative positions 3,5 in naphthalene skeletons. Only formula LVIa has such a structure though LVId might result from the oxidation of a methyl group in the 3-position. A most important fact is that a substantial quantity of acetic acid can be isolated along with formic and isobutyric acids, by the limited permanganate oxidation of gossypol.[19] The aldehyde group may be the source of the formic acid and the isopropyl group with a carbon atom from the ring the source of the isobutyric acid. The formation of the acetic acid can be explained only on the basis of LVIa and LVIc. Attempted isolation of suc-

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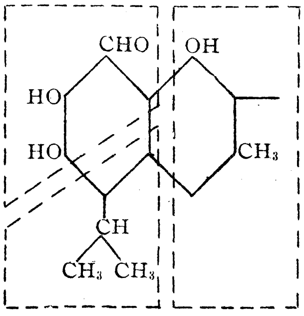
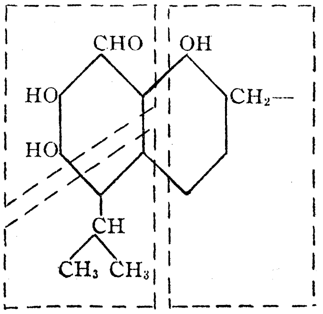
(19) Clark, *J. Biol. Chem.*, **77**, 81 (1928).



LVII (Ia)



LVIII

cinic acid which should result from LVIb and LVId by a similar oxidation was unsuccessful. Since LVIc is less likely because it does not have the 3-methyl-5-isopropyl arrangement, LVIa is considered as the most acceptable. It is obvious that other combinations in the 2,3-positions may be written but none other than those mentioned would result in a completely symmetrical molecule.

In view of these facts, formula Ia has been tentatively adopted for gossypol and is 2,2-bi-1,6,7-trihydroxy-5-isopropyl-8-aldehydonaphthyl.

The structure of gossypol (Ia) accounts for the anomalous results found by Clark[20] in carrying out a Zeisel determination. Gossypol gave a value of 5.7% though it contains no methoxyls. In the investigations from this Laboratory, methoxyl values of most of the gossypol derivatives were very frequently high. These can be accounted for by the fact that hydriodic acid removes, partially at least, the isopropyl groups as isopropyl iodide. The removal of an isopropyl group from a naphthalene by means of hydriodic acid is not entirely to be unexpected for it is reported in the literature that α-isopropylnaphthalene can be converted by means of hydriodic acid into naphthalene and isopropyl iodide.[21]

The definite establishment of structure Ia for gossypol must await (1) the synthesis of one or more of the benzene derivative degradation products, (2) a further study of gossypolone tetramethyl ether and gossypolonic acid tetramethyl ether, (3) knowledge concerning the arrangement of linkages and groups at the 2,3-positions.

Two oxidation products of gossypol dimethyl ether which have not been discussed are (1) that obtained by passing air through an alkaline solution, and (2) that resulting from treatment with ferric chloride.[11] These are of less significance in connection with the gossypol structure and consequently their further investigation is of secondary importance. The same is true of the oxidation product of demethylated apogossypolic acid in alkaline solution by means of air.[15]

The red gossypol hexamethyl ether requires further study.[3] This substance is not easily isolated in a pure state and consequently there is some doubt as to its exact empirical formula. The yellow product formed along with gossypol hexaacetate or from the latter by the action of acetic anhydride falls into the same category.[12] The complex compounds[4] from gossypol and certain substituted anilines need clarification. The character of the nitration products of gossypol hexamethyl ether and gossypolonic acid tetramethyl ether has not yet been determined. The structure of red gossypol may be Ic though no evidence for this is available.[22]

No simple naphthalene compounds have ever been isolated by degradation of gossypol except that reported by Schmid[23] as β-isoamylnaphthalene, obtained by exhaustive hydrogenation of gossypol and distillation of the reaction mixture with excess zinc dust. The identification of the product mentioned was not convincing and the formula for gossypol proposed would not give β-isoamylnaphthalene by the procedure used. Schmid also reported the isolation of *n*-butyric acid, a compound which could not be obtained from formula Ia.

The character of gossypolic acid reported by Karrer and Tobler[24] cannot be determined until a satisfactory method is found for its preparation.

The authors desire to express their sincere thanks to the Proctor and Gamble Company for furnishing through their subsidiary, the Buckeye Cotton Oil Company, the cottonseed meats from which the gossypol is being extracted for use in these investigations.

Summary

1. The correlation of the results of the study of gossypol has been made. The deductions from (1) the color reactions and salts, (2) the anilino

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[20] Clark, THIS JOURNAL, **51**, 1479 (1929).

[21] Meyer and Bernhauer, *Monatsh.*, **54**, 721 (1929).

[22] Podolskaja, *Biochem. Z.*, **284**, 401 (1936); *Fettchemische Umschau*, **42**, 96 (1935).

[23] Schmid and Margulies, *Monatsh.*, **65**, 391 (1934).

[24] Karrer and Tobler, *Helv. Chim. Acta*, **15**, 1204 (1932).

and amino derivatives, (3) anhydrogossypol and its derivatives, (4) the esters, (5) the ethers and their degradation products, (6) apogossypol and its degradation products, (7) desapogossypol and its degradation products lead to the postulation that gossypol is 2,2-bi-1,6,7-trihydroxy-3-methyl-5-isopropyl-8-aldehydonaphthyl.

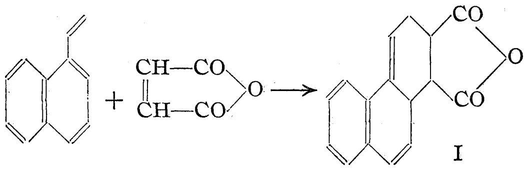
Urbana, Illinois Received June 27, 1938

[Contribution from the Chemistry Laboratory of the University of Michigan]

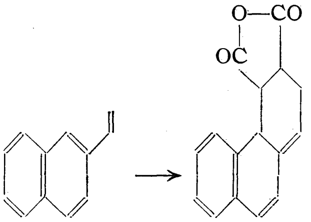
The Diels–Alder Reaction between Naphthylcyclopentenes and Maleic Anhydride

By W. E. Bachmann and M. C. Kloetzel[1]

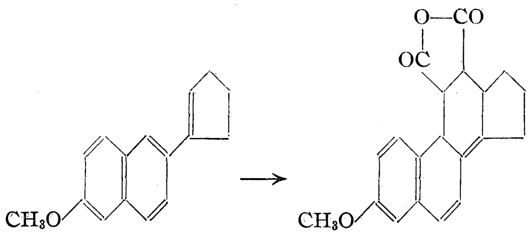
Cohen and Warren[2] have shown recently that 1-vinylnaphthalene and 2-vinylnaphthalene undergo the Diels–Alder reaction with maleic anhydride to give 1,2,3,10a-tetrahydrophenanthrene-1,2-dicarboxylic acid anhydride (I) and 2,3,4,4a-tetrahydrophenanthrene-3,4-dicarboxylic acid anhydride (II), respectively. A similar addition of maleic anhydride to 1-(6′-methoxy-2′-naphthyl)-cyclopentene-1 (III) would be expected to form a compound (IV) having the sterol skeleton, but it has been reported by Bergmann and Bergmann[3] that maleic anhydride reacts neither with 1-(α-naphthyl)-cyclopentene-1 (V) nor with (III). We have now found that (III) and (V) can be made to react practically quantitatively with maleic anhydride. Similarly, 1-(β-naphthyl)-cyclopentene-1 (VI) can be made to react with maleic anhydride to the extent of 92%.



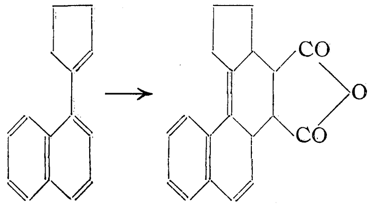
I



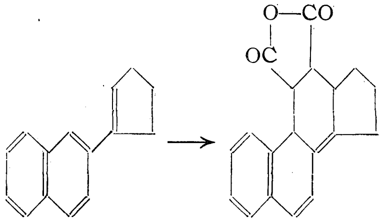
II



III IV



V Va



VI VIa

When a xylene solution of equimolecular proportions of (V) and maleic anhydride was refluxed for two hours and allowed to cool, a mixture of 3,4-cyclopentano-1,2,3,10a-tetrahydrophenanthrene-1,2-dicarboxylic acid and the corresponding acid anhydride (Va) was deposited. Under these conditions, reaction was found to have gone to the extent of 63%. A quantitative yield of the adduct could be obtained by fusing (V) with ten mole equivalents of maleic anhydride for twenty hours on a steam-bath.

When 1-(β-naphthyl)-cyclopentene-1 (VI) was refluxed for two hours in xylene solution with maleic anhydride and the solution was allowed to cool, 1,2-cyclopentano-2,3,4,4a-tetrahydrophenanthrene-3,4-dicarboxylic acid anhydride (VIa) was deposited as a resin, but (VIa) and (IV) were best prepared by fusing (VI) or (III), respectively, with ten mole equivalents of maleic anhydride on a steam-bath for twenty hours, dissolving the adduct in aqueous potassium hydroxide and precipitating by acidification with hydrochloric acid.

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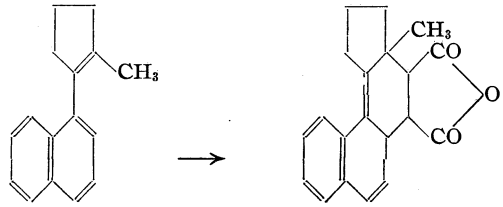
[1] Du Pont Post-Doctorate Fellow.

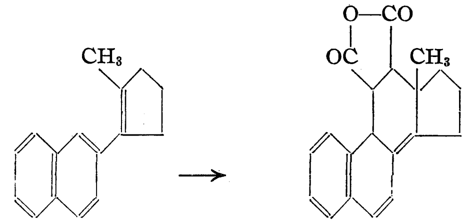
[2] Cohen and Warren, *J. Chem. Soc.*, 1318 (1937).

[3] Bergmann and Bergmann, This Journal, **59**, 1443 (1937).

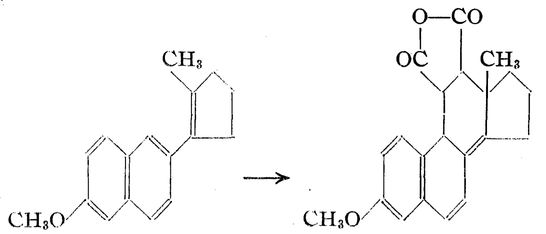
We have shown recently[4] that methyl groups in the *meso* positions of anthracene derivatives markedly activate the diene systems involved in the reaction with maleic anhydride. We therefore prepared 1-(α-naphthyl)-2-cyclopentene-1 (VII), 1-(β-naphthyl)-2-methylcyclopentene-1 (VIII) and 1-(6′-methoxy-2′-naphthyl)-2-methylcyclopentene-1 (IX) and tested their reactivity with maleic anhydride. These naphthylcyclopentenes reacted to give (VIIa), (VIIIa) and (IXa), respectively, but, contrary to expectation, the presence of the methyl groups actually decreased the rates of reaction.



VII VIIa



VIII VIIIa



IX IXa

The compounds (IV), (Va), (VIa), (VIIa), (VIIIa) and (IXa) are in each instance proposed as the primary addition products with the realization that they may be isomerized to the corresponding naphthalenic isomers. This isomerization was actually demonstrated by Cohen and Warren,[2] who converted (I) into (X) by the action of hot acetic acid saturated with hydrogen chloride.

The extent of reaction of each of these naphthylcyclopentenes with maleic anhydride was determined by refluxing a xylene solution (2 cc. of xylene/g. of cyclopentene) containing equimolecular proportions of the reactants for periods of one and two hours, respectively. In each instance, also, the naphthylcyclopentene was fused with ten mole equivalents of maleic anhydride on a steam-bath for twenty hours. The results, which are based upon the weight of unreacted cyclopentene recovered, are presented in Table I. It is important, however, that in most instances of long refluxing, although the extent of reaction is greater, the adduct is contaminated with decomposition products, so that a shorter period of reflux is generally desirable for preparative purposes.

TABLE I

THE EXTENT OF REACTION OF NAPHTHYLCYCLOPENTENES WITH MALEIC ANHYDRIDE

	Percentage of reaction after		
	Period of reflux		Fusion
Naphthylcyclopentene	1 hour	2 hours	20 hours
1-(α-Naphthyl)-cyclopentene-1 (V)	45	63	98
1-(α-Naphthyl)-2-methylcyclopentene-1 (VII)	9	16	32
1-(β-Naphthyl)-cyclopentene-1 (VI)	55	58	92
1-(β-Naphthyl)-2-methylcyclopentene-1 (VIII)	18	19	77
1-(6′-Methoxy-2′-naphthyl)-cyclopentene-1 (III)	45	56	98
1-(6′-Methoxy-2′-naphthyl)-2-methylcyclopentene-1 (IX)	12	14	94

The naphthylcyclopentenes necessary for this investigation were all prepared in a similar manner. First of all, the tertiary cyclopentanols were prepared by means of the Grignard reaction: thus, α-naphthylmagnesium bromide with cyclopentanone and 2-methylcyclopentanone gave 1-(α-naphthyl)-cyclopentanol-1 and 1-(α-naphthyl)-2-methylcyclopentanol-1, respectively; β-naphthylmagnesium iodide with the same two ketones gave 1-(β-naphthyl)-cyclopentanol-1 and 1-(β-naphthyl)-2-methylcyclopentanol-1, respectively; and 6-methoxy-2-naphthylmagnesium bromide gave 1-(6′-methoxy-2′-naphthyl)-cyclopentanol-1 and 1-(6′-methoxy-2′-naphthyl)-2-methylcyclopentanol-1, respectively. These carbinols were then dehydrated to the corresponding naphthylcyclopentenes by warming for a short time with anhydrous formic acid.

It may be observed that the use of (VIII) and (IX) in the reaction with maleic anhydride offers a convenient method of obtaining compounds containing angular methyl groups; thus, (IXa) is an isomer of the methyl ether of deoxoequilenin-11,12-dicarboxylic acid anhydride. It was therefore of interest to attempt the decarboxylation of our adducts with the hope of obtaining derivatives closely related to naturally occurring compounds.

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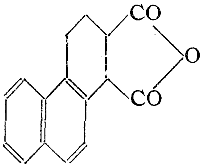
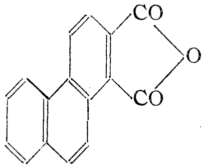
(4) Bachmann and Kloetzel, THIS JOURNAL, **60**, 481 (1938).

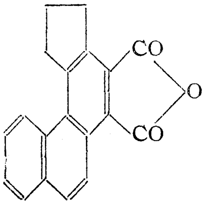
When a mixture of (I) or (Va) with the theoretical amount of sulfur necessary to remove four hydrogen atoms was heated to 250–270° for a period of thirty to forty-five minutes, phenanthrene-1,2-dicarboxylic acid anhydride (XI) or 3,4-cyclopentenophenanthrene - 1,2 - dicarboxylic acid anhydride (XII) were obtained, respectively. Dehydrogenation of (IV), (VIa), (VIIa), (VIIIa) or (IXa) with sulfur did not proceed smoothly under these same conditions.



X



XI

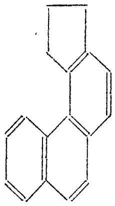


XII

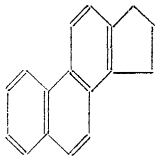
An attempt then was made to decarboxylate (XII) by refluxing in quinoline solution with basic copper carbonate. This method gave erratic results, however, and in no case was the yield of 3,4-cyclopentenophenanthrene (XIII) greater than 19%. Dry distillation of the dipotassium salt of 3,4 - cyclopentenophenanthrene - 1,2 - dicarboxylic acid with potassium hydroxide at 430° likewise gave 3,4-cyclopentenophenanthrene in extremely poor yield. When, however, the calcium salt of (XI) was dry distilled with a mixture of calcium oxide and zinc dust, a 30% yield of phenanthrene was obtained.

When the latter method of decarboxylation was applied to the adducts themselves it was found that dehydrogenation as well as decarboxylation took place, even when no zinc dust was employed in the distillation of the calcium salts. Dry distillation of the calcium salt of 1,2,3,10a-tetrahydrophenanthrene - 1,2 - dicarboxylic acid (from I) with calcium oxide alone gave a 67% yield of phenanthrene. When zinc dust was included in the distillation mixture, the yield of phenanthrene was reduced to 28%, and the product, moreover, was contaminated with impurities which were difficult to remove. The calcium salt of 3,4-cyclopenteno-1,2,3,10a-tetrahydrophenanthrene-1,2-dicarboxylic acid (from Va) was distilled with a mixture of calcium oxide and zinc dust, resulting in a 62% yield of 3,4-cyclopentenophenanthrene (XIII). Addition of 1-(α-naphthyl)-cyclopentene-1 to maleic anhydride, followed by decarboxylation of the resulting adduct, therefore offers a second convenient synthesis of 3,4-cyclopentenophenanthrene.[5]

In like manner, the addition of 1-(β-naphthyl)-cyclopentene-1 to maleic anhydride, followed by decarboxylation of the resulting adduct, offers a convenient synthetic route to 1,2-cyclopentenophenanthrene (XIV), for the dry distillation of the calcium salt of 1,2-cyclopentano-2,3,4,4a-tetrahydrophenanthrene-3,4-dicarboxylic acid (from VIa) with a mixture of calcium oxide and zinc dust resulted in an 80% yield of 1,2-cyclopentenophenanthrene, even when crude adduct was employed.



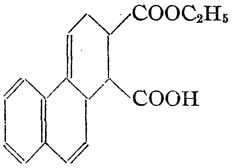
XIII



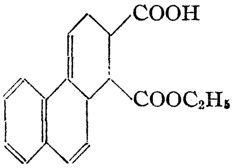
XIV

When this method of decarboxylation was extended to 2-methyl-1,2-cyclopentano-2,3,4,4a-tetrahydrophenanthrene-3,4-dicarboxylic acid anhydride (VIIIa), a good yield of distillate was obtained. Although the product formed a picrate (m. p. 123–124°), its identity was not ascertained. Similarly, the distillation of the calcium salts of those adducts containing methoxyl or angular methyl groups produced no identifiable products.

The reaction of 1-vinylnaphthalene with ethyl hydrogen maleate was investigated in the hope of obtaining an adduct which might be readily decarboxylated without simultaneous aromatization. When a mixture of equimolecular proportions of the hydrocarbon and ester was heated on the steam-bath for fifteen hours, addition took place to the extent of 72%, and the adduct, (XV) or (XVI), was isolated as a colorless solid. Dehydrogenation of this with sulfur gave phenan-



XV



XVI

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[5] Bachmann and Kloetzel, This Journal, **59**, 2207 (1937).

threne-1,2-dicarboxylic acid anhydride (XI). Attempted decarboxylation by refluxing in quinoline solution with basic copper carbonate gave, however, only an unidentified, crystalline product.

Experimental

The effect of concentration, time and temperature on the yields of adducts was determined by means of a procedure outlined in a previous paper.[4] Xylene solutions containing equivalent quantitites of the reactants (2 cc. of xylene/g. of naphthylcyclopentene) were heated to the boiling points of the solutions for periods of one hour and two hours, respectively. Forty per cent. potassium hydroxide solution was then added to hydrolyze the addition product (anhydride) and the potassium salt of the dicarboxylic acid was dissolved in hot water. Benzene was added to dissolve unreacted naphthylcyclopentene and the two solutions were separated. Evaporation of the benzene in a weighed container gave the amount of unreacted naphthylcyclopentene; acidification of the aqueous solution with dilute hydrochloric acid precipitated the dicarboxylic acid.

Experiments also were carried out in which the naphthylcyclopentene and ten mole equivalents of maleic anhydride were fused together on a steam-bath for twenty hours without the addition of any solvent. These reaction mixtures were worked up as before in order to determine the extent of reaction. The results of these experiments, which are accurate to a few per cent., are presented in Table I.

1-Vinylnaphthalene and Maleic Anhydride.—The adduct of 1-vinylnaphthalene was prepared according to the method of Cohen and Warren[2] with some modifications. The yellow solution obtained by heating 8.5 g. of 1-vinylnaphthalene, 5.7 g. of maleic anhydride and 17 cc. of anhydrous xylene on a steam-bath began to deposit the adduct within ten minutes. Heating was continued for three hours, after which the mixture was allowed to stand at 0° for twelve hours and the precipitate was filtered off; yield 13.0 g. This crude product began to sinter at 130° and finally melted with decomposition at 185–190°. A portion of the product was soluble in hot acetic acid, and on being cooled the solution deposited colorless crystals of **1,2,3,10a-tetrahydrophenanthrene-1,2-dicarboxylic acid.** The portion insoluble in acetic acid was presumably the corresponding dicarboxylic acid anhydride (I).[3]

Decarboxylation and Dehydrogenation of 1,2,3,10a-Tetrahydrophenanthrene-1,2-dicarboxylic Acid to Phenanthrene.—A 2.5-g. sample of the crude adduct from 1-vinylnaphthalene and maleic anhydride was dissolved by warming in 80 cc. of water containing 1.0 g. of sodium hydroxide, 1.5 g. of calcium oxide was added, and the mixture was boiled for five minutes in order to form the calcium salt of 1,2,3,10a-tetrahydrophenanthrene-1,2-dicarboxylic acid. The suspension was evaporated to dryness and the calcium salt was mixed intimately with 8.5 g. of calcium oxide and dry distilled in a hard glass test-tube. The yellow, crystalline product (1.2 g.) which condensed in the cold part of the tube was sublimed in vacuum (130° at 0.6 mm.) and crystallized from ethanol, yield 0.8 g., m. p. 97–98°, giving no depression of melting point when mixed with an authentic sample of phenanthrene. The picrate (m. p. 144–145°) was likewise identical with phenanthrene picrate.

In a similar experiment, when the calcium salt of the dicarboxylic acid was dry-distilled with a mixture of 8.5 g. of calcium oxide and 6.3 g. of zinc dust, the phenanthrene obtained (0.5 g.) was contaminated with other products.

Phenanthrene-1,2-dicarboxylic Acid Anhydride (XI).—A mixture of 1.0 g. of the crude adduct obtained from 1-vinylnaphthalene and maleic anhydride was mixed with 260 mg. of sulfur and heated to 255° for forty minutes. The product was sublimed in vacuum (240° at 1 mm.) and recrystallized from chlorobenzene; yield, 320 mg. of yellow needles; m. p. 310–311° (Fieser and Hershberg[6] give 311–312°).

The **diethyl ester of phenanthrene-1,2-dicarboxylic acid** was prepared by refluxing for six hours a mixture of 200 mg. of phenanthrene-1,2-dicarboxylic acid anhydride, 10 cc. of absolute ethanol and 1 cc. of concentrated sulfuric acid. A clear yellow solution was obtained within one hour. Most of the alcohol was evaporated and the ester was precipitated with water. When the precipitate was warmed with a small quantity of ethanol the ester dissolved, leaving behind some unchanged dicarboxylic acid anhydride which was filtered off. The ester was vacuum sublimed (140° at 0.6 mm.) and crystallized from ethanol in pale yellow needles, m. p. 132°; yield, 63 mg.

Anal. Calcd. for $C_{20}H_{18}O_4$: C, 74.5; H, 5.6. Found: C, 74.0; H, 5.8.

Decarboxylation of Phenanthrene-1,2-dicarboxylic Acid.—A 0.47-g. sample of phenanthrene-1,2-dicarboxylic acid was converted to the calcium salt in the same manner as described for the conversion of 1,2,3,10a-tetrahydrophenanthrene-1,2-dicarboxylic acid, and was then dry distilled with a mixture of 1.7 g. of calcium oxide and 1.3 g. of zinc dust. The crude **phenanthrene** (100 mg.) was purified by picration, and was identical with an authentic sample.

1-Vinylnaphthalene and Ethyl Hydrogen Maleate.—A mixture of 2.6 g. of 1-vinylnaphthalene and 2.5 g. of ethyl hydrogen maleate[7] was heated on a steam-bath for fifteen hours. Water, potassium carbonate and benzene were then added and the layers were separated. Evaporation of the benzene left 0.74 g. of unreacted vinylnaphthalene, indicating 72% reaction. Acidification of the aqueous layer with dilute hydrochloric acid precipitated the adduct (XV or XVI) as a pale yellow solid (4 g.), which was digested with warm ether and filtered. The colorless powder so obtained is very soluble in ethyl acetate, chloroform, acetic acid or hot ethanol; insoluble in ether, hot benzene or hot *n*-butyl ether. Partial purification of the adduct was accomplished by solution in hot acetone (in which it is slightly soluble) and reprecipitation with ether, but the compound was not successfully crystallized.

When a sample of the aforementioned adduct (1.5 g.) was heated at 250–260° for thirty minutes with sulfur (330 mg.) and the product vacuum sublimed, there was obtained 100 mg. of **phenanthrene-1,2-dicarboxylic acid anhydride** (XI).

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[6] Fieser and Hershberg, THIS JOURNAL, **57**, 1508, 1853 (1935).

[7] Shields, *J. Chem. Soc.*, **59**, 740 (1891).

A solution of the aforementioned adduct (2 g.) in quinoline (20 cc.) was refluxed with basic copper carbonate (400 mg.) for thirty minutes, and after being cooled was diluted with ether and filtered. The ethereal solution was washed with dilute hydrochloric acid, dilute sodium carbonate and finally with water. Evaporation of the ether left only a yellow crystalline compound which crystallized from acetic acid in broad, yellow needles; m. p. 246–247°; yield 600 mg. The compound (C, 81.1; H, 4.3) gives a red-orange color with concentrated sulfuric acid, and is soluble in hot, aqueous potassium hydroxide with difficulty.

1-(α-Naphthyl)-cyclopentanol-1 was prepared by adding 42 g. of cyclopentanone dropwise to a solution of α-naphthylmagnesium bromide prepared from 116 g. of α-bromonaphthalene, 12.5 g. of pure magnesium ribbon and 300 cc. of anhydrous ether. The cyclopentanone was added at such a rate that the mixture refluxed gently from heat of reaction. The crystalline addition product which separated after standing at 0° for twelve hours was filtered off and hydrolyzed with ice water and ammonium chloride. When an ethereal solution of the hydrolyzed product was allowed to evaporate spontaneously at room temperature the carbinol was obtained in colorless crystals which were then washed with petroleum ether (60–70°); yield, 50 g. (42%). From 30–40° petroleum ether **1-(α-naphthyl)-cyclopentanol-1** crystallized in colorless, rectangular prisms, m. p. 75.5–76°. Concentrated sulfuric acid gives a purple-red color with this carbinol.

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.9; H, 7.6. Found: C, 84.5; H, 7.1.

1-(α-Naphthyl)-cyclopentene-1 (V) was obtained when the corresponding naphthylcyclopentanol was dehydrated with either potassium acid sulfate or anhydrous formic acid.

A mixture of 5 g. of the carbinol and 7.5 g. of potassium acid sulfate was heated in a Pyrex test-tube at 165° for forty-five minutes. Water and benzene were then added, the benzene layer was separated and evaporated and the residual oil was distilled in vacuum (165–168° at 1 mm.); yield, 3.7 g. (81%) of a colorless oil which solidified when placed in a refrigerator at −2°.

Dehydration with anhydrous formic acid was accomplished by dissolving 20 g. of finely powdered 1-(α-naphthyl)-cyclopentanol-1 in 50 cc. of the acid at room temperature. Within several minutes the solution became cloudy and the hydrocarbon separated as an oil. After warming the mixture on a steam-bath for five minutes to complete the reaction, 200 cc. of water was added and the 1-(α-naphthyl)-cyclopentene-1 was extracted with benzene; yield, 18 g. (98%).

The naphthylcyclopentene prepared by either method yielded a picrate which crystallized from methanol in vermilion needles, m. p. 79–80°.[3]

Anal. Calcd. for $C_{21}H_{17}O_7N_3$: N, 9.93. Found: N, 9.98.

1-(α-Naphthyl)-cyclopentene-1 and Maleic Anhydride.—A solution of 8.5 g. of 1-(α-naphthyl)-cyclopentene-1 and 4.5 g. of sublimed maleic anhydride in 17 cc. of anhydrous xylene was refluxed for two hours, the solvent was evaporated and the residue was dissolved in 13 cc. of hot acetic acid. After standing for twelve hours the solution deposited 2.8 g. of a mixture of **3,4-cyclopentano-1,2,3,10a-tetrahydrophenanthrene-1,2-dicarboxylic acid** and the corresponding acid anhydride (Va). The dicarboxylic acid crystallizes from acetic acid in colorless, diamond-shaped plates, m. p. 211–213° dec. (in nitrogen).

Anal. Calcd. for $C_{19}H_{18}O_4$: C, 73.5; H, 5.8. Found: C, 73.2; H, 5.9.

The dicarboxylic acid is soluble in acetone, dioxane or hot benzene, slightly soluble in cold benzene, and insoluble in ether. It dissolves in dilute potassium hydroxide and the cold alkaline solution reduces potassium permanganate instantaneously. Acidification of the alkaline solution yields the dicarboxylic acid as a yellow gum. Recrystallization from acetic acid or from acetic anhydride partially converted the acid to the corresponding anhydride, as was shown by analysis.

3,4-Cyclopentenophenanthrene-1,2-dicarboxylic Acid Anhydride (XII).—A mixture of 500 mg. of 3,4-cyclopentano-1,2,3,10a-tetrahydrophenanthrene-1,2-dicarboxylic acid and 100 mg. of sulfur was heated to 230–240° for forty-five minutes in an atmosphere of carbon dioxide. The product was sublimed in vacuum (250–280° at 0.4 mm.) and crystallized from chlorobenzene (65 cc./g.) in yellow needles; m. p. 321°; yield, 270 mg. (54%).

Anal. Calcd. for $C_{19}H_{12}O_3$: C, 79.1; H, 4.2. Found: C, 78.9; H, 4.2.

3,4-Cyclopentenophenanthrene (XIII). (a) Decarboxylation and Dehydrogenation of 3,4-Cyclopentano-1,2,3,10a-tetrahydrophenanthrene-1,2-dicarboxylic Acid.—A 1.2-g. sample of 3,4-cyclopentano-1,2,3,10a-tetrahydrophenanthrene-1,2-dicarboxylic acid was converted to the calcium salt as in the case of 1,2,3,10a-tetrahydrophenanthrene-1,2-dicarboxylic acid, and dry distilled with 4 g. of calcium oxide and 3 g. of zinc dust. The yellow distillate obtained (0.56 g.) was dissolved in 4 cc. of absolute ethanol and 0.6 g. of picric acid was added to the hot solution. When the solution was cooled, 1.0 g. of **3,4-cyclopentenophenanthrene picrate** crystallized; m. p. 133–134° alone and when mixed with an authentic sample of the same melting point.

The picrate was decomposed with dilute ammonium hydroxide, and the **3,4-cyclopentenophenanthrene** liberated was crystallized from acetone–methanol, m. p. 69–71° alone and when mixed with an authentic sample.[5]

(b) Decarboxylation of 3,4-Cyclopentenophenanthrene-1,2-dicarboxylic Acid Anhydride.—A mixture of 70 mg. of 3,4-cyclopentenophenanthrene-1,2-dicarboxylic acid anhydride, 14 mg. of basic copper carbonate and 2 cc. of quinoline was refluxed for thirty minutes, a large volume of ether was added and the solution was filtered from a dark sludge. The ethereal solution was shaken with dilute hydrochloric acid, dilute potassium hydroxide and finally with water. Evaporation of the ethereal solution left a residue which, when dissolved in acetone–alcohol, yielded 10 mg. of yellow needles of m. p. 240°. These were discarded and the remaining residue was sublimed in vacuum (up to 150° at 0.4 mm.) and crystallized from acetone–alcohol; yield, 10 mg. of **3,4-cyclopentenophenanthrene** in colorless plates, m. p. 71.5–72° alone and when mixed with an authentic sample. The picrate of the hydrocarbon obtained was likewise identical with an authentic sample of 3,4-cyclopentenophenanthrene picrate.

3,4-Cyclopentenophenanthrene-1,2-dicarboxylic acid also was decarboxylated with poor yield by dry distillation of its dipotassium salt. A mixture of 100 mg. of 3,4-cyclopentenophenanthrene-1,2-dicarboxylic acid anhydride, 100 mg. of potassium hydroxide and 5 cc. of water was heated in a test-tube until complete solution was obtained. The solution was then evaporated to dryness and the residue was heated for thirty minutes at 430°. The white sublimate obtained from the cool part of the tube was dissolved in ethanol and picric acid was added; yield, 5 mg. of **3,4-cyclopentenophenanthrene picrate**, m. p. 134–135°.

1-(α-Naphthyl)-2-methylcyclopentene-1 (VII).—To the cooled solution of α-naphthylmagnesium bromide prepared from 31 g. of α-bromonaphthalene, 3.8 g. of pure, powdered magnesium and 100 cc. of anhydrous ether, was added dropwise a solution of 15 g. of 2-methylcyclopentanone[8] in 15 cc. of anhydrous benzene. The clear green solution obtained was refluxed on a steam-bath for two hours, cooled and then hydrolyzed with cold, aqueous ammonium chloride. To the residual 1-(α-naphthyl)-2-methylcyclopentanol-1 obtained when the organic layer was evaporated was added 85 cc. of anhydrous formic acid, and the resulting blue-green solution was warmed on a steam-bath for ten minutes. The solution was poured into 400 cc. of water, ether was added and the ethereal extract was washed with 10% sodium carbonate. After removal of the ether the residue was fractionated three times in vacuum, and the fraction boiling at 165–168° (1 mm.) finally was collected as **1-(α-naphthyl)-2-methylcyclopentene-1**; yield, 6 g. of pale yellow oil. Concentrated sulfuric acid gives a red color with this hydrocarbon. The compound was not obtained analytically pure.

1-(α-Naphthyl)-2-methylcyclopentene-1 and Maleic Anhydride.—A mixture of 1.0 g. of 1-(α-naphthyl)-2-methylcyclopentene-1 and 4.7 g. of maleic anhydride was heated on a steam-bath for twenty hours. **3-Methyl-3,4-cyclopentano-1,2,3,10a-tetrahydrophenanthrene-1,2-dicarboxylic acid** (0.25 g.) was obtained in the form of a brown gum when the reaction mixture was extracted with aqueous potassium hydroxide and the extract was acidified with dilute hydrochloric acid.

1-(β-Naphthyl)-cyclopentene-1 (VI).—To the solution of Grignard reagent prepared by refluxing 25.4 g. of β-iodonaphthalene, 2.5 g. of pure magnesium powder and 75 cc. of anhydrous ether for three hours, was added dropwise a solution of 8.5 g. of cyclopentanone in 10 cc. of ether. The mixture was allowed to warm up from heat of reaction, and then allowed to stand at room temperature for two hours. To the crude 1-(β-naphthyl)-cyclopentanol-1 obtained by hydrolysis of the Grignard reaction mixture was added 50 cc. of anhydrous formic acid, and the solution was heated on a steam-bath for ten minutes. **1-(β-Naphthyl)-cyclopentene-1** separated in crystalline form when the solution was cooled. The crude hydrocarbon was crystallized twice from ethanol (separating from a yellow, insoluble by-product) and formed thin, colorless plates, m. p. 85–86°; yield, 5.2 g. The compound gives a rose-red color with concentrated sulfuric acid.

Anal. Calcd. for $C_{15}H_{14}$: C, 92.7; H, 7.3. Found: C, 92.6; H, 7.35.

1-(β-Naphthyl)-cyclopentene-1 and Maleic Anhydride.—A mixture of 1.0 g. of 1-(β-naphthyl)-cyclopentene-1 and 5 g. of maleic anhydride was fused on a steam-bath for twenty hours. A red color was produced immediately when the reactants were mixed. The reaction product was hydrolyzed with water and potassium hydroxide, the aqueous solution was extracted with benzene to remove unreacted hydrocarbon, and was then acidified with dilute hydrochloric acid; yield, 1.4 g. (92%) of cream-colored adduct.

Decarboxylation and Dehydrogenation of 1,2-Cyclopentano-2,3,4,4a-tetrahydrophenanthrene-3,4-dicarboxylic Acid.—The calcium salt of 1,2-cyclopentano-2,3,4,4a-tetrahydrophenanthrene-3,4-dicarboxylic acid was prepared as before from a 2.0-g. sample of the crude adduct, and was dry distilled with 8 g. of calcium oxide and 6 g. of zinc dust. **1,2-Cyclopentenophenanthrene** (1.2 g.) crystallized in the cold part of the tube, and was recrystallized from ethanol; yield, 0.6 g. of nearly colorless leaflets, m. p. 135–136° alone and when mixed with an authentic sample of hydrocarbon melting at 134°. **1,2-Cyclopentenophenanthrene picrate** was prepared and crystallized from ethanol in orange-yellow needles, m. p. 130–132°.

1-(β-Naphthyl)-2-methylcyclopentene-1 (VIII) was prepared in the same manner as its α-naphthyl isomer, from β-naphthylmagnesium iodide and 2-methylcyclopentanone. The crude hydrocarbon was fractionated four times in vacuum, and the fraction boiling at 180–182° (1 mm.) finally was collected as **1-(β-naphthyl)-2-methylcyclopentene-1**; yield, 5.5 g. of yellow oil (from 38 g. of β-iodonaphthalene). Concentrated sulfuric acid produces a red color with this hydrocarbon. Like its α-naphthyl isomer. the hydrocarbon was not obtained analytically pure.

1-(β-Naphthyl)-2-methylcyclopentene-1 and Maleic Anhydride.—The adduct was prepared by fusing the naphthylmethylcyclopentene with ten mole equivalents of maleic anhydride on a steam-bath for twenty hours, as described for 1-(β-naphthyl)-cyclopentene-1; yield, 58% of cream-colored powder.

1-(6′-Methoxy-2′-naphthyl)-cyclopentene-1 (III).—1-(6′-Methoxy-2′-naphthyl)-cyclopentanol-1 was prepared from 6-methoxy-2-naphthylmagnesium bromide and cyclopentanone, and then dehydrated with anhydrous formic acid as described in the preparation of 1-(β-naphthyl)-cyclopentene-1. The crude product was fractionated in vacuum, and the fraction boiling at 200–240° (1 mm.) was crystallized from ethanol. Boiling for fifteen minutes with an equivalent weight of maleic anhydride in xylene solution removed the last traces of colored impurities, and the **1-(6′-methoxy-2′-naphthyl)-cyclopentene-1** finally crystallized from ethanol in colorless leaflets, m. p. 141–142°; yield, 10 g. from 22 g. of 6-bromo-2-methoxynaphthalene. Bergmann and Bergmann,[3] who prepared this hydrocarbon by dehydrating the carbinol with potassium acid sulfate, reported a melting point of 148° for this compound.

1-(6′-Methoxy-2′-naphthyl)-cyclopentene-1 and Maleic Anhydride.—When 1.0 g. of 1-(6′-methoxy-2′-naphthyl)-cyclopentene-1 and 4.4 g. of maleic anhydride were melted together on a steam-bath the mixture quickly became brown-red. Heating was continued for twenty hours and

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[8] Cornubert and Borrel, *Bull. soc. chim.*, (*IV*) **47**, 310 (1930).

the reaction mixture was hydrolyzed as previously described. Acidification of the alkaline solution precipitated 0.52 g. of **7-methoxy-1,2-cyclopentano-2,3,4,4a-tetrahydrophenanthrene-3,4-dicarboxylic acid** in the form of a cream-colored solid. The adduct was not crystallized successfully, but was partially purified by solution in cold acetic acid and reprecipitation with xylene. It then formed a colorless powder which sintered and darkened at 280° and finally melted at 310°, dec. The compound is nearly insoluble in hot xylene or hot chlorobenzene, but is readily soluble in cold acetic acid. Molecular weight (by neutralization) was 300; calculated, 340.

1-(6′-Methoxy-2′-naphthyl) - 2 - methylcyclopentene - 1 (IX).—This compound was prepared in the usual manner by dehydrating the carbinol obtained from 6-methoxy-2-naphthylmagnesium bromide and 2-methylcyclopentanone. The crude product was distilled twice in vacuum, and the fraction boiling at 200–205° (0.9 mm.) was crystallized from ethanol. Boiling for one hour with an equivalent weight of maleic anhydride removed the colored impurities and the **1-(6′-methoxy-2′-naphthyl)-2-methylcyclopentene-1** finally crystallized from methanol in clusters of colorless needles; m. p. 74–75°; yield 4.0 g. The compound gives an orange-red color with concentrated sulfuric acid.

Anal. Calcd. for $C_{17}H_{18}O$: C, 85.7; H, 7.6. Found: C, 85.6; H, 7.7.

1-(6′-Methoxy-2′-naphthyl) - 2 - methylcyclopentene - 1 and Maleic Anhydride.—When a mixture of 0.7 g. of the methoxy derivative and 2.94 g. (ten mols) of maleic anhydride was heated on a steam-bath for twenty hours and the alkaline solution of the hydrolyzed product was acidified with dilute hydrochloric acid, 0.9 g. (92%) of **7 - methoxy - 2 - methyl - 1,2 - cyclopentano - 2,3,4,4a - tetrahydrophenanthrene-3,4-dicarboxylic acid** was obtained in the form of a colorless, granular precipitate. The adduct is practically insoluble in hot xylene but is readily soluble in cold acetic acid. It was partially purified by solution in cold acetic acid, and reprecipitation with xylene: the colorless powder so obtained sintered and darkened at 275° and finally melted at 292°, dec.

Summary

Maleic anhydride reacts with 1-(α-naphthyl)-cyclopentene-1, 1-(α-naphthyl)-2-methylcyclopentene-1, 1-(β-naphthyl)-cyclopentene-1, 1-(β-naphthyl)-2-methylcyclopentene-1, 1-(6′-methoxy-2′ - naphthyl)-cyclopentene - 1 and 1-(6′ - methoxy-2′- naphthyl) - 2 - methylcyclopentene-1. In these reactions one of the double bonds of the diene system is part of the aromatic naphthalene ring.

Dry distillation of the calcium salt of 3,4-cyclopentano-1,2,3,10a-tetrahydrophenanthrene-1,2-dicarboxylic acid or 1,2-cyclopentano-2,3,4,4a-tetrahydrophenanthrene-3,4-dicarboxylic acid with a mixture of calcium oxide and zinc dust produces excellent yields of 3,4-cyclopentenephenanthrene or 1,2-cyclopentenophenanthrene, respectively. This reaction offers a convenient route to the synthesis of these two hydrocarbons.

ANN ARBOR, MICHIGAN RECEIVED JULY 14, 1938

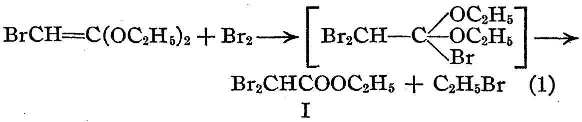
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Ketene Acetals. III. The Bromination of Bromoketene Diethylacetal. Other Halogenated Ketene Acetals

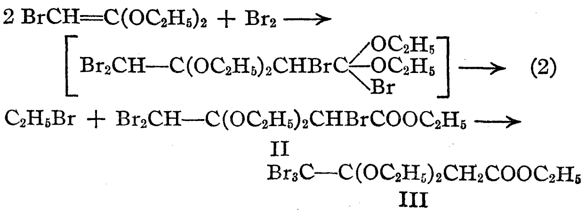
BY ARTHUR MAGNANI[1] AND S. M. MCELVAIN

A continuation of the study of various halogenated ketene acetals led to an investigation of the bromination of bromoketene diethylacetal.[2] Although the bromination did not prove to be of any value from the standpoint of preparing other ketene acetals, it seems to be of sufficient interest to report at this time.

Bromoketene diethylacetal absorbs bromine rapidly at 0–5° but the absorption stops abruptly after approximately 0.7 of an equivalent of bromine has reacted. No further absorption of bromine occurs even if the temperature of the reactants is allowed to rise to 25°. The products that were isolated from the resulting reaction mixture can be explained on the basis that slightly less than one-half of the bromoketene acetal reacts according to reaction (1) while somewhat more than one-half of the acetal follows the course shown in reaction (2)



$$BrCH{=}C(OC_2H_5)_2 + Br_2 \longrightarrow \left[Br_2CH{-}C\begin{matrix} OC_2H_5 \\ OC_2H_5 \\ Br \end{matrix} \right] \longrightarrow \underset{\text{I}}{Br_2CHCOOC_2H_5} + C_2H_5Br \quad (1)$$



$$2\,BrCH{=}C(OC_2H_5)_2 + Br_2 \longrightarrow \left[Br_2CH{-}C(OC_2H_5)_2CHBrC\begin{matrix} OC_2H_5 \\ OC_2H_5 \\ Br \end{matrix} \right] \longrightarrow \quad (2)$$

$$C_2H_5Br + \underset{\text{II}}{Br_2CH{-}C(OC_2H_5)_2CHBrCOOC_2H_5} \longrightarrow \underset{\text{III}}{Br_3C{-}C(OC_2H_5)_2CH_2COOC_2H_5}$$

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[1] Du Pont Post-doctorate Research Assistant, 1937–1938.

[2] Beyerstedt and McElvain, THIS JOURNAL, **59**, 2266 (1937).

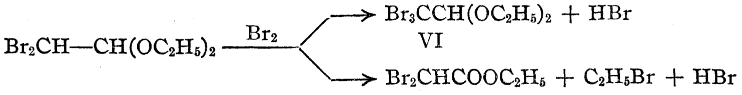
In addition to these main reaction products, small and practically equivalent amounts of ethyl tribromoacetate (IV) and the dibromoacetoacetic ester acetal (V) were found in the reaction mixture. These products appear to have been formed by the interaction of I and II, thus

$$\mathrm{Br_2CHCOOC_2H_5 + Br_2CHC(OC_2H_5)_2CHBrCOOC_2H_5 \longrightarrow \underset{IV}{Br_3CCOOC_2H_5} + \underset{V}{Br_2CHC(OC_2H_5)_2CH_2COOC_2H_5}} \quad (3)$$

It may be seen that reaction (1) requires one equivalent of bromine per mole of the bromoketene acetal while reaction (2) requires only one-half of this quantity of bromine. These ratios of reactants explain the failure of the ketene acetal to absorb more than about 0.7 of an equivalent of bromine.

The brominated acetic esters (I and IV) were identified as amides; the brominated acetals of acetoacetic ester (III and V) were hydrolyzed to the corresponding brominated acetones which were identified.

The other halogenated ketene acetals which have been prepared in this work are monochloro-, dichloro-, and dibromoketene diethylacetal. Each of these ketene acetals was prepared by the procedure which has been used previously in this Laboratory, *viz.*, the elimination of hydrogen halide from the properly halogenated acetaldehyde acetal. Dichloroacetal was prepared by the direct chlorination of acetal. Trichloroacetal was prepared by treating α,β,β,β-tetrachlorodiethyl ether ($Cl_3CCHCl\text{-}O\text{-}C_2H_5$) with alcohol; the tetrachloro ether was obtained by the action of phosphorus pentachloride on chloral alcoholate.[3] Tribromoacetal VI could not be prepared successfully by the procedure which was used for the corresponding chloro compound. It was finally prepared by the bromination of dibromoacetal. This reaction gave a very low yield (12–15%) of the desired tribromoacetal, partly because of the fact that the hydrogen attached to the carbon atom carrying the ethoxyl groups was replaced by bromine as easily as was the hydrogen on the carbon carrying the bromine atoms, thus



$$\mathrm{Br_2CH{-}CH(OC_2H_5)_2 \xrightarrow{Br_2} \begin{cases} \underset{VI}{Br_3CCH(OC_2H_5)_2} + HBr \\ Br_2CHCOOC_2H_5 + C_2H_5Br + HBr \end{cases}}$$

The yield of ethyl bromide (90%), however, was very much greater than that of ethyl dibromoacetate (17%). This discrepancy in yields, and the fact that a large amount of bromal (45%) was found among the reaction products, indicate that the main reaction that takes place is the splitting of the acetal linkages of tribromoacetal or some of the starting acetal by the hydrogen bromide to yield ethyl bromide and the free aldehyde which, in the case of dibromoacetaldehyde, is brominated further to bromal.

The halogenated acetaldehyde acetals are converted smoothly by potassium in *t*-butyl alcohol into the corresponding halogenated ketene diethylacetals. The yields range from 55 to 85% of the theoretical. These ketene acetals show the same vigorous reaction with water and alcohol that was observed with ketene diethylacetal[4] and bromoketene diethylacetal.[2]

In the second paper of this series[2] it was pointed out that these ketene acetals are ethers of the enolic forms of esters and their boiling points, in general, are considerably higher than those of the corresponding esters.[5] The table below lists the analyses and properties of the halogenated ketene acetals and compares their boiling points with those of the corresponding esters. The monobromoketene diethylacetal is included for comparison.

Experimental

Bromination of Bromoketene Diethylacetal.—In a 1-liter 3-necked flask, fitted with a stirrer, a dropping funnel and a reflux condenser carrying a drying tube, was placed 176 g. (0.90 mole) of bromoketene diethylacetal.[2] The flask was cooled in an ice–salt bath until the contents reached a temperature of 0–5° and then a solution of 145 g. (0.90 mole) of bromine in 150 cc. of carbon tetrachloride was added to the stirred solution at such a rate that the temperature did not rise above 5°. After about one and a half hours, when 0.61 mole of bromine (68% of the theoretical) had been added, the bromine was no longer decolorized.

The contents of the reaction flask were allowed to come to room temperature and the ethyl bromide and carbon tetrachloride were distilled from the slightly yellow solution at atmospheric pressure. The remaining products were then fractionated through a Widmer column (26 cm. spiral) under reduced pressure. The following compounds, in the amounts indicated, were obtained: 64.3 g. (0.59 mole) ethyl bromide, b. p. 37–38°; 81.9 g. (0.33 mole) of ethyl dibromoacetate, b. p. 66–70°

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(3) (a) Paternò and Pisati, *Gazz. chim. ital.*, **2**, 334 (1872); (b) Pergami, *ibid.*, **26**, II, 468 (1896).

(4) Beyerstedt and McElvain, THIS JOURNAL, **58**, 529 (1936).

(5) Due to an oversight a ketene acetal which has been described in the recent literature was omitted from the table of known ketene acetals that appeared in this paper. This ketene acetal is dicarbomethoxylketene dimethylacetal, $C(COOCH_3)_2{=}C(OCH_3)_2$, which was described by Martius and Arndt [*Ann.*, **499**, 268–270 (1932)] as boiling at 142–145° (13 mm.). The corresponding ester, tricarbomethoxymethane ($HC(COOCH_3)_3$), boils at 130° (16 mm.).

PROPERTIES AND ANALYSES OF HALOGENATED KETENE ACETALS AND THE BOILING POINTS OF THE CORRESPONDING ESTERS

Compound	Analyses Calcd. Cl(or Br)	Analyses Calcd. OC_2H_5	Analyses Found Cl(or Br)	Analyses Found OEt	d^{25}_{25}	n^{25}_D	B. p., °C. 732–740 (mm.)	°C. Difference
$ClCH{=}C(OC_2H_5)_2$	23.59	59.80	23.42	59.51	1.0534	1.4375	166	21
$ClCH_2COOC_2H_5$	...	...	...	...	...	...	145	
$Cl_2C{=}C(OC_2H_5)_2$	38.38	48.65	38.05	48.46	1.1672	1.4350	177	23
$Cl_2CHCOOC_2H_5$	...	...	...	...	...	...	154	
$BrCH{=}C(OC_2H_5)_2$	...	...	...	...	...	...	180–182	24
$BrCH_2COOC_2H_5$	...	...	...	...	...	...	158	
$Br_2C{=}C(OC_2H_5)_2$	58.39	32.84	58.34	32.18	1.5790	1.4895	206–208	20
$Br_2CHCOOC_2H_5$	...	...	...	...	...	...	188	

(7 mm.); 11.9 g. (0.038 mole) of ethyl tribromoacetate, b. p. 65–69° (2 mm.); 17.4 g. (0.048 mole) of ethyl β,β-diethoxy-γ,γ-dibromobutyrate (V), b. p. 114–117° (3 mm.); and 77.2 g. (0.175 mole) of ethyl β,β-diethoxy-γ,γ,γ-tribromobutyrate (III), b. p. 135–139° (3 mm.).

The ethyl bromide was identified by its boiling point and by its conversion to propionanilide, m. p. 105–106°, through the formation of ethylmagnesium bromide and the reaction of this compound with phenyl isocyanate. Both ethyl dibromoacetate and ethyl tribromoacetate were converted to the corresponding amides, m. p. 154–155°[6] and 119–120°,[7] respectively. These amides were compared with authentic specimens obtained from known esters and found to be identical. The tribromo ester was identified further by hydrolysis with dilute sodium hydroxide into bromoform which was characterized by conversion into carbon tetrabromide, m. p. 91°.[8]

Ethyl β,β-diethoxy-γ,γ-dibromobutyrate, as obtained from the reaction, contained 45.50% of bromine (calcd. 44.20) and showed a molecular weight of 356 (calcd. 362) in benzene. Hydrolysis in 40% sulfuric acid for three hours yielded a dibromoacetone, b. p. 90–93° (12 mm.), which contained 75.44% (calcd. 76.23) of bromine. Reduction of this dibromoacetone with zinc and hydrochloric acid yielded acetone, identified as the dibenzilidene derivative, m. p. 110–111°. Both bromine atoms were assumed to be on the same carbon atom of the dibromoacetone and its precursor on account of the report[9] that the symmetrical dibromoacetone is a solid and also because of their analogy to ethyl β,β-diethoxy-γ,γ,γ-tribromobutyrate.

Ethyl β,β-diethoxy-γ,γ,γ-tribromobutyrate.—This product showed a bromine content of 57.10% (calcd. 54.42) and a molecular weight in benzene of 482 (calcd. 441). On hydrolysis with 40% sulfuric acid, 13.7 g. of this ester yielded 3.75 g. of tribromoacetone,[10] b. p. 105–108° (8 mm.), which contained 81.07% (calcd. 81.36) of bromine. This tribromoacetone was reduced to acetone as described above and was converted by alkaline hydrolysis into bromoform.

Dichloroacetal.—Into a 3-liter 4-necked flask fitted with a condenser carrying a calcium chloride tube, a thermometer, an efficient stirrer and a 7-mm. inlet tube for chlorine, was placed 745 g. of anhydrous acetal. Chlorine was passed into the acetal at such a rate that a temperature of 34–36° was maintained by the heat of the reaction for about two hours. The acetal was stirred vigorously throughout the entire run. An exit tube from the condenser led to a 1-liter flask in which the characteristic green chlorine color could be seen against a white background.

At the end of two hours the rate of chlorine addition was increased until the temperature of the acetal reached 70° where it was held by the heat of the reaction for about six hours. After this time the temperature began to drop, whereupon heat was supplied from a steam-bath to maintain a temperature of 70° in the flask while chlorine was added slowly over an additional four-hour period. After this chlorination period the acetal was cooled to room temperature. The volume amounted to approximately 1000 cc. It was washed once with water, three times with 300 cc. of a 10% solution of sodium bicarbonate, once with 250 cc. of a 10% solution of sodium thiosulfate, and twice with water. The volume of the reaction product at this point amounted to approximately 800 cc. After drying over anhydrous potassium carbonate the product was fractionated through a 38-cm. Widmer column.

From this fractionation 314 g., b. p. 35–66° (12 mm.), and 440 g., b. p. 66–71° (12 mm.), were obtained. This latter fraction is practically pure dichloroacetal. The yield amounts to 37% of the theoretical. This acetal boils at 178–181° at atmospheric pressure. On standing dichloroacetal appears to decompose to a slight extent to yield hydrogen chloride. Chlorine analyses are generally high on freshly distilled material unless the latter portion of the distillate is taken. Three fractions collected at 69–70, 70–70.5 and 70.5–71° (12 mm.) showed chlorine contents of 46.75, 40.88 and 38.98%, respectively (calcd. 37.94). Each of these fractions, however, gave practically the same yields of chloroketene acetal (see below).

Several attempts to prepare dichloroacetal by the procedure of Fritsch[11] were made. This method involves simply the chlorination of ethyl alcohol. In none of these attempts was an appreciable amount of the dichloroacetal obtained.

Trichloroacetal (Chloral Diethylacetal).—This compound was prepared by the procedure of Paternò and Pisati,[3(a)] from chloral, by first preparing the alcoholate, converting this compound into α,β,β,β-tetrachlorodiethyl ether by the action of phosphorus pentachloride, and finally treating the tetrachloro compound with absolute alcohol. The yield of the alcoholate from the chloral is quantitative, of the tetrachlorodiethyl ether from the alcoholate 25–33% of the theoretical, and of the chloral acetal from the tetrachloro ether about 70%. The acetal so obtained boils at 84–85° (10 mm.).

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(6) Steinkopf, *Ber.*, **38**, 2695 (1905).

(7) Broche, *J. prakt. Chem.*, [2] **50**, 100 (1894).

(8) Fuson, Farlow and Stehman, THIS JOURNAL, **53**, 4102 (1931).

(9) Volker, *Ann.*, **192**, 96 (1878).

(10) Étard, *Compt. rend.*, **114**, 754 (1892).

(11) Fritsch, *Ann.*, **279**, 300 (1894).

Tribromoacetal (Bromal Diethylacetal).—In a 1-liter 3-necked flask carrying a reflux condenser, a stirrer and a dropping funnel was placed 552 g. (2 moles) of dibromoacetal.[2] The flask was heated on a steam-bath while 320 g. (2 moles) of bromine was added over a period of two hours. After approximately one-half of the bromine had been added, the evolution of hydrogen bromide started and ethyl bromide began to reflux in the condenser. A carbon dioxide snow trap was used to catch any ethyl bromide that was carried from the reaction by the hydrogen bromide. After all of the bromine had been added the reaction mixture was fractionated. The following compounds, in the amounts indicated, were obtained from this fractionation: 1.8 mole of ethyl bromide, b. p. 36–38°; 0.29 mole of dibromoacetaldehyde, b. p. 46–54° (19 mm.); 0.90 mole of bromal, b. p. 69–73° (19 mm.); 0.34 mole of ethyl dibromoacetate, b. p. 88–95° (19 mm.); 0.14 mole of recovered dibromoacetal, b. p. 105–112° (19 mm.); 0.23 mole of tribromoacetal, b. p. 132–135° (19 mm.).

The tribromoacetal upon refractionating boiled at 85–86° (1 mm.). It contained 68.18% (calcd. 67.61) bromine and 25.29% (calcd. 25.35) ethoxyl; n^{25}_D 1.5158; d^{25}_{25} 1.8721.

Halogenated Ketene Acetals.—Chloro-, dichloro- and dibromoketene diethyl acetals were prepared in yields of 85, 76 and 56%, respectively, from the corresponding halogenated acetals by means of potassium in *t*-butyl alcohol.[2] The properties of these compounds are listed in the table in the introductory portion of this paper.

The authors wish to acknowledge their indebtedness to Mr. Donald G. Kundiger for the development of the preparation of dichloroacetal.

Summary

The bromination of bromoketene diethylacetal has been carried out and the course of the reaction elucidated. The preparation and properties of chloro-, dichloro- and dibromoketene diethyl acetals and of the intermediate halogenated acetaldehyde acetals have been described.

MADISON, WISCONSIN RECEIVED JUNE 16, 1938

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Enol Content of Some β-Keto Esters

BY ARTHUR B. NESS AND S. M. MCELVAIN

Over a period of years a number of β-keto esters have accumulated in this Laboratory from studies of the acetoacetic ester condensation. It seemed worth while to determine the enol content of certain of these esters in the hope that some correlation between this property and the structure of the keto ester might be revealed.

The esters which were studied in this work are of two general types, (a) alkyl acetoacetates[1] and (b) ethyl α,γ-dialkyl acetoacetates.[2] In this latter group are two keto-esters, ethyl α-isovalerylisovalerate and ethyl α,γ-di-*t*-butylacetoacetate, that are of special interest on account of the fact that they cannot be made from the condensation by means of sodium ethoxide,[3] of the substituted acetic ester, $RCH_2COOC_2H_5$, but are readily formed from these esters by the action of mesitylmagnesium bromide.[2c]

The determinations of the enol content were made in 0.1 *M* hexane solution at 25° since the work of Conant and Thompson[4] indicates that this particular solvent has the least solvation effect on the true thermodynamic equilibrium between the keto and enol forms. For the β-keto esters carrying no α-substituent the indirect method[5] of titration was used, while for the α-substituted esters the direct method[5] was employed.

The results that were obtained are summarized in the following table. Data for ethyl acetoacetate, ethyl α-butylacetoacetate, and ethyl α-benzylacetoacetate (nos. 2, 8 and 9) are included for comparison with results obtained by previous workers.

It may be seen from the above table that the alkyl acetoacetates, with the exception of the ethyl ester, have practically the same enol content. The ethyl ester stands out in striking contrast to the other esters of this type by having a decidedly lower enol content.

α-Substitution, as expected, lowers considerably the enol content of the β-keto esters. Distribution of the substituent carbon atoms between the α- and γ-carbon atoms of the keto ester appears to have about the same effect as having

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(1) Fischer and McElvain, THIS JOURNAL, **56**, 1766 (1934).

(2) (a) McElvain, *ibid.*, **51**, 3124 (1929); (b) Briese and McElvain, *ibid.*, **55**, 1697 (1933); (c) Spielman and Schmidt, *ibid.*, **59**, 2009 (1937); *cf.* also Hauser and Renfrow, *ibid.*, **59**, 1823 (1937).

(3) Roberts and McElvain, *ibid.*, **59**, 2007 (1937).

(4) Conant and Thompson, *ibid.*, **54**, 4039 (1932).

(5) Meyer, *Ber.*, **45**, 2843 (1912).

ENOL CONTENT OF β-KETO ESTERS, $RCH_2COCHR'COOR''$, IN 0.1 *M* HEXANE SOLUTION AT 25°

No.	R	R′	R″	% enol, range of values found	Detns.
1	H	H	CH_3	55.5–56.3	11
2[a]	H	H	C_2H_5	46.4–47.4	12
3	H	H	*n*-C_3H_7	53.8–55.3	11
4	H	H	*i*-C_3H_7	53.7–54.5	11
5	H	H	*n*-C_4H_9	54.7–55.7	11
6	H	H	*i*-C_4H_9	57.4–59.4	12
7	H	H	*s*-C_4H_9	55.7–56.4	10
8[a]	H	*n*-C_4H_9	C_2H_5	7.1– 7.9	11
9[a]	H	$C_6H_5CH_2$	C_2H_5	7.1– 7.5	12
10	CH_3	CH_3	C_2H_5	9.9–10.2	12
11	C_2H_5	C_2H_5	C_2H_5	7.7– 8.0	11
12	*n*-C_3H_7	*n*-C_3H_7	C_2H_5	5.8– 6.2	10
13[b]	*i*-C_3H_7	*i*-C_3H_7	C_2H_5	2.3– 2.6	7
14[b]	*t*-C_4H_9	*t*-C_4H_9	C_2H_5	1.8– 2.1	11
15	*n*-C_5H_{11}	*n*-C_5H_{11}	C_2H_5	4.1– 4.8	12
16[c]	*n*-C_7H_{15}	*n*-C_7H_{15}	C_2H_5	4.8– 4.9	3
17	*n*-$C_{12}H_{25}$	*n*-$C_{12}H_{25}$	C_2H_5	2.8– 3.0	5

[a] Values for the keto esters nos. 2, 8 and 9 as reported by Conant and Thompson[4] are 48.0–50.0, 9.0–11.0 and 11.0–13.0%, respectively; in alcoholic solution these workers reported 9.0–11.0, 5.7–6.4 and 5.0–5.5% enol content, respectively, for the same esters. [b] In alcoholic solution these esters show no enol content. [c] The sample of this keto ester that was used was not pure in that it contained small amounts of the corresponding ketone.[2]

all of them (as a normal chain) on the α-carbon (*cf.* nos. 8 and 11). An increase in size of the normal α- and γ-alkyl substituents causes a progressive lowering of the enol content of the substituted β-keto ester (nos. 10–12, 15–17). The work of Conant and Thompson shows that an increase in the size of a single normal α-alkyl substituent does not produce the same progressive lowering of the enol content of the β-keto ester.[6] Branching of the carbon chain that substitutes the α- and γ-carbons of the keto ester causes a further lowering of the enol content (*cf.* nos. 13 and 14 with 12 and 15). Conant and Thompson found that a similar effect was produced by branched substituents.[7]

It should be noted that ethyl isovalerylisovalerate (no. 13) contains almost as much of the enol form as does ethyl myristyl-myristate (no. 17). The latter ester may be prepared with sodium ethoxide as the condensing agent but the former ester (as well as no. 14) cannot be so prepared.[3] It must be concluded, therefore, that the failure of these esters that contain branched substituents, to be formed from condensations using sodium ethoxide cannot be attributed to their inability to enolize. It should be pointed out also that these keto esters with branched substituents seem to enolize very slowly as compared to those having *n*-alkyl substituents. In the direct titration of the latter type of keto esters the bromine coloration disappears in less than one minute after the end-point has been reached. With the branched chain substituted keto esters (13 and 14), however, the bromine coloration persisted for several (three to five) minutes before it was finally discharged. That this slow loss of the bromine color was due to a slow rate of enolization rather than to bromine substitution seems likely for the reason that neither of these keto-esters (13 and 14) showed any measurable absorption of bromine when absolute alcohol instead of hexane was used as a solvent. This observation is in line with that of previous investigators[4] who found that β-keto esters in general are enolized to a considerably less extent in alcohol than they are in hexane (*cf.* footnote *a* of the above table).

The present work has demonstrated that ferric chloride cannot be depended upon as an indicator when the enol content of a β-keto ester is low. At some point between an enol content of 7–8 and 4–5% it fails. Ethyl α-butyrylbutyrate (no. 11) gives a satisfactory ferric chloride test in aqueous suspension or alcoholic solution. The keto esters, nos. 12 to 16, inclusive, in the above table, give no coloration with ferric chloride under these conditions, nor do they show any coloration at the interface when their solutions in hexane, which have stood for several days, are treated with an aqueous or aqueous-alcoholic solution of ferric chloride.

Experimental

The β-keto esters that were used in this work were freshly distilled from samples that had been prepared[2] previously in this Laboratory. Two hundred and fifty cc. of a 0.1 *M* solution of each of these esters in hexane was made and allowed to stand for at least seventy-two hours to attain equilibrium. A 20-cc. sample of this hexane solution was transferred to a 125-cc. Erlenmeyer flask and placed in a thermostat at 25° for several hours. For both the direct and indirect method of titration 50 cc. of 95% alcohol, cooled to −7 to −10°, was added to the hexane solution before titration to freeze the equilibrium.

In the direct method of titration this cold alcoholic solution was titrated immediately with an approximately 0.1 *N* solution of bromine in absolute, aldehyde-free alcohol to a faint yellow color that remained for ten seconds. Exactly the same amount of this bromine solution was run

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(6) For example, Conant and Thompson[4] reported 10.3–12.9, 14–15, 14.3–14.5 and 9–11% enol for α-methyl-, α-ethyl-, α-*n*-propyl- and α-*n*-butylacetoacetic ester, respectively, in 0.1 *M* hexane solution.

(7) The α-isopropylacetoacetic ester and α-*s*-butylacetoacetic ester showed enol contents of 5.85–6.1 and 8.6–9.9%, respectively, in 0.1 *M* hexane (*cf.* values for the *n*-propyl and *n*-butyl compounds in footnote 6).

into a flask containing 50 cc. of water and 10 cc. of a 10% aqueous solution of potassium iodide. The liberated iodine then was titrated with 0.1 *N* sodium thiosulfate.

For the indirect method of titration an excess of the 0.1 *N* bromine solution in alcohol, which had been cooled to −7 to −10°, was added to the cold alcohol–hexane solution of the keto ester. The excess bromine was decolorized immediately by titration with a 10% solution of β-naphthol in absolute alcohol. To this point approximately fifteen seconds were required from the time the equilibrium was frozen by the cold alcohol. Then 15 cc. of a 10% solution of potassium iodide was added and the resulting solution warmed to 25–30° for five minutes, after which time the liberated iodine was titrated with 0.1 *N* sodium thiosulfate.

Summary

The enol contents of a number of alkyl acetoacetates and of some α,γ-dialkyl substituted ethyl acetoacetates are reported.

MADISON, WISCONSIN RECEIVED JUNE 16, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BRYN MAWR COLLEGE]

The Precipitation of Phenylmagnesium Bromide by Pyridine and by Dioxane

BY ARTHUR C. COPE

The accuracy of the Schlenk dioxane precipitation method[1] for determining the position of Grignard equilibria ($2RMgX \rightleftarrows R_2Mg + MgX_2$) is still open to question. The method depends upon precipitation of insoluble dioxanates of the RMgX and MgX_2 components, and this precipitation must be rapid compared to the rate of equilibration in order to avoid shifting the equilibrium in the direction of the less soluble dioxanate during precipitation. Recent work has shown that the compositions of the solution and the precipitate change if the two remain in contact,[2] presumably because of the reaction: $2RMgX \cdot$ dioxane (insoluble) $\rightleftarrows R_2Mg$ (soluble) $+ MgX_2 \cdot$ dioxane (insoluble). If the precipitation is used as an analytical method for determining the position of the original Grignard equilibrium, the latter reaction must be minimized by rapid removal of the precipitate.

In this investigation a number of ethers, sulfides and tertiary amines were added to ether solutions of phenylmagnesium bromide in an effort to find other precipitants for the halomagnesium components, thus making it possible to compare analyses obtained with two or more precipitants. Phenylmagnesium bromide was chosen because in this Laboratory arylmagnesium halides have given consistent analyses by dioxane precipitation.

Pyridine produces a precipitate with phenylmagnesium bromide which is grossly similar to the one obtained with dioxane. The precipitate can be separated by centrifuging, and the solution analyzed for basic magnesium and halogen. Typical data are plotted in Fig. 1, which shows the percentage of basic magnesium and bromide ion left in solution after the addition of a definite number of equivalents of pyridine, together with similar data for dioxane. The behavior of the two precipitants is very different in several respects. Dioxane precipitates the halomagnesium components more completely than does pyridine. Diphenylmagnesium is not precipitated by dioxane even when the latter is in large excess and high concentration. Pyridine precipitates only

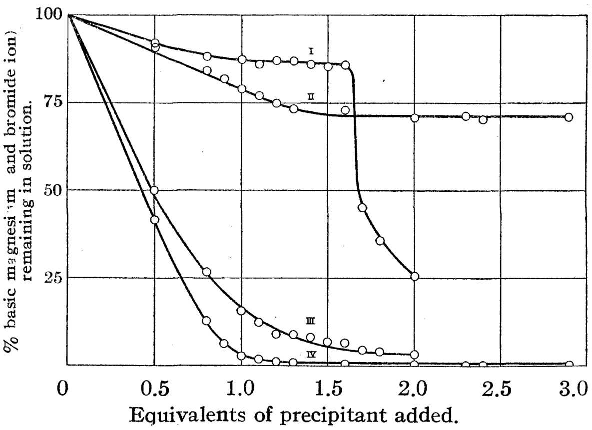

Fig. 1.—Precipitation of a phenylmagnesium bromide solution 0.2325 *N* in basic magnesium and 0.2402 *N* in bromide ion. The equivalents of precipitants are based on the normality in bromide ion. Curve I, % basic magnesium remaining in solution after precipitation with pyridine; II, % basic magnesium in solution after dioxane precipitation; III, % bromide in solution after pyridine precipitation; IV, % bromide in solution after dioxane precipitation.

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[1] Schlenk and Schlenk, *Ber.*, **62**, 920 (1929); Schlenk, *ibid.*, **64**, 734 (1931).

[2] (a) Noller and White, THIS JOURNAL, **59**, 1354 (1937); (b) Cope, *ibid.*, **57**, 2238 (1935).

phenylmagnesium bromide and magnesium bromide up to a molar ratio of pyridine to bromide ion of 1.6, with the concentrations employed; with ratios higher than 1.6 diphenylmagnesium is also precipitated, and in large amount (note the point of inflection in Curve I).

A comparison of the dioxane and pyridine precipitation data (Table I) gives two independent evaluations of the extent of disproportionation of phenylmagnesium bromide. The most accurate analyses should be those in which there is least bromide ion left in solution, or those with 1.2 to 20.0 equivalents of dioxane and 1.2 to 1.6 equivalents of pyridine. These dioxane and pyridine values show 70–74% and 78–79% disproportionation,[3] respectively. The results do not indicate a high degree of accuracy for the dioxane precipitation method, but the approximate checks obtained with the two precipitants suggest that in this case the order of magnitude at least is correct.

TABLE I

DISPROPORTIONATION OF PHENYLMAGNESIUM BROMIDE

	% disproportionation[a]			
	from dioxane precipitation		from pyridine precipitation	
Molar ratio precipitant/Br^-	A	B	A	B
1.0	76.2	78.9	71.7	87.3
1.1	75.2	77.0	73.6	86.0
1.2	73.8	74.9	78.1	87.1
1.3	72.5	73.3	77.9	86.8
1.4	..	..	77.8	85.9
1.5	..	..	78.5	85.3
1.6	72.4	72.9	79.3	85.8
2.0 to 20.0	70–72	70–72	..	..

[a] In this calculation it is necessary to make some assumption concerning the bromide ion left in solution, which is an appreciable quantity in all cases with pyridine, and with dioxane if less than 1.2 equivalents is used. The values recorded are calculated from the data of Fig. 1. The values in the columns headed A are calculated assuming that all the remaining bromide ion is present as phenylmagnesium bromide, and those headed B assuming that it is all magnesium bromide. The A values are more nearly correct, since magnesium bromide dioxanate appears to be less soluble than phenylmagnesium bromide dioxanate, but the true values are probably somewhere between the two extremes.

Pyridine cannot be recommended as a precipitant for preparing dialkylmagnesium solutions from Grignard reagents for synthetic purposes, because it does not remove bromide ion as completely as does dioxane, nor is it as convenient a reagent for use in analyses. If its behavior with phenylmagnesium bromide is typical of Grignard reagents in general, it may serve a useful purpose in checking analyses made by the Schlenk method.

Oddo[4] has reported that the addition of two moles of pyridine to an ether solution of phenylmagnesium bromide causes precipitation of the definite compound, $C_6H_5MgBr\cdot(C_2H_5)_2O\cdot2C_5H_5N$. This and most of the other work on addition compounds of tertiary amines and other "donor" molecules with Grignard reagents[5] was done prior to Schlenk's demonstration of the existence of the Grignard equilibrium, and the addition compounds were usually analyzed after some purification, with no thought of a possible separation of the supposedly homogeneous reagent during precipitation. It is possible that in other cases like the above, where definite compounds are reported, analysis of the original precipitate or the residual solution after precipitation would disclose a differential precipitation of the components of the equilibrium.

Experimental Part[6]

The phenylmagnesium bromide solutions were prepared in the usual manner under dry nitrogen in a flask fitted with a filter tube,[2b] and filtered with nitrogen pressure directly into the reservoir of a specially designed buret (Fig. 2). During filtration the reagent was protected by a counter current of nitrogen introduced through the tip of the buret, the top half of the ground glass seal being removed and tube A stoppered temporarily. The solutions were standardized by acidimetric[7] and Volhard titrations.

Among the substances investigated which gave no precipitate with phenylmagnesium bromide in ether solution were the following: dimethyldioxane,[8] *p*-thioxane, *p*-dithiane, diphenylpiperazine, dimethylaniline, diethylaniline, N-phenylmorpholine and nicotine. Quinoline, α-picoline, N-methylmorpholine and diphenyl sulfoxide gave varying amounts of oily or gelatinous precipitates which could not be handled quantitatively.

The pyridine and dioxane analyses were made in the following manner. Twenty cubic centimeters of the Grignard solution (at 20°) was measured from the buret into a dry, nitrogen-filled centrifuge tube of 50-cc. capacity, made with a constricted neck. The access of air during transfer was prevented by a nitrogen mantle (shown in Fig. 2), and the tube was tightly stoppered as soon as it was removed from the mantle. Solutions of pyridine or dioxane were made up to contain the desired number of equivalents of precipitant in 10 cc. of dry ether solution, and this volume was added to the 20-cc. samples as rapidly as possible from a buret with a wide orifice, the sample

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(3) According to assumption A above. With assumption B the values are 70–75% and 85–87%.

(4) Oddo, *Atti accad. Lincei,* [5] **13**, II, 100 (1904); *Gazz. chim. ital.*, **34**, II, 420 (1904).

(5) *Cf.* the references given by Hepworth, *J. Chem. Soc.*, **119**, 1249 (1921).

(6) The author wishes to express his indebtedness for a grant from the Wolcott Gibbs fund of the National Academy of Sciences for apparatus essential to this investigation.

(7) Gilman, Zoellner and Dickey, THIS JOURNAL, **51**, 1576 (1929).

(8) Kindly furnished by the Carbide and Carbon Chemicals Corp.

again being protected from the air with a nitrogen mantle. The tubes were stoppered immediately, shaken vigorously and centrifuged at 2800 r. p. m. for ten minutes. The clear supernatant liquid was decanted into a flask containing 75 cc. of water. A 20-cc. portion of dry ether was added to the solid residue remaining in the centrifuge tube, which was again shaken, centrifuged for five minutes and decanted into the flask containing water. Further washing of the precipitate with ether failed to remove significant quantities of basic magnesium or halogen, showing that there was little if any occlusion, except in analyses using pyridine in quantities sufficient to precipitate diphenylmagnesium. In the latter case the amount of basic magnesium taken into solution increased with each washing of the precipitate, so that the analyses with more than 1.6 equivalents of pyridine have no exact quantitative significance.

In the pyridine analyses, the ether was first boiled off, after which the aqueous mixture was boiled for thirty minutes to remove the pyridine, acidified with an excess of standard sulfuric acid, again boiled for five minutes and back titrated with standard alkali. Bromide analyses were made on the same samples, after cooling, by Volhard titration. The method was proved to be accurate by analysis of a Grignard reagent of known normality after the addition of pyridine. The end-points in the acidimetric titration were not as sharp as in the dioxane analyses. Solutions precipitated with dioxane were acidified initially with an excess of standard sulfuric acid and boiled long enough to expel completely the ether before back titrating with standard alkali.

Precipitations with Isoquinoline.—Isoquinoline gives a bulky solid precipitate with phenylmagnesium bromide in ether solution. The precipitate may be separated by centrifuging, and the solutions analyzed as in the pyridine procedure if they are boiled for one hour before acidification, although the end-points are obscure in the acidimetric titration. Interpretation of the analyses is difficult, because a relatively large proportion of the bromide ion remains in solution. The following data are representative. A solution of phenylmagnesium bromide 0.2060 *N* in basic magnesium and 0.2138 *N* in bromide ion was precipitated as described above with 1.0 and 1.1 equivalents of isoquinoline. The solutions after centrifuging contained: (1 equivalent of isoquinoline) basic magnesium 0.1720 *N* (with respect to the volume of the original sample); bromide ion 0.0522 *N;* (1.1 equivalents of isoquinoline) basic magnesium 0.1690 *N;* bromide ion 0.0443 *N.*

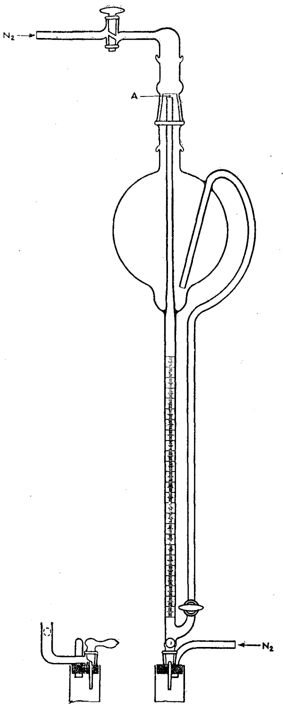


Fig. 2.—Apparatus.

Summary

Pyridine behaves like dioxane in precipitating the halomagnesium components of the equilibrium, $2C_6H_5MgBr \rightleftarrows (C_6H_5)_2Mg + MgBr_2$. The two precipitants indicate 78–79% and 70–74% disproportionation in the above equilibrium, respectively. This rough check with two different precipitants indicates that the Schlenk dioxane precipitation method, for this Grignard reagent at least, gives approximately correct results.

BRYN MAWR, PENNSYLVANIA RECEIVED JUNE 18, 1938

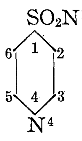
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE CALCO CHEMICAL COMPANY, INC.]

Sulfanilamide Derivatives. I. Aminoarylsulfonamidoarylsulfonic Acids and Aminoarylsulfonamidoarylcarboxylic Acids*

BY M. L. CROSSLEY, E. H. NORTHEY AND MARTIN E. HULTQUIST

Nomenclature of Sulfanilamide Derivatives.—Chemical and medical literature on sulfanilamide derivatives suffers from a confusion of names and naming systems which is bewildering to the medical reader and often misleading to chemists. The name "sulfanilamide" has been adopted officially by the American Medical Association and is now generally used. It would seem desirable, therefore, to continue with this and relate the names of new derivatives, where possible, to the parent sulfanilamide. In the interest of setting up such a system, we have corresponded with Austin M. Patterson, who has given valuable suggestions on the following:

a. Naming as substituted sulfanilamides



In sulfanilamide the sulfonamide group, being the principal functional group, occupies the 1-posi-

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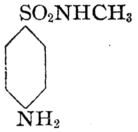
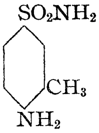
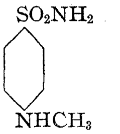
(*) Presented in part before the Division of Medicinal Chemistry, A. C. S., April 20, 1938.

tion in the ring. The nitrogens are differentiated by superscripts: N^1 referring to substituents on the amide nitrogen and N^4 to substituents on the amino nitrogen.

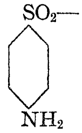
The following examples illustrate the method

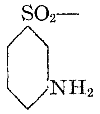

N^1-Methylsulfanilamide

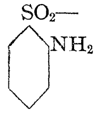

3-Methylsulfanilamide

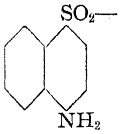

N^4-Methylsulfanilamide

b. Radical names.—For simple derivatives the above method should be used, but it becomes unwieldy in naming compounds with complex substituents. In such cases radical names are useful. The following radicals are suggested


Sulfanilyl-


Metanilyl-

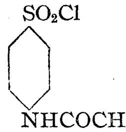

Orthanilyl-


Naphthionyl-

These names follow directly from the corresponding amino acids.

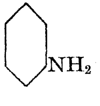
An example of their usefulness is shown by the compound

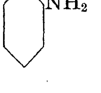
which we name N,N′-disulfanilylbenzidine-2,2′-disulfonic acid. This seems preferable to the name, N,N′-*bis*-(4-aminobenzenesulfonyl)-4,4′-di-aminobiphenyl-2,2′-disulfonic acid. A simpler case is



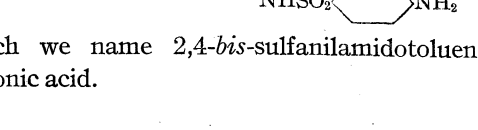
an important intermediate, which we call N-acetylsulfanilyl chloride instead of *p*-acetamidobenzenesulfonyl chloride. Other useful radicals are


Sulfanilamido-


Metanilamido-

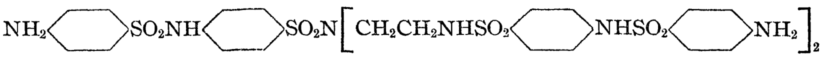

Orthanilamido-

An example is



which we name 2,4-*bis*-sulfanilamidotoluene-5-sulfonic acid.

An example of the use of all three types of names is the following


N^1,N^1-*bis*[2-(N^4-Sulfanilylsulfanilamido)-ethyl]-N^4-sulfanilylsulfanilamide

New Derivatives.—In spite of the fact that the literature on sulfanilamide and its derivatives now numbers over 300 references, a relatively few outstanding publications summarize most of the published work on new derivatives.[1–5]

The published work has indicated the following generalities on the relationship of structure and antistreptococcal activity. (1) Little or no activity was found in mononuclear compounds in which either the amino or sulfonamide groups of sulfanilamide were replaced. (The highly active diamino- and dinitrodiphenylsulfones, sulfoxides and sulfides have two rings joined through a sulfur linkage.) (2) Shifting the amino group to the meta or ortho position resulted in marked loss of activity. (3) A third group on the ring lowered the activity. (4) Substitution of the amino group with alkyl, aralkyl, substituted alkyl or aryl, acyl and alkylidene groups had less effect, but in general lowered the activity. (5) Substitution of the amide nitrogen had a variable effect. Methyl and ethyl groups did not change the activity while higher alkyl groups decreased the activity. *p*-Amino- and *p*-nitrophenyl groups increased the activity.

The low solubility of sulfanilamide and its toxicity at effective dosage levels led us to attempt new derivatives of increased solubility which might also have a higher therapeutic index. Our first attempts were to combine N-acetylsulfanilyl chloride with various aminobenzenesulfonic acids and aminobenzenecarboxylic acids in aqueous solution at *p*H 8–10. The reaction went smoothly and after hydrolysis of the acetyl group with acid or base gave us the desired sulfanilyl derivative.

Orthanilyl and metanilyl derivatives were made by treating the corresponding nitrobenzenesulfonyl chlorides with the desired amino acid, followed by reduction of the nitroamide with ammonium polysulfide or in some cases iron in neutral solution.

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(1) Tréfouël, Nitti and Bovet, *Ann. Inst. Pasteur*, **58**, 30 (1937).

(2) Buttle, Gray and Stephenson, *Lancet*, I, 1286 (1936); *Biochem. J.*, **31**, 724 (1937).

(3) Mietzsch, *Ber.*, **71**, 15 (1938).

(4) Bauer and Rosenthal, *U. S. Treasury Dept., Pub. Health Repts.*, **53**, 40 (1938).

(5) I. G. Fr. 817,034; *C. A.*, **32**, 1714 (1938).

Compound	Formula	Therapeutic effect	Melting range, °C.
Sodium N-sulfanilylsulfanilate[a]	$C_{12}H_{11}O_5N_2S_2Na$	+	>300 dec.
N-Sulfanilylmetanilic acid	$C_{12}H_{12}O_5N_2S_2$	++	>300 dec.
N-Sulfanilylorthanilic acid	$C_{12}H_{12}O_5N_2S_2$	+++	>300 dec.
2-Methyl-N-sulfanilylsulfanilic acid	$C_{13}H_{14}O_5N_2S_2$	0	>300 dec.
3-Methyl-N-sulfanilylsulfanilic acid	$C_{13}H_{14}O_5N_2S_2$	+	>280 dec.
Sodium 5-methyl-N-sulfanilylorthanilate	$C_{13}H_{13}O_5N_2S_2Na$	0	>300 dec.
Sodium 2,5-dimethyl-N-sulfanilylsulfanilate	$C_{14}H_{15}O_5N_2S_2Na \cdot H_2O$	0	>300 dec.
6-Ethoxy-N-sulfanilylmetanilic acid	$C_{14}H_{16}O_6N_2S_2 \cdot H_2O$	0	>245 dec.
Sodium 2,4-*bis*-sulfanilamidobenzenesulfonate	$C_{18}H_{17}O_7N_4S_3Na$	+++	>320 dec.
Sodium 2,4-*bis*-sulfanilamidotoluene-5-sulfonate	$C_{19}H_{19}O_7N_4S_3Na$	0	>300 dec.
2,5-*bis*-Sulfanilamidobenzenesulfonic acid	$C_{18}H_{18}O_7N_4S_3 \cdot H_2O$	+++	>240 dec.
Sodium 3,4-*bis*-sulfanilamidobenzenesulfonate	$C_{18}H_{18}O_7N_4S_3Na$	±	
2-Sulfanilamidosulfanilic acid	$C_{12}H_{13}O_5N_3S_2 \cdot {}^1/_2H_2O$	0	>270 dec.
Sodium-4-sulfanilamidonaphthalenesulfonate	$C_{16}H_{13}O_5N_2S_2Na \cdot {}^1/_2H_2O$	++	>245 dec.
2-Sulfanilamidonaphthalene-6-sulfonic acid	$C_{16}H_{14}O_5N_2S_2$	−	>300 dec.
Sodium 5-sulfanilamidonaphthalene-1-sulfonate	$C_{16}H_{13}O_5N_2S_2Na \cdot 2H_2O$	+	>300 dec.
N,N′-Disulfanilylbenzidine-2,2′-disulfonic acid	$C_{24}H_{22}O_{10}N_4S_4$	0	>300 dec.
4,4′-Disulfanilamidostilbene-2,2′-disulfonic acid	$C_{26}H_{24}O_{10}N_4S_4 \cdot 4H_2O$	0	>330 dec.
4-Sulfanilamidobenzoic acid[a,4]	$C_{13}H_{12}O_4N_2S$	+	198–200.5
3-Sulfanilamidobenzoic acid[a]	$C_{13}H_{12}O_4N_2S$	+	197.0–198.5
2-Sulfanilamidobenzoic acid[a]	$C_{13}H_{12}O_4N_2S$	+++	225 dec.
2-Metanilamidobenzoic acid	$C_{13}H_{12}O_4N_2S$	++	191.5–193.5
2-Orthanilamidobenzoic acid	$C_{13}H_{12}O_4N_2S$	−	176.7–178
2-Hydroxy-5-sulfanilamidobenzoic acid	$C_{13}H_{12}O_5N_2S$	−	>285 dec.

[a] Kolloff, THIS JOURNAL, 60, 950 (1938).

Purity by nitrite, %	Analyses									
	Calculated					Found				
	C	H	N	S	Na	C	H	N	S	Na
99.9	41.2	3.14	8.00	18.21	6.57	41.3	3.5	8.0	18.1	6.2
100.3	43.8	3.68	8.55	19.53		43.6	3.8	8.45	19.4	
96.3	43.8	3.68	8.55	19.53		41.3	4.2	8.53	18.8	
99.4	45.6	4.17	8.16	18.7		45.2	4.4	8.17	18.7	
100.1	45.65	4.15	8.18	18.7		44.5	4.3	7.9	18.1	
100.2			7.68	17.6	6.31			7.7	16.8	5.84
100.2	42.4	4.32	7.07	16.18	5.8	42.4	4.6	6.87	16.3	
103.0	42.9	4.61	7.15	16.3		43.0	4.9	7.2	16.2	
100.0	41.5	3.26	10.7	18.4	4.4	41.6	3.9	9.9	17.9	
100.4	42.7	3.6	10.5	18.0	4.3	42.1	3.9	10.7	17.7	
100.2	41.9	3.91	10.86	18.6		41.9	4.03	11.5	19.1	
100.4	41.5	3.29	10.77	18.3	4.42				18.4	4.3
101.0	40.9	4.0	11.9	18.2		40.8	4.3	12.5	18.1	
101.1	44.9	3.79	6.55	15.05	5.38	44.5	3.72	5.72	14.4	5.4
100.5	50.8	3.74	7.42	16.95		49.7	3.7	7.5	16.5	
	44.1	3.92	6.43	14.7	5.27	44.0	3.79	6.77	14.9	5.24
100.0	44.05	3.4	8.58	19.57		43.5	3.4	8.7	19.4	
100.5	41.5	3.75	7.54	17.05		41.2	3.81	7.53	17.06	
100.0	53.4	4.14	9.58	10.98		52.6	4.1	9.7	10.9	
100.0	53.4	4.14	9.58	10.98		52.8	4.2	9.31	10.8	
101.9	53.4	4.14	9.58	10.98		53.7	3.7	9.3	10.8	
100.0	53.4	4.14	9.58	10.98		52.6	4.5	9.7	11.0	
99.8										
	50.6	3.93	9.08	10.42		50.5	4.4	9.0	9.7	

In the form of the neutral salts of the sulfonic or carboxylic acids, these derivatives had high water solubility, while the free acids were, in general, only slightly soluble.

The table shows the derivatives and the results of preliminary tests in mice infected with β-hemolytic streptococci. The signs and their meaning are: +++ indicates compounds superior to sulfanilamide, ++ equal to, + somewhat inferior to sulfanilamide; while ± designates compounds with very slight activity, 0 no activity, and − identifies compounds which killed the animals faster than the controls died.[6,7]

The compounds are named as substituted sulfonic or carboxylic acids. The acid function, therefore, occupies the 1-position in the ring.

Sodium N-sulfanilylsulfanilate is extremely water soluble—so much so that a solution of it may be evaporated to a very thick sirup. The addition of benzene to a moderately concentrated aqueous solution caused precipitation of a white crystalline compound containing benzene of crystallization. This was stable to drying at 60°, but was decomposed on dissolving in boiling water, when the benzene was evolved with effervescence, like a carbonate dissolving in acid.

While sodium N-sulfanilylsulfanilate was synthesized primarily for trial in bacterial diseases, this unusual property gave us the idea that it might be effective against viruses, for if it had the power of coördinating with an inert substance such as benzene, might it not coördinate with, or inactivate, the infinitely more complex molecules of a virus?

We suggested, therefore, to Dr. Dochez that he try it against the common cold and influenza viruses. The latter being capable of investigation in experimental animals was tried first and the compound found ineffective. The thing might have died a natural death at this point but, fortunately, Dr. Dochez tried it against dog distemper virus, with striking results.[8]

We have tested other of the above compounds in other virus diseases with promising results. Our most interesting compound in this respect is 2,5-*bis*-sulfanilamidobenzenesulfonic acid, which not only appears to be more efficient than sulfanilamide in antistreptococcal effect, but which shows definite activity against the Francis strain of influenza virus in mice.

Attempts to correlate antistreptococcal activity with structure, based on the above series, indicate that in the parent aminobenzenesulfonamide the para position gives the greater therapeutic effect with the meta position next and the ortho position least. In the second ring, however, this is reversed completely and the more effective compounds are obtained when a carboxyl or sulfonic group is ortho to the amido group. These compounds, in fact, seem to be more effective than sulfanilamide.

Addition of a methyl, chlorine, OH or OR to these derivatives gives less active compounds.

Addition of NH_2 also gives an inactive derivative. However, a very active derivative is obtained by placing an additional sulfonamido group on this ring as in 2,4-*bis*-sulfanilamidobenzenesulfonic acid. Addition of a fourth group, CH_3, to this ring again completely destroys the activity.

Further interesting evidence on the relation of structure to therapeutic effect in these compounds is furnished by 1,3-*bis*-sulfanilamidobenzene which rates only ± while its sulfonic acid is +++; 1,4-*bis*-sulfanilamidobenzene rates ++, while its sulfonic acid as stated above has a superior antistreptococcal effect coupled with viruscidal activity.

In the naphthalene series position isomerism also has a pronounced effect on the therapeutic activity. The 1,4-position was much superior to the 1,5-, while the 2,6-derivative was toxic. An attempt to prepare N-sulfanilyl-2-naphthylamine-1-sulfonic acid failed when the sulfonic group was lost during hydrolysis of the acetyl derivative. This compound would have been of interest in view of our results in the benzene series.

Experimental

Preparation of Sulfanilyl Derivatives.—The general method of preparing sulfanilyl derivatives of aminoarylsulfonic acids and aminoarylcarboxylic acids is illustrated below for the synthesis of sodium N-sulfanilylsulfanilate.

Sodium N-Sulfanilylsulfanilate.—One hundred seventy-three grams (1 mole) of sulfanilic acid, 40 g. (1 mole) sodium hydroxide and 20 g. sodium carbonate were dissolved in 800 cc. of water. The solution was cooled to 40° and 1 mole of N-acetylsulfanilyl chloride in the form of a freshly prepared and analyzed paste was added over one hour, with vigorous agitation. The temperature was held at 40–45° by addition of ice, and the *p*H maintained between 8 and 11 by addition of 50% sodium hydroxide solution as required.

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(6) The pharmacological study was carried out by D. R. Climenko and will be reported elsewhere.

(7) Micro-analyses were made under the direction of G. L. Royer.

(8) Dochez and Slanetz, *Science*, **87**, 142 (1938).

After stirring for fifteen minutes a 2-cc. sample of the reaction mixture was diluted to 50 cc., acidified and titrated with 0.1 *N* sodium nitrite at about 20°. This gave an estimation of unreacted amino nitrogen. If the value corresponded to more than 5% of the starting amount, more N-acetylsulfanilyl chloride was added until the nitrite titration reached a minimum, or until 25% excess had been added.

Isolation of N-acetylsulfanilylsulfanilic acid at this point offered no advantage in purity of the final compound. Hydrolysis was therefore made by adding 100 g. (2.5 moles) of sodium hydroxide and boiling the solution for one and one-half hours, or until there was no further increase in diazotizable amine.

N-Sulfanilylsulfanilic acid was isolated from the hydrolysate by acidifying to about *p*H 1 with hydrochloric acid, filtering the precipitate and washing five or six times with 100-cc. portions of water at 80–90° to remove sulfanilic acid.

The crude N-sulfanilylsulfanilic acid was dissolved as the sodium salt at *p*H 5–6, treated with decolorizing carbon and reprecipitated twice. The resulting filter cake was dissolved with solid sodium hydroxide to give a 2.2 *N* solution having a *p*H of 6.5. An equal volume of 95% ethyl alcohol was added to the warm solution. On cooling, crystallizing, filtering, washing with alcohol and drying finally at 100°, 110 g. of anhydrous sodium-N-sulfanilylsulfanilate resulted. Approximately an equal amount was recovered from the mother liquor, giving a yield over all of 60%.

Notes on General Procedure. **1.**—This type procedure was followed with the other sulfanilyl derivatives listed, substituting an equivalent amount of the corresponding amino or diaminosulfonic acid. Some variation was necessary in concentration because of the difference in solubility of intermediates and final compounds. Thus, in the case of N-sulfanilylorthanilic acid, N-sulfanilylmetanilic acid and 6-ethoxy-N-sulfanilylmetanilic acid, the free acids were moderately soluble and were therefore recrystallized from water without passing through the sodium salt. Sodium salts listed, with the exception of sodium-N-sulfanilylsulfanilate, were crystallized from concentrated aqueous solutions without use of alcohol.

2.—Yields averaging 60–70% were obtained in most cases but were of no special significance since recoveries from the numerous mother liquors were not made unless these contained more than 10% of the yield as determined by nitrite titration. Yields of derivatives where a sulfonic acid or other large group was in the ortho position to the sulfanilamido group were generally poor, probably because of steric hindrance.

3.—In making sulfanilyl derivatives of aminonaphthalenesulfonic acids, and diaminosulfonic acids, care was taken to prepare or purify these immediately before use, since highly colored impurities were difficult to remove later. Use of small amounts of sodium hydrosulfite following treatment with decolorizing carbon was helpful in removing color and preventing further oxidation, both on intermediates and final compounds.

4.—Usage of sodium hydroxide in hydrolysis was based on one mole for each acetyl group, plus one mole for each —SO_2NH— (or other acidic group not neutralized), plus one-half mole excess. This excess was sufficient to promote complete hydrolysis of the acetyl groups in about one hour at 102–103°, for the concentrations used.

5.—Hydrolysis of acetyl groups was also effected by boiling in 15% hydrochloric acid, but this was generally less satisfactory since many of the products were only slightly soluble in acid. The resulting thick slurry bumped on boiling and was otherwise difficult to handle. Hydrolysis did not proceed to completion in some cases because the particles of intermediate were protected by a coating of the product.

2-Sulfanilamidosulfanilic Acid.—This was prepared by the type procedure starting with 1 mole of 2-amino-4-acetylaminobenzenesulfonic acid per mole of N-acetylsulfanilyl chloride; 3.5 moles of sodium hydroxide was used for hydrolysis of the acetyl groups.

Orthanilyl and Metanilyl Derivatives.—These derivatives were made following the general procedure outlined above but with substitution of *o*-nitrobenzenesulfonyl chloride or *m*-nitrobenzenesulfonyl chloride in equivalent amount for N-acetylsulfanilyl chloride. Since these acid chlorides were somewhat more resistant to hydrolysis, the reaction temperature was raised to 45–50°. The resulting nitrosulfonamide was isolated by acidification of the reaction mixture and reduced to the amino derivative by the method illustrated below.

2-Metanilamidobenzoic Acid.—The 2-(*m*-nitrobenzenesulfonamido)-benzoic acid resulting from one mole of anthranilic acid was dissolved in 500 cc. of 28% ammonia. A stream of hydrogen sulfide was passed in with vigorous agitation and cooling. When the initial reaction had moderated, the flask contents were heated to a gentle boil under a reflux condenser with a continued slow stream of hydrogen sulfide, for an hour and a half. Boiling was then maintained while a rapid stream of air was passed through the solution until sulfides had been oxidized to sulfur and most of the excess ammonia removed. Sulfur was removed by filtration. The filtrate was acidified slowly with hydrochloric acid and the crude product filtered off. This was twice recrystallized by dissolving as the sodium salt, treating with activated charcoal and reprecipitating. A yellow color still persisted. The material was dissolved as the sodium salt, made slightly acid with acetic acid and boiled with about 1 g. of zinc dust. This decolorized the solution. The product was isolated as the acid and recrystallized twice from 1 liter of alcohol using activated charcoal.

Attempts to reduce the nitro compound with iron failed because of the formation of an insoluble iron salt.

Summary

A naming system for sulfanilamide derivatives is proposed which relates the names where possible to the parent sulfanilamide. For more complex derivatives, the radicals "sulfanilyl,"  and "sulfanilamido,"  are used.

Highly soluble salts of sulfanilamidobenzenesulfonic acids and sulfanilamidobenzenecarboxylic acids are described. Preliminary tests in mice indicate that while in the parent ring highest antistreptococcal activity is found in the para derivative, this is reversed completely in the second ring, where compounds in which the acid function is ortho to the nitrogen have the highest activity.

Addition of —CH_3, —OH, —OR or —Cl to the second ring greatly lowers or destroys the activity.

Sodium 2,4-*bis*-sulfanilamidobenzenesulfonate and 2,5-*bis*-sulfanilamidobenzenesulfonic acid appear to have activity against influenza virus in mice, as well as to have high antistreptococcal powers.

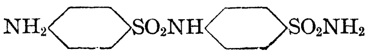
BOUND BROOK, N. J. RECEIVED APRIL 27, 1938

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE CALCO CHEMICAL COMPANY, INC.]

Sulfanilamide Derivatives. II. Disulfanilamides and Related Compounds[1]

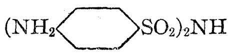
BY M. L. CROSSLEY, E. H. NORTHEY AND MARTIN E. HULTQUIST

The compound called by Rosenthal[2] "Disulfanilamide"



is incorrectly named. We suggest that it be called N⁴-sulfanilylsulfanilamide.

We have synthesized true disulfanilamide



and have prepared a number of derivatives having the disulfonamide linkage, —SO_2NHSO_2—. These compounds as a class behave as strong acids, forming neutral sodium salts of the type —SO_2NNaSO_2—. The salts have high water solubility and are very stable to heat, decomposing at temperatures above 300°. However, if the hydrogen of the disulfonamide is replaced by alkyl, the compound becomes water and alkali insoluble and is broken down more readily by strong acids or bases.

Disulfanilamide was synthesized by treating more than two moles of N-acetylsulfanilyl chloride with one mole of ammonia, keeping the *p*H at 10–11 by addition of sodium hydroxide solution and holding the temperature below 45°. It was also made starting with N-acetylsulfanilyl chloride and N^4-acetylsulfanilamide. The resulting N^1-sodium-N^4,$N^{4'}$-diacetyldisulfanilamide was hydrolyzed by boiling with sodium hydroxide and was purified by recrystallization as the sodium salt.

Alkylation was accomplished by boiling the N^1-sodium-N^4,$N^{4'}$-diacetyldisulfanilamide with excess dimethyl sulfate in xylene. The resulting N^1-methyl-N^4,$N^{4'}$-diacetyldisulfanilamide was hydrolyzed to N^1-methyldisulfanilamide by adding the theoretical amount of 36% hydrochloric acid, dropwise, to a boiling alcoholic solution so that the acidity at no time was sufficient to give a green spot on methyl violet paper. Boiling aqueous 20% hydrochloric acid caused rapid breakdown at the amide linkage giving sulfanilic acid and N^1-methylsulfanilamide. The same type of decomposition occurred during hydrolysis with sodium hydroxide but at a much slower rate.

Dimetanilamide was made by treating an excess of *m*-nitrobenzenesulfonyl chloride with *m*-nitrobenzenesulfonamide at 50–60° in aqueous solution and at *p*H 10–11. The *p*H was maintained by addition of sodium hydroxide as necessary. The resulting 3,3′-di-*m*-nitrodibenzenesulfonamide was reduced to dimetanilamide with ammonia and hydrogen sulfide.

The compounds synthesized and their relative effectiveness as indicated by preliminary studies on β-hemolytic streptococcal infections in mice are shown in the table, where sulfanilamide = ++.[3,4]

The inferences drawn from the results are:

1. Acetylation of the amino groups lowered the therapeutic effect. This was in agreement with all other work on sulfanilamide derivatives.

2. Alkylation of the amide nitrogen had no apparent effect on the therapeutic efficiency although the compound had lost its water solubility almost completely.

3. Metanilyl derivatives had a lower effectiveness than the corresponding sulfanilyl derivatives. However, dimetanilamide had about the same activity as sulfanilamide.

In addition to the sodium and magnesium salts

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(1) Presented in part before the Division of Medicinal Chemistry, A. C. S., April 20, 1938.

(2) Rosenthal, *et al.*, *Pub. Health Repts.*, *U. S. Treas. Dept.*, **52** 662 (1937); *ibid.*, **53**, 40 (1938).

(3) A complete report on the pharmacology will be presented by Dr. D. R. Climenko, elsewhere.

(4) Microanalyses were made under the direction of G. L. Royer.

TABLE I

Compound	Formula	Therapeutic effect	Melting range, °C.	Assay by nitrite, %	Analyses, % Calculated C	H	N	S	Found C	H	N	S
Disulfanilamide	$C_{12}H_{13}O_4N_3S_2$		260.5–261.0	99.8	44.0	4.01	12.86	19.6	43.6	4.2	12.8	19.1
N^1-Sodium-N^4,$N^{4'}$-diacetyldisulfanilamide	$C_{16}H_{16}O_5N_3S_2Na$	++					9.68	Na, 5.3			9.81	Na, 5.5
N^1-Methyldisulfanilamide	$C_{13}H_{15}O_4N_3S_2$	+++	180.0–181.0	99.3	45.7	4.45	12.3	18.75	46.1	4.6	12.1	18.6
N^1-Methyl-N^4,$N^{4'}$-diacetyldisulfanilamide	$C_{17}H_{19}O_6N_3S_2$	±	228.5–229–230		48.0	4.5	9.9	15.1	47.9	4.5	10.1	15.0
N^1-Ethyldisulfanilamide	$C_{14}H_{17}O_4N_3S_2$	+++	153.3–154.7	100.3	47.3	4.84	11.85	18.03	47.25	5.04	12.3	18.0
N^1-Ethyl-N^4,$N^{4'}$-diacetyldisulfanilamide	$C_{18}H_{21}O_6N_3S_2$		229.5–230.5		49.2	4.8	9.7	14.6	49.38	4.94	9.7	14.8
Dimetanilamide	$C_{12}H_{13}O_4N_3S_2$	++	>300 dec.	100.0	44.0	4.0	12.86	19.6	43.9	3.7	12.8	19.1
N^1-Magnesium disulfanilamide	$C_{24}H_{24}O_8N_6S_4Mg \cdot H_2O$	++		98.4			Mg, 3.40			Mg, 3.35		
N^1-Sodium disulfanilamide	$C_{12}H_{12}O_4N_3S_2Na \cdot H_2O$	+++	>340 dec.	100.2	Sodium		6.28		Sodium		6.35	

TABLE II

SALTS OF DISULFANILAMIDE

Salt	Method of preparation	Appearance	Water solubility Hot	Water solubility Cold
Lithium	DSA + $LICO_3$	Small white flat rods or plates	v. s.	v. s.
Sodium	DSA + NaOH	White prisms	ext. s.	v. s.
Magnesium	Sod. DSA + $MgCl_2$	White rectangular plates	v. s.	mod. s.
Calcium	DSA + $Ca(OH)_2$	Rods or needles	ext. s.	v. s.
Barium	Sod. DSA + $BaCl_2$	Needles	mod. s.	sl. s.
Cupric	Sod. DSA + $CuSO_4$	Light green needles[a]	mod. s.	sl. s.
Nickel	Sod. DSA + $NiCl_2$	Pale green thin plates	ext. s.	v. s.
Silver	Sod. DSA + $AgNO_3$	White grains[b]	sl. s.	v. sl. s.
Plumbous	Sod. DSA + $Pb(NO_3)_2$	White fine needles	sl. s.	v. sl. s.
Mercuric	Sod. DSA + $HgCl_2$	White diamond shaped plates	sl. s.	v. sl. s.
Zinc	DSA + ZnO	Thin white plates	v. s.	s.
Ammonium	DSA + NH_4OH	White needles	v. s.	v. s.
Diethylammonium	DSA + $(C_2H_5)_2NH$	Rectangular prisms	v. s.	sl. s.
Monoamylammonium	DSA + $C_5H_{11}NH_2$	Needles, tetrahedra and spherical segments	s.	mod. s.
Diamylammonium	Sod. DSA + $(C_5H_{11})_2NH \cdot HCl$	Feathers	sl. s.	v. sl. s.
Triethanolammonium	DSA + $(HOCH_2CH_2)_3N$	Not readily crystallizable sirup	ext. s.	ext. s.

[a] In cold solution was precipitated as bronze scales which spontaneously changed to the above. [b] Apparently light stable.

of disulfanilamide we have prepared (but have not analyzed) the other salts shown in Table II. The method of preparation for sparingly soluble salts was double decomposition between N^1-sodium disulfanilamide (sod. DSA) and a soluble salt of the metal. For soluble salts disulfanilamide (DSA) was neutralized with the corresponding hydroxide or carbonate of the metal.

The cupric salt is of interest since in the cold it was precipitated first as bronze scales which spontaneously changed over to light green needles. There was no evidence of the deep blue copper–ammonium coördination complex which might have been expected. The silver salt was white and apparently light stable. The monoamylammonium salt was peculiar in that it crystallized in unusual forms, one of which appeared to consist of spherical segments like the sections of an orange. The monoamylamine was obtained from the Sharples Solvent Corp. and was a mixture of isomers.

Of this series, N^1-sodium disulfanilamide and N^1-methyldisulfanilamide appeared very interesting and their pharmacology is being studied extensively. We have tested disulfanilamides of this type, successfully, in certain of the virus diseases. N^1-Methyl- and N^1-ethyldisulfanilamide are most outstanding, since they have shown promising results on infections caused by the Francis strain of influenza in mice.

Experimental

N^1-Sodium-N^4,$N^{4'}$-diacetyldisulfanilamide.—To one mole of ammonia dissolved in 150 cc. of water at 10° there was added over one hour with vigorous agitation, 2.5 moles of freshly prepared and analyzed N-acetylsulfanilyl chloride. Sufficient 50% sodium hydroxide solution was added to maintain the *p*H between 10 and 12. Ice was added to hold the temperature at 35–40°. After all of the N-acetylsulfanilyl chloride was added, stirring was continued for about an hour. The mixture was cooled to 10° and filtered. The crude product was recrystallized twice from concentrated aqueous solutions with use of activated charcoal, after adjusting the *p*H to 6–7. Under these conditions, N^4-acetylsulfanilamide was very slightly soluble while N^1-sodium-N^4,N$^{4'}$-diacetyldisulfanilamide was very soluble, so that a separation was obtained readily. N^4,N$^{4'}$-Diacetyldisulfanilamide was recovered from the mother liquors by acidifying to *p*H 1–2. It was sparingly soluble in cold water. Anhydrous N^1-sodium-N^4,N$^{4'}$-diacetyldisulfanilamide was obtained by drying the hydrated salt at 130° *in vacuo*.

The same product was obtained starting with 1 mole of N^4-acetylsulfanilamide and 1 mole of N-acetylsulfanilyl chloride under similar conditions.

N^1-Sodium Disulfanilamide.—The filter cake of crude N^1-sodium-N^4,N$^{4'}$-diacetyldisulfanilamide prepared as above was hydrolyzed by boiling with 200 g. of sodium hydroxide and 200 cc. of water until there was no further increase in diazotizable amine (one to two hours). The mixture was then cooled to 10° and crude N^1-sodium disulfanilamide filtered. This was purified by recrystallization from concentrated aqueous solutions at *p*H 6–7 with use of activated charcoal. Solubility of N^1-sodium disulfanilamide in water was 9.6 g. per 100 cc. at 10° and 20 g. per 100 cc. at 37°. The anhydrous salt was obtained by drying at 100°.

Crude disulfanilamide was recovered from the mother liquors by acidification to *p*H 2–3 where it had a minimum solubility. Additional hydrochloric acid formed the more soluble hydrochloride or dihydrochloride. Disulfanilamide was only moderately soluble in boiling water. Disulfanilamide dihydrochloride was readily tetrazotized and this reaction served as a means of analyzing both disulfanilamide and its salts.

Dimetanilamide.—One mole of *m*-nitrobenzenesulfonamide was dissolved in 1600 cc. of water containing 16 g. of anhydrous sodium carbonate and 30 g. of sodium hydroxide at 45°; 1.3 moles of *m*-nitrobenzenesulfonyl chloride was then added with vigorous agitation at 45–60° over one-half hour while maintaining a *p*H of 10–11 by addition of 50% sodium hydroxide solution as required. After stirring for an hour the reaction mixture was cooled to 10° and the crude product filtered. Sodium di-(*m*-nitrobenzenesulfon)-amide was obtained by recrystallization from water.

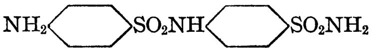
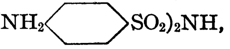
The nitro compound was reduced in two and one-half times its weight of 28% ammonia by passing a stream of hydrogen sulfide through the suspension while stirring vigorously. Cooling was necessary at first but after the reaction moderated, the mixture was held at a slow boil under a reflux condenser with constant passage of hydrogen sulfide for one hour. A rapid stream of air was then passed through the solution at the boil, to remove excess ammonia and oxidize sulfides to sulfur. The mixture was made alkaline to phenolphthalein with sodium hydroxide, and sulfur removed by filtration. The solution was acidified with hydrochloric acid to *p*H 4.5 to 5 and crude dimetanilamide obtained. This was purified by dissolving as the sodium salt, treating with activated charcoal and reprecipitating. Dimetanilamide melts to a characteristic blue-green liquid above 330°.

N^1-Methyl-N^4,N$^{4'}$-diacetyldisulfanilamide.—One mole of anhydrous N^1-diacetyldisulfanilamide was suspended in 2 liters of dry xylene containing two moles of dimethyl sulfate. The mixture was heated with constant agitation under a reflux condenser for two hours. The solid material was removed by filtration and the filtrate discarded. The solid was suspended in 3 liters of water and warmed with addition of sodium hydroxide solution until it remained alkaline to phenolphthalein. The insoluble material was filtered off and twice retreated with warm dilute sodium hydroxide. The final residue was the crude methylated product. It was purified by dissolving in glacial acetic acid, treating with activated charcoal and diluting with water. The yield of N^1-methyl-N^4,N$^{4'}$-diacetyldisulfanilamide was about 50%.

N^1-Methyldisulfanilamide.—One-half mole of N^1-methyl-N^4,N$^{4'}$-diacetyldisulfanilamide was suspended in 1200 cc. of 95% alcohol; 1.05 moles of 36% hydrochloric acid was added dropwise over one and one-half hours to the boiling, well agitated suspension. The liquid was spot tested on methyl violet paper frequently. Insufficient hydrochloric acid was present at any time to give a green spot. This was important since excess acid would have caused cleavage at the sulfonamide linkage. At the end a complete solution was obtained, which was exactly neutralized with 50% sodium hydroxide solution. After removal of salt the filtrate was evaporated to low volume and gradually diluted with water under agitation, so as to induce crystallization and avoid precipitation of the product as an amorphous mass. The crystals were suspended in 700 cc. of water at 35°, treated with excess sodium hydroxide and filtered, to remove any N^1-methylsulfanilamide. The crude product was then recrystallized several times from 80% alcohol (in which it was considerably more soluble than in 95%) using activated charcoal. N^1-Methyldisulfanilamide was water insoluble but readily dissolved in strong hydrochloric acid, in which it could be tetrazotized quantitatively. Yield in the hydrolysis was about 60%.

N^1-Ethyldisulfanilamide.—This was made by the same procedure using diethyl sulfate instead of dimethyl sulfate. Yields were somewhat lower.

Summary

The compound  has been misnamed "disulfanilamide." Synthesis of true disulfanilamide, , is reported, and it is suggested that the first compound be named N^4-sulfanilylsulfanilamide to avoid confusion.

Disulfanilamide reacts with many bases to form a series of neutral salts, most of which are highly water soluble.

N^1-Alkyl derivatives have been made which are water insoluble and which do not form salts with bases.

These compounds appear from preliminary experiments in mice to have high antistreptococcal activity, and in the case of the N^1-alkyl derivatives, viruscidal activity as well.

Bound Brook, N. J. Received April 27, 1938

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE CALCO CHEMICAL COMPANY, INC.]

Sulfanilamide Derivatives. III. *strepto*-N-Polysulfanilylsulfanilamides and Related Compounds[1]

BY M. L. CROSSLEY, E. H. NORTHEY AND MARTIN E. HULTQUIST

Fourneau and his co-workers[2] describe the compound which we would name N^4-(N-acetylsulfanilyl)-sulfanilamide as having little therapeutic effect. Later Rosenthal[3] studied N^4-sulfanilylsulfanilamide and more recently[4] N^1-(2-hydroxyethyl)-N^4-sulfanilylsulfanilamide, and *strepto*-N^4-disulfanilylsulfanilamide.

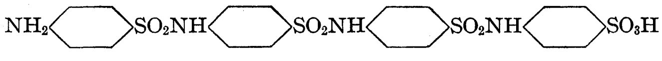
In the meantime investigators at the I. G. had studied N^4-sulfanilylsulfanilamide and its N^4-mono- and dimethyl derivatives.[5]

Gray, Buttle and Stephenson[6] also made N^4-sulfanilylsulfanilamide, which they named *p*-aminobenzenesulfonyl - *p*′ - sulfonamidophenylamide. This is an example of what one encounters in trying to name such derivatives by conventional methods. The name is sufficiently formidable to make even chemists think twice, or reach for paper and pencil.

We have synthesized, independently of the others, not only the parent compound but a large number of derivatives using as starting materials many of the compounds described in the first two papers of this series.

The method of synthesis was to treat N-acetylsulfanilyl chloride with sulfanilamide or any of its N^1-derivatives at *p*H 8–10, followed by hydrolysis of the acetyl group with either acid or base depending on the character of the compound.

By increasing the chain of sulfanilyl groups the compounds become increasingly difficult to crystallize. Thus *strepto*[7]-N-trisulfanilylsulfanilic acid



forms an emulsion in water which is difficult to work with. However, its sodium salt is nearly impossible to handle, since it forms a pearly dispersion closely resembling a vanishing cream, which resists all attempts to filter.

In the synthesis of N^1-hydroxyalkyl-*strepto*-N-polysulfanilylsulfanilamides crystallization of the product is difficult not only because of the tendency of the desired compound to form tars or oils, but because the crude products are often contaminated by sulfanilic esters. However, after crystals once have been obtained subsequent crystallizations are easy. In general, these compounds were purified by dissolving in alcohol, treating with activated carbon, and slowly diluting with water so as to prevent immediate precipitation of the bulk of the material as an oil.

The derivatives made and their pharmacology are indicated in the following table, where sulfanilamide = ++, comparison being made on β-hemolytic streptococcic infections in mice.[8,9]

Inferences which can be drawn from a study of the present results and the results described in our first two papers are:

1. There is an apparent increase of activity by adding a sulfanilyl group to the amino group in sulfanilamide, N-sulfanilylsulfanilic acid, N^1-(2-hydroxyethyl)-sulfanilamide and N^1-(2-hydroxypropyl)-sulfanilamide.
2. Activity is decreased by adding a sulfanilyl group to 2-sulfanilamidobenzoic acid, N^1,N^1-*bis*-2-hydroxyethylsulfanilamide, and disulfanilamide.
3. Addition of a third sulfanilyl group decreases the activity in N^1-2-hydroxyethyl-N^4-sulfanilylsulfanilamide; increases it in *strepto*-N-disulfanilylsulfanilic acid.
4. The much better activity of N^3-sulfanilylmetanilamide as compared with N^4-metanilylsulfanilamide is significant and was predicted. The first compound is behaving as a sulfanilamide substituted on the amido nitrogen while the second is behaving as a sulfanilamide substituted on the amino nitrogen. All previous results, including our own, indicate that new *sulfanilamide* derivatives of greater activity will be substituted by groups on the amido nitrogen and probably not elsewhere.
5. Certain of these compounds have been found effective against virus diseases.

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[1] Presented in part before the Division of Medicinal Chemistry, A. C. S., April 20, 1938.

[2] Fourneau, *et al.*, *Compt. rend., soc. biol.*, **122**, 258 (1936).

[3] Rosenthal, *et al.*, *Pub. Health Repts., U. S. Treas. Dept.*, **52**, 662 (1937).

[4] Rosenthal, et al., *ibid.*, **53**, 40 (1938).

[5] Mietzsch, *Ber.*, **71**, 15 (1938); French Patent, 817,034, Aug. 24, 1937.

[6] Gray, Buttle and Stephenson, *Biochem. J.*, **31**, 724 (1937).

[7] We have used the prefix "*strepto*" to indicate that the sulfanilyl- groups are in a chain rather than separately attached. It has no therapeutic connotation as used.

[8] The pharmacology will be reported by D. R. Climenko elsewhere.

[9] Microanalyses were made under the direction of G. L. Royer.

Compound	Formula	Therapeutic effect	Melting range, °C.	Assay by nitrite, %	Analyses, %							
					Calcd.				Found			
					C	H	N	S	C	H	N	S
N^4-Sulfanilylsulfanilamide[a]	$C_{12}H_{13}O_4N_3S_2$	+++	132.5–136	99.6	44.0	4.0	12.86	19.6	43.3	4.3	12.9	19.2
strepto-N^4-Disulfanilylsulfanilamide[a,b]	$C_{18}H_{18}O_6N_4S_3$	+++	210.0–211.5	100.4	44.8	3.76	11.62	19.9	44.8	4.0	11.6	19.4
N^4-Metanilylsulfanilamide	$C_{12}H_{13}O_4N_3S_2$	+	142–144	100.0	44.1	4.01	12.86	19.6	43.7	4.0	12.7	19.5
N^3-Sulfanilylmetanilamide	$C_{12}H_{13}O_4N_3S_2\cdot{}^1/_2H_2O$	++	134–156	100.0	42.9	4.2	12.5	19.1	43.4	4.6	12.5	
Sodium-*strepto*-N-disulfanilylsulfanilate	$C_{18}H_{16}O_7N_3S_3Na$	+	>220 dec.	99.5	42.72	3.18	8.32	Na, 4.55	42.1	3.9	8.22	Na, 4.3
strepto-N-Trisulfanilylsulfanilic acid	$C_{24}H_{22}O_9N_4S_4\cdot 2H_2O$	++	>250 dec.	105	42.6	3.89	8.32	19.6	42.4	4.6	8.24	
2-(N^4-Sulfanilylsulfanilamido)-benzoic acid	$C_{19}H_{17}O_6N_3S_2$	++	200–203	100.2	51.0	3.83	9.40	14.32	49.3	4.4	9.3	12.9
N^1-(2-Hydroxyethyl)-N^4 sulfanilylsulfanilamide[b]	$C_{14}H_{17}O_5N_3S_2$	+++	140–143	100.2	45.3	4.61	11.31	17.28	45.2	4.8	11.2	17.3
N^1-(2-Hydroxyethyl)-N^3 metanilylmetanilamide	$C_{14}H_{17}O_5N_3S_2$	±	125–127.2	100.4	45.3	4.61	11.31	17.28	44.7	4.9	11.31	
N^1-(2-Hydroxyethyl)-*strepto*-N^4-disulfanilylsulfanilamide	$C_{20}H_{22}O_7N_4S_3$	±	137–143	99.1	45.6	4.21	10.65	18.27	45.35	4.27	11.1	
N^1,N^1-*bis*-2-Hydroxyethyl-N^4-sulfanilylsulfanilamide[a]	$C_{16}H_{21}O_6N_3S_2$	+	122.5–128	96.4	46.25	5.16	10.1	15.41	46.3	5.6	10.0	14.9
N^1,N^1-*bis*-2-Hydroxyethyl-*strepto*-N^4-disulfanilylsulfanilamide	$C_{22}H_{26}O_8N_4S_3$	+	115.5–120.5	99.5	46.3	4.6	9.81	16.84	45.5	5.0	9.8	16.1
N^1-(2-Hydroxypropyl)-N^4 sulfanilylsulfanilamide	$C_{15}H_{19}O_5N_3S_2$	+	127.3–129.6	100.2	46.8	5.00	10.9	16.6	45.5	4.82	10.95	16.8
N^1-Phenyl-N^1-(2-hydroxyethyl)-N^4-sulfanilylsulfanilamide	$C_{20}H_{21}O_5N_3S_2$	++	183–185	100.0	53.0	4.0	9.47	14.38	52.8	5.0	9.55	14.3
N^1,N^1-*bis*-2-Hydroxyethyl-N^4-*p*-toluenesulfonylsulfanilamide	$C_{17}H_{22}O_6N_2S_2$	±	187–190									
N^1-Sodium-N^1,N^4-dimetanilylsulfanilamide	$C_{18}H_{17}O_6N_4S_3Na$	+	280 dec.	100.4	42.8	3.39	11.1	Na, 4.57	41.4	3.5	11.1	Na, 3.9
N^1,N^4,$N^{4\prime}$-Trisodium-N^4,$N^{4\prime}$-disulfanilyldisulfanilamide	$C_{24}H_{20}O_8N_5S_4Na_3$	0	340 dec.	100.4		Na, 9.81				Na, 9.05		
N^4-Sulfanilyldisulfanilamide	$C_{18}H_{18}O_6N_4S_3$	+	198.5–206	99.2	44.7	3.72	11.6	19.8	43.4	3.7	11.1	19.8

[a] I. G. Fr. 817,034, Aug. 24, 1937.

[b] Bauer and Rosenthal, ref. 4.

It should be pointed out that the therapeutic effectiveness of these various sulfanilamide compounds is described in terms of a series of preliminary pharmacological experiments carried out on large groups of mice experimentally infected with a very virulent strain of β-hemolytic streptococci, using massive infecting doses and single protective doses of the therapeutic agent. In all cases the control animals died in sixteen hours. Reported results are in terms of animals surviving at the end of seventy-two hours. Much further experimental evidence will be needed to establish the usefulness of these products in human medication, since acute toxicity studies in mice tell nothing of the complications of human administration, such as fever, cyanosis, dermatitis, acidosis and peripheral neuritis.

Experimental

General Method of Preparation.—The general method for making the present derivatives was the same as that described in the first paper of this series for the preparation of sodium N-sulfanilylsulfanilate.[10] Syntheses of compounds involving important variations of this method are given below.

N^4-Metanilylsulfanilamide.—Seven-tenths mole of sulfanilamide was dissolved in 500 cc. of water at about 95°; 0.5 mole of freshly prepared *m*-nitrobenzenesulfonyl chloride was added rapidly with vigorous agitation. When the mixture had crystallized (ten to fifteen minutes) sufficient sodium hydroxide was added to dissolve the solid. The solution was clarified and poured into 400 cc. of concentrated hydrochloric acid. N^4-*m*-Nitrobenzenesulfonylsulfanilamide precipitated while excess sulfanilamide remained dissolved. The precipitate was filtered and washed with hot water. It was reduced with ammonia and hydrogen sulfide by the general procedure for metanilyl derivatives.[11]

Attempts to prepare this compound by the usual procedure lead to N^1,N^4-di-(*m*-nitrobenzenesulfonyl)-sulfanilamide as the main product.

N^1-(2-Hydroxyethyl)-N^4-sulfanilylsulfanilamide and similar derivatives were made by the general method while maintaining a *p*H of 7–9 (when foaming occurred sufficient sodium hydroxide solution was added to give a faint pink spot test on phenolphthalein paper). It was thought that a somewhat lower *p*H led to formation of less of the sulfanilic esters which gave difficulty in purification of the final products. The crude hydrolyzed products were oils or sticky masses which were partially purified by dissolving as the sodium salts in water, treating with activated charcoal, and reprecipitating with acid. Initial crystallization was frequently very slow, extending in some cases to weeks. Most favorable conditions found for inducing initial crystallization were established by dissolving the material in about twice the amount of 60–80% alcohol, treating with decolorizing carbon, and diluting with water

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(10) Crossley, Northey and Hultquist, THIS JOURNAL, **60**, 2220 (1938).

(11) Crossley, Northey and Hultquist, THIS JOURNAL, **60**, 2220 (1938).

at room temperature until the solution remained slightly milky. It was then allowed to stand with occasional agitation and scratching of the walls until crystallization started. Once seed crystals were obtained subsequent recrystallizations were comparatively easy.

N^4-Sulfanilyldisulfanilamide.—One-half mole of sulfanilamide was dissolved in 500 cc. of water with sufficient sodium hydroxide to give a *p*H of 10–12; 1.2 moles of freshly prepared N-acetylsulfanilyl chloride was added over half an hour at 35–40° while maintaining the above *p*H by addition of 50% sodium hydroxide as necessary. Stirring was continued for one hour, then 100 g. of sodium hydroxide was added, and the mixture boiled for two hours. The hydrolysis mixture was neutralized with concentrated hydrochloric acid, cooled, crystals of crude N^1-sodium-N^4-sulfanilyldisulfanilamide filtered off, and recrystallized several times from water, using activated charcoal. The free amide was made by acidification of a solution of the sodium salt. The initial amorphous mass was crystallized by rubbing in alcohol.

$N^1,N^4,N^{4'}$-Trisodium $N^4,N^{4'}$-disulfanilyldisulfanilamide.—This was made by the general procedure starting with an equivalent of N^1-sodium disulfanilamide. Attempts to prepare a crystalline monosodium salt or crystalline free amide failed. The trisodium salt (actually a mixture with some of the disodium salt) was crystallized from a concentrated aqueous solution at *p*H 9–10, by dilution with alcohol.

N^1-(2-Hydroxyethyl)-N^3-metanilylmetanilamide.—One-third mole of N^1-(2-hydroxyethyl)-metanilamide was dissolved in 300 cc. of water containing 30 g. of boric acid; $^1/_3$ mole of *m*-nitrobenzenesulfonyl chloride was added over an hour at 55–65° with vigorous agitation while maintaining a *p*H of 6–8 by addition of 50% sodium hydroxide solution as required. The nitro compound which separated on cooling was reduced with 150 g. of fine iron, 500 cc. of water, and 1 cc. of glacial acetic acid at 95–100°. After complete reduction excess sodium hydroxide was added to dissolve completely the product, the mixture was filtered, and the filtrate neutralized. A sticky mass separated which crystallized on standing overnight. This crude product was recrystallized by dissolving in hot alcohol, treating with activated charcoal, then diluting gradually with water, cooling and seeding. After several recrystallizations, colorless crystals were obtained.

Boric acid was used in the hope that by forming a complex with the hydroxyl groups, it would aid in preventing formation of sulfonic esters. Success in obtaining a crystalline product through its use, where previously there had been failure, leads us to believe that it was of value.

Summary

A series of *strepto*-N-polysulfanilyl derivatives of aminobenzenesulfonic acids and carboxylic acids, hydroxyalkylamines, sulfonamides, and disulfonamides are described, together with preliminary results of the pharmacological study of their effect in mice infected with β-hemolytic streptococci.

No general conclusions can be drawn concerning the effect of increasing the number of sulfanilyl groups.

Better activity was shown by N^3-sulfanilylmetanilamide than by N^4-metanilylsulfanilamide. This was predicted from previous results.

Certain of these compounds appear effective in virus diseases, but caution is expressed against assuming that the results of these preliminary studies in mice are translatable to human therapy.

BOUND BROOK, N. J.

RECEIVED APRIL 27, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF WISCONSIN]

Ethylenediamine and Propylenediamine Vanadates

BY EUGENE H. HUFFMAN

In the course of an investigation, some diamine vanadates were desired. A search of the literature did not reveal the previous preparation of these, though some alkyl amine vanadates[1] and a pyridinium vanadate[2] have been described. This paper describes the preparation and some properties of hydrated hexavanadates of ethylenediamine and propylenediamine and the metavanadate of ethylenediamine.

Preparation

Ethylenediamine and Propylenediamine Hexavanadates.—Ten grams of vanadium pentoxide (either C. P. grade or prepared by gently heating ammonium metavanadate) is added to a solution of 5 cc. of 69.8% ethylenediamine and 15 cc. of water, or 8 g. of vanadium pentoxide to 5 cc. of 70–75% propylenediamine and 15 cc. of water. Then 15 cc. of 30% hydrogen peroxide is added slowly, with stirring, over a period of half an hour, while keeping the temperature below 60°. The mixture is filtered, washed with 25 cc. of water, to which is added 3 cc. of 30% hydrogen peroxide, and the filtrate and washings diluted to 150 cc. After just neutralizing the solution to

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(1) Bailey, *J. Chem. Soc.*, **45**, 690 (1884); *Compt. rend.*, **104**, 1844 (1887).

(2) Katzoff and Roseman, THIS JOURNAL, **58**, 1785 (1936).

litmus with the corresponding diamine, crystallization usually begins in thirty minutes. It can be hastened by the addition of a small amount of the diamine dihydrochloride. The bright brownish-yellow product is filtered off, washed with water, and air-dried at room temperature.

Ethylenediamine Metavanadate.—This compound may be prepared by the following three methods. (1) Solid ethylenediamine dihydrochloride is added slowly to a saturated solution of ammonium metavanadate (prepared by heating to boiling, cooling, and filtering) until precipitation is complete. About 3 g. of the hydrochloride is required for every 100 cc. of saturated metavanadate solution. The golden-yellow product is washed on a filter with water until free from chloride and dried over calcium chloride.

(2) Three grams of vanadium pentoxide is added to a mixture of 5 cc. of ethylenediamine (69.8%) and 10 cc. of water. The mixture is heated to 90° for five minutes, filtered, and cooled to 20°. The brown turbid appearance is discharged by adding 2 drops of 30% hydrogen peroxide and allowing to stand for ten minutes. The vanadate is precipitated either by diluting to 200 cc. and passing carbon dioxide into the solution or by diluting to 40 cc. and slowly adding, with stirring, 150 cc. of 95% ethyl alcohol. The white product is washed first with four 10-cc. portions of alcohol to remove excess amine, and then with water to remove carbonate. If it is washed with water before the amine is removed, the precipitate redissolves.

(3) Two grams of the hexavanadate is dissolved in 6 cc. of ethylenediamine (69.8%) and 30 cc. of water. The orange color of the solution changes to colorless in forty minutes. The solution is diluted to 50 cc. and 100 cc. of 95% ethyl alcohol added, with stirring, to precipitate the white metavanadate. The product is filtered, washed with four 10-cc. portions of alcohol and then with water.

Similar attempts to prepare propylenediamine metavanadate gave discordant results which approached the hexavanadate in composition.

Analysis

The compounds were analyzed for vanadium and diamine. (1) Vanadium is determined readily by direct ignition to vanadium pentoxide in a platinum crucible. The fluid vanadium pentoxide should be allowed to run off the un-oxidized part to ensure complete oxidation.

(2) The diamine can be determined by a modified Kjeldahl method. A sample (0.4 to 0.6 g.) is digested with sulfuric acid and potassium sulfate, but without the addition of any other oxidation catalyst. The vanadium pentoxide brings about complete oxidation in one and a quarter hours. The ammonia is then distilled and titrated in the usual manner. The results[3] allow the ratio between vanadium and diamine to be determined quite accurately.

The water content was based upon the vanadium and diamine determinations. The results were: (1) ethylenediamine metavanadate, 38.99, 38.99, 39.08, and 39.13% vanadium and 23.24, 23.02, 23.73, and 22.90% ethylenediamine; calculated for $C_2H_4(NH_2)_2 \cdot 2HVO_3$, 39.19% vanadium and 23.11% ethylenediamine; (2) ethylenediamine hexavanadate, 39.46 and 39.50% vanadium and 15.31 and 15.25% ethylenediamine; calculated for $2C_2H_4(NH_2)_2 \cdot H_4V_6O_{17} \cdot 4H_2O$, 39.50% vanadium and 15.53% propylenediamine; (3) propylenediamine hexavanadate, 39.75, 39.99, and 40.10% vanadium and 19.56 and 19.20% propylenediamine; calculated for $2C_3H_6(NH_2)_2 \cdot H_4V_6O_{17} \cdot 2H_2O$, 39.91% vanadium and 19.35% propylenediamine.

Properties

Ethylenediamine metavanadate is golden-yellow in color when prepared by precipitation from an ammonium metavanadate solution or white when precipitated from an ethylenediamine solution. Both hexavanadates are brownish-yellow. All three compounds are insoluble in alcohol, ether, acetone, dioxane, and benzene, and are not appreciably soluble in water. All are soluble in aqueous solutions of ammonia, ethylenediamine, propylenediamine, and 30% hydrogen peroxide.

The compounds undergo no detectable change in composition on standing in diffused light for one month, but turn dark when exposed to direct sunlight. The hexavanadate and yellow metavanadate of ethylenediamine change to the white metavanadate when allowed to remain in a solution of ethylenediamine until just colorless.

Summary

The preparation and some properties of ethylenediamine hexavanadate, propylenediamine hexavanadate, and ethylenediamine metavanadate have been described. Attempts to prepare propylenediamine metavanadate gave discordant results.

MADISON, WISCONSIN RECEIVED JUNE 2, 1938

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[3] The method was checked by determining the diamine content of ethylenediamine dihydrochloride, carefully purified by recrystallization and dried over calcium chloride. For this purpose about 0.2 g. of vanadium pentoxide was used as a catalyst in the digestion. The variation amounts to 0.5 to 0.8% of the diamine content.

[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY OF YALE UNIVERSITY]

The Elimination of Liquid Junction Potentials. I. The Solubility Product of Silver Chloride from 5 to 45°

BY BENTON BROOKS OWEN

There are two types of liquid junctions commonly encountered in electrochemical studies: homoionic junctions formed by juxtaposition of solutions differing only in ionic concentrations, and heterionic junctions involving differences in ionic species. The potentials of heterionic junctions are not subject to simple thermodynamic definition,[1] which accounts for the necessity of their "elimination" when such junctions occur in cells used for thermodynamic purposes. This elimination has been attempted by both mathematical and physical means, but it always involves some extra-thermodynamic hypothesis which remains to be justified on empirical grounds. In the method described in this communication, the essential hypothesis is so simple in principle, and direct in operation, that the possibility of its adequate experimental verification is unusually high. A variety of data may be used in this connection, and will be presented in this paper, and elsewhere.[2]

Outline of the Method

The method involves the study of series of cells containing solutions of varying concentrations of the dissimilar ions giving rise to the junction potentials, but maintained at constant total ionic strength by the presence of an additional electrolyte which takes no part in the electrode reactions. Extrapolation to zero concentration of the dissimilar ions eliminates the junction potentials. The effect of the inert electrolyte can be eliminated by subsequent extrapolation to zero ionic strength. Somewhat similar schemes have been used, or implied, in the work of previous investigators,[3] but the simplicity of linear extrapolations was not obtained. This practical advantage of the present method is probably a consequence of the simple behavior of electrolytes in mixtures at constant ionic strength,[4] and the attainment of maximum symmetry in the electrode–electrolyte systems.

The determination of the solubility product of silver chloride was selected to illustrate the method because the results may be used as an independent check on the standard potential of the silver electrode.[2] The cells can be represented as follows

$$\text{Ag, AgCl}\left|\begin{matrix}\text{KCl}(x)m\\ \text{KNO}_3(1-x)m\end{matrix}\right|\ \text{KNO}_3(m)\ \left|\begin{matrix}\text{AgNO}_3(x)m\\ \text{KNO}_3(1-x)m\end{matrix}\right|\text{AgCl, Ag}^+$$

The total ionic concentration in each solution is m, but a fraction, x, of this is composed of chloride ion in the left-hand compartment, and silver ion in the right. The e. m. f. of such a cell is given by

$$E = k \log a'_{\text{Ag}}/a_{\text{Ag}} \pm E_{\text{j}} \qquad (1)$$

E_{j} is the sum of the unknown liquid junction potentials, $k = 0.00019844T$, and a'_{Ag} and a_{Ag} represent the activities of the silver ion in the right-hand and left-hand solutions, respectively. The solubility product

$$K = a_{\text{Ag}}a_{\text{Cl}} \qquad (2)$$

can be used to eliminate a_{Ag} in the left-hand solution, and equation (1) becomes

$$E - k \log a'_{\text{Ag}}a_{\text{Cl}} = -k \log K \pm E_{\text{j}} \qquad (3)$$

The introduction of the concentrations, xm, and the individual ionic activity coefficients leads to

$$E - 2k \log xm = -k \log K + k \log \gamma_{\text{Cl}}\gamma'_{\text{Ag}} \pm E_{\text{j}} \qquad (4)$$

The last two terms of this equation are not *independently* defined by thermodynamics alone, and this fact constitutes the essential limitation on the use of cells with heterionic liquid junctions.

Inspection of equation (4), and consideration of the symmetry of the electrochemical system it represents, shows that if m is held constant while x is varied, extrapolation to $x = 0$ must yield

$$[E - 2k \log (xm)]_{x=0} = -k \log K + [k \log \gamma_{\text{Cl}}\gamma'_{\text{Ag}}]_{x=0} \qquad (5)$$

because E_{j} becomes zero under this condition. Since it is no longer necessary to retain the prime on γ'_{Ag} when $x = 0$, the last term is amenable to thermodynamic treatment, and can be expressed as a function of m similar to that for any uni-univalent strong electrolyte.

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[1] Harned, *J. Phys. Chem.*, **29**, 433 (1926); Taylor, *ibid.*, **31**, 1478 (1927); Guggenheim, *ibid.*, **34**, 1758 (1930); **33**, 842 (1929).

[2] Owen and Brinkley, THIS JOURNAL, **60**, 2233 (1938).

[3] Linhart, THIS JOURNAL, **38**, 2356 (1916); Lewis and Randall, "Thermodynamics," McGraw-Hill Book Co., New York, 1923, p. 418; Harned and Robinson, THIS JOURNAL, **50**, 3157 (1928); Popoff and Kunz, *ibid.*, **51**, 382 (1929).

[4] Güntelberg, *Z. physik. Chem.*, **123**, 199 (1926); Harned, THIS JOURNAL, **48**, 326 (1926).

To allow compact graphical representation of the experimental results, the term $2k\alpha\sqrt{m}$ will be added to both sides of equation (5) (α = Debye–Hückel limiting slope). Since this term is not a function of x, the extrapolation function may be rewritten as follows

$$[E - 2k \log (xm) + 2k\alpha\sqrt{m}]_{x=0} = -k \log K + [k \log \gamma_{Cl}\, \gamma_{Ag} + 2k\alpha\sqrt{m}]_{x=0} \quad (6)$$

The determination of $[E - 2k \log (xm) + 2k\alpha\sqrt{m}]_{x=0}$ by extrapolation at various values of m is shown in Fig. 2. The determination of $-k \log K$ by subsequent extrapolation of these intercepts to $m = 0$ is given in Fig. 3. This final step is equivalent to the familiar Hitchcock[5] extrapolation.

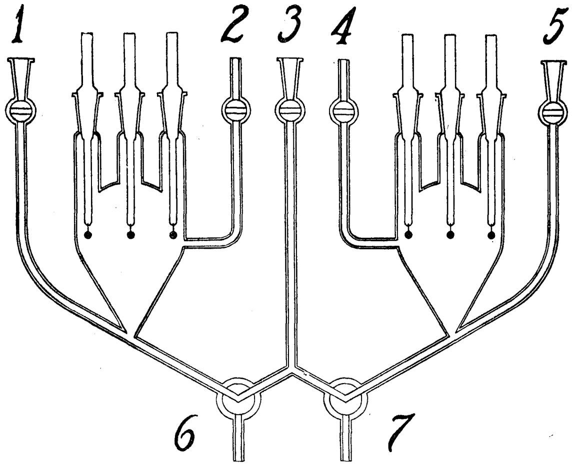

Fig. 1.—Cell assembly.

Materials and Technique

Water from an electrically heated Barnstead still was used in the purification of chemicals, and the preparation of stock solutions. "Jena" sintered glass mats were used in all filtrations. Concentrations of stock solutions were based upon weights of water and dry salts. Vacuum corrections were applied throughout.

The silver nitrate was Merck "Reagent" grade, recrystallized once, and air dried at 85 to 95° for twenty-four hours. Just before use, it was heated for five hours to 100° under reduced pressure (<1 mm.). The 0.05 molal stock solution was shielded carefully from light, and protected from contact with reducing substances and laboratory fumes.

The potassium chloride was Baker "Analyzed" grade, recrystallized twice. It was dried for two days at 95° followed by three days at 115°. The potassium nitrate was from the same source as the chloride, and received the same treatment.

The electrodes were prepared by decomposition of well-washed silver oxide at 450°, followed by electrolysis (series) in 0.5 m hydrochloric acid solutions at 3 m. a. for two or three hours. They were shielded from strong light at all times. An effort was made to have them very similar to those used by Harned and Ehlers,[6] because the standard potentials reported by them are to be combined with the present results to obtain the standard potential of the silver electrode.

The cell construction is illustrated in Fig. 1. The inlets numbered 1 and 5 are connected to flasks containing the air-free chloride and silver solutions, and number 3 is connected to the pure potassium nitrate junction solution. All connections which come in contact with cell solutions are ground glass joints, lightly greased with vaseline which had been boiled with silver nitrate solution, and subjected to numerous rinsings with hot water. The cells are evacuated through the lower outlets to stopcocks 6 and 7. Then nitrogen, freed of oxygen by copper turnings at 700°, is introduced through 2 and 4. By successive evacuation and admission of nitrogen, the air is completely displaced from the cells and connections to solution flasks. After a final evacuation, cell solutions are admitted, under slight pressure, through 1 and 5 until the pressure inside exceeds the atmospheric. The electrodes are lifted slightly, one at a time, to allow the ground glass joints to be rinsed by overflowing cell solutions. After half an hour the cells are emptied through 6 and 7, and fresh solutions admitted. About twelve hours later, this rinsing process is twice repeated before e. m. f. readings are begun at 5°. Since equilibrium is slowly attained at this temperature, the readings usually extended over two or three hours. At higher temperatures one hour is quite sufficient. The temperature of the water-bath varied by ± 0.02° at 5 and 15°, but was controlled within 0.01° at the higher temperatures.

After each reading, the junctions (3-mm. bore of stopcocks) were flushed through the outlets of 6 and 7, but as an additional precaution against contamination by diffusion, or otherwise, the cells and ground glass joints were rinsed several times with fresh solutions during the course of the measurements, usually at 25 and 45°.

Experimental Results and Discussion

The experimental data are collected in Table I. The results of all measurements are included except two early ones in which the product xm was 0.002, or less. Erratic results were obtained with silver ion concentrations of this order unless the electrodes were rinsed thoroughly with the solution, and extra time allowed for equilibrium at the lower temperatures. The recorded values of E are the means of pair-wise combinations of the six electrodes. These were ordinarily concordant well within 0.1 mv. The over-all reproducibility of a cell was also of this order at the higher concentrations, but irregularities as high as 0.1 and 0.15 mv. were sometimes observed at m = 0.02 and m = 0.01, respectively. The effects of these irregularities can be seen in Fig. 2, where the radii of the plotted circles are 0.1 mv.

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(5) Hitchcock, This Journal, **50**, 2076 (1928).

(6) Harned and Ehlers, *ibid.*, **55**, 2179 (1933).

The plots for all values of m and T show that a linear extrapolation is indicated on purely empirical grounds. Because of experimental difficulties when $xm < 0.002$, a rather long extrapolation is required at low values of m, but when $m = 0.05$ the linearity of the extrapolation function seems definitely established down to $x = 0.05$. These observations are corroborated by analogous plots from a study of buffer solutions.[2] This is an important point because *the possibility of this extrapolation, and its linearity* (or form ultimately arrived at by further study) *constitute the extrathermodynamic hypothesis upon which this method of eliminating liquid junction potentials is based.*

The intercepts obtained from the extrapolations in Fig. 2 are recorded in Table I to the nearest 0.05 mv.

TABLE I

OBSERVED ELECTROMOTIVE FORCES AND INTERCEPTS FROM THE FIRST EXTRAPOLATION (FIG. 2)

x	$t°$ 5°	15°	25°	35°	45°
			$m = 0.05$		
0.4	0.38790	0.37623	0.36503	0.35455	0.34445
.2	.35432	.34166	.32935	.31771	.30635
.1	.32105	.30720	.29370	.28086	.26836
.05	.28774	.27272	.25807	.24408	.23036
Int.	.58700	.58295	.57930	.57635	.57375
			$m = 0.03$		
0.5	0.37641	0.36436	0.35285	0.34185	0.33129
.3	.35153	.33868	.32632	.31455	.30318
.2	.33205	.31841	.30543	.29289	.28082
.1	.29854	.28386	.26962	.25592	.24273
Int.	.58620	.58200	.57835	.57525	.57270
			$m = 0.02$		
0.6	0.36739	0.35492	0.34302	0.33170	0.32091
.4	.34742	.33440	.32185	.30989	.29825
.3	.33345	.32000	.30695	.29436	.28238
.2	.31371	.29946	.28593	.27286	.26017
Int.	.58560	.58140	.57780	.57465	.57200
			$m = 0.01$		
0.6	0.33592	0.32239	0.30930	0.29683	0.28482
.4	.31610	.30203	.28829	.27520	.26256
.3	.30206	.28725	.27318	.25965	.24655
.2	.28249	.26708	.25226	.23806	.22431
Int.	.58535	.58100	.57730	.57420	.57150

Figure 3 shows the plots of these intercepts against m, which according to equation (6) permits the evaluation of $-k \log K$ by extrapolation to $m = 0$. These extrapolations are also linear within the estimated uncertainty of ± 0.1 mv. for the plotted points, which are drawn with 0.1-mv. radii. It will be noted that the straight lines intersect all the points except two at 5° where experimental difficulties were high, and the accuracy correspondingly low. It appears from the plots that the purely extrapolative uncertainty in $-k \log K$ might exceed 0.2 mv. at 5°, but not at the other temperatures.

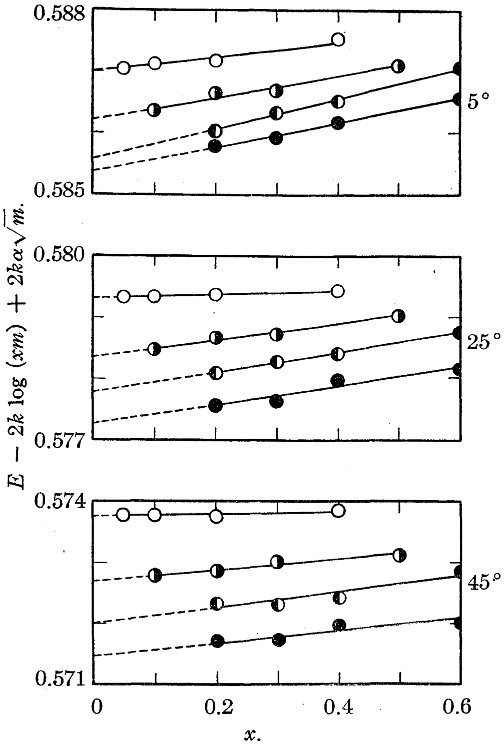

Fig. 2.—Elimination of E_j by extrapolation; ○, $m = 0.05$; ◑, $m = 0.03$; ◐, $m = 0.02$; ●, $m = 0.01$.

The intercepts, $-k \log K$, from the extrapolations in Fig. 3 are recorded in the second column of Table II to the nearest 0.1 mv. Their variation with temperature is satisfactorily expressed by

$$k \log K = -0.5768 + 345\,(t - 25)\,10^{-6} - 25\,(t - 25)^2 10^{-7} \quad (7)$$

or

$$\log K = 9.2496 - 4544.4/T - 0.012598T \quad (8)$$

Values calculated by these equations are given in the third and fourth columns, respectively. The solubility of silver chloride in pure water was calculated by the equation

$$\log m_0 = {}^1/_2 \log K + \alpha\sqrt{c_0} \quad (9)$$

which assumes the applicability of the Debye–Hückel limiting law at such high dilutions. The solubility, m_0, is in moles per kilogram of water, and c_0 is the corresponding value in moles per liter of solution.

The absolute accuracy of the results depends mainly upon three factors. These are the accuracy with which the concentrations are known,

TABLE II

INTERCEPTS FROM SECOND EXTRAPOLATION (FIG. 3) AND SOLUBILITY OF SILVER CHLORIDE

t°	$-k \log K$ Int.	$-k \log K$ Eq. (7)	$-\log K$ Eq. (8)	Solubility $m_0 \times 10^5$	Solubility $c_0 \times 10^5$
5	0.5848	0.5847	10.5950	0.505	0.505
15	.5805	.5805	10.1536	0.841	0.840
25	.5768	.5768	9.7508	1.338	1.334
35	.5736	.5736	9.3818	2.048	2.036
45	.5709	.5709	9.0440	3.026	2.997

the physical state (and purity) of the silver chloride, and the validity of the extension of the plots in Fig. 2. The uncertainties in the concentrations could hardly cause an error greater than 0.1 mv.

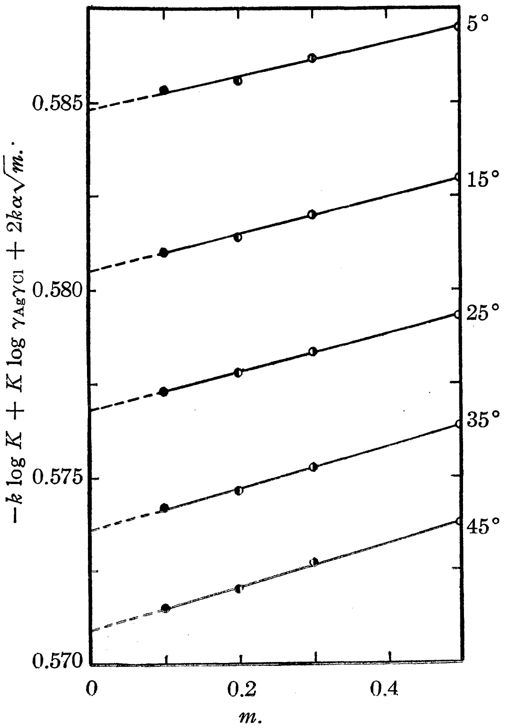

Fig. 3.—Evaluation of $-k \log K$ by extrapolation to infinite dilution.

The preparation of the electrolytic silver chloride has been described in the foregoing section. A review[7] of the determinations of the standard potential of the electrolytic silver–silver chloride electrodes shows that the results of the several independent investigators agree within 0.1 to 0.4 mv. This may be taken as indicative of high thermodynamic reproducibility of electrolytic silver chloride, because this agreement must also include uncertainties in analysis and extrapolation, and possible differences in the physical state and purity of the metallic silver. In the present solubility product determination the thermodynamic properties of the metallic silver cancel in the operation of the cell, so long as they are the same in all of the electrodes. It was to ensure this identity that all six of the electrodes used in any cell were electrolyzed in series, without distinction as to which were to be used in the silver and which in the chloride solutions. It is therefore probable that the absolute accuracy of the final results is of the same order as that of the two extrapolations. This seems to be better than ±0.2 mv. on the basis of the plots as drawn, but if linearity is not strictly maintained, then, in the absence of further data at high dilutions, the uncertainty might easily be twice as great.

Although comparison with values previously recorded in the literature constitutes a satisfactory check upon the essential correctness of the results, it does not furnish a dependable criterion of their absolute accuracy, because the discordance among such values appears to be much greater than the combined experimental errors of the various measurements. Variability in the physical condition of precipitated silver chloride is responsible for most of the difficulty. There are several papers which review[8,9] the literature, and discuss possible explanations of the discrepancies, so this matter need not be elaborated. Three previous investigations cover a considerable temperature range. Kohlrausch[10] determined the solubility of well-aged, precipitated silver chloride conductometrically from 1.55 to 34.12°. His values are about 3% lower than the present results. The results of the electrometric titrations of Hahn and Klockmann[11] (15 to 40°) are in good agreement, while the nephelometric values (0 to 50°) of Dave and Krishnaswami[9] are 3 to 4% higher. This is representative of the agreement to be expected when precipitated silver chloride is involved. Accordingly the score of determinations at single temperatures will not be discussed further than to consider one particular experiment in which electrolytic silver chloride was employed.

Brown and MacInnes[12] found that the solubility of silver chloride is 1.570×10^{-5} mole per liter in a 0.0286 normal solution of potassium nitrate at 25°. Although precipitated silver chlo-

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[7] Prentiss and Scatchard, *Chem. Rev.*, **13**, 139 (1933).

[8] Glowczynski, *Kolloidchem. Beihefte*, **6**, 147 (1914).

[9] Dave and Krishnaswami, *J. Indian Inst. Sci.*, **16**, 153 (1933); *cf.* also Johnson and Hulett, THIS JOURNAL, **55**, 2258 (1933).

[10] Kohlrausch, *Z. physik. Chem.*, **64**, 129 (1908).

[11] Hahn and Klockmann, *ibid.*, **A146**, 394 (1930).

[12] Brown and MacInnes, THIS JOURNAL, **57**, 459 (1935).

ride was formed during the course of their electrometric titrations, the electrodes were coated with the electrolytic variety. If the concentration of silver chloride in the immediate neighborhood of the electrodes was successfully controlled by the electrolytic variety, the results should be comparable with those of the present research. Interpolation based on Fig. 3 leads to 1.577×10^{-5}, in excellent agreement with the above, but the value for the solubility in pure water reported by Brown and MacInnes is 1.314×10^{-5}, which is 1.5% lower than that given in Table III. The discrepancy is caused by the difference between the activity coefficients used by Brown and MacInnes[13] and those which may be obtained from consideration of equation (6) and Fig. 3. The slope of the 25° plot in Fig. 3 is 0.051, which leads to the expression

$$\log \gamma = -0.506 \sqrt{\mu} + 0.43\mu \qquad (10)$$

for the activity coefficient of silver chloride. On the basis of this equation, the result of Brown and MacInnes would be increased to 1.332×10^{-5}.

Although this concordance leaves little to be desired, it should be borne in mind that two electrometric determinations of the solubility of identical samples would not be strictly comparable unless the extra-thermodynamic hypotheses used to eliminate liquid junction potentials could be verified experimentally, or shown to be equivalent. It therefore seems necessary to reserve final judgment upon the absolute accuracy of the results reported in this paper until the reliability of the hypothesis represented by Fig. 2 has been established, or discredited, by further experimental work. Some familiar indirect checks upon the accuracy of solubilities and their temperature coefficients will be considered in a later communication.[2]

Summary

A method is proposed by which heterionic liquid junction potentials may be eliminated by extrapolation. Experimental data are presented which indicate that the junction extrapolation is linear as a first approximation.

The method is applied to the determination of the solubility product of electrolytic silver chloride in water at 5, 15, 25, 35, and 45°.

NEW HAVEN, CONN. RECEIVED JUNE 11, 1938

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[13] Values obtained by Neuman [THIS JOURNAL, **54**, 2195 (1932)] from solubility measurements in which presence of precipitated silver chloride was determined by Tyndall beam.

[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY OF YALE UNIVERSITY]

The Elimination of Liquid Junction Potentials. II. The Standard Electrode Potential of Silver from 5 to 45°, and Related Thermodynamic Quantities

BY BENTON BROOKS OWEN AND STUART R. BRINKLEY, JR.[1]

In the first paper of this series,[2] an extrapolation method for eliminating heterionic liquid junction potentials was described, and employed in a determination of the solubility product of silver chloride. It was considered desirable to test the validity and generality of the method by applying it to a comparison of the silver and hydrogen electrodes in buffer solutions. The results of these two investigations are interrelated through the potential of the silver–silver chloride electrode, and can be used to check one another. By the use of identical measuring equipment and technique, and consistent supplementary data, the concordance of these results becomes a necessary, but not a sufficient, condition to the validity of the extra-thermodynamic extrapolation upon which the method is based. Complete demonstration of its validity is contingent upon further direct investigation of the extrapolation, and comparison of its consequences with thermodynamic data obtained without recourse to liquid junctions. Several such comparisons can be made with the data at hand, and others will be available in the future.

Buffer solutions were used to depress and stabilize the hydrogen ion concentration, so that transfer of electricity across the liquid junction would be accomplished, for the most part, by ions other than hydrogen. The cell may be represented as follows

$$H_2 \mid HAc_{(m)}, NaAc_{(m)} \mid HAc_{(m)}, NaAc_{(m-mx)}, AgAc_{(mx)} \mid Ag^+$$

The ionic strength, $\mu \simeq m$, is practically identical

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[1] This communication embodies part of the experimental material to be presented by Stuart R. Brinkley, Jr., to the Graduate School of Yale University in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] Owen, THIS JOURNAL, **60**, 2229 (1938).

on both sides of the junction, but a small fraction, x, of the total salt in the right-hand solution is silver acetate. The electromotive force of this cell is given by

$$E = -E^0_{Ag} - k \log a_H/a'_{Ag} \pm E_j \qquad (1)$$

where $k = 0.00019844T$, and a_H and a'_{Ag} denote the activities of the hydrogen and silver ion in the left and right-hand solutions, respectively. The ionization of acetic acid requires that

$$a_H = Ka_{HAc}/a_{Ac} \qquad (2)$$

and by substitution, equation (1) becomes

$$E = -E^0_{Ag} + k \log a'_{Ag}a_{Ac}/a_{HAc} - k \log K \pm E_j \quad (3)$$

With a buffer ratio unity, it is permissible to write $m_H = K$ throughout the concentration range investigated. Accordingly equation (3) becomes

$$E - k \log mx(m + K)/(m - K) + k \log K = -E^0_{Ag} + k \log \gamma'_{Ag}\gamma_{Ac}/\gamma_{HAc} \pm E_j \quad (4)$$

by rearrangement, and introduction of concentrations and the corresponding ionic activity coefficients.

It is evident that when $x = 0$ the solutions are identical, and E_j vanishes. At constant m, a plot of the left-hand member against some convenient function of x yields the intercept

$$[E - k \log mx(m + K)/(m - K) + k \log K]_{x \doteq 0} = -E^0_{Ag} + k \log \gamma_{Ag}\gamma_{Ac}/\gamma_{HAc} \quad (5)$$

Since the two solutions are identical, it is no longer necessary to retain the prime on the activity coefficient term. At high dilutions, this term becomes equal to $-2k\alpha\sqrt{m}$, where α is the Debye–Hückel limiting slope. Therefore we may add $2k\alpha\sqrt{m}$ to the values of the bracketed term of equation (5), and extrapolate[3] the resulting quantities to zero ionic strength. The intercept is $-E^0_{Ag}$.

Materials and Technique

Baker C. P. glacial acetic acid was purified further by one partial freezing, and two distillations from chromic oxide in an all-glass still. The acid was diluted with conductivity water to form a stock solution approximately 0.2 molal. It was standardized by comparison with Bureau of Standards potassium acid phthalate and an independently standardized hydrochloric acid solution. The titer was known to ±0.04%. The solution was stored under hydrogen. Eimer and Amend C. P. silver acetate was analyzed gravimetrically, as silver bromide, and found to be 99.45 ± 0.03% silver acetate. It was used on this basis without further purification. Baker and Adamson sodium bicarbonate was recrystallized once from distilled water saturated with carbon dioxide, and dried in an atmosphere of carbon dioxide. Commercial nitrogen and hydrogen were freed from oxygen by passing them over copper turnings at 700°. Sodium carbonate was prepared fresh for each cell solution by heating the bicarbonate, in a platinum dish, in an electric furnace at 290 ± 10° for at least ten hours.

The calculated amounts of sodium carbonate, silver acetate, acetic acid stock solution and water were weighed into the solution flasks to obtain solutions with the desired values of x, m and a buffer ratio of unity. Conductivity water was used, and vacuum corrections applied. The solutions for the hydrogen half-cell were swept with hydrogen which had passed through a saturator of large volume, and they were then kept under hydrogen. The silver half-cell solutions were swept with nitrogen, and stored under this gas. The silver solutions were protected from light.

The essential features of the cell have been described by Owen.[2] No intermediate solution was required, and our cell differs from his only in the elimination of one of the junction stopcocks, and the necessary modifications for the electrodes employed. The silver electrodes were prepared by the thermal decomposition of silver oxide at 450°. The sample of silver oxide which was used was the same as for the previous investigation.[2] The hydrogen electrodes were of the usual type employed in work from this Laboratory. The measuring equipment was the same as that of the previous investigation, and the technique was practically identical. The cells were filled twelve hours before the first measurement, the usual vacuum technique being employed. Measurements were made from 5 to 45° at 10° intervals, and the cells were refilled frequently during the course of the measurements.

Discussion of the Results

The observed electromotive forces of the cells were corrected to a partial pressure of hydrogen of one atmosphere, and to round temperatures. They are recorded in Table I. The reported values are the mean of two cells (of four cells, in a few cases) differing by no more than 0.03 mv. In one case ($m = 0.05$, $x = 0.089$), the value represents two independent runs. The first group of cells were taken from 5 to 45° in one day. The second were taken from 5 to 25°, maintained at 25° for three days, returned to 5° and then taken to 45°. All values for the two runs agree within the deviation noted above. The cells therefore appear to be very stable once equilibrium is attained. Reproducible results were not obtained for silver concentrations below 0.002 molal, and these results have been discarded.

The values for the dissociation constant of acetic acid were taken from a paper by Harned and Ehlers.[4] The left-hand member of equation (4) is plotted against x in Fig. 1 at the five temperatures investigated. The results at 25° are similarly plotted on a larger scale in Fig. 2 to illustrate

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[3] Hitchcock, THIS JOURNAL, **50**, 2076 (1928).

[4] Harned and Ehlers, *ibid.*, **55**, 652 (1933), Equation 7.

TABLE I

OBSERVED ELECTROMOTIVE FORCES AND INTERCEPTS FROM THE FIRST EXTRAPOLATION (FIG. 1)

x	$t°$......5°	15°	25°	35°	45°
			m = 0.05		
0.2299	0.96085	0.95477	0.94944	0.94452	0.93977
.1660	.95428	.94793	.94258	.93748	.93252
.1299	.94917	.94265	.93717	.93166	.92659
.0892	.94101	.93413	.92837	.92283	.91737
.0652	.93389	.92626	.92083	.91493	.90938
.0475	.92612	.91944	.91296	.90696	.90109
Intercept	.80910	.79830	.78805	.77740	.76630
			m = 0.03		
0.40	0.96512	0.95960	0.95461	0.95021	0.94598
.30	.95893	.95323	.94807	.94347	.93892
.2299	.95312	.94718	.94177	.93675	.93202
.1299	.93990	.93350	.92789	.92234	.91716
.10	.93385	.92725	.92141	.91572	.91029
Intercept	.81070	.80015	.79015	.77950	.76870
			m = 0.02		
0.50	0.96302	0.95748	0.95248	0.94801	0.94367
.40	.95807	.95235	.94708	.94245	.93796
.30	.95143	.94549	.94006	.93513	.93042
.20	.94222	.93583	.93018	.92491	.91983
.15	.93544	.92887	.92295	.91750	.91222
Intercept	.81195	.80155	.79145	.78105	.77040
			m = 0.01		
0.60	0.95285	0.94691	0.94165	0.93657	0.93202
.40	.94370	.93739	.93175	.92642	.92146
.30	.93701	.93055	.92468	.91918	.91402
.20	.92748	.92073	.91458	.90878	.90334
Intercept	.81370	.80335	.79330	.78315	.77255

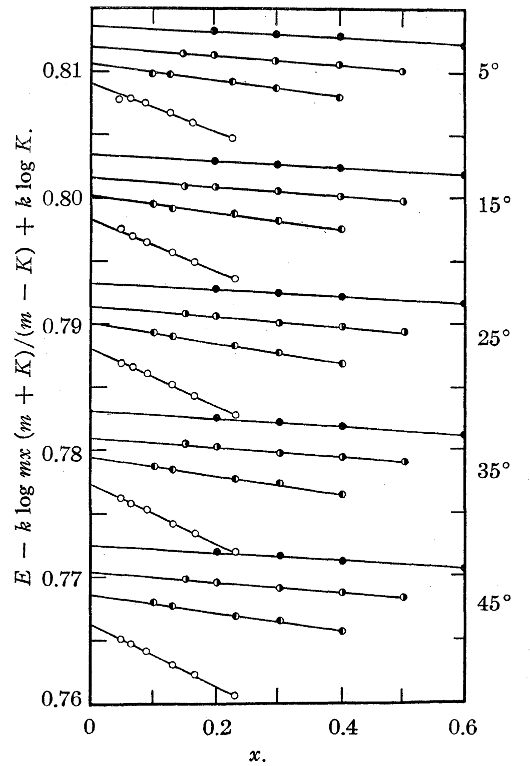

Fig. 1.—Extrapolation to eliminate liquid junction potentials: ○, m = 0.05; ◐, m = 0.03; ◑, m = 0.02; ●, m = 0.01.

the accuracy of the extrapolation. In Fig. 2, the radius of the experimental points represents an uncertainty of 0.1 mv. With the exception of a single point at 5° (m = 0.05, x = 0.047), the deviations from linearity are in no cases greater than 0.10 mv. This result for cells with buffer solutions corroborates the linearity previously observed[2] without buffer solutions. In that investigation, the slope of the extrapolation function increases with increase in ionic strength; in this investigation, the slope has the opposite sign, and shows an algebraic decrease with increasing ionic strength that is more rapid than in the former case. By reason of its steeper slope, the extrapolation at m = 0.05 is probably of no greater accuracy than that at m = 0.02, although in the former case it was possible to extend the measurements to a lower value of x. It should be noted that a plot of the electromotive forces of these cells against x does not form a basis for the estimation of the magnitude of the liquid junction potential, or of its variation with total ionic strength or temperature, since these plots also contain the variation of the unknown activity coefficient term, $\log \gamma'_{Ag^+}\gamma_{Ac^-}/\gamma_{HAc}$. The linearity of the extrapolation *function* seems established within the experimental error for the concentration range which has been investigated with both types of cells.

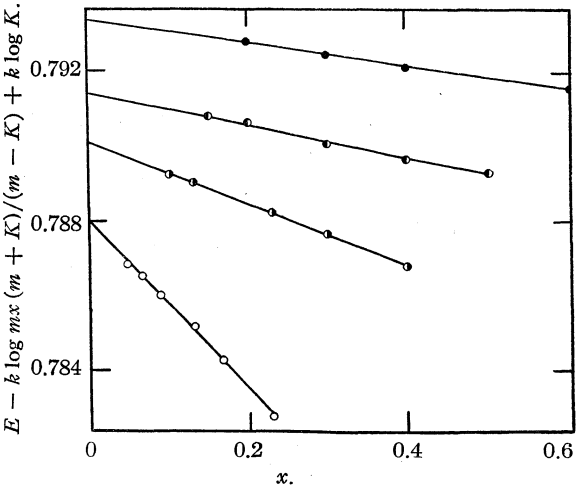

Fig. 2.—Extrapolation to eliminate liquid junction potentials at 25°. Radius of circles is 0.1 mv.: ○, m = 0.05; ◐, m = 0.03; ◑, m = 0.02; ●, m = 0.01.

The intercepts from the extrapolation in Fig. 1 are recorded in Table I to the nearest 0.05 mv. The term $2k\alpha\sqrt{m}$ is added to these intercepts as explained above, and the resulting quantities ex-

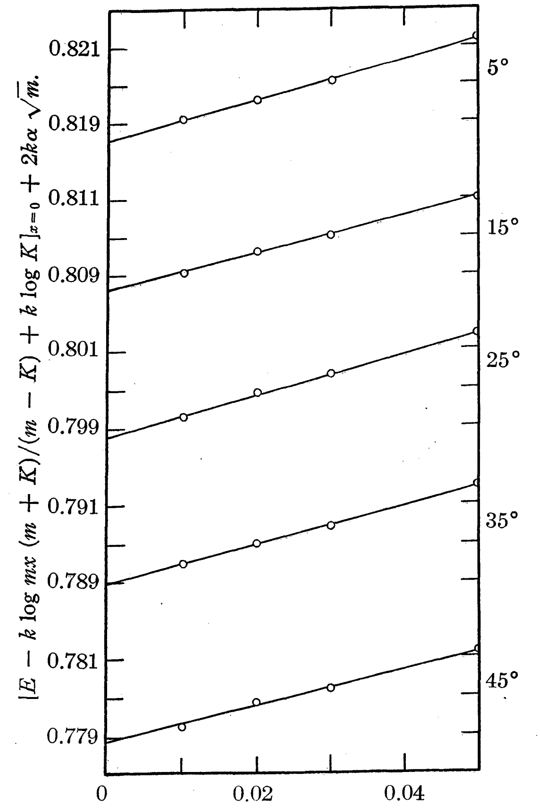

Fig. 3.—Extrapolation to eliminate activity coefficients.

trapolated to infinite dilution in Fig. 3. The values of E^0_{Ag} thus obtained are recorded in Table II. Uncertainties in concentrations, temperature and the measurement of the electromotive force are not likely to cause an error as great as 0.1 mv. and hence the uncertainties in E^0_{Ag} may be assigned to that of the two extrapolations, which we estimate to be less than ±0.2 mv.

TABLE II

STANDARD ELECTRODE POTENTIAL OF SILVER, AND DERIVED THERMODYNAMIC QUANTITIES FOR THE ELECTRODE REACTION

t, °C.	$-E^0_{\mathrm{Ag}}$ Obsd.	$-E^0_{\mathrm{Ag}}$ Ref. 2	$-E^0_{\mathrm{Ag}}$ Eq. (7)	ΔS^0	ΔH^0	$\Delta C_p{}^0$
5	0.8185_5	0.8187	0.8185_8	...	....	..
15	.8087	.8090	$.8089_1$	22.46	25,127	9.30
25	.7990	.7992	$.7991_0$	22.79	25,221	9.62
35	.7891	.7892	$.7891_5$	23.10	25,319	9.95
45	.7788	$.7791_5$	$.7790_6$	...	....	..

In the previous paper,[2] values of the logarithm of the solubility product of silver chloride have been tabulated. E^0_{Ag} can be calculated from the relation

$$E^0_{\mathrm{Ag}} = k \log K + E^0_{\mathrm{AgCl}} \qquad (6)$$

We have employed Harned and Ehlers' values[5] of E^0_{AgCl} because their investigation led to the values of the dissociation constant of acetic acid[4] which we have used above. The result of this calculation is given in column three of Table II. The two sets of data constitute a satisfactory check on the precision of the measurements. The difference between the two sets of values is well within the combined experimental uncertainties of the two determinations. Accordingly, we consider the best values of E^0_{Ag} to be the mean of the two determinations. This can be expressed satisfactorily by the equation

$$E^0_{\mathrm{Ag}} = -0.7991 + 0.000988(t - 25) + 7 \times 10^{-7}(t - 25)^2 \qquad (7)$$

Values calculated from this equation are given in Table II, column 4. The maximum deviation of observed from calculated values is 0.26 mv., and the average deviation is 0.11 mv. for both series of results. Since the temperature coefficient of E^0_{Ag} is of particular interest, it should be remarked that by a change in the constant term this equation will reproduce either set of values with a maximum deviation of 0.1 mv., and an average deviation of 0.05 mv. The values from the equation are used in all subsequent calculations.

Lewis[6] and Noyes and Brann[7] have compared the silver electrode in a 0.1 normal silver nitrate solution with the 0.1 normal calomel electrode. On the basis of various values for the reference electrode potential, and of various assumptions regarding the liquid junction potential and ionic activities, different authors have obtained the values −0.7995[6-8] and −0.7978[9] for E^0_{Ag} at 25° from these data. Chloupek and Daneš[10] have compared the silver electrode in a silver sulfate solution with the decinormal calomel electrode, using various bridge solutions. They obtain −0.7996 for E^0_{Ag} at 25°. Considering the diversity of the methods used to eliminate liquid junction potentials, the agreement of these values with ours seems satisfactory.

Differentiation of equation (7) yields

$$\mathrm{d}E^0_{\mathrm{Ag}}/\mathrm{d}T = 0.000988 + 1.4 \times 10^{-6}(t - 25) \qquad (8)$$

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[5] Harned and Ehlers, THIS JOURNAL, **55**, 2179 (1933), Equation 7.

[6] Lewis, *ibid.*, **28**, 158 (1906).

[7] Noyes and Brann, *ibid.*, **34**, 1016 (1912).

[8] Lewis and Randall, "Thermodynamics and the Free Energy of Chemical Substances," McGraw-Hill Book Co., New York, N. Y., 1923, p. 414; Gerke, *Chem. Rev.*, **1**, 377 (1925).

[9] "International Critical Tables," Vol. VI, p. 333.

[10] Chloupek and Daneš, *Coll. Czech. Chem. Comm.*, **4**, 124 (1932).

Skotnický[11] has measured the temperature coefficient of various half-cells against reference electrodes maintained at constant temperature. His method involves a thermal e. m. f. in the bridge solution, and a correction for the change in activity of the electrolyte with temperature, which is estimated from conductance measurements. He obtained the value 0.978 mv./deg. for dE^0_{Ag}/dT at 25°. Lingane and Larson[12] have measured the temperature coefficient of the cell

$$\text{Quinhydrone} \mid \text{HClO}_4c_1 \mid \text{HClO}_4c_1,\ \text{AgNO}_3c_2 \mid \text{Ag}$$

They obtain the value 0.967 mv./deg. for dE^0_{Ag}/dT at 25°. Their lowest concentration is 0.04 molar, and they made no extrapolation to infinite dilution. Their silver ion concentrations are lower than those with which we could obtain reproducible results, and no account was taken of liquid junction potentials. In view of the nature of the calculations employed by Skotnický, and by Lingane and Larson, we regard our value, 0.000988, as the most reliable figure.

Derived Thermodynamic Quantities

By application of familiar thermodynamic relations to equations (7) and (8), ΔS^0, ΔH^0 and ΔC^0_p are computed readily for the electrode reaction

$$\text{Ag} + \text{H}^+ \longrightarrow {}^1/_2\text{H}_2 + \text{Ag}^+$$

The values of these quantities are given in Table II for 15, 25 and 35°, the three temperatures at which equation (7) best reproduces the experimental results.

The solubility products of the silver halides may be computed from the relation

$$k \log K_{AgX} = E^0_{Ag} - E^0_{AgX} \qquad (6a)$$

By substitution of equation (7) from this paper, and the equations for the temperature variation of the standard silver halide electrode potentials[5,13,14] into equation (6a), the following expressions for the logarithm of the solubility product are obtained

$$k \log K_{AgCl} = -0.57671 + 0.00034248(t-25) - 2.584 \times 10^{-6}(t-25)^2 + 9.948 \times 10^{-9}(t-25)^3$$
$$k \log K_{AgBr} = -0.72776 + 0.000490(t-25) - 2.9 \times 10^{-6}(t-25)^2 \qquad (9)$$
$$k \log K_{AgI} = -0.95129 + 0.000660(t-25) - 2.9 \times 10^{-6}(t-25)^2$$

or

$$-\log K_{AgCl} = 5905.8/T - 22.8538 + 0.057854T - 5.0131 \times 10^{-5}T^2$$
$$-\log K_{AgBr} = 5702.2/T - 11.1822 + 0.014610T \qquad (10)$$
$$-\log K_{AgI} = 7084.0/T - 12.0389 + 0.014610T$$

Values of the logarithms of the solubility products and the corresponding solubilities are given in Table III. The solubilities have been converted into moles per liter of solution in order to facilitate comparison with the literature. Activity coefficients were calculated by the Debye–Hückel limiting law.

TABLE III

SOLUBILITY PRODUCTS AND SOLUBILITIES OF THE SILVER HALIDES

t, °C.	AgCl		AgBr		AgI	
	$-\log K$	$c \times 10^5$	$-\log K$	$c \times 10^6$	$-\log K$	$c \times 10^8$
5	10.5945	0.506	13.3860	0.203	17.4980	0.178
15	10.1520	0.842	12.8201	.380	16.7598	.417
25	9.7492	1.337	12.3026	.704	16.0813	.908
35	9.3809	2.038	11.8280	1.213	15.4562	1.859
45	9.0425	3.002	11.3920	1.997	14.8792	3.599

The discordance between the values in the literature for the solubility of silver chloride has been discussed in the previous paper.[2] The same considerations apply to the bromide and iodide. Comparison with previously recorded results does not, therefore, constitute a criterion of the absolute accuracy of the results in Table III. Our values do constitute a self-consistent set of solubilities which have been derived from e. m. f. methods alone. It is important to note in this connection that identical values of the standard potential of the silver–silver chloride electrode[5] were used in all of the supplementary data[13,14] involved in the construction of Table III. The solubilities in Table III are 0.25% higher than those recorded by the first paper[2] due to the combination of those data with ours in equation (7). The values in the literature for the solubility of silver bromide and silver iodide consist of determinations at a single temperature. The mention of a few of these will be sufficient. The determination of the solubility of silver bromide at 21.1° by Kohlrausch and Dolezalek[15] is 5% lower than our interpolated value. That of Bodländer and Fittig[16] at 25° is 2% higher than ours. The discordance with other values is considerably greater. The disagreement with the few recorded values of the solubility of silver iodide is even greater. The value of Goodwin[17] at 25° is 5% higher than ours, and that of Thiel[18] at the same temperature is 15% higher than ours.

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[11] Skotnický, *Coll. Czeck. Chem. Comm.*, **8**, 498 (1936).

[12] Lingane and Larson, THIS JOURNAL, **59**, 2271 (1937).

[13] Owen and Foering, *ibid.*, **58**, 1575 (1936). Equation 2.

[14] Owen, *ibid.*, **57**, 1526 (1935). Equation 5.

[15] Kohlrausch and Dolezalek, *Berl. Sitzber.*, 1021 (1901).

[16] Bodländer and Fittig, *Z. physik. Chem.*, **39**, 605 (1902).

[17] Goodwin, *ibid.*, **13**, 646 (1894).

[18] Thiel, *Z. anorg. Chem.*, **24**, 57 (1900).

TABLE IV

DERIVED THERMODYNAMIC QUANTITIES FOR THE REACTION

$AgX \longrightarrow Ag^+ + X^-$

	AgCl			AgBr			AgI		
t, °C.	ΔS^0	ΔH^0	ΔC_p^0	ΔS^0	ΔH^0	ΔC_p^0	ΔS^0	ΔH^0	ΔC_p^0
15	9.19	16,022	−34.7	12.64	20,542	−38.5	16.56	26,865	−38.5
25	7.90	15,653	−35.5	11.30	20,150	−39.9	15.22	26,473	−39.9
35	6.77	15,313	−36.3	9.96	19,749	−41.2	13.88	26,068	−41.2

TABLE V

SUPPLEMENTARY THERMODYNAMIC DATA[23]

	C_p^0					S^0				
t, °C.	½ H_2	Ag	AgCl	AgBr	AgI	½ H_2	Ag	AgCl	AgBr	AgI
15	3.43	6.09	12.05	12.38	12.87	15.50	10.00	22.59	25.16	26.66
25	3.43	6.10	12.14	12.52	13.01	15.61	10.20	23.00	25.60	27.10
35	3.44	6.12	12.23	12.66	13.15	15.73	10.40	23.40	26.03	27.53
	6.62	5.65	9.37	8.81	8.81 = a					
	0.81	1.50	9.29	14.1	14.1 = $b \times 10^3$					

TABLE VI

RELATIVE IONIC ENTROPIES AND HEAT CAPACITIES

t, °C.	$S^0_{Ag^+}$	$S^0_{Cl^-}$	$S^0_{Br^-}$	$S^0_{I^-}$	$C^0_{pAg^+}$	$C^0_{pCl^-}$	$C^0_{pBr^-}$	$C^0_{pI^-}$
15	16.96	14.82	20.84	26.26	12.0	−34.6	−38.1	−37.6
25	17.38	13.52	19.52	24.94	12.3	−35.7	−39.6	−39.2
35	17.87	12.30	18.12	23.54	12.6	−36.7	−41.2	−40.7

By application of the usual thermodynamic relations to equations (9) or (10), it is possible to compute ΔS°, ΔH° and ΔC_p^0 for the reaction, $AgX \longrightarrow Ag^+ + X^-$. The values of these quantities for the silver halides are given in Table IV for 15, 25 and 35°. Pitzer and Smith[19] have calculated the heat of solution at 25° of silver chloride from the heat of precipitation data of Lange and Fuoss.[20] They obtain the value $\Delta H^0 =$ 15,740 cal. Latimer, Schutz and Hicks[21] report 26,710 cal. for the heat of solution of silver iodide, at 25° using the data of Lange and Shibata.[22]

The supplementary thermodynamic data necessary for the computation of relative ionic entropies and heat capacities are summarized in Table V.[23] Using the convention that the entropy of the hydrogen ion is zero at all temperatures, the relative ionic entropies and heat capacities of the silver and halide ions have been calculated from the values in Tables II, IV and V. These quantities are summarized in Table VI at 15, 25 and 35°.

Skotnický's[11] value of dE^0_{Ag}/dT leads to 17.0 cal./deg. mole for $S^0_{Ag^+}$ at 25°. Lingane and Larson[12] obtain 16.7 cal./deg. mole for the same quantity. A more reliable value from calorimetric methods is from the recent heat capacity data for silver oxide of Pitzer and Smith.[19] They obtained 17.46 ± 0.2 cal./deg. mole for $S^0_{Ag^+}$ at 25°. They have also recalculated the value given by Latimer, Schutz and Hicks,[21] based upon the heat of precipitation data of Lange and Fuoss,[20] and obtained 17.62 ± 0.2. They proposed the mean of these two figures as the best value, but in view of the approximate heats of dilution used to correct the data of Lange and Fuoss, and the close agreement with our value, we suggest the adoption of 17.4 ± 0.2 cal./deg. mole as the most probable value of $S^0_{Ag^+}$ at 25°.

From a number of sources, Latimer, Schutz and Hicks[21] have selected 13.5 ± 0.1, 19.4 ± 0.4 and 25.7 ± 0.7 cal./deg. mole for the best values[24] of $S^0_{Cl^-}$, $S^0_{Br^-}$ and $S^0_{I^-}$, respectively, at 25°. The agreement with the values in Table VI is well within the estimated uncertainties for the chloride and bromide ions, and is probably also satisfactory in the case of the iodide ion.

Summary

A method for the elimination of heterionic liq-

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(19) Pitzer and Smith, THIS JOURNAL, **59**, 2633 (1937).

(20) Lange and Fuoss, *Z. physik. Chem.*, **125**, 431 (1927).

(21) Latimer, Schutz and Hicks, *J. Chem. Phys.*, **2**, 82 (1934).

(22) Lange and Shibata, *Z. physik. Chem.*, **A149**, 456 (1930).

(23) The entropy and heat capacity data at 25°, except for hydrogen, are from the review of Kelley, *Bur. Mines*, Bull., 394, 35 (1935). The heat capacity of hydrogen [*cf.* Murphey, *J. Chem. Phys.*, **5**, 637 (1937)] and the temperature coefficients of all heat capacities are from the review of Kelley, *ibid.*, Bull. 371 (1934), being described by the equation, $C_p^0 = a + bT$. "a" was recalculated from "b" and C_p^0 at 298.1°K. (given in Bull. 394). The entropy at temperatures other than 298.1°K. is then given by $S^0 = S^0_{298.1} + a(2.303 \log T/298.1) + b(T - 298.1)$.

(24) While this paper was in press, Latimer, Pitzer and Smith [THIS JOURNAL, **60**, 1829 (1938)] have published another review of the subject. Their revised "best" values are 13.5 ± 0.1, 19.7 ± 0.2 and 25.3 ± 0.5 for the entropies of the halide ions, and 17.54 ± 0.15 for the silver ion.

uid junction potentials by extrapolation has been tested in cells with buffer solutions. Experimental data are presented which indicate that the junction extrapolation is linear as a first approximation.

The method is applied to the determination of the standard potential of the silver electrode at 5, 15, 25, 35 and 45°. Values of ΔS^0, ΔH^0 and ΔC_p^0 have been calculated for the electrode reaction at 15, 25 and 35°.

By combination of the normal potentials of the silver and silver–silver halide electrodes, the solubility products and solubilities of (electrolytic) silver chloride, bromide and iodide have been computed from 5 to 45°. Values of ΔS^0, ΔH^0 and ΔC_p^0 for the reaction $AgX = Ag^+ + X^-$ have been recorded at 15, 25 and 35°.

A self-consistent table of relative ionic entropies and heat capacities from electromotive force data has been made for the silver ion, chloride ion, bromide ion and iodide ion at 15, 25 and 35°.

NEW HAVEN, CONN. RECEIVED JUNE 29, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Infrared Absorption Studies. V. Association in the Carboxylic Acids

BY A. M. BUSWELL, W. H. RODEBUSH AND M. F. ROY

The electron conception of valence proposed some twenty years ago led to the prediction in 1920 of two types of associated liquids.[1] In one of these the molecules should be combined with the formation of definite polymers (dimers in the case of acetic acid) while in the other type polymers of indefinite molecular weight and structure were anticipated. Radically different behavior, especially in the case of solvent properties, was predicted in the two cases. The liquids composed of polymers of indefinite molecular weight comprised the typically polar solvents such as water or alcohol, while in those having definite polymer molecules non-polar properties were to be expected.

Since then a great deal of additional evidence has been accumulated to emphasize this difference. For example, acetic acid shows no dipole moment in benzene solution whereas alcohols show an increasing polarization with increasing concentration. Alcohols also form glasses at low temperatures, which have been shown by Zachariasen[2] to involve polymerization with hydrogen bond formation. It is not possible, of course, to anticipate or predict in every case the type of polymer to be expected and that problem is one which still holds the greatest interest. The data from which conclusions could be drawn have been available for a long time; witness the excellent review by Lassettre[3] based entirely upon the ordinary data of physical chemistry. More recently a study of simple solubility by Zellhoefer, Copley and Marvel[4] has yielded a surprising amount of additional confirmatory data along these lines.

The existence of these two types of association has perhaps contributed to the confusion which for many years characterized the attempts of physical chemists to discuss the behavior of the so-called "normal" and "associated" liquids. This confusion was all the more inevitable because it is now obvious that the normal or unassociated liquid lies intermediate in its properties between the two types of associated liquids.

It should be mentioned at this point that a third type of association through hydrogen, namely, intramolecular association or chelation, may occur, which has the result of producing a "normal" behavior in a molecule which would otherwise show abnormal behavior as a liquid and solvent. This type of association has been much studied by Sidgwick[5] and his collaborators. The conditions under which it occurs are well defined, and one of the important ones is apparently the possibility of two configurations of the molecule with respect to the hydrogen, thus giving an opportunity for resonance.

All of the types of association of interest in the liquid state appear to involve hydrogen bonding. The formation of polymers depends upon potential cross linkages or additional valences between

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(1) W. M. Latimer and W. H. Rodebush, THIS JOURNAL, **42**, 1432 (1920).

(2) W. H. Zachariasen, *J. Chem. Phys.*, **3**, 158 (1935).

(3) E. N. Lassettre, *Chem. Rev.*, **20**, 259 (1937).

(4) G. F. Zellhoefer, M. J. Copley and C. S. Marvel, THIS JOURNAL, **60**, 1337 (1938); G. F. Zellhoefer and M. J. Copley, *ibid.*, **60**, 1343 (1938).

(5) N. V. Sidgwick, "The Electronic Theory of Valency," Oxford University Press, 1929.

molecules. In the typical organic polymers these cross linkages are strong and irreversible and lead to the formation of inert solids. Because of the low energies of activation and dissociation of the hydrogen bond, the polymers formed may be liquid or if the unit molecules are large, substances capable of colloidal dispersion as in the case of the proteins may be formed.

While it is possible to determine from a study of the physical data the type of association present, it is not possible to explain or predict such association without more direct information as to the molecular structure. The first important advance in this type of study was made by Pauling and Brockway[6] when they confirmed the prediction of Latimer and Rodebush, showing by means of electron diffraction that the dimer of formic acid has a symmetrical ring structure involving both carboxyls. The methods of electron diffraction do not, of course, lend themselves to the study of solutions and a further great advance was made when Wulf[7] and his collaborators began the study of the infrared absorption of organic substances in an inert solvent. They noted the absence of the second harmonic in the case where hydrogen bonding, particularly of the chelated type, was to be anticipated.

After the work of Wulf and his collaborators came to our attention, experiments were begun in this Laboratory[8] upon the infrared absorption of certain types of compounds in which hydrogen bonding was present. We investigated a large number of compounds in the region where the fundamental of hydroxyl was to be expected and found the very important generalization that the formation of a hydrogen bond is accompanied by a very considerable increase in the absorption and a marked change in frequency, the shift being in the direction of longer wave lengths. This work has been amply confirmed by other investigators working independently,[9] at least in the case of polymerization. So far as we know, we were the first to call attention to the shift in absorption accompanying the formation of an intramolecular hydrogen bond. In previous publications we have reported the investigation of the shifts in the fundamental frequency of a considerable variety of compounds, following more or less the lines laid down by Wulf and his collaborators in their investigation of the harmonic absorption. In the present paper we wish to report results which have to do mainly with association and which include the formation of hydrogen bonds where the hydrogen is linked to atoms other than oxygen and, in particular, the formation of hydrogen bonds between different types of molecules, a subject which is of the greatest interest and which has not been studied to any considerable extent.

Hydrogen bonds are known to be formed readily when hydrogen is attached to nitrogen, oxygen and fluorine. Certain types of compounds such as ether hydrochloride and chloroform–ether suggest that carbon and the other halogens should be included in the list. It is certain that for bond formation the hydrogen must be active to some degree, which means, of course, ionizable in the proper solvents. Hydrogen attached to carbon in an ordinary hydrocarbon is incapable of forming a bond; likewise apparently there is little tendency for the hydrogen of ammonia of the amines to form bonds. All the physical properties of the amines indicate[10] the lack of association and our infrared studies do not indicate any bonding in the case of aniline for example. On the other hand, the hydrogen of chloroform shows a strong tendency toward bonding, even with the oxygen of ether. The question as to whether the hydrogen of chloroform is more "active" than the hydrogen of an amine, such as aniline, is one to which it is difficult to make an answer. Data upon the ionization constants must be applied in non-polar solvents with a good deal of caution. Certainly our conclusions show that the hydrogen of chloroform and all the hydrogens which are more active will form hydrogen bonds either with another molecule of the same kind or with one which is perhaps more basic. There seems to be no evidence, for example, that hydrogen chloride is associated but the ether hydrochloride complex is a clear case of hydrogen bonding. On the other hand, moderately acidic substances such as the amides or carboxylic acids show a very strong tendency toward association.

One important generalization that has been suggested by Venkateswaran[11] from a study of the Raman and infrared spectra appears to be con-

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[6] L. Pauling and L. O. Brockway, *Proc. Nat. Acad. Sci. U. S.*, **20**, 336 (1934).

[7] G. E. Hilbert, O. R. Wulf, S. B. Hendricks and U. Liddel, This Journal, **58**, 248 (1936).

[8] A. M. Buswell, V. Deitz and W. H. Rodebush, *J. Chem. Phys.*, **5**, 84, 501 (1937).

[9] J. Errera and P. Mollet, *Nature*, **138**, 882 (1936); J. J. Fox and A. E. Martin, *Proc. Roy. Soc.* (London), **A162**, 419 (1937).

[10] W. D. Kumler, This Journal, **57**, 600 (1935).

[11] C. S. Venkateswaran, *Proc. Indian Acad.*, **7**, 13 (1938).

firmed here. When a bond is formed, the more acidic the hydrogen, the greater the shift in frequency toward the longer wave length and the broader the resulting absorption band. The foregoing statement applies to the stretching frequency. Our evidence on the bending frequency is limited to the case of chloroform, and since there is possibly some uncertainty concerning it, we will discuss the behavior of the bending frequency in connection with the experimental work on chloroform compounds in a subsequent paper.

The question as to the strength of the bond formed between various types of molecules is one upon which we have only qualitative evidence. Qualitatively, the bond strengths appear to be all of the same order of magnitude. This can scarcely be true, but a study of the heats of mixing under various conditions would be very desirable.

In the foregoing discussion we have tacitly assumed that such a thing as hydrogen "bond" exists and have ignored the fact that some believe it to be nothing more than an attraction due to dipole interaction. One might evade the argument by simply stating that the association takes place through hydrogen without further implication as to the nature of the interaction. We believe, however, that the evidence warrants a much more detailed picture. The characteristic effect of hydrogen bonding on the fundamental in infrared absorption is the increase in absorption coefficient and the shift of frequency to longer wave length. The increase in absorption coefficient is presumably due to an increase in dipole moment. All of these effects would be accounted for by an increase in the internuclear distance of the hydrogen from its original partner accompanied by a transformation toward the ionic type of bonding. In the case where the hydrogen is not active as in chloroform this transformation is small but in the case of the carboxylic acids the result is the formation of a symmetrical eight-membered ring which can hardly be considered as anything short of a chemical reaction. One may say therefore that all degrees of interaction are to be found but that in general the interaction is more than could be predicted from a simple dipole theory. It must be remembered that the hydrogen bond is formed in non-polar solvents and in the vapor state so that no question of ionization is involved.[12]

One may say, therefore, that the formation of a hydrogen bond involves a definite alteration in molecular structure which is scarcely envisaged in the term dipole interaction; this structure is sufficiently rigid to justify the use of the term bond. The fact that the bond is easily broken does not invalidate the use of the term.

The colligative and other physical properties of the molecule still furnish the best evidence as to the type of association. For example, when dimers are formed the dipole moments tend toward zero while in the case of polymers the polarization is increased. Thus alcohol has a much higher dielectric constant than acetic acid. One may hope, however, that when sufficient data have been obtained on the infrared absorption, vibrational analysis will give a definite picture of the structure in all types of association.

In this paper we shall report the results obtained on the carboxylic acids. Hydrogen bonding between other types of molecules will be discussed in subsequent papers.

Experimental

The infrared spectrograph and other equipment has been described briefly in a previous paper.[8] In the spectrograph a 75-mm. rock salt prism is used with a Littrow mounting. The source of radiation is a 220-volt Nernst glower, and the deflections are read directly from a high sensitivity galvanometer. The resolving power and accuracy of calibration are such as to make all details shown in the accompanying absorption curves significant and reproducible.

In the region in which these results were obtained thin glass proved satisfactory for all windows. The results reported here are mainly for solutions, carbon tetrachloride being the solvent. For absorption in solution the molal absorption coefficient K is calculated, as defined arbitrarily by the expression

$$K = \frac{1}{cd} \log \frac{I_0}{I}$$

Here I is the intensity (as measured by galvanometer deflection) through the solution and I_0 the intensity through an equal thickness of pure solvent; c is the concentration expressed as moles per liter of solution and d is the cell length. Because of insufficient resolving power and other factors

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[12] Scatchard and Raymond [THIS JOURNAL, **60**, 1278 (1938)] recently have discussed negative evidence for hydrogen bond formation in chloroform–alcohol solutions. The evidence here is unquestionably that the association of the alcohol is so strong that there is no tendency toward the formation of an intermolecular compound with chloroform. This is because the hydrogen of the alcohol is more active than the hydrogen of the chloroform; *cf.* the article by Zellhoefer, Copley and Marvel referred to above.

K is not independent of the product $c \times d$. In order to make comparisons at different concentrations it is necessary therefore to maintain the product $c \times d$ constant; this was accomplished by using cells of various lengths. When $c \times d$ is maintained constant, the value of K for a static group such as C–H was found to be quite independent of concentration.

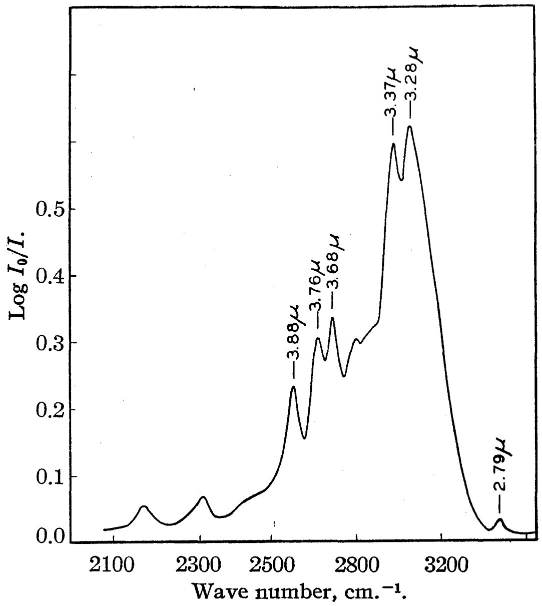

Fig. 1.—Acetic acid vapor: air saturated with acetic acid at 21° in 10.18 cm. cell.

The utmost care was exercised in the preparation and purification of materials, including the solvent material. Benzoic acid was purified by recrystallization from alcohol–water solutions. Acetic acid, benzoyl chloride and trichloroacetic acid were purified by distillation at low pressures.

The deuterobenzoic acid was prepared by heating benzoyl chloride with a fivefold excess of 99.6% deuterium oxide in a sealed tube at 100° for two hours. The deuterium chloride and excess deuterium oxide were removed by distillation at low pressures. The carbon tetrachloride used as solvent was dried over phosphorus pentoxide. After the absorption curve of the deuterated acid was obtained the acid was reconverted to ordinary benzoic acid by exposure to moist air. The absorption curve was identical with ordinary benzoic acid.

The association of acetic acid in the vapor has been recognized for a very long time and many references could be cited to the effect that a dimer is formed. The first direct experimental evidence as to the structure of this dimer was obtained by Pauling and Brockway, as cited above. Electron diffraction does not, however, give information about the hydrogen atoms. Studies have also been made of the Raman spectrum but the method *par excellence* for the observation of the behavior of hydrogen in molecules is infrared spectroscopy.

The infrared absorption spectra of the carboxylic acids have been investigated by a number of workers in recent years, particularly in the vapor. We shall refer here only to work dealing with the absorption due to hydrogen.

Gillette and Daniels[13] observed a complicated spectrum in the region of 3.0 μ which they attributed to C–H and to overtone and combination frequencies. Badger and Bauer[14] have studied the infrared spectrum of acetic acid by photographic methods and have observed what they believe to be shifts in the second overtone frequency which they believe to be due to hydrogen bonding. Davies and Sutherland[15] have studied the effect of temperature on the infrared absorption of solutions of the carboxylic acids. They find that increasing temperature increases the monomeric O–H frequency and report a broad "association" band in trichloroacetic acid at 3.3 μ. Herman and Hofstadter[16] have published a curve showing the infrared absorption of deuteroacetic acid, CH_3COOD, and have suggested that the absorption band at 4.3 μ is due to deuterium bonding. Only a very weak C–H absorption was observed.

In the accompanying curves are shown the infrared absorption in the region of the C–H and O–H fundamental for acetic acid, trichloroacetic acid, benzoic acid and deuterobenzoic acid. One curve is shown for acetic acid vapor. Comparison with the curve for acetic acid in carbon tetrachloride solution shows that the absorption is the same in solution except that there is a shift of 0.01–0.02 μ toward longer wave lengths in solution. We may therefore assume that any conclusions drawn from our observations in solution apply to the vapor of acetic acid.

An examination of the curves in Fig. 2 shows that acetic acid is slightly dissociated into single

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[13] R. H. Gillette and F. Daniels, This Journal, **58**, 1139 (1396); R. H. Gillette, *ibid.*, **58**, 1143 (1936).

[14] R. M. Badger and S. H. Bauer, *J. Chem. Phys.*, **5**, 369, 605, 839, 852 (1937).

[15] M. M. Davies, G. B. and B. M. Sutherland, *Nature*, **141**, 372 (1938).

[16] R. C. Herman and R. Hofstadter, *J. Chem. Phys.*, **6**, 110 (1938).

molecules at 0.0005 *M* solution; much less so in 0.008 *M* solution. The unbounded hydroxyl band is at 2.82 μ; the slight absorption at 2.67 μ being due to water. A study of Figs. 3 and 4 shows that the absorption due to C–H must be very slight. This is a point about which Daniels and Gillette were uncertain but it is clear that both benzoyl chloride and deuterobenzoic acid have very little absorption in this region and some of the absorption in the case of the deuterobenzoic acid is undoubtedly due to the presence of a small amount ($\sim$1%) of ordinary benzoic acid. It will be further noted that the absorption of trichloroacetic is very similar to that for acetic and benzoic acids.

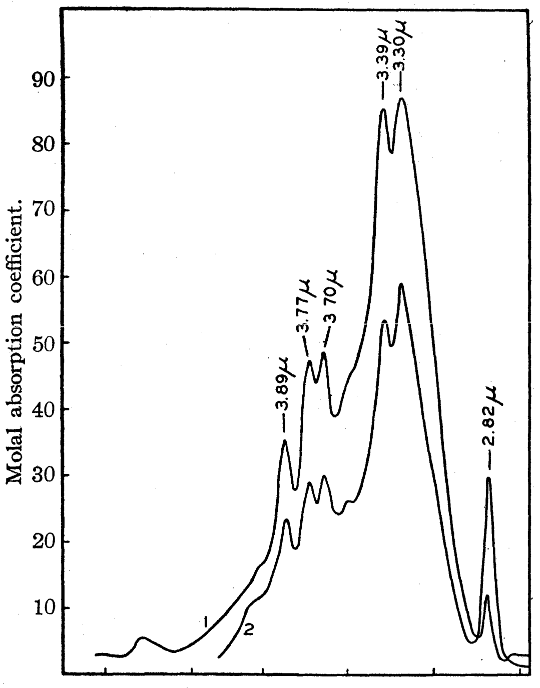

Fig. 2.—Acetic acid: (1) 0.008 *M* in 0.640 cm. cell; (2) 0.0005 *M* in 10.18 cm. cell.

One may therefore conclude that the strong absorption in the neighborhood of 3.3 μ is due mainly to the hydrogen bonding as Herman and Hofstadter suggest. In deuterobenzoic acid the absorption band is narrower and apparently simpler in structure, although the shift in the principal peak is just what one would calculate for deuterium substitution.

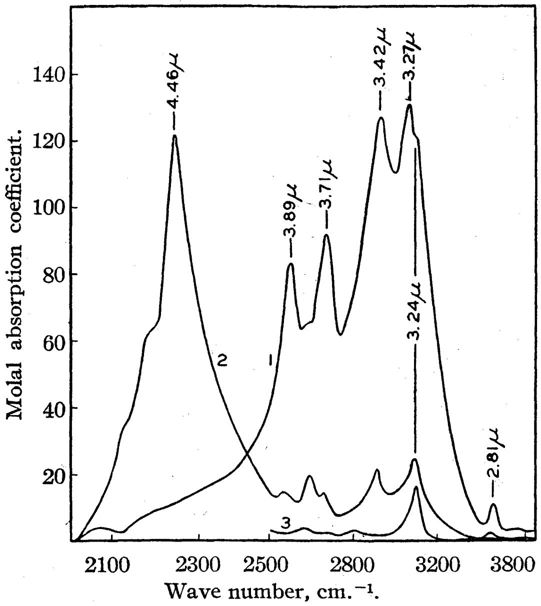

Fig. 3.—(1) Benzoic acid, 0.008 M solution in 0.640 cm. cell; (2) deuterobenzoic acid, 0.008 *M* solution in 0.640 cm. cell; (3) benzoyl chloride, 0.008 *M* solution in 0.640 cm. cell.

It is evident that the absorption band for the acids contains two or more pairs of doublets. The exact identification of these doublets must await the vibrational analysis of the carboxylic dimer. This has been undertaken by Dr. F. T. Wall of this Laboratory. Meanwhile one may speculate as to the probable cause of the doublet

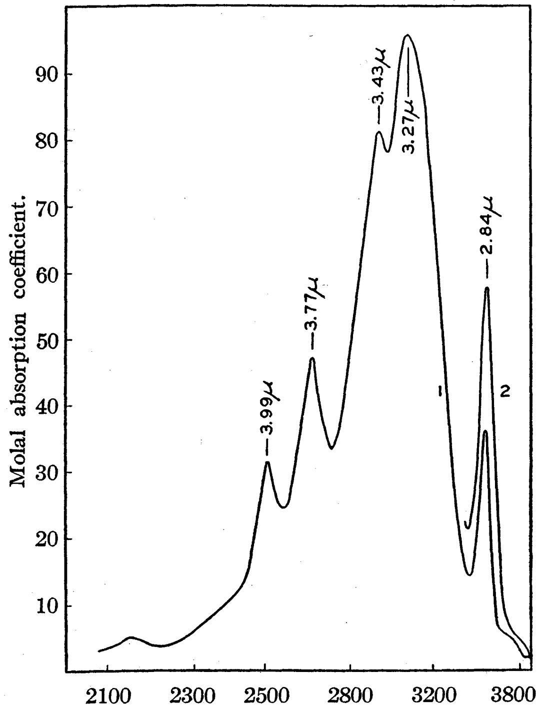

Fig. 4.—Trichloroacetic acid: (1) 0.008 *M* in 0.640 cm. cell; (2) 0.0005 *M* in 10.18 cm. cell.

structure observed. If we assume that the hydrogen atoms are placed unsymmetrically in the eight-membered ring formed by the two carboxyl groups, *i. e.*, each hydrogen being nearer to the oxygen to which it was originally attached, then there are two modes of vibration involving the stretching of the hydrogen bonds which are active in infrared absorption. Each vibration is antisymmetric with respect to a center of symmetry but they differ in the relative motions of the oxygen atoms on either side of the hydrogen atoms. These two frequencies might be guessed to differ by the separation of the two pairs of doublets, *viz.*, 50 cm.$^{-1}$. Because of the fact that there are alternative positions for each hydrogen and consequently, a double minimum in the potential energy curve, the doublets themselves might be expected. Their separation varies from 10 to 20 cm.$^{-1}$. This is, of course, to say nothing of the possibility of resonance between the O–H and C–H vibrations which have nearly the same frequency. Since the C–H absorption is small this effect is probably unimportant although the C–H absorption might be considerably increased by the resonance itself.[17]

Some plausibility is lent to the foregoing explanations by the much simpler structure observed in the absorption peak for deuterobenzoic acid. Here the last effect is absent and because of the greater mass of the deuterium atom the doublet separation would be too small for resolution. There would remain only the two modes of vibration differing markedly in absorption coefficients and these appear to be present.

It has been noted by various authors that formic acid in the liquid state has a dielectric constant some ten times that of liquid acetic acid. Because of the difficulty of purification no studies have been made upon formic acid but there can be little doubt that in the liquid state the dimers are transformed into higher polymers perhaps through the hydrogen attached to the carbon. In a subsequent paper this possibility will be discussed again in connection with formamide. The high dielectric constant which results from polymerization such as occurs in formamide probably offers a clue to the explanation of the greatly reduced solubility of chloroform in this solvent.

The authors wish to acknowledge their indebtedness to the Rockefeller Foundation for funds which enabled them to conduct this research.

Summary

The general character of the infrared absorption spectra indicative of hydrogen bonding is discussed. Curves are shown for the absorption of the active or bonding hydrogen in acetic, benzoic and deuterobenzoic acids under various conditions. The generalization of Venkateswaran in regard to the shift of the hydroxyl frequency is confirmed and some suggestions are made to explain the complex absorption characteristic of association in the carboxylic acids.

URBANA, ILLINOIS RECEIVED JUNE 30, 1938

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[17] In a previous note [THIS JOURNAL, **59**, 176 (1937)] the authors reported on the lack of evidence for the enolization of dibenzoylmethane. This molecule shows absorption resembling that of the carboxylic acids and it is possible to write a hydrogen bonded structure for the enolic form that resembles one-half of the dimeric ring of the acids. The matter therefore requires further investigation.

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

The Negative Temperature Coefficient in the Rate of Propane Oxidation

BY ROBERT N. PEASE

In the early work[1] on the slow combustion of propane and the butanes, it was noted that under certain conditions the rate of oxidation decreased markedly with increasing temperature, although eventually (at a higher temperature) explosion occurred. Similar observations have since been made by Beatty and Edgar[2] on heptane–air mixtures, by Aivazov and Neumann[3] on pentane–oxygen mixtures, and by Newitt[4] on propane–oxygen mixtures.

The beginnings of an explanation of this anomalous behavior follow from the latter investigation. It had been found by Townend[5] that mixtures of air with vapors of hydrocarbons, alcohols, or aldehydes show, in addition to a "true ignition" region (higher pressures and temperatures), a region of limited explosibility giving rise to so-

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[1] Pease, THIS JOURNAL, **51**, 1839 (1929).

[2] Beatty and Edgar, *ibid.*, **56**, 102 (1934).

[3] Aivazov and Neumann, *Acta Physicochimica* (U. R. S. S.), **4**, 575 (1936).

[4] Newitt, *et al.*, *J. Chem. Soc.*, 1656, 1665, 1669 (1937).

[5] Townend, *Chem. Rev.*, **21**, 259 (1937).

called "cool-flames." In a pressure–temperature plot, the latter region appears as a tongue or peninsula pointed toward lower pressures over a limited temperature range in the neighborhood of 300°.

Now it so happens that much of the work which has been done on the oxidation of hydrocarbons apparently has fallen in or near the region of cool flames. Hence the anomalies which have appeared in such work (including the negative temperature coefficient) are in effect incidental to the anomaly of the limited cool-flame region itself.

With the above in mind, Newitt investigated in some detail the characteristics of the cool-flame region for propane–oxygen mixtures. He found among other effects that at temperatures immediately above the cool-flame limit (∽350°), the rate of reaction dropped abruptly to a fairly flat minimum (∽425°) and then rose abruptly to the ignition point (∽450°). The negative temperature coefficient was thus identified with the crossing of the cool-flame limit on the high temperature side.

The region of negative temperature coefficient is more accurately described as a region of minimum rate, bounded at lower and higher temperatures by explosion limits. It would thus appear to be a region of transition from one to another mechanism of oxidation. One should then expect a corresponding change in the kinetics of the process, and this can in fact be observed.

The author[6] has reported measurements of the rate of propane oxidation at a temperature (270°) well below the lower cool-flame limit. With an uncoated[7] Pyrex bulb, it was found that the maximum rate was nearly independent of the oxygen concentration but varied with a power of the propane concentration between one and two, as shown in Table I.

TABLE I

RATE OF PROPANE OXIDATION AT 270° (5 MM. CH_3CHO ADDED)

Initial pressure, mm. C_3H_8	O_2	N_2	Total pressure change, mm.	$[dP/dt]_{(max.)}$ mm./min.
199	202	.	61	9.93
212	197	202	61	11.03
205	384	.	119	10.62
300	301	.	92	23.5
408	202	.	65	34.8

On the other hand, Newitt found that above the cool-flame limit (but below the ignition point), the equimolecular mixture is the most reactive (total pressure constant at 360 mm.; temp. 408°) *i. e.*, the rate is roughly proportional to the product of propane and oxygen concentrations.

In order to make sure that this difference is real, the author has repeated Newitt's experiments under somewhat different conditions as follows.

A reaction bulb like that used for the low temperature experiments was prepared, and washed out with nitric acid and then with distilled water. This was mounted in an electric heater and connected with sources of tank gases, with a manometer, and with vacuum pumps. A series of runs was then carried out at 400° with results as shown in Table II.

It is clear from these results that the rate now depends on *both* propane and oxygen concentrations, the powers being rather higher than the first. There is thus excellent evidence from the kinetics of the reaction that there are two mechanisms of oxidation, one predominating at low temperatures (and leading to cool-flames under optimum conditions), and the other predominating above the cool-flame region and leading to true ignition.

TABLE II

RATE OF PROPANE OXIDATION AT 400°

Initial pressure, mm. C_3H_8	O_2	N_2	Total pressure change, mm.	$[dP/dt]_{max.}$ mm./min.
105	103	.	59	15.9
101	103	104	60	15.6
207	101	.	67	42.
102	203	.	115	51.
102	103	.	59	14.2

In order the better to visualize these two alternative reactions, a series of runs was made at 10° intervals between 300 and 430° (Fig. 1). These runs were made with 100 mm. each of propane and oxygen. With such a mixture, one would (according to Newitt's results) just cut the tip of the cool-flame peninsula at about 290–320°. As, however, Newitt worked with a reaction vessel 5.5. cm. in diameter, whereas the one here used was 2.0 cm. in diameter, it is probable that the experiments were outside the cool-flame region entirely. Certainly there was nothing in the pressure records to indicate the occurrence of cool-flames.

The procedure was to measure rates at 20° intervals from 300 to 420°, then to return to 310° and again proceed upward (to 430°) by 20° intervals. The second set of measurements are lower

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[6] Pease, *Chem. Rev.*, **21**, 279 (1937).

[7] That is, *not* treated with potassium chloride solution.

than the first but the general form of the curve is evident (Fig. 1.).

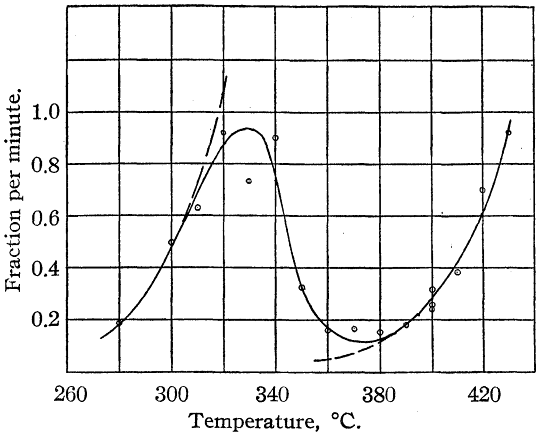

Fig. 1.—Variation of rate of oxidation of propane with temperature for 1:1 mixture at 200 mm. The rates are maximum rates corresponding to the inflection points of the pressure–time curves.

Individual rate curves were of the familiar S-shaped type, with an induction period which decreased regularly with increasing temperature. The values of the rate given are the maximum rates as read from the curves.

This maximum rate rises to an upper level at about 340°, and then drops to a fairly flat minimum. Subsequently, it rises again, and would terminate in true ignition.

Two curves have been sketched in Fig. 1 to emphasize the existence of two mechanisms of oxidation. These curves were drawn on the basis of points read from a log rate–reciprocal temperature plot. The one for lower temperatures corresponds to an activation energy of 29,000 cal.; that for the higher temperature range corresponds to an activation energy of 38,000 cal.

Between these two curves lies the transition region within which the rate passes through a minimum as the temperature increases. If we assume with von Elbe and Lewis[8] that the low-temperature reaction at least is of the branched-chain type, the rather sharp suppression of reaction as temperature rises may be attributed to suppression of branching. The subsequent development of reaction at higher temperatures would then represent the same or a new reaction proceeding by an unbranched chain. In bare outline, one might write

$$\text{Intermediate} \begin{cases} \nearrow \text{Branched chain} \\ \searrow \text{Unbranched chain} \end{cases}$$

the balance between the two alternatives being determined by the temperature, other things being equal. The experimental work here reported appears to be in general accord with the speculations of von Elbe and Lewis.

Summary

A further study of the negative temperature coefficient in the rate of oxidation of propane has been carried out. It is shown that the rate passes through a minimum at 360–380° (100 mm. of each gas). At low temperatures, the steady-state rate is independent of oxygen concentration (uncoated reaction bulb), whereas at higher temperatures it depends upon the concentrations of both gases, the powers being between one and two.

It is suggested that a low-temperature branched-chain reaction is suppressed in the transition region and gives place to an unbranched chain.

PRINCETON, N. J.

RECEIVED MAY 25, 1938

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[8] Von Elbe and Lewis, THIS JOURNAL, **59**, 976 (1937).

The Structure of the Insulin Molecule

BY D. M. WRINCH AND IRVING LANGMUIR

The cyclol hypothesis has yielded a cage structure C_2 for the insulin molecule.[1,2,3] This structure has a skeleton framework lying on the surface of a truncated tetrahedron (hereafter called the C_2 polyhedron) whose faces are parallel to those of a regular octahedron having 6 corners S, as shown in Fig. 1a. The arrangement of the carbon and nitrogen atoms in the skeleton (cyclol fabric) which forms two of the faces of the C_2 polyhedron is shown in Fig. 1b.

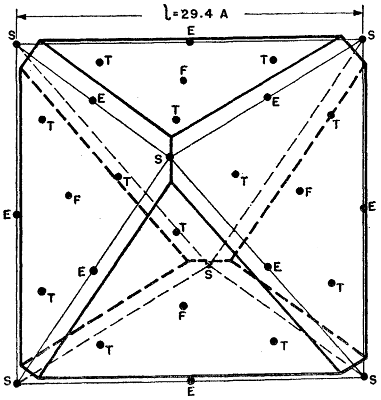

Fig. 1a.—The C_2 truncated tetrahedron (heavy lines) and the C_2 octahedron (light lines), showing on the front half the centers of lacunae at the midpoints of edges E, the centers of faces F and at points T midway between F and S.

The dimensions are determined by a, the only metrical parameter of the cyclol structure, which, being a mean between the C–C and the C–N bond lengths, was taken as $a = 1.50$ Å. The shortest distance between the centers of lacunae in the cyclol fabric is $4\sqrt{2a} = 8.48$ Å.; the length of the sides of the triangular faces of the C_2 polyhedron is $7\sqrt{6a} = 25.7$ Å.; the length of the slits which form the 3 short sides of the hexagonal faces is $\sqrt{6a} = 3.68$ Å., and the distance between the parallel opposite faces of the polyhedron is $16a = 24.0$ Å.

For many calculations we shall find it convenient to replace the C_2 polyhedron by an equivalent regular octahedron which we shall call the C_2 octahedron whose side length is $l = 8\sqrt{6a} = 29.4$ Å. This size is so chosen that the distance between the opposite faces is the same ($16a = 24.0$ Å.) as the corresponding distance in the C_2 polyhedron.

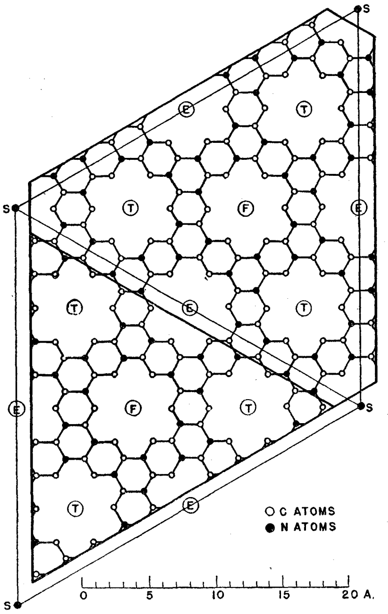

Fig. 1b.—The C, N skeleton of the cyclol fabric on two faces of the C_2 polyhedron, whose boundaries are given by heavy lines. The light lines are the projections of the boundaries of the faces of the C_2 octahedron which, after folding, lie 1 Å. above or below the faces of the C_2 polyhedron.

The faces and corners of the C_2 octahedron are shown in Figs. 1a and 1b. The distance SE between a corner S of a triangular face and E the center of an opposite side of the same triangle is $12\sqrt{2a} = 25.5$ Å., which is three times the shortest distance between lacunae. Thus there are lacunae at E, the midpoints of edges; at F, the centers of faces; and at T, the midpoints between F and S.

The faces of the C_2 polyhedron and the corresponding faces of the C_2 octahedron are parallel and are separated by the distance $(2/3)a = 1.0$ Å.; four of the faces of the polyhedron lie within and the other four lie outside the octahedron. The surface area and volume of the C_2 polyhedron are,

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(1) D. M. Wrinch, *Nature*, **137**, 411 (1936); *Proc. Roy. Soc.* (London), **160A**, 59 (1937).

(2) D. M. Wrinch, *Nature*, **139**, 972 (1937); *Proc. Roy. Soc.* (London), **161A**, 505 (1937).

(3) D. M. Wrinch, *Science*, **85**, 566 (1937); *Trans. Faraday Soc.*, **33**, 1368 (1937).

respectively, $762\sqrt{3}a^2 = 2970$ Å.^{2} and $2003\sqrt{3}a^3 = 11{,}710$ Å.^{3}, which differ very little from the corresponding values for the C_2 octahedron $768\sqrt{3}a^2 = 2993$ Å.^{2} and $2048\sqrt{3}a^3 = 11{,}970$ Å.^{3}, respectively.

The final test for the correctness of a structure of molecules which form a crystal lattice is that it should be in agreement with deductions properly made from X-ray data. It was found[3] that the C_2 molecules, each having a trigonal axis parallel to the trigonal axis of the insulin lattice, fit the rhombohedral cell of the insulin lattice given by an X-ray analysis.[4] They can be arranged with any orientation δ in the corresponding hexagonal cell, and this single parameter was necessarily left undetermined until further information should be obtained from X-ray studies.

The necessary data are now available through Crowfoot's recent measurements[5] of insulin crystals (59 terms). Her data were summarized in five Patterson–Harker diagrams, which are reproduced herewith[6] in Figs. 1c to 5.

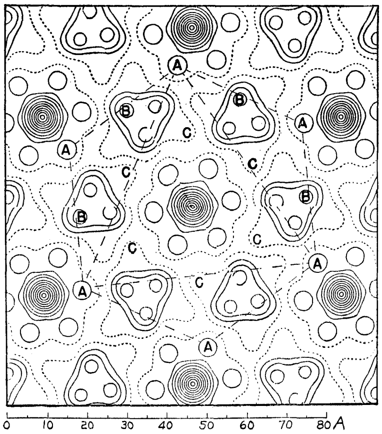

Fig. 1c.—P(xyo) projection of Patterson–Harker map for insulin. Origin in center.

Diagrams of this kind must be sharply distinguished from electron density maps which have played so large a part in establishing the structures of molecules containing relatively few atoms. The Patterson–Harker maps represent not distributions of matter in space but of vectors erected at a common point or origin, each vector giving in magnitude and direction the distance between two atoms in the original stucture. The Patterson–Harker diagrams obtained from the X-ray data are essentially sections or projections of a three-dimensional map showing the distribution of these vectors in space. They constitute an intermediate step between the X-ray photograph and the determination of the molecular structure. Whereas the electron density maps make it possible to confirm a structure directly, the Patterson–Harker diagrams need to be interpreted before they become of use.

In the case of the insulin lattice, Crowfoot has performed the transition from the X-ray pictures to the Patterson–Harker diagrams but has not accomplished their interpretation.

In a recent preliminary investigation,[7] however, it has been found that all the 18 peaks per molecule on Crowfoot's xy-plane projection (A, B, and C in Fig. 1c) lie in the positions to be expected if the insulin molecule is characterized by regions of high electron density at the 6 corners (S) of the C_2 octahedron shown in Fig. 1a.

Thus, taking in turn each of the 6 corners of the C_2 octahedron of side l, and drawing lines to the other 5 corners, we obtain 30 vectors. Erecting these from a common origin, we find that 6 give points at the corners of a similarly oriented octahedron of side $2l = 58.8$ Å. and the other 24 give two points at each of the midpoints of the 12 edges of the same octahedron. These points thus constitute the Patterson–Harker diagram of the S points of the C_2 octahedron.

If we project these 30 points upon a plane parallel to any face of the octahedron (the xy-plane), we find that 6 lie at the corners of a regular hexagon of side length $16\sqrt{2}\,a = 33.9$ Å., 2 at each midpoint of a side (lines connecting *adjacent* corners) and 2 at each midpoint of lines connecting *alternate* corners. A hexagon of this size has been drawn in Fig. 1c having its center at the origin with its axes turned through 6° corresponding to the previously undetermined[3] angle δ. The points, designated A, B, and C by Crowfoot, in Fig. 1c lie in positions which correspond to the projections of the Patterson–Harker diagram of the slits S of the C_2 molecule.

The Patterson–Harker diagram given by points

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(4) D. Crowfoot, *Nature*, **135**, 591 (1935).

(5) D. Crowfoot, *Proc. Roy. Soc.* (London), **164A**, 580 (1938).

(6) The figures given by Crowfoot map the contours within a single rhombohedral cell. Since we wish to consider the molecular rather than the crystal structure, we have fitted together four photographic enlargements of each of Crowfoot's figures and have so obtained maps of the whole neighborhood around the central molecule. The lettering, the scales, and the polygons corresponding to the projections of the Patterson–Harker octahedron, of side $2l$, were drawn in on these composite enlargements and they were rephotographed for the figures of this paper.

(7) D. M. Wrinch, THIS JOURNAL, **60**, 2005 (1938); *Science*, **88**, 148 (1938).

which lie on or within the C_2 octahedron of side l thus consists of points on or within a similarly oriented octahedron (the PH octahedron) of side $2\,l$. In Fig. 2 the cross section of the PH octahedron, through its center and parallel to the xy-plane, has been drawn about the origin. This hexagon is obtained by joining the midpoints of adjacent sides of the hexagon in Fig. 1c. In Figs. 4 and 5 the projections of the edges of the PH octahedron on to the plane of the section are shown, neglecting the effect of the slight rotation of the PH octahedron through $\delta = 6°$.

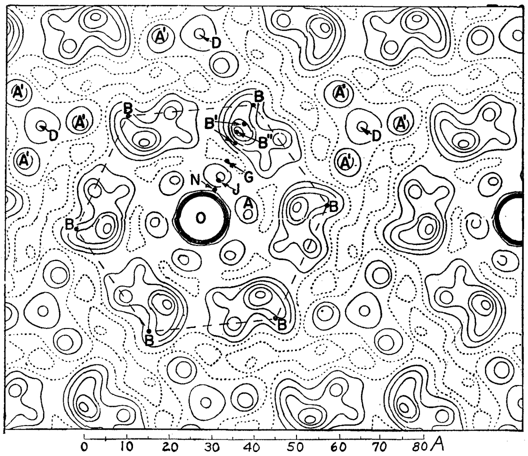

Fig. 2.—P(xyo) section of Patterson–Harker map for insulin.

Crowfoot used rectangular coördinates x, y, z to describe the position of peaks, and we shall describe the sections cut through the Patterson–Harker maps in this way; but, because of the trigonal symmetry of the lattice and molecule, we prefer for other purposes to use polar coördinates z, θ, ρ where θ is $\tan^{-1} y/x$ and ρ is the distance from the z-axis.

We shall use M to designate molecular centers: M_0 for that at the origin, M' for the next one along the z-axis at $z = c = 30.9$ Å., and M_1, M_2, . . . M_6 for the 6 nearest neighbors near the x, y plane in the positions indicated in Fig. 3. Thus M_1 and M_6 are located, respectively, at $z = \pm 10.3$ Å., $\theta = \pm 30°$, $\rho = 43.2$ Å., while the positions of the others are obtained by successive rotations through 120°. The distance M_1 to M_3 is 74.8 Å.

The agreement we have noted between the projection of Fig. 1c and the projection of the PH octahedron suggests that the A, B, and C peaks represent the S points of the C_2 octahedron. However, the points on the PH octahedron are not all in one plane. The A and C points lie at $z = \pm 24$ and the B points at $z = 0$. The calculated coördinates are given in Table II.

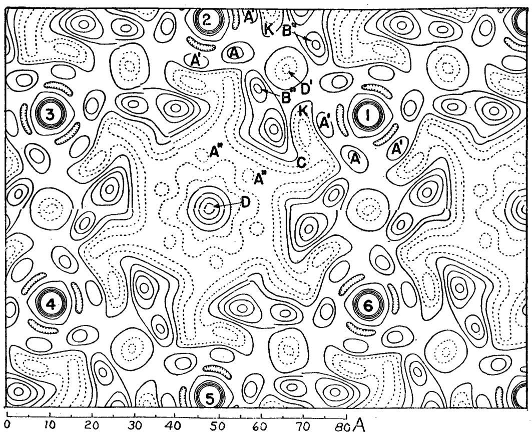

Fig. 3.—P($xy^1/_2c$) section of Patterson–Harker map.

It is thus important to examine the sections of Figs. 2–5 to see if the maxima whose projections give the A, B, and C points in Fig. 1c really lie at the proper values of z.

We are handicapped in this study by the fact that the sections of Figs. 4 and 5 are taken at $\theta = 0$ and 90°, while the maxima are to be expected at 6 and 96°. Figure 2 is a section which, for different molecules, corresponds to values of $z = 0$, and ± 10.3. Similarly, Fig. 3 gives $z = \pm 5.2$, and 15.5. None of these sections comes at $z = 24$, where the A or C peaks lie. However, the section at $z = 25.8$ is close enough to locate the peaks reasonably well.

Referring to Fig. 5, we see in fact that the A peak for M_0 lies close to the upper M_2 molecule at $z = +24$ and at a value of ρ only a few per cent. less than $\rho = 33.9$ which corresponds to the calculated PH octahedron (see Table II).

In Fig. 4 at $z = +3$ Å., $\theta = 0°$, $\rho = 10$ Å., there is a well-defined peak which we identify as the A peak belonging to M_1 (which lies at $z = -20.6$). With respect to M_1 this peak lies at $z = +23.6$. From Figs. 1c and 2 we see that its position with respect to M_1 corresponds to $\theta = 216°$, for which z should be $+24$.

The A peaks appear in their proper positions in Figs. 1c, 2, 3, 4 and 5, and these sections all show that the A peaks are comparatively isolated. Figure 4 shows, however, that in one direction, parallel to the z-axis, the A maximum is connected through a point J to another maximum A′, which, although really a separate peak, contributes to the

A peak seen in the projection of Fig. 1c. We shall discuss the origin of J and A′ later.

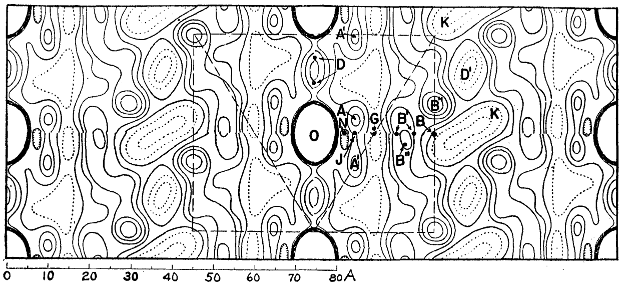

Fig. 4.—P(xoz) section of Patterson–Harker map. $\theta = 0°$.

The data prove that the A peaks lie alternately above and below the x, y plane at distances ± 24 Å., which is the distance between opposite parallel faces of the C_2 octahedron. We note from the section $\theta = 90°$ (Fig. 5) that the *molecule* at the origin must have one of its slits S at $\theta = 96°$, $z = +12$ Å., but there is no slit at -12 Å. for this value of θ. Since there is only one molecule in each rhombohedral cell, we conclude that all the molecules in the crystal lattice given by these diagrams are so oriented that an apex of the triangle forming the upper face of the C_2 octahedron is located at $\theta = 96$ but none at 276°.

The points in the PH octahedron which correspond to the B peaks lie at $z = 0$ on the corners of the hexagon shown in Fig. 2. There is, in fact, a prominent extension of the contours toward this point B, but the presence of other maxima B′ and B″ prevents us from estimating the exact contribution of B. We shall discuss the factors that cause these complications in this region.

The calculated coördinates for the C points in Table II give values of θ which are the same as for A, but the values of ρ are half as great, and z is of opposite sign although it has the same magnitude (24 Å.). Examination of Fig. 5 shows a maximum at $z = -27$, $\theta = 90°$, $\rho = 20$, not far from the calculated position of C at $z = -24$, $\theta = 96°$, $\rho = 17$. The agreement might be much better if the section had been taken at $\theta = 96°$.

Although the A, B, and C peaks in all the sections agree satisfactorily with the positions calculated from the slits of the C_2 octahedron, it will be recognized that the 6 slits provide a very incomplete description of the C_2 structure. It is reasonable to hope that the 62 additional maxima and minima per molecule listed in Table II, which are seen only in the sections of Figs. 2–5, correspond to other characteristic features of the C_2 molecule, such as the polyhedral nature of the skeleton. We may also expect to detect effects due to the 44 hexagonal lacunae in the positions shown in Figs. 1a and 1b by F, T, and E.

Density Deviations in Insulin.—Each molecule in the insulin crystal contains several thousand atoms of an average atomic weight of about 7. The heaviest atoms are 3 zinc atoms per molecule, and there are about 36 sulfur atoms. With the exception of these heavy atoms and a few groups of atoms having slightly higher or lower density than the average, we may look upon the volume distribution of electrons as being substantially uniform or at least as varying continuously in such a way as to show no fine structure. A slowly varying electron distribution would contribute to the general scattered X-ray radiation, but its effects would be eliminated automatically when the Patterson–Harker analysis is made by taking only photographic lines whose intensity is estimated visually. The finer structure given by the lines, which is the basis of the Patterson–Harker diagrams, can thus be regarded as representing positive and negative deviations from this assumed smooth volume distribution of electrons.

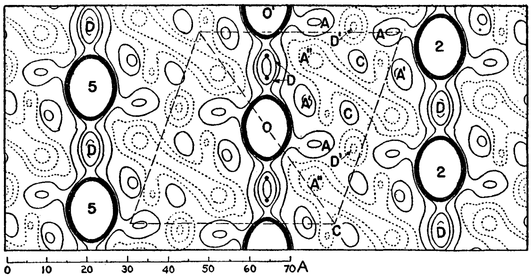

Fig. 5.—P(oyz) section of Patterson–Harker map. $\theta = 90°$.

In the protein molecule we may roughly assume 0.50 electron per unit of molecular weight, whereas in a water molecule we have 0.56 electron per unit. Considering that the density of the insulin crystal as a whole is about 1.32 and that of water is 1.0, it appears that water has an electron density about 16% lower than that of the average of the protein molecule. Thus low density may be expected in regions where the water content is high or where there are actual voids. Similarly, side chains comprising aliphatic or aromatic hydrocarbons would also correspond to minima, while the groups containing many oxygen or

TABLE I

DENSITY DEVIATIONS IN THE INSULIN LATTICE

Symbol	Description (L = lacunae)	No. per molecule	Coördinates Z, Å.	θ deg.	ρ Å.	Symmetry	Density	Relative magnitude (approx).
O	Center	1	0		0	...	$-o$	-4
S	Slit (corner)	6	± 12	6 ∓ 30	17.0	3	$+s$	$+5$
E	L in edge	12	± 12	6 ± 30	8.5	3	$-e$	-1
			0	6	14.7	6		
F	L in face center	8	± 12	...	0	...	$-f$	-3
			± 4	6 ± 30	11.3	3		
T	Other L in faces	24	± 12	6 ∓ 30	8.5	3	$-t$	-1
			± 8	(6 ∓ 6) and (6 ± 66)	12.3	3		
			± 4	6 ∓ 30	14.1	3		
Z	Zinc complex	6/2	± 5	± 30	21.6	3	$+z$	$+4$
U	Group near Z	3 or 6	± 5	40 ∓ 30	17	3	$+u$	$+3$
V	Group near Z	3 or 6	± 3	38 ± 30	22	3	$-v$	-5
Q	Midpoints between L	144	..	...	...	...	$+q$	$+0.1$

especially sulfur atoms correspond to maxima.

In Table I we have listed the points associated with the C_2 molecule where density deviations are to be expected. Thus, the center O of the molecule is probably a region of negative density deviation $-o$, since the side chains within the cage are not long enough to reach the center, a distance of 12 Å. from the surface of the C_2 octahedron. To the slits S we assign an intensity $+s$, since even apart from side chains the atoms forming the skeleton are crowded at these points. To the lacunae F, T, and E, presumably regions of negative deviations, intensities $-f$, $-t$, and $-e$ are assigned. Furthermore, we note from symmetry considerations, and for reasons already given,[3] that the zinc atoms are located near the midpoints along lines connecting the centers of adjacent molecules (except along the z-axis). These zinc atoms and the polar oxygen or sulfur atoms probably associated with them we designate by Z (intensity $+z$). We shall find later that there are two regions U and V having deviations $+u$ and $-v$, respectively, probably associated with side chains contributed by neighboring molecules which bind the zinc.

If the lacunae are regions of low density, the spaces between them must be of comparatively higher density. We therefore may consider that the midpoints Q between the centers of lacunae are regions having a positive density deviation $+q$.

The foregoing assumptions regarding density distribution are designed as a description of the characteristic features of the C_2 structure. The effects of individual side chains (except U and V) have been neglected. The C_2 structure is not actually an octahedron and has at least 2 kinds of trigonal faces (Fig. 1a). The trigonal symmetry characteristic of insulin could be preserved even if the C_2 molecule had faces of four kinds,[3] *i. e.*, with 4 different distributions of side chains. It may be hoped that the effects of these features may also ultimately be taken into account in analyzing the X-ray data.

Construction of Patterson–Harker Diagrams.—To consider the Patterson–Harker diagrams given by any distribution of atoms in space, we take first two points a and b of intensities α and β, respectively. The diagram associated with these two points comprises the vectors of a on a, of b on b, of a on b, and of b on a. Each has associated with it the product of the intensities of its two constituents. We therefore write

$$V([\alpha a + \beta b]^2) = \alpha^2 V(a^2) + \beta^2 V(b^2) + \alpha\beta V(ab) + \alpha\beta V(ba)$$

The terms $V(a^2)$ and $V(b^2)$ correspond to locations at the origin. It will be noticed that the cross terms $V(ab)$ and $V(ba)$ will be positive if α and β have the same sign, negative if they have different signs. Thus a positive cross term will result both when two points of positive intensity are concerned and when two points of negative intensity are concerned. On the other hand, the cross terms will be negative only when a point with positive intensity is associated with a point of negative intensity. These are located at positions ab and ba with respect to the origin.

The A, B, and C peaks that we have previously considered have the intensities s^2, $2s^2 - e^2$, and $2s^2 - e$ as given in Table II. It hardly seems possible at present to compare the relative intensities of the A, B, and C peaks to get the actual ratio in the coefficients.

Let us now consider the peak A′. This point

TABLE II

MAXIMA AND MINIMA IN THE PATTERSON–HARKER MAPS FOR INSULIN

The coördinates give the positions with reference to the center of the molecule to which they are associated.

Symbol	Character[a]	Vector	Symmetry	Coördinates			Intensities
				z, Å.	θ, deg.	ρ, Å.	
A	Max. I	OA	3	± 24	6 ∓ 30	33.9	$+s^2$
A′	Max. I	$^1/_3$ OA	3	± 8	6 ∓ 30	11.3	$+4f^2$
A″	Min. I	$^1/_2$ OC	3	± 12	6 ± 30	8.4	$-4es + 4e^2 + 4t^2 + 2eo$
B	Max. II	OB	6	0	6	29.4	$+2s^2 + e^2$
B′	Max. III	$^2/_3$ OB	6	0	6	19.6	$+2f^2$
	Max. III	$^5/_6$ OB	6	0	6	24.5	$+4t^2$
B″	Max. I	....	3 or 6	± 3	ca 38 ± 30	ca 22	$+2ov$
C	Max. II	OC	3	± 24	6 ± 30	17.0	$+2s^2 + e^2$
D	Max. I	$^1/_2$ OM′	...	± 12	...	0	$+fo$
D′	Min. I	$^1/_2$ OM	3	± 5	± 30	21.6	$-2oz$
G	Min. I	$^1/_2$ OB	6	0	6	14.7	$-4es + 4e^2 + 4t^2 + 2eo$
J	Max. II	$^1/_3$ OB	6	0	6	9.8	$+2t^2$
K	Min. II	....	3	± 5	ca 40 ∓ 30	ca 17.	$-2ou$
N	Min. I	$^1/_4$ OB	6	0	6	7.4	$-32lq$

[a] In the second column of Table II, maxima or minima shown in the diagrams are classed as follows: I, well-defined isolated maxima or minima; II, maxima or minima whose effects are observable although partly masked by neighboring maxima or minima; and III maxima or minima which contribute to but are individually masked by neighboring terms.

(Fig. 5) lies close to the z-plane about one-third of the way from the origin to A (vector $^1/_3$ OA). We note that in the C_2 octahedron of Fig. 1a the lines connecting F points in adjacent faces lie parallel to the lines S–S between opposite corners and are of one-third the length of S–S. There are four such vectors, corresponding to each of the diagonals between opposite points, so that the intensity of A′ corresponds to $4f^2$. This is necessarily positive and produces a maximum. The point A′ in Fig. 5 at $z = +8$, $\rho = 11.3$ Å. is, in fact, a maximum and happens to come almost directly above one of the A points, at $z = -4$, although it is unrelated since A′ belongs to M_0, while A belongs to M_2.

At point D′ there is a well-defined and very symmetrical minimum, shown in Figs. 3, 4, and 5. Since it lies at the midpoint along the line connecting adjacent molecules, it must receive equal contributions from these. This appears to result from the interaction between O and Z, giving a minimum of intensity $-2oz$ at D′. Since the two molecular faces adjacent to the zinc are not of identical structure, it is possible that the zinc atom is not exactly at the midpoint between the two molecules. However, the contours around the point D′ (Fig. 5) are not elongated along the line connecting the atoms, so that the zinc atom is probably not far from this midpoint. The observed spheroidal nature of the D′ minimum may be an effect of neighboring A maxima.

The maximum D seen in Figs. 3, 4, and 5 lies approximately halfway between centers of adjacent molecules along the z axis from which it must receive equal contributions. The interaction between O and F lacunae in the upper and lower faces gives a maximum of intensity $+fo$ at $z = \pm 12$ Å. Thus we recognize that the maximum D represents the overlapping of two peaks at $z = \pm 12$ Å., the elongation in the vertical direction being due to the composite nature of this maximum. The size of the maximum gives a rough estimate of the maximum dimensions of the low density region O. The D′ minimum is of about the same size as the D minimum, both being dependent on the dimensions of O.

The well-defined minimum at A″ (Figs. 3 and 5) corresponds to the vector $^1/_2$ OC, and appears to be due principally to the interaction of E and S points along the edges between adjacent lateral faces of the C_2 octahedron. This gives an intensity $-4es$. However, we find that there are other terms which contributed to the intensity at this point: four vectors EE, four TT, and two DE, so that the total intensity is $-4es + 4e^2 + 4t^2 + 2eo$. The fact that we have here a minimum indicates that the $4es$ term must predominate.

This, and similar observations, enable us to make the rough estimates of the relative intensities of the various points given in the last column of Table I which seem consistent with all the observed maxima and minima of Table II. Accurate values of these intensities must probably await knowledge of the distribution of the side chains on the surface of the C_2 molecule.

The minimum G in Figs. 2 and 4 corresponds to the vector $^1/_2$ OB and contains exactly the same terms as the A″ minimum and should thus have the same relative intensity.

Figs. 1c, 2, 3, and 4 show high vector concentrations in 6 regions symmetrically arranged about the z-axis. This "B complex" lies between $\rho = 19$ and $\rho = 31$ Å., covers the range of angles θ from $-20°$ to $+20°$, and extends over all values of z. Figure 5, which corresponds to $\theta = 30°$, $90°$, etc., shows that in these planes the B complex is wholly absent. We recognize several definite maxima within the B complex. The principal one, B″, seen best in Fig. 4, appears to be due to the interaction of the low density regions O and V. Since O is at the origin, the OV term is located at V (see Tables I and II). The very strong maximum B″ at $z = +7$, $\theta = 0°$, $\rho = 29$ belongs to M_1, which lies at $z = 10.3$ Å. Another of the B″ points, the one belonging to M_0, thus lies at $z = -3$ Å., $\theta = 8°$, and $\rho = 22$ Å. The point marked B″ in approximately this position in Fig. 4 is really 3 Å. in front of the true B″ maximum, and this fact accounts for its lower intensity as compared to the B″ point located at $z = +7$, $\rho = 29$.

This maximum corresponds to a strong negative density deviation near the zinc atom Z. Perhaps it is associated with the phenyl group of one or two tyrosine side chains which bind the zinc atom.

In Table II we have listed two other maxima (B′) which correspond to the vectors $^2/_3$ OB and $^5/_6$ OB and result from FF and TT terms. They contribute to the B complex at $z = 0$ and ± 10.3.

The rest of the B complex, extending as it does over all values of z, is most readily interpreted as due to the interactions of T lacunae with other rather distant T, F, or E lacunae. With a total of 44 E, F, and T lacunae, there would be over 1900 vectors connecting them. We have attempted in Table II to consider particularly the single terms which are of greatest intensity because they contain the more important factors S, F, O, or U or because they involve a large number of contributing vectors as a result of symmetry. The terms of most significance have been those between extreme points in the molecules, such as the S points, for the Patterson–Harker map of these points has a simple structure with widely separated points.

We have naturally not attempted to analyze in detail all the terms involving T, E, and F. It does appear, however, from numerous trials that a particularly large fraction of the vectors which involve the more distant lacunae give terms that lie within the B complex, well distributed over various values of z. The terms are individually of small intensity but add up to substantial values because of their large number.[8]

We have now considered in Table II 80 well-defined points shown in the Crowfoot diagrams. These include nearly all points which might be expected to have high intensities. The total number of points per molecule for which we have assumed characteristic density deviations (neglecting the Q points), as shown in Table I, is 60 to 66 which corresponds to a total of about 3600 vectors. Many of these, however, coincide. We have not attempted to consider all the maxima and minima which would result from these vectors. We have considered a large number not given in Table II and in no case have we found that they conflict seriously with the Crowfoot diagrams. Some of the points come in positions where they are masked by neighboring maxima or minima, but many fall in positions where their effect is to modify the contour lines in a manner which improves the agreement with the Crowfoot diagrams.

It should be noted that the sections of the Patterson–Harker diagrams given by Crowfoot are chosen with reference to axes of the crystal lattice. The x, y projection and the sections in this plane show that the trigonal axis of crystal and molecule coincide, but that the hexagonal axes of the molecule do not coincide with those of the crystal but are turned through an angle about the z-axis of $\delta = +6°$.

The Patterson–Harker sections chosen with reference to the crystal lattice are, of course, useful in determining the symmetry of the crystal as a whole. For example, Crowfoot showed that the insulin crystal has symmetry corresponding to the R3 space group. She was not able, however, to determine the symmetry or orientation of the molecule itself.

These sections through the crystal lattice are also useful in determining the positions and the

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[8] (Note added by I. Langmuir, August 14, 1938.) An alternative and perhaps preferable although nearly equivalent interpretation of the B complex is to regard it as being the result of the interaction of the slits S with a uniform positive density deviation over the faces of the C_2 octahedron. This gives a PH distribution very closely like that of the B complex. Upon this uniform positive surface distribution over the faces there is then to be superposed the negative deviations corresponding to the lacunae which have already been considered. This suggests that in Table I q should be taken larger than 0.1 so as to give a positive value for the average density deviation over the whole surface.

structure in the neighborhood of all atoms which lie midway between the adjacent molecules in the crystal. Thus Figs. 3, 4, and 5 give various sections through the maximum at D which is due to the overlapping of the EO vectors contributed by neighboring molecules along the z-axis. Furthermore, the maximum D′ is located approximately midway between other pairs of adjacent molecules and so furnishes direct information regarding the location of the zinc atoms and the groups which bind them to adjacent molecules. In other words, the crystal lattice sections give the location of the molecules and intermolecular structure.

To determine the intramolecular structure, however, sections should be chosen with reference to the axes of the C_2 octahedra. The projection of the x, y plane, in Fig. 1c, gives directly the value of δ. If sections parallel to the z-axis had then been taken at $\theta = 6°, 21°, 36°$, etc., simply related to the axes of the C_2 octahedron, the diagrams would have shown the intramolecular structure in far greater detail. For this purpose it would also be desirable to have x, y sections at the height $z = h = +24$ Å. and at halves, thirds, and sixths of this distance. To obtain these sections needed to bring out the molecular structure, it will not be necessary to obtain new X-ray data. These Patterson–Harker sections can be calculated directly from Crowfoot's data on the intensities of the X-ray reflections.

It has been shown[3] that the distance between faces of adjacent C_2 structures (not along the c-axis) varies from 7 to 13 Å. as δ varies. Since the zinc atoms and their attached groups lie between these faces, it appears that the angle δ is determined by the zinc atom. If we should substitute cadmium or if possible mercury for the zinc, we should expect to obtain different values of δ. This would change in marked degree the Patterson–Harker sections chosen with reference to the crystal lattice but would leave unchanged many of the intramolecular features characteristic of the sections which have been chosen with reference to the molecular orientation.

Attention should be called to the particular features of the Patterson–Harker diagrams near D′, the midpoint between neighboring molecules. The cross terms between the zinc atom and all the other points in the C_2 molecules reproduce about D′ as a center, an image of the whole of the C_2 structure of unaltered size and of intensity proportional to z. The minimum at D′ is merely the image of the hollow at the center of the C_2 molecule transposed to the point D′. If we could substitute a much heavier atom than zinc and so increase the factor z, this image should become more distinct and show more clearly all the features of the molecular structure.

We have examined the diagrams in the neighborhood of D′ to see if the 6 S points in this transposed image of the C_2 molecule are observable as maxima of intensity $+ sz$ in planes given by $z = \pm 5 \pm 12$ Å. We find that points in 3 locations are obtained: 2 of these fall at the edges of the B complex at $z = \pm 7$ and are masked by it. The third set of maxima lie with hexagonal symmetry at $\theta = 10°$ and $\rho = 5$ Å. and so appear to account exactly for the hexagonal form of the outermost of the closed curves that surround the molecular centers in Fig. 1c.

Just as we have seen that a high density point half way between molecular centers gives about that point an undistorted image of the whole molecule, so we must conclude that the vectors between a low density point O at the center of each molecule and all the other points in the molecule will produce another undistorted molecular image about O as a center but of intensity proportional to $-o$. The central part is, of course, lost because of the high central density, but the terms of intensity $-os$ resulting from the interaction of O and S should be present as minima in the diagrams. These 6 points occur at $^1/_2$ OA and in Fig. 5 all lie in the deep trough connecting the A″ points. The OE interactions we have already taken into account in points A″ and G.

The molecular image produced by the zinc around D′ could be greatly enhanced if a very heavy atom such as mercury could replace the zinc. It is conceivable that in this way simple structural analyses may be made of very complicated molecules.

The foregoing analysis shows that all the prominent features of the Crowfoot diagram are deducible from the C_2 structure whose octahedron has a side 29.4 Å. if $a = 1.50$ Å. During the development of this analysis we repeatedly found that as we introduced one by one the more delicate features of the C_2 molecule the more perfect became the concordance between the Patterson–Harker diagrams and the Crowfoot pictures. We feel therefore that these X-ray data, in giving so perfect a picture of the C_2 structure, provide the experimental basis for the cyclol theory.

Summary

Crowfoot's data on X-ray reflections from insulin crystals, as summarized in a set of Patterson–Harker vector maps, are found to correspond in great detail to the C_2 polyhedral structure predicted for the insulin molecule on the basis of the cyclol theory. The features of the insulin molecule confirmed by the X-ray data include: (1) six high density points at the corners of an octahedron of side 29.4 Å., which is the size given by the cyclol theory; (2) low density regions near the centers of the 44 lacunae in the cyclol fabric that are located in definite positions in the edges and faces of the polyhedron; (3) a comparative hollow at the molecular center, *i. e*, a cage structure; (4) three zinc atoms per molecule on lines connecting molecular centers (except along the *z*-axis) and low and high density groups attached to these zinc atoms outside the C_2 structure.

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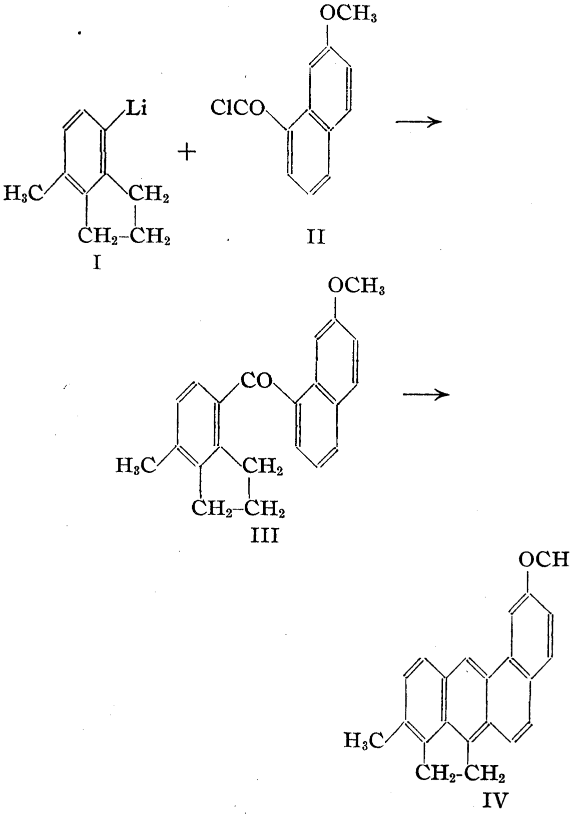
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Synthesis of 2- and 6-Substituted Derivatives of 20-Methylcholanthrene[1]

BY LOUIS F. FIESER AND VICTOR DESREUX[2]

Derivatives of carcinogenic hydrocarbons having active functional groups are of interest to the general problem of attempting to correlate structure and biological activity, and if, among such compounds, derivatives can be found which possess marked carcinogenic activity they may be of value in providing a route to the preparation of interesting glycosides or conjugated proteins.

The only functional derivatives of methylcholanthrene previously known are 3-hydroxy-20-methylcholanthrene,[3,4] and its ether and acetate, 3-chloro-,[4] and 3-cyano-20-methylcholanthrene.[4] These were all made available by application of the Fieser–Seligman methylcholanthrene synthesis[5] to suitable methoxy- and chloro-substituted ketones, and the successful outcome of the syntheses shows that these substituent groups are capable of withstanding the pyrolytic conditions of the Elbs reaction when located in a position corresponding to the 3-position of methylcholanthrene. This is a β-position and is located in the terminal angular nucleus at a point rather remote from the site of ring closure, and it seemed likely that the other β-position 2 in this ring also would offer an environment favorable for the retention of an active functional group. Consequently, as a next step in the search for compounds of the type desired we synthesized the ketone III and investigated its behavior on pyrolysis. For the preparation of the ketone the lithium derivative



I from 4-methyl-7-chlorohydrindene[5,6] was condensed with the chloride of 7-methoxy-1-naph-

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[1] This investigation was conducted as part of a program of research receiving support from the National Cancer Institute.

[2] Fellow of the Belgian American Foundation; Aspirant du Fonds National de la Recherche Scientifique Belgique.

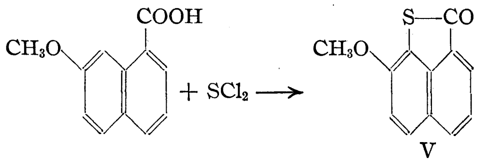
[3] Cook and de Worms, *J. Chem. Soc.*, 1825 (1937).

[4] Fieser and Riegel, THIS JOURNAL, **59**, 2561 (1937).

[5] (a) Fieser and Seligman. *ibid.*, **57**, 942 (1935); (b) **58**, 2482 (1936).

[6] If the condensation of such a lithium derivative with a suitable nitrile constitutes a "modification of the original method of Fieser and Seligman," as stated by Cook and de Worms,[3] it may be noted that the modification was introduced not by these workers but by Fieser and Hershberg, *ibid.*, **59**, 394 (1937).

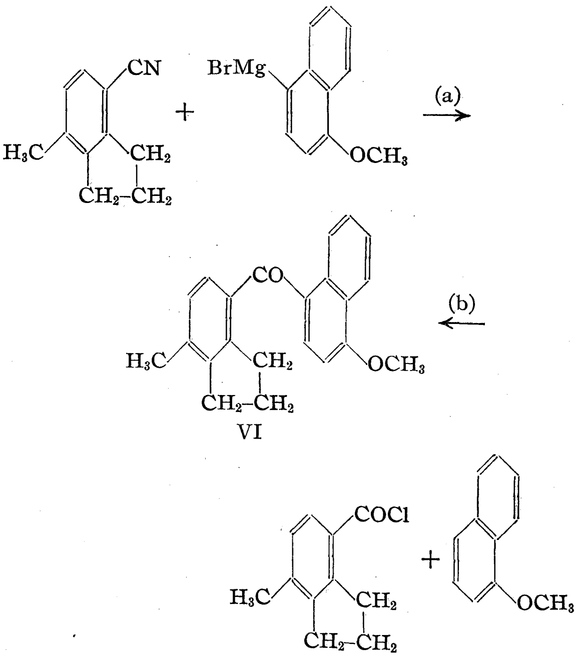
thoic acid, prepared by the synthesis described by Fieser and Holmes.[7] The 7-methoxy-1-naphthoyl chloride was prepared satisfactorily with the use of phosphorus pentachloride, but an unexpected difficulty was encountered on employing a commercial lot of thionyl chloride which, being colorless, had not been further purified. The acid chloride in this case was contaminated with a persistent yellow impurity, and when this was isolated it was found to contain sulfur and to have the properties of a lactone (insoluble in cold alkali, slowly dissolved by alcoholic alkali). From the analyses and properties it is probable that the yellow substance has the structure V and that it arises from the condensation of sulfur dichloride, present in the commercial thionyl chloride, into the activated 8(α)-position of the acid or acid chloride, with subsequent ring closure.



V

The pyrolysis of the ketone III proceeded satisfactorily and pure 2-methoxy-02-methylcholanthrene (IV) was obtained in 40% yield, which is practically the same as that obtained in this Laboratory[4] in the preparation of the isomeric 3-methoxy compound. The hydrolysis, however, presented special difficulties, for the 2-ether is unusually resistant to acid cleavage and the free hydroxy compound is very sensitive and decomposes extensively under the influence of acids or bases, or when heated in the presence of oxygen. The hydrolysis consequently could not be carried to completion without destruction of all of the product formed and it was necessary to work with mixtures. It was found, however, that after acetylation of the crude mixture the more stable acetate can be separated from the ether and purified satisfactorily, and careful saponification of the pure acetate afforded the hydroxy compound in such a condition that it could be purified.

The synthesis of the 2- and 3-methoxy compounds having been accomplished successfully by the Elbs reaction, we investigated the possibility of preparing 6-methoxy-20-methylcholanthrene by the pyrolysis of the ketone VI. As indicated in the formulas, this was synthesized by two different methods, the first of which fully establishes the structure of the ketone. The 4-bromo-1-naphthol required for this synthesis (a) was prepared by the bromination of α-naphthol with iodine bromide according to Militzer,[8] but the purification was very tedious and the yield of satisfactory material was only 23%. The Friedel and Crafts synthesis (b) was therefore investigated and found to give the identical ketone in excellent yield. The 4-methylhydrindene-7-carboxylic acid required was prepared conveniently by heating the corresponding 7-chloro compound with cuprous cyanide, pyridine, and water at 210°; this gave some acid and some amide, and the latter was easily converted into acid by alkaline hydrolysis.



Since the methoxyl group of the ketone VI is in an α-position of a ring involved in the cyclization, there is more opportunity here than with the previously investigated compounds for disturbance of the substituent in the course of the Elbs reaction conducted at a temperature above 400°. Such disturbance evidently occurred, for in several experiments the only product that could be isolated was methylcholanthrene, and when the total crude product was submitted to acid hydrolysis no trace of a phenolic substance was obtained. We are not prepared to say that conditions cannot be found permitting retention of the methoxyl group, but record merely that under the conditions found most satisfactory for the pyroly-

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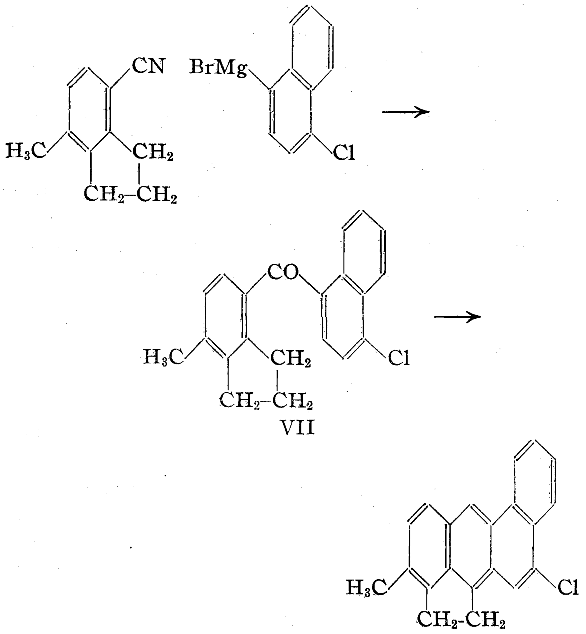
[7] Fieser and Holmes, THIS JOURNAL, **58**, 2319 (1936).

[8] Militzer, *ibid.*, **60**, 256 (1938).

sis of related ketones the methoxy group in this position is easily eliminated.

It was of interest to learn whether a chlorine atom in the same position would suffer a similar fate, and for this purpose we required 5-methyl-7-(4′-chloro-1′-naphthoyl)-hydrindene (VII). The synthesis was accomplished by the Grignard reaction indicated in the chart, the 1-bromo-4-chloronaphthalene being prepared conveniently in a very pure form from the known[9] acetyl-4-bromo-1-naphthylamine.

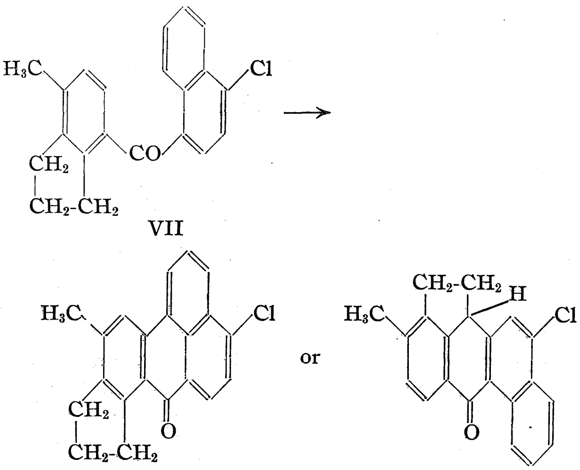


VII

VIII

The direct bromination of α-chloronaphthalene was also tried but gave a mixture from which the desired isomer was isolated in only very poor yield. When the chloro ketone VII is heated no change occurs until a critical temperature of about 410° is reached and at that point a vigorous reaction sets in with loss of water and evolution of hydrogen chloride. The reaction is exothermic, and if the external temperature is not decreased the product is largely destroyed. By quickly lowering the bath temperature as soon as the reaction had started, it was possible to conduct the pyrolysis with sufficient success to permit the isolation of 6-chloro-20-methylcholanthrene (VIII) in a pure condition, if in only 1.2% yield. The reaction mixture contained in addition a considerable quantity of methylcholanthrene, but the sparing solubility of the chloro compound made possible its isolation in a condition believed to be free from contamination with the carcinogenic hydrocarbon. The chloro compound is rather sensitive and decomposes when heated at the melting point in the presence of air, but it is nevertheless transformed very smoothly into the nitrile when heated with cuprous cyanide in pyridine. The nitrile is very resistant to hydrolysis, and in a few trial experiments we did not succeed in preparing the corresponding acid. 6-Chloro- and 6-cyano-10-methylcholanthrene are of particular interest because the position of substitution corresponds to that of 3-substituted 1,2-benzanthracenes, some of which have been found to possess carcinogenic activity.[10]

An interesting observation was made in the course of a preliminary attempt to prepare the chloro ketone VII by the Friedel and Crafts reaction between 4-methylhydrindene-7-carboxylic acid chloride and α-chloronaphthalene. Little reaction took place at −10°, but at room temperature in tetrachloroethane solution there was produced a yellow substance having two hydrogen atoms less than the expected ketone VII. After the latter compound had been made available by the Grignard synthesis it was found that the same yellow condensation product can be obtained by the action of aluminum chloride on the ketone in tetrachloroethane solution at 25°. From the composition of the condensation product and the structure of the intermediate from which it can be obtained, it would seem that the substance is probably either a benzanthrone derivative IX or the cholanthrone X.



VII

IX

X

While conclusive evidence of the structure cannot

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[9] Meldola, *Ber.*, **11**, 1904 (1878).

[10] Fieser, Hershberg, Long, Jr., and Newman, This Journal, **59**, 475 (1937).

be given, the following observations appear to be significant. If the substance were a cholanthrone, it would be expected to yield a cholanthranol acetate on treatment with acetic anhydride in pyridine, but the yellow compound failed to react under these conditions and was recovered unchanged. The alternate structure IX, on the other hand, is consistent with the behavior of the substance in a qualitative test with zinc dust, sodium acetate and acetic anhydride. It has been observed recently in this Laboratory that benzanthrones can be converted by this method of reductive acetylation into easily hydrolyzed dihydrobenzanthrone-enol acetates,[11] and the compound in question gave evidence of reacting in this manner, although the product proved to be quite unstable and was not isolated in a pure condition. The structure therefore is probably that of formula IX, and the observations suggest that the α-benzoylnaphthalene derivative VII undergoes the Scholl peri-condensation under the influence of aluminum chloride in tetrachloroethane solution at a temperature lower than is required to produce benzanthrones by the usual process using aluminum chloride alone or sodium aluminum chloride.

In connection with the attempt to synthesize the ketone VII by the Friedel and Crafts reaction, we investigated the action of aluminum chloride on α-chloronaphthalene in tetrachloroethane at room temperature and found that a part of the material was isomerized to β-chloronaphthalene. This isomerization was observed some time ago by Roux,[12] but at a considerably higher temperature. There was also a higher boiling fraction probably similar to that obtained by Weitzenböck and Seer[13] at a higher temperature and found to contain perylene and dinaphthyl derivatives.

Experimental Part[14]

2-Hydroxymethylcholanthrene

Preparation of Starting Materials.—In the preparation of **β-(4-methoxybenzoyl)-propionic acid** by the procedure of Fieser and Hershberg[15] it was found unnecessary to keep the mixture at 0–5° after adding the aluminum chloride; we allowed the mixture to stand at room temperature for three days and obtained purified acid, m. p. 146.5–147°, in 90% yield. Reduction (Martin[16]) gave **γ-(4-methoxyphenyl)-butyric acid,** m. p. 60.5°, in 90% yield, and the ethyl ester (96% yield) boiled at 176.5–177° (15 mm.). **α-Keto-δ-(4-methoxyphenyl)-valeric acid** was prepared by condensing the ester and ethyl oxalate with the use of sodium ethylate following the procedure of Fieser and Holmes,[7] but our observations indicated that the time specified for the condensation is insufficient for complete conversion. Probably a longer period should be allowed also for effecting decarboxylation. The following method of purification gave a better product than that previously described and made possible the recovery of starting material. After decarboxylation, the crude keto acid was treated with dimethyl sulfate in warm alkali and after clarifying the solution with Norite the sodium salt of the keto acid was allowed to crystallize. After this purification through the crystalline salt, the liberated acid was obtained directly in a very pure condition and melted sharply at 76–77°. The material failing to crystallize as the sodium salt was refluxed again with 15% sulfuric acid (five hours) and put through the above process, but as the product seemed to be a mixture it was esterified and distilled. The main fraction (b. p. about 160° at 2 mm.) after saponification was found to consist chiefly of γ-(4-methoxyphenyl)-butyric acid, while the fraction boiling at 190–200° (2 mm.) was a mixture of the ester of this acid and the keto ester. A separation was accomplished easily by taking advantage of the greater ease of saponification of the keto ester, and by purifying the keto acid as sodium salt. In all 444 g. of ethyl γ-(4-methoxyphenyl)-butyrate gave 223 g. (50%) of very pure keto acid and 110 g. (25%) of recovered starting material.

7-Methoxy-Δ'-dihydro-1-naphthoic acid was prepared as described[7] except that the acid was used for cyclization rather than the ester. The crude material was remethylated in alkali and the solution was clarified and acidified. Acetone proved unsatisfactory as a solvent for crystallization and this was done from water, giving pure acid, m. p. 117.5°, in 65% yield. **7-Methoxy-1-naphthoic acid** was prepared as described[7] and purified by remethylation of the sodium salt; m. p. 169–170°, yield 87%.

In preparing **4-methyl-7-chlorohydrindene**[5b] it was found convenient, after cyclizing the β-chloropropionyl derivatives, to take up the ketone mixture in benzene and wash the solution with saturated sodium chloride solution at 50–60°. Decantation was then easily accomplished and after removing the solvent the product was distilled quickly; yield 60%. No other changes were made in the procedure and the yields agreed closely with those reported.

Action of Thionyl Chloride on 7-Methoxy-1-naphthoic Acid.—The acid was treated with 3–4 equivalents of commercial thionyl chloride (Fraenkel and Landau, colorless), and after it had dissolved the solution was warmed for about one-half hour longer. The excess reagent was removed in vacuum and the product was distilled at 2 mm. (liberation of hydrogen chloride noted). The distillate was a yellow, unhomogeneous solid, m. p. 75–85°, and as trial crystallizations were not promising the material was saponified with a hot sodium hydroxide–acetone mixture. Distillation of the acidic material gave a yellow solid, m. p. 158–168°, and on crystallization from dilute acetone this yielded a product melting at 167° and giving no de-

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(11) Fieser and Hershberg, unpublished observation.

(12) Roux, *Ann. chim.*, [6], **12**, 349 (1887).

(13) Weitzenböck and Seer, *Ber.*, **46**, 1994 (1913).

(14) All melting points are corrected. Analyses by Mrs. Verna R. Keevil, Dr. C. Fitz and the Arlington Laboratories.

(15) Fieser and Hershberg, THIS JOURNAL, **58**, 2314 (1936).

(16) Martin, *ibid.*, **58**, 1438 (1936).

pression when mixed with methoxynaphthoic acid. The material was still yellow, however, and it was noted that it dissolved with difficulty in alkali, and only on warming, and that it contained sulfur. Six crystallizations from benzene served to remove the impurity and gave pure white methoxynaphthoic acid, m. p. 170° (neut. equiv. 200; calcd. 202). The yellow benzene mother liquors were extracted three times with 10% alkali to remove the remaining acid, and on concentrating the benzene solution the by-product was obtained in a nicely crystalline condition. Purified further for analysis, the **sulfur compound (V?)** formed bright yellow needles melting constantly at 143.5–144°. The substance is attacked only very slowly by boiling aqueous alkali; it dissolves in hot alcoholic alkali with almost complete loss of color and precipitates in the original condition on acidification of the diluted solution.

Anal. Calcd. for $C_{12}H_8O_2S$: C, 66.63; H, 3.73; S, 14.83; mol. wt., 216. Found: C, 66.87; H, 3.82; S, 14.76; mol. wt. (micro Rast), 221, 231.

7-Methoxy-1-naphthoyl Chloride.—A mixture of 10 g. of the acid and 12 g. of phosphorus pentachloride was warmed at 50° until solution was complete and the phosphorus oxychloride was removed in vacuum at 50°. As the clear mixture was found to darken rapidly even at this temperature it seemed inadvisable to attempt to distil the acid chloride, and the mixture therefore was cooled and extracted with 150 cc. of dry petroleum ether (b. p. 30–60°). Evaporation gave 8 g. (73%) of pale yellow crystalline product, m. p. 65–75°, and titration with alkali indicated the presence of 90% of the desired acid chloride. When prepared immediately before use, this material was satisfactory for the Grignard reaction, but it is subject to ready hydrolysis and does not keep well. It dissolves readily in warm alkali, but not in the cold. A recrystallized sample melted at 78.5°.

4-Methyl-7-(7′-methoxy-1′-naphthoyl)-hydrindene (III).—A three-necked flask provided with a stirrer, condenser and funnel was charged under nitrogen with 1 g. of lithium (cut under dry ether into small pieces), 10 cc. of ether and 1 g. of 4-methyl-7-chlorohydrindene. The reaction started after warming and stirring for about ten minutes, and in the course of three hours 7 g. more of the chloro compound in 90 cc. of ether was introduced, adding benzene as required to keep the lithium compound in solution. After twenty hours the reaction was complete; the solution was then forced under nitrogen pressure into a stirred benzene solution of 9 g. of 7-methoxy-1-naphthoyl chloride, while cooling to 0°. The mixture was eventually brought to boiling, the ether was allowed to distil and refluxing was continued for two hours. After the careful addition of dilute acid, the mixture was neutralized and steam distilled in the presence of soda. The solid residue, after being dried in ether, distilled at 260–270° (3 mm.), but in order to remove traces of acid or acid chloride the distillate was taken into an acetone-alkali mixture and boiled for two hours. A second distillation, followed by crystallization from ether–petroleum ether, gave colorless prisms melting at 91.4–91.6°; yield 7 g. (48%).

Anal. Calcd. for $C_{22}H_{20}O_2$: C, 83.51; H, 6.37. Found: C, 83.60; H, 6.27.

2-Methoxy-20-methylcholanthrene (IV).—One gram of the above ketone was heated in a bath kept at 405° for fifteen minutes and the temperature was then rapidly raised to 420°. Once this temperature had been reached the mixture was cooled and distilled at 3 mm. The distillate was taken into benzene and the solution filtered through a tower of activated alumina and concentrated. Satisfactory crystalline material was in this way obtained without difficulty in total yield of 40%. When the ketone (2 g.) was heated in the presence of zinc dust (0.5 g.) loss of water occurred at exactly the same temperature as above and the total yield was 36%.

The methoxy compound on recrystallization from benzene–ether formed yellow prisms melting constantly at 163–163.4°. Like the 3-methoxy isomer,[4] the substance exists in two crystalline forms, for on standing in contact with the mother liquor the prisms are slowly transformed into needles; both forms have the same melting point.

Anal. Calcd. for $C_{22}H_{18}O$: C, 88.56; H, 6.08. Found: C, 88.43; H, 5.95.

The picrate crystallizes from alcohol as brown-black needles, m. p. 185.5–186°.

Anal. Calcd. for $C_{22}H_{18}O \cdot C_6H_4O_7N_3$: N, 7.97. Found: N, 7.72.

2-Acetoxy-20-methylcholanthrene.—Because of the great resistance of the methoxy derivative to hydrolysis and the sensitivity of the hydroxy compound to acid, alkali, and oxidation, the isolation of the hydrolysis product could only be accomplished by way of the acetate. In the first successful method found the conditions were similar to those employed by Cook and de Worms[3] for the 3-isomer, but somewhat more drastic. A suspension of 95 mg. of the ether in 3 cc. of glacial acetic acid and 0.5 cc. of constant boiling hydrobromic acid was sealed in a tube in an atmosphere of nitrogen and heated at 140° for three hours. The product was precipitated with water, collected and dried, and treated directly with acetic anhydride and sodium acetate under nitrogen. Dried in ether and fractionally crystallized from ethyl acetate, the product yielded in all 26 mg. (25%) of pure acetate. Some unchanged methoxy compound was still present but the acetate can be separated from this without difficulty by fractional crystallization. The pure acetate forms yellow micro prisms melting, when sealed into an evacuated capillary tube and introduced at a bath temperature of 210°, at 218–219°. When heated in the presence of air the sample turns black at about 210°.

Anal. Calcd. for $C_{23}H_{18}O_2$: C, 84.63; H, 5.56. Found: C, 84.59; H, 5.72.

In an attempt to increase the yield the methoxy compound (500 mg.) was warmed in a sealed tube on the steam-bath with 13 cc. of glacial acetic acid and 5 cc. of hydrobromic acid solution under nitrogen for fifteen hours. The solution became highly colored, but unchanged ether was still present. After acetylating the crude product, purification by fractional crystallization and sublimation in high vacuum at 210° gave 130 mg. (23.5%) of pure acetate.

In other trials it was found that demethylation does not occur at either 25 or 40° on shaking for several days. At higher temperatures decomposition to dark products invariably occurred and some ether always escaped hydrolysis. Attempts to isolate the hydroxy compound by chromatographic adsorption on alumina and elution of a pale blue fluorescent zone with benzene–alcohol gave no crystalline product, and separation with alkali led to extensive oxidation. Demethylation with aluminum chloride was tried without success.

2-Hydroxy-20-methylcholanthrene.—For hydrolysis a mixture of 200 mg. of the acetate, 35 cc. of alcohol and 2 cc. of 50% aqueous sodium hydroxide solution was sealed in a tube under nitrogen and heated at 40°. In about five minutes the acetate dissolved, and the deep orange-red solution was then diluted and acidified. The crude precipitated material was dried and sublimed in high vacuum, giving 120 mg. of crystalline yellow material, but this was still impure. A product of constant melting point was obtained by fractional crystallization from benzene, in which the hydroxy compound is sparingly soluble, but the yield of pure product was only 49 mg. (28%). The substance forms fine yellow needles which, when heated in an evacuated capillary in a bath preheated to 220°, melt at 225.5–226°. In concentrated sulfuric acid the substance gives an orange color turning blue on heating.

Anal. Calcd. for $C_{21}H_{16}O$: C, 88.70; H, 5.67. Found: C, 88.63; H, 5.55.

The picrate forms brown needles from benzene and melts, under the above conditions, at 204°.

Anal. Calcd. for $C_{21}H_{16}O{\cdot}C_6H_4O_7N_3$: N, 8.19. Found: N, 8.04.

Synthesis and Pyrolysis of 4-Methyl-7-(4′-methoxy-1′-naphthoyl)-hydrindene

Preparation of Starting Materials.—For the preparation of **4-bromo-1-naphthol** the procedure of Militzer[8] was modified in the following respects. The solution of bromine and iodine in acetic acid was added dropwise to a vigorously stirred solution of α-naphthol in an atmosphere of nitrogen at 10°, and at the end of the reaction the solution was added by drops to the sulfite solution under mechanical stirring, which avoids occlusion of iodine by the precipitate. After complete precipitation with sodium bicarbonate the washed and dried product was crystallized once from chloroform and several times from aqueous alcohol. The purification is very tedious and the yield of pure material, m. p. 120° (constant), was only 23%. **4-Bromo-1-methoxynaphthalene,** prepared with the use of excess dimethyl sulfate, was obtained in 60% yield as an oil, b. p. 182° (15 mm.).

4-Methyl-7-cyanohydrindene was prepared as described by Fieser and Seligman[5b] (E. B. H. procedure) except that a few cc. of acetonitrile was added to take up traces of water and the heating was conducted at 240–245°. It was found advisable to use very pure chloro compound. The yield in several experiments was close to 90%. **4-Methylhydrindene-7-carboxylic acid**[5b] was most conveniently prepared directly from the chloro compound. A mixture of 12.5 g. of 4-methyl-7-chlorohydrindene, 7 g. of anhydrous cuprous cyanide, 10 cc. of pyridine and 2 cc. of water was heated in a sealed tube at 200–210° for twenty hours (probably a longer period would be better). The mixture was treated with aqueous ammonia, the solid material was collected and extracted with benzene and the ammoniacal filtrate was extracted with the same solvent. The ammonia solution was evaporated until copper oxide precipitated, and on acidifying the filtered solution methylhydrindene-carboxylic acid precipitated (1.6 g.). The combined benzene extracts, after being washed with bicarbonate solution and dried, afforded 8 g. of the corresponding amide on concentration, and the amide was transformed into acid by refluxing with 20% sodium hydroxide solution, the total over-all yield of acid being 75%. The Rosenmund reaction[17] was tried without success, no acid being found on acidification. **4-Methylhydrindene-7-carboxylic acid chloride** was obtained without difficulty from the acid (4.5 g.) and phosphorus pentachloride (5.2 g.) at 40–50° (ten minutes), distilling the product (low melting solid) in vacuum; yield 4 g. (80%).

Grignard Synthesis.—The reaction between 4-bromo-1-methoxynaphthalene (12.5 g. in 60 cc. of ether) and magnesium (1.5 g.) started very easily and was complete in three hours, some benzene being added to keep the complex in solution. The Grignard solution was cooled in ice and 8.5 g. of 4-methyl-7-cyanohydrindene was added in benzene; after distilling the ether the mixture was refluxed for three hours and allowed to stand overnight. After adding water and acid the benzene was removed by distillation, and hydrolysis of the ketimine was accomplished by adding toluene, acetic acid and concentrated hydrochloric acid and refluxing for four hours. The toluene solution was dried and distilled, the ketone boiling at about 262° (2 mm.). Crystallized from ether, **4-methyl-7-(4′-methoxy-1′-naphthoyl)-hydrindene** formed colorless prisms, m. p. 121.5–122°; yield, 11 g. (66%).

Anal. Calcd. for $C_{22}H_{20}O_2$: C, 83.51; H, 6.37. Found: C, 83.26; H, 6.30.

Friedel and Crafts Synthesis.—A mixture of 4 g. of the chloride of 4-methylhydrindene-7-carboxylic acid, 30 cc. of purified tetrachloroethane and 4 g. of 1-methoxynaphthalene was stirred at 0° and 6.5 g. of aluminum chloride was added in portions over six hours. After standing overnight at room temperature, the mixture was decomposed with acid, steam distilled, and the product distilled in vacuum. To remove traces of acid, the distillate was heated with acetone–alkali and the recovered material melted at 118.5°; yield, 5.2 g. (82%). Crystallized from ether, the substance melted at 121.5° and did not depress the melting point of the above sample.

Pyrolysis.—In a typical experiment 2 g. of the ketone was heated at 405° for fifteen minutes and the product then was distilled in vacuum. A solution of the distillate in benzene was filtered through a tower of alumina, and after many crystallizations there was obtained a crystalline yellow substance melting at 174.5° and giving no depression when mixed with a sample of methylcholanthrene, m. p. 175.5°. No other substance was encountered, and the following observation indicates that the desired methoxy compound was not present. The material (150 mg.) obtained from a pyrolysis similar to that described and purified by passage through an adsorption tower was boiled with 10 cc. of glacial acetic acid and 1 cc. of hydrobromic acid for two hours, the solution was diluted and extracted with benzene. On extraction with dilute alkali there was no coloration in the alkali layer and no precipitate on acidification.

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(17) Rosenmund and Struck, *Ber.*, **52**, 1749 (1919).

Pyrolysis in the presence of zinc dust gave the same results.

6-Chloro-20-methylcholanthrene

1-Bromo-4-chloronaphthalene. (a) **By Direct Bromination.**—As no mention of this possible method was found in the literature, a trial was made in which 50 cc. of bromine was added in twenty-four hours to a stirred solution of 162 g. of carefully fractionated (1-meter column) α-chloronaphthalene in 1 liter of carbon tetrachloride at 50–60°. After refluxing overnight the solvent was removed with steam and the residue was treated with steam in the presence of alkali, fractionated at 3 mm. and crystallized from acetic acid. After six crystallizations the 1-bromo-4-chloro compound was obtained in a pure condition, m. p. 67° (compare 66.5–67°[18]), but the yield was only 6.5 g.

(b) **From Acetyl-α-naphthylamine.**—The acetyl compound (200 g.) was brominated in glacial acetic acid solution with vigorous stirring at about 10° according to Meldola,[9] and the crystallized product was hydrolyzed[19] by refluxing with 3 liters of alcohol and 300 cc. of concentrated hydrochloric acid for three hours. Most of the resulting amine hydrochloride crystallized on cooling in a very pure form, and a further crop was obtained on concentrating the solution. The total yield was 215 g. (overall yield, 77%). The amine liberated from the salt melted at 102.5° (compare[19] 102°).

For diazotization 35 g. of 4-bromo-1-naphthylamine hydrochloride in 650 cc. of water and 65 cc. of concentrated hydrochloric acid was stirred at 0° and treated with a cold aqueous solution of 20 g. of sodium nitrite. After one hour a cold aqueous solution of 10 g. of urea was added and after forty-five minutes the solution was added slowly to a stirred solution of 33 g. of cuprous chloride in 350 cc. of concentrated hydrochloric acid at 5–10°. The mixture was allowed to come to room temperature, with continued stirring, and at 15–20° there was a color change and decomposition of the complex occurred. After heating on the steam-bath until the reaction product melted, the mixture was cooled and extracted with benzene. On distillation the product boiled at 159–160° (3 mm.) and melted at 65–66°. One crystallization gave very pure 1-bromo-4-chloronaphthalene, m. p. 67.5°, and the yield was 82–84% in several experiments.

When copper powder was used as catalyst in the Sandmeyer reaction the yield was the same and the only difference noted was that there was a shorter induction period before evolution of nitrogen commenced, although the decomposition occurred at the same temperature.

4-Methyl-7-(4′-chloro-1′-naphthoyl)-hydrindene (VII).—The reaction of 1-bromo-4-chloronaphthalene (6.5 g.) in ether (60 cc.) and magnesium (0.7 g.) started very easily and was complete in two hours, some benzene being added to keep the complex dissolved. The solution was cooled in ice and 4.2 g. of 4-methyl-7-cyanohydrindene in benzene solution was added with stirring. After removing the ether and refluxing for three hours, the product was decomposed with dilute acid and the ketimine hydrolyzed by refluxing with toluene, acetic and hydrochloric acids, as above. The hydrolysis proceeded very slowly and sometimes refluxing had to be continued for fifteen hours. The toluene layer was washed with water and with bicarbonate solution and the aqueous layer was extracted with ether. The material from the toluene–ether solutions was distilled at 3 mm. and the product crystallized from benzene–ether. The yield of very satisfactory ketone was 6.2 g. (72%), and the purest sample formed prisms, m. p. 144.5–145°.

Anal. Calcd. for $C_{21}H_{17}OCl$: C, 78.62; H, 5.34. Found: C, 78.62; H, 5.47.

In one experiment the ketimine hydrochloride was collected before hydrolysis, and in this case the distilled ketone was directly pure (m. p. 144.5–145°) and required no crystallization; the yield, however, was slightly lower (65%).

6-Chloro-20-methylcholanthrene (VIII).—The Elbs reaction with the above ketone proceeds very poorly, and in order to obtain any of the desired chloro-hydrocarbon it is necessary to control the temperature very carefully. Otherwise the sole product that can be isolated is methylcholanthrene. A critical temperature must be reached before loss of water begins and at this temperature considerable hydrogen chloride is evolved and the reaction proceeds exothermally with extensive decomposition.

In the most successful experiment 80 g. of ketone was pyrolyzed in two lots as follows. The bath was heated to 410° and as soon as the reaction started the temperature was decreased to 360–370°. Evolution of water continued to occur at this temperature for about ten minutes, after which the bath was again heated to 410°. The very dark, tarry mixture was then distilled at 3 mm. pressure and a solution of the distillate was passed through an adsorption tower of alumina. Concentration of the solution afforded a clean, crystalline product, but this proved to be a mixture which was separated only by a tedious process of fractional crystallization. Chloromethylcholanthrene is but sparingly soluble in benzene and was obtained as the top fraction, the yield of thoroughly purified material, m. p. 233.5–233.8° (see below), being 940 mg. (1.2%). There was a second fraction of nearly pure material (140 mg.), m. p. 230°, and 450 mg. of a mixture of the chloro compound and the hydrocarbon. From the residue there were isolated 1.7 g. of nearly pure methylcholanthrene and 8 g. of very impure hydrocarbon picrate.

After very careful purification to remove traces of the hydrocarbon, 6-chloro-20-methylcholanthrene formed glistening, pale yellow needles, m. p. 233.5–233.8° (evacuated capillary, preheated bath).

Anal. Calcd. for $C_{21}H_{15}Cl$: C, 83.29; H, 4.99; Cl, 11.71. Found: C, 83.28; H, 5.18; Cl, 11.77.

A pure picrate could not be obtained from the chloro compound, possibly because of the low solubility of the substance in the usual solvents The separation of the pyrolysis mixture through the picrate was tried but found unsatisfactory.

We tried carrying out the Elbs reaction by distilling the ketone through a glass coil heated at 520° in a nitrate bath but little pyrolysis occurred under these conditions.

6-Chano-10-methylcholanthrene.—A mixture of 120 mg. of the pure chloro compound, 50 mg. of cuprous cyanide, 0.2 cc. of pyridine and a trace of acetonitrile was heated in a sealed tube at 230–240° for twenty hours. The

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(18) Beattie and Whitmore, *J. Chem. Soc.*, 50 (1934).

(19) Gomberg and Blicke, THIS JOURNAL, **45**, 1765 (1923).

cooled mixture, which was very clean and partly crystalline, was washed out with water and ammonia and the precipitated cyano compound was collected, washed with ammonia water and dried. It was crystallized from glacial acetic acid (sparingly soluble) and from pyridine-benzene and obtained in the form of long yellow needles m. p. 268–268.5° (evacuated capillary, preheated bath). The yield was 75 mg. (66%).

Anal. Calcd. for $C_{22}H_{15}N$: C, 90.07; H, 5.15. Found: C, 89.87; H, 5.29.

The nitrile is very resistant to hydrolysis and was recovered unchanged after being heated with concentrated hydrochloric acid in a tube at 118° for one day. On attempting to convert the chloro compound (140 mg.) directly into the acid with cuprous cyanide, pyridine and water at 230° (twenty hours), the chief product appeared to be the amide (insoluble in dilute ammonia, decomposes when heated above 300°) and only 10 mg. of an acidic product was obtained.

Condensation Product, Probably 2-Chloro-7-methyl-5,6-cyclopenteno-1,9-benzanthrone-10 (IX). **(a) By the Friedel and Crafts Reaction.**—In a first attempt to condense the chloride of 4-methylhydrindene-4-carboxylic acid with α-chloronaphthalene in the presence of aluminum chloride, the chloro compound was taken in excess and no other solvent was employed. No condensation was observed. In another experiment a mixture of 3.5 g. of the acid chloride, 30 cc. of α-chloronaphthalene and 10 cc. of tetrachloroethane was stirred in ice and 6 g. of aluminum chloride was added during six hours. After standing for several hours at room temperature the mixture was decomposed and the product distilled at 3 mm. By careful distillation it was possible to obtain a certain amount of a crystalline yellow product (b. p. 260°, m. p. 210°, dec.), although the substance is very sensitive to heat and much of the material present was destroyed. Crystallization from benzene (moderate solubility) gave 150 mg. of the pure substance. This forms yellow needles melting at 215° (evacuated capillary, preheated bath). It is insoluble in hot alkali and gives a positive test for chlorine. Decomposition occurred in an attempted molecular weight determination in camphor.

Anal. Calcd. for $C_{21}H_{15}OCl$: C, 79.11; H, 4.74. Found: C, 79.02; H, 4.84.

It may be noted that the Friedel and Crafts reaction is complicated by the sensitivity of α-chloronaphthalene to aluminum chloride. A solution of the substance (5 g.) in tetrachloroethane (40 cc.) was treated at 0° with aluminum chloride (7 g.), and after standing overnight at room temperature the product was recovered and distilled. From the first fraction there was isolated a solid product melting, after crystallization, at 56.5° and identified by mixed melting point determinations as β-chloronaphthalene. There was also considerable high boiling material present, but this appeared to be a mixture and pure components were not isolated.

(b) From the Ketone VII.—The action of aluminum chloride (4 g.) on the ketone (5 g.) in tetrachloroethane (40 cc.) was tried at −10°, but most of the ketone was recovered unchanged. In a second experiment (3.5 g. of ketone) the aluminum chloride was added at 5° and the solution was then allowed to stand overnight at room temperature. On working up the mixture and distilling the product as above, there was obtained 150 mg. of the yellow condensation product melting at 213° (as above, 215° when further purified) and giving no depression when mixed with the first sample. Another fraction (500 mg.) proved to be a mixture of the yellow substance and the original ketone.

On attempted acetylation by boiling the yellow product in pyridine with acetic anhydride for five minutes, the starting material was recovered quantitatively in an unchanged condition. On treatment of the yellow compound (80 mg.) with acetic anhydride, sodium acetate and zinc dust a reaction occurred even on moderate heating and a practically colorless solution was obtained. The addition of water precipitated an amorphous product which became more and more yellow as attempts were made to purify it by crystallization, and no satisfactory product could be obtained.

Summary

The general cholanthrene synthesis developed in this Laboratory has been extended to the preparation of 2-methoxy-20-methylcholanthrene. The Elbs reaction proceeded satisfactorily and the corresponding hydroxy compound was obtained, if with some difficulty, on hydrolysis. In an attempt to synthesize 6-methoxy-20-methylcholanthrene by the same method the methoxyl group was completely eliminated. A similar lability of the substituent was noted with the corresponding chloro ketone, but 6-chloro-20-methylcholanthrene was isolated in a pure condition if in poor yield. This was transformed in good yield into the 6-nitrile by reaction with cuprous cyanide in pyridine.

It was noted that 4-methyl-7-(4′-chloro-1′-naphthoyl)-hydrindene suffers dehydrogenation in the presence of aluminum chloride in solution at room temperature and is converted into a yellow substance which probably is a benzanthrone derivative.

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[COMMUNICATION FROM THE RESEARCH LABORATORY OF MERCK AND COMPANY, INC., AND THE RESEARCH LABORATORY OF THE McLEOD INFIRMARY]

Synthesis, Isolation and Identification of Cocarboxylase

BY JOHN WEIJLARD AND HENRY TAUBER

From the reaction mixture recently described[1] cocarboxylase may be isolated in pure state by a procedure to be described in the present communication. A series of experiments will be presented which show that the synthetic cocarboxylase as obtained from synthetic thiamin chloride is in every respect identical with the natural cocarboxylase isolated by Lohmann and Schuster[2] from bottom yeast.

Experimental

Synthesis.—One gram of sodium pyrophosphate was placed in a Pyrex test-tube and heated until all of the water of crystallization was removed. Two cc. of orthophosphoric acid (c. P. 85%) was placed in another large Pyrex tube and heated until a slight amount of solid deposit formed on the side of the tube. Then the pyrophosphate was added and the mixture gently heated until solution took place. After cooling 1 g. of thiamin was added. The tube was placed in an oil-bath of 155°, kept there for fifteen minutes and constantly stirred. Then the tube was removed and after cooling the solid mass was dissolved in 15 cc. of cold water. Cold saturated barium hydroxide solution was added until no more precipitate formed and the solution just commenced to turn yellow. The precipitate was centrifuged out and the supernatant fluid was decanted. The precipitate was extracted four times with 80 cc. of cold water. The supernatant fluids (five) were united and 3% sulfuric acid was added to slight blue reaction of congo red paper. The barium sulfate was centrifuged off and discarded. The barium-free solution was concentrated to 30 cc. in vacuum at 25°. It was cooled in ice water and 15 volumes of a mixture of one part of absolute alcohol and two parts of ether were added which precipitated the cocarboxylase in the form of microscopic needles. Sometimes a gummy mass formed which turned into long macroscopic needles on short standing in the cold. The yield was about 1 g. of crude cocarboxylase.

Isolation.—One and one-half grams of crude cocarboxylase was dissolved in 150 cc. of water, neutralized to congo red with ammonium hydroxide and treated with 3 cc. of *N* silver nitrate. This first precipitate was mainly silver chloride and, accordingly was discarded. The clear solution was made neutral to litmus with ammonium hydroxide and 15 cc. of *N* silver nitrate was added. A copious yellow precipitate appeared. It contained most of the active cocarboxylase in the form of the silver salt. This was centrifuged and washed with water, suspended in 150 cc. of water and decomposed with hydrogen sulfide. The precipitate was centrifuged and washed with 20 cc. of water. The liquids were united and the hydrogen sulfide removed by aëration. To the neutral, hydrogen sulfide-free solution 96 cc. of 2.5 *N* hydrochloric acid was added and the mixture was diluted to 300 cc. with water. A moderate excess of a 25% phosphotungstic acid solution was added and the mixture centrifuged. The supernatant liquid was discarded. The precipitate was treated with 150 cc. of acetone which dissolved the phosphotungstic acid whereas the cocarboxylase separated as an oil which tended to crystallize on scratching. The cocarboxylase was centrifuged off and the acetone fraction was discarded. The precipitate was extracted twice more with 50 cc. of acetone. The residue was then extracted with 20 cc. of 0.1 *N* hydrochloric acid and filtered. The insoluble part was treated with 75 cc. of acetone and the acetone discarded. The residue was extracted with 15 cc. of 0.1 *N* hydrochloric acid. To the total (35 cc.) 0.1 *N* hydrochloric acid solution, 350 cc. of acetone was added and the mixture placed in the refrigerator overnight. The supernatant fluid was discarded and the residue dissolved in 15 cc. of 0.1 *N* hydrochloric acid; 150 cc. of acetone was added and the mixture allowed to crystallize in the refrigerator for twenty-four hours. The crystalline precipitate was dissolved in 15 cc. of 0.1 *N* hydrochloric acid and 30 cc. of absolute alcohol and 120 cc. of acetone added. The mixture was allowed to crystallize in the refrigerator for twenty-four hours; yield 180 mg.

Analysis.—The synthetic, practically pure cocarboxylase dried in a vacuum over sulfuric acid had a slightly yellowish color similar to the natural product and melted at 240°. Its elementary composition agrees well with that found for the natural cocarboxylase by Lohmann and Schuster. Calcd.: C, 30.08; H, 4.42; N, 11.71; P, 12.96; Cl, 7.40. Found: C, 30.62; H, 4.20; N, 11.82; P, 12.37; Cl, 7.95.

One more crystallization (50 mg. in 1 cc. of 0.1 *N* hydrochloric acid with 3 cc. of alcohol) gave a cocarboxylase which may be considered to be 100% pure. Found: C, 30.36; H, 4.24; N, 11.30; P, 12.83.

Acid Hydrolysis.—3.206 mg. of synthetic cocarboxylase with 2 cc. of *N* hydrochloric acid was placed in a bath of boiling water for forty minutes. The solution was then evaporated to dryness in vacuum at room temperature, and the ionized phosphate determined: found, 12.978 mg. of ammonium phosphomolybdate (5.89% P) or 47.6% of the total phosphorus. The second phosphate radical is more firmly bound, as also found by Lohmann and Schuster for natural cocarboxylase. Twenty-five micrograms of cocarboxylase in 1 cc. of 0.1 *N* hydrochloric acid boiled for sixty minutes at 100° lost 50% of its coenzyme activity.

Enzymic Hydrolysis.—To 4 g. of minced kidney tissue, 50 micrograms of cocarboxylase in 4 cc. of water was added and incubated at 37°. In thirty minutes 58% of the cocarboxylase was hydrolyzed by the kidney phosphatase, as determined enzymatically, using alkaline washed, cocarboxylase-free dry brewers' yeast.

Thiamin Content and Thiochrome Formation.—It is well known that thiamin may be oxidized to thiochrome

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[1] H. Tauber, THIS JOURNAL, **60**, 730 (1938).

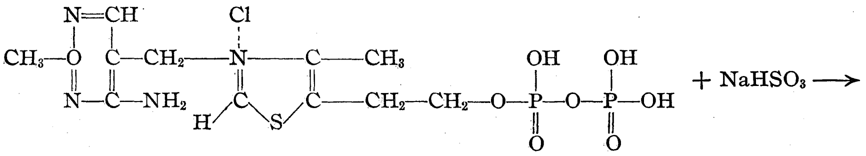
[2] K. Lohmann and P. Schuster, *Biochem. Z.*, **294**, 188 (1937).

by an alkaline potassium ferricyanide solution. Tauber[3] found that the ferrocyanide formed during the reaction may be converted quantitatively to Prussian blue and the color measured colorimetrically. The same is true for cocarboxylase. Its thiamin portion may be converted quantitatively to thiochrome. Cocarboxylase also forms thiochrome on the addition of alkali alone. The thiochrome compound, however, is inactive. It becomes enzymatically active again on acidification.

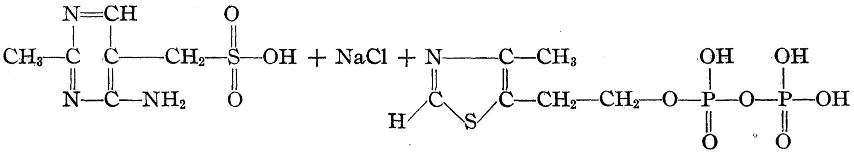
Formaldehyde–Azo Test.—The formaldehyde-azo test[4] gave an intense yellow color with cocarboxylase. Thiamin gave a red color.

Coenzyme Activity.—Synthetic cocarboxylase is as active as natural cocarboxylase (very kindly furnished by Professor Lohmann). Exact comparisons can only be made, however, if the same yeast preparation is employed as the source of carboxylase. The carboxylase content of various yeasts differs considerably.

Sulfite Cleavage.—The synthetic cocarboxylase should split in the same manner as the natural cocarboxylase, *e. g.*, into a phosphorus-free pyrimidine and a thiazolpyrophosphate:



Cocarboxylase (Pyrophosphoric acid ester of thiamin)



Pyrimidine portion

Thiazole pyrophosphate

One hundred and twenty-three mg. of cocarboxylase was dissolved in 2 cc. of water and adjusted to *p*H 5 by the addition of 0.27 cc. of *N* sodium hydroxide; 200 mg. of solid sodium bisulfite was added and the mixture allowed to stand for three days at room temperature. In less than one hour crystallization began and after concentration in vacuum at room temperature to 0.5 cc., the crystals were filtered off, washed with 3 drops of water and dried in vacuum to constant weight; yield 44.6 mg., calcd. 52 mg. It was recrystallized by dissolving in hot water, cooling, filtering, washing with several portions of water, and drying.

Anal. Calcd. for the P-free pyrimidine $C_6H_9O_3N_3S$ (m. w. 203.2): C, 35.44; H, 4.46; N, 20.68. Found: C, 35.37; H, 4.45; N, 20.51.

The filtrate from the pyrimidine portion was made slightly alkaline to litmus with ammonium hydroxide; 3 drops of hydrogen peroxide was added and the solution warmed in order to oxidize the sulfite ions to sulfate ions. The solution was then made acid to congo red with 10% nitric acid (5 drops). A slight excess of concd. barium nitrate solution and a slight excess of 10% silver nitrate solution were added. The sulfate and chloride precipitate was discarded and the filtrate was made neutral to congo red with dilute ammonium hydroxide. It was then concentrated to 3 cc. in vacuum at room temperature. An excess of 60% silver nitrate solution was added until no further precipitation occurred. The precipitate was filtered off, washed with 50%, then 90%, then 100% alcohol and finally with ether, and then dried in vacuum; yield 150 mg. silver salt, calcd. 184 mg.

The silver salt was dissolved in 3 cc. of 5% nitric acid, neutralized with ammonium hydroxide and excess 60% silver nitrate was added. The precipitate was filtered, washed with alcohol and ether as above. Analyses indicate the approximate formula: $C_6H_8O_7NSP_2Ag_3(AgOH \cdot AgNO_3)6/10 \cdot 3H_2O$ (m. w. 854.75).

Calcd.: C, 8.42; H, 1.72; total N, 2.62; N as nitrate, 0.98; Ag, 54.8; P, 7.26. Found: C, 8.21; H, 1.45; total N, 2.61; nitrate N, 0.87; Ag, 53.0; P, 7.64.

Mild Hydrolysis in *N* Nitric Acid.—3.395 mg. of the cleavage product was heated at 100° for twenty minutes with 1 cc. of *N* nitric acid: found 9.717 mg. of ammonium phosphomolybdate = 4.10% P, hence 53.6% of the total P was hydrolyzed. This indicates that only one of the phosphate radicals is removed readily from the phosphorylated thiazole.

Lohmann and Schuster evidently obtained their cleavage product in a more acid solution since their analysis indicates the formula $C_6H_8O_7NSP_2Ag_3(HNO_3)6/10 \cdot 3H_2O$, whereas we obtained a basic double salt.

The nitrate was reduced with Devarda's metal and determined colorimetrically. Nitrogen was determined according to Hayman and Adler.[5]

The analytical work was carried out by D. F. Hayman, W. Reiss and H. Levy, to whom we are indebted. We wish also to express our appreciation to Dr. R. T. Major, for his advice and interest throughout this investigation.

Summary

Synthetic cocarboxylase has been prepared in pure form and identified. Its behavior toward mild acid hydrolysis and its cleavage products as well as its coenzyme activity are identical with those of the natural cocarboxylase, the pyrophosphoric acid ester of thiamin.

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RECEIVED JULY 12, 1938

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(3) H. Tauber, *Mikrochim. Acta*, **3**, 108 (1938).

(4) H. W. Kinnersley and R. A. Peters, *Biochem. J.*, **28**, 667 (1934).

(5) Hayman and Adler, *Ind. Eng. Chem., Anal. Ed.*, **9**, 197 (1937).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

The Preparation of Chlorides from Certain Aliphatic Branched Chain Secondary Carbinols[1,2]

BY FRANK C. WHITMORE AND FRANKLIN JOHNSTON

It has long been known that carbinols containing a grouping $R_3C{-}CHOH{-}$ fail to give the corresponding halide when the hydroxyl is replaced. Instead, a rearrangement occurs. Thus pinacolyl alcohol gives a tertiary chloride in at least 90% yield,[3] $Me_3CCHOHMe \longrightarrow Me_2CXCHMe_2$. In spite of nearly seventy years[2] (note 2) of study of the replacement of the hydroxyl in methylisopropylcarbinol, the course of the reaction and its products are still not clear. This condition induced the present study of two types of aliphatic secondary carbinols (1) with a fork next to the carbinol group and (2) with the fork farther removed. Even under the mildest conditions the first gave almost entirely the tertiary chloride formed by shift of the tertiary hydrogen atom adjacent to the carbinol group; thus $(CH_3)_2CHCHOHCH_3 \longrightarrow (CH_3)_2CXCH_2CH_3$. The stability recently proven for the secondary chloride[2] indicates that the tertiary chloride is formed during the replacement of hydroxyl and not through the secondary chloride as an intermediate either by direct shift of chlorine or by loss and addition of hydrogen chloride as have been suggested by the earlier workers.[2] At room temperature, without a catalyst, the second type of carbinol gave no detectable rearrangement with hydrogen chloride. Thus a secondary hydrogen does not shift appreciably under these mild conditions.

The chlorides were distilled under reduced pressure below 30° to avoid any thermal change in the products. *Thus any rearrangement which took place occurred during the replacement of hydroxyl and not by a shift of the chlorine after the replacement.* The rearrangements observed with the halides themselves take place at much higher temperatures (above 200°).[4]

In the present study, methylisopropylcarbinol has been treated with (1) zinc chloride and hydrochloric acid (Lucas) at 0°, (2) thionyl chloride and pyridine at 20°, (3) phosphorus pentachloride at 20°, (4) phosphorus trichloride at 0°, and (5) hydrogen chloride below 20° for ten weeks. The phosphorus trichloride gave only a phosphite. The other methods gave *t*-amyl chloride with only traces of material which might contain the secondary chloride. The low temperature treatment with hydrogen chloride repeatedly gave yields of over 90% of *t*-amyl chloride. This method was adopted as standard procedure with the other alcohols studied. In this way ethylisopropylcarbinol, *n*-propylisopropylcarbinol and diisopropylcarbinol gave the tertiary chlorides, dimethyl-*n*-propyl-, dimethyl-*n*-butyl- and dimethylisobutylcarbinyl chlorides, respectively. In each case the crude chloride was distilled below 30° to avoid the suspicion of temperature effects. Similarly methylisobutylcarbinol, methylisoamylcarbinol and methylneopentylcarbinol (2,2-dimethylpentanol-4) were converted to chlorides. In each case the product was the secondary chloride formed by simple replacement of hydroxyl by chlorine. No trace of tertiary chloride was detected in any of the compounds having the fork not adjacent to the carbinol group.

Experimental

Conversion of Methylisopropylcarbinol to *t*-Amyl Chloride.—Isopropyl alcohol (Petrohol supplied by Stanco, Inc.) was converted to the chloride by $ZnCl_2 \cdot HCl$ treatment in 75% yield; b. p. 33–36° (737 mm.), $n^{20}D$ 1.377. Nine moles of the chloride was converted to the Grignard reagent using 1.7 liters of ether; yield 90%. Treatment with acetaldehyde and fractionation of the product through a packed column, 2.2 × 85 cm.,[5] gave the desired carbinol; yield 56%, b. p. 110–111° (727 mm.), $n^{20}D$ 1.4090, d^{20}_4 0.818.

1. **By Zinc Chloride–Hydrochloric Acid Mixture.**—To a cooled solution of 546 g. of fused zinc chloride and 335 cc. of concd. hydrochloric acid, saturated with hydrogen chloride gas, and cooled to −10° by dry ice, was added 176 g. (2 moles) of methylisopropylcarbinol with mechanical stirring. After two hours, hydrogen chloride gas was introduced in a slow stream. Soon the mixture solidified. After standing overnight, the mixture was allowed to melt and was saturated with hydrogen chloride gas below 0°. After a total time of twenty-four hours, the chloride layer was separated and dried with 50 g. of anhydrous sodium sulfate and freed from excess hydrogen chloride by dry nitrogen; yield, 172 g. (80%).

The chloride was distilled under reduced pressure through a column with a partial condenser. Between

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[1] Original manuscript received April 3, 1934.

[2] *Cf.* Whitmore and Johnston, THIS JOURNAL, **55**, 5020 (1933).

[3] Whitmore and Rothrock, *ibid.*, **55**, 1106 (1933).

[4] Faworsky, *Ann.*, **354**, 325–89 (1907); Michael and Zeidler, *ibid.*, **385**, 227–92 (1911).

[5] Whitmore and Lux, THIS JOURNAL, **54**, 3448 (1932).

the column and pump were placed a manometer, a spiral trap cooled with dry ice, a 12-liter bottle to minimize changes in pressure and an adjustable leak for controlling the pressure. During a typical distillation the partial condenser was kept at about 3° with mechanically circulated ice water, the temperature in the flask was 25–26° and in the room 28–30°. Reflux from the partial condenser was kept at about 200 drops per minute. Fractions were taken every thirty minutes. The fractions, pressures (mm.), wts., g. and $n^{20}\text{D}$ were as follows: 1, (35), 3.5, 1.4049; 2, (32), 8.8, 1.4051; 3–10, (31), 127.0, 1.4052; 11, (29), 6.0, 1.4053; 12, (24), 13.4, 1.4060; residue, 2.0, 1.4340. The main fractions boiled at 84–84.5° (734 mm.). A sample hydrolyzed with distilled water[6] for thirty minutes, and titrated by the Volhard method showed 95% hydrolysis. A known sample of *t*-amyl chloride, b. p. 51° (238 mm.), $n^{20}\text{D}$ 1.4055 showed the following percentages of hydrolysis at fifteen, thirty and sixty minutes, 88.6, 94.9 and 95.4. Thus the product of the action of zinc chloride and hydrochloric acid with methylisopropylcarbinol was *t*-amyl chloride. No product having the properties of secondary isoamyl chloride, b. p. 91.9° (736 mm.), $n^{20}\text{D}$ 1.4095, was obtained.

2. By Thionyl Chloride.—A mixture of 103 g. of dry pyridine (b. p. 112–120°) and 88 g. (1 mole) of the carbinol cooled to 0° was treated during four hours with vigorous stirring with 143 g. (1.2 moles) of thionyl chloride. The mixture was stirred for three hours at room temperature. The top layer was decanted. The bottom layer consisted of a crystalline solid and a viscous oil. The top layer was diluted with low boiling hydrocarbon (b. p. 0–30°)[7] and washed with sodium bicarbonate solution and water until neutral. After drying over 10 g. of calcium chloride the solvent was removed at 300 mm. pressure and the residue was fractionated through a 1.4 × 50 cm. column of the type used in this Laboratory.[5] The temperature was 27–23° and the pressure 90–55 mm. Most of the fractions had $n^{20}\text{D}$ 1.4050–1.4060. The yield was 73%. A sample treated with water[6] showed 92% hydrolysis.

3. With Phosphorus Pentachloride.—To 214 g. (1.05 mole) of phosphorus pentachloride and 200 cc. of 0–30° hydrocarbon[7] cooled to 0° was added with stirring during two hours 88 g. (1 mole) of the carbinol. After stirring for three and one-half hours the evolution of hydrogen chloride had ceased. Two 50-g. portions of cracked ice were added. The chloride layer was washed and dried as usual and distilled to a 76% yield of crude chloride. This was distilled at 27–24° and 95–60 mm. to give mainly a product with $n^{20}\text{D}$ 1.4069 which was 83% hydrolyzed by cold water.[6] A Michael determination for secondary and tertiary halides gave 84%. Attempts to prove the presence of secondary isoamyl chloride failed.

5. With Hydrogen Chloride.—The pure carbinol was saturated with dry hydrogen chloride gas at 0° and sealed in pressure bottles. After four weeks at about 20° the bottles were opened and again saturated at 0°. After six weeks more, the chloride layer showed no further increase. It was separated, dried and distilled as usual at low pressure. Four runs with a total of 580 g. of carbinol absorbed 264 g. of hydrogen chloride and gave 676 g. of crude chloride, yield 97%. Distillation of 305 g. of the chloride at 25–26° and 33–28 mm. gave fractions with wts. (g.) and $n^{20}\text{D}$ as follows: 3–6, 83, 1.4051; 7–12, 111, 1.4053; 16–19, 42, 1.4058; 20, 14, 1.4069; residue, 13, 1.4410. Analyses for tertiary chloride and for tertiary and secondary chloride[6] on the fractions gave the values, 7, 95.6% tertiary; 18, 82% tertiary, 86.5% tertiary and secondary; 100.2% total amyl chloride (Carius); 20, 33.4% tertiary; 44.9% tertiary and secondary. The possible presence of traces of secondary and primary chlorides in the later fractions is being further investigated.

Conversion of Ethylisopropylcarbinol to Dimethyl-*n*-propylcarbinyl Chloride.[8]—The carbinol was prepared from isopropylmagnesium chloride and propionaldehyde in 52% yield, b. p. 125–126° (742 mm.), $n^{20}\text{D}$ 1.4170, d^{20}_4 0.824.[9] From 404 g. of the carbinol and hydrogen chloride was obtained 430 g. of crude chloride, 89% yield. This was distilled at reduced pressure with the water in the partial condenser at 12–13° and the heating bath at 39–42°. Fractionation of 410 g. of the chloride gave a 68% yield of material, b. p. (Cottrell) 110–111° dec. (734 mm.), $n^{20}\text{D}$ 1.4125–1.4130, d^{20}_4 0.863. These properties correspond to those of dimethyl-*n*-propylcarbinyl chloride.[10]

The structure of the chloride was proved further by conversion to the Grignard compound, treatment with oxygen[5] and conversion in 48% yield[11] to dimethyl-*n*-propylcarbinol, b. p. 93.5° (265 mm.); (Cottrell), 119.5–120.5° (738 mm.), $n^{20}\text{D}$ 1.4103, d^{20}_4 0.808. These properties correspond to the values in the literature.

When saturated with hydrogen chloride gas for fifteen minutes the carbinol was converted back to the chloride, thus confirming its tertiary nature.

Conversion of *n*-Propylisopropylcarbinol to Dimethyl-*n*-butylcarbinyl Chloride.—The carbinol was prepared from *n*-butyraldehyde, b. p. 72–74°, $n^{20}\text{D}$ 1.379 (from Butalyde supplied by Commercial Solvents Corp.), and isopropylmagnesium chloride in 62% yield, b. p. 144–145° (734 mm.), $n^{20}\text{D}$ 1.4213, d^{20}_4 0.822.[8] A total of 435 g. of the carbinol was saturated with dry hydrogen chloride at 0° as usual. The crude chloride was dried and distilled at 3 mm. pressure. Fractionation of 476 g. gave an 80% yield of chloride, b. p. (Cottrell) 133° dec. (734 mm.), $n^{20}\text{D}$ 1.4200–1.4210, d^{20}_4 0.863. These agree with the properties of dimethyl-*n*-butylcarbinyl chloride.[12]

The structure of the chloride was confirmed by conversion to dimethyl-*n*-butylcarbinol through the Grignard reagent.[5] A half-mole run gave a 42% yield of carbinol, b. p. 110° (250 mm.) 139.5–140.5° (741 mm.) (Cottrell), $n^{20}\text{D}$ 1.4173, d^{20}_4 0.813.[12] The residue of $n^{20}\text{D}$ 1.4400 amounted to only 3 g. The carbinol was changed to the chloride by hydrogen chloride gas at 0°.

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[6] Michael and Leupold, *Ann.*, **379**, 294 (1911).

[7] From the Viking Corporation, Charleston, W. Va.

[8] Grigorowitch and Pawlow, *J. Chem. Soc.*, **64**, I, 124 (1893), claim to have obtained the secondary chloride by means of phosphorus pentachloride. Van Risseghem, *Bull. soc. chim. Belg.*, **32**, 144–150 (1923), has reported the secondary chloride as a by-product of the action of chlorine with 2-methylpentene-2.

[9] *Cf.* Pickard and Kenyon, *J. Chem. Soc.*, **101**, 628 (1912).

[10] *Cf.* Schreiner, *J. prakt. Chem.*, [2], **82**, 294 (1910).

[11] The low yields of carbinols from the tertiary chlorides are due to olefin formation as indicated in the lower fractions. *Cf.* Whitmore and Badertscher, THIS JOURNAL, **55**, 1559 (1933).

[12] Whitmore and Woodburn, *ibid.*, **55**, 363 (1933).

Conversion of Diisopropylcarbinol to Dimethylisobutylcarbinyl Chloride.—The carbinol was kindly supplied by the du Pont Ammonia Department. It was fractionated through a 2.2 × 90 cm. column; b. p. 137–8° (738 mm.), n^{20}_{D} 1.4246, d^{20}_{4} 0.831.[12] The carbinol (464 g.) absorbed hydrogen chloride gas more slowly than the other carbinols studied. At first a pale purple color was formed. This gradually changed to brownish yellow. Reaction was complete in ten weeks at 20° and the yield of chloride was quantitative. It was distilled at 3 mm. to give 272 g. of chloride, b. p. (Cottrell) 127–128° dec. (733 mm.), n^{20}_{D} 1.4180, d^{20}_{4} 0.861. These properties correspond to dimethylisobutylcarbinyl chloride.[11] The identity was confirmed by conversion of the chloride, in 32% yield,[13] to dimethylisobutylcarbinol, b. p. (Cottrell) 130–131° (738 mm.), n^{20}_{D} 1.4166, d^{20}_{4} 0.811.[14] Treatment of fraction 7 with hydrogen chloride at 0° gave the tertiary chloride. No color appeared.

Conversion of Methylisobutylcarbinol to its Chloride.[15]—The carbinol was made in 42% yield from isobutylmagnesium bromide and acetaldehyde: b. p. 129.5° (734 mm.), n^{20}_{D} 1.4111, d^{20}_{4} 0.807.[16] Treatment of 408 g. of the carbinol with dry hydrogen chloride in the usual way for eighteen weeks gave 398 g. of crude chloride, 82% yield. Fractionation and refractionation gave methylisobutylcarbinyl chloride, b. p. (Cottrell) 111–112° (733 mm.) n^{20}_{D} 1.4113, d^{20}_{4} 0.861. The identity was substantiated further by conversion to the carbinol in 62% yield through the Grignard reagent.[5] The methylisobutylcarbinol was identified by b. p. 68° (64 mm.), n^{20}_{D} 1.4112 and conversion to the α-naphthylurethan, m. p. and mixed m. p. 96–97°.

Conversion of Methylisoamylcarbinol to its Chloride.—The carbinol was prepared in 65% yield from acetaldehyde and isoamylmagnesium chloride; b. p. 150.5–151° (742 mm.), n^{20}_{D} 1.4180, d^{20}_{4} 0.814. In the usual way hydrogen chloride gas was passed into 464 g. of the carbinol. After six weeks the chloride was separated and treated as usual. The partial condenser was kept at 14–15° and the heating bath at 50–52°. Fractionation gave a 90% yield of chloride, b. p. 138° dec. (735 mm.), d^{20}_{4} 0.863. Conversion of the chloride through the Grignard reagent and oxygen gave methylisoamylcarbinol in 60% yield, b. p. 151–152° (736 mm.), n^{20}_{D} 1.4180, α-naphthylurethan, m. p. and mixed m. p. 84–85°.

Conversion of Methylneopentylcarbinol to its Chloride.—The carbinol was prepared in 64% yield by reduction of methyl neopentyl ketone,[17] b. p. 136.5° (738 mm.), n^{20}_{D} 1.4180. The carbinol (36 g.) saturated with hydrogen chloride and allowed to stand for eight weeks gave a 90% yield of chloride which was distilled through a 1.1 × 70 cm. column[5] to give mainly methylneopentylcarbinyl chloride, b. p. 93° (250 mm.), n^{20}_{D} 1.4180; d^{20}_{4} 0.855. Only 2 g. of low boiling material was obtained. The chloride was converted to the carbinol in the usual way and the latter was converted to the α-naphthylurethan, m. p. 83°, mixed m. p. 84°.

Summary

1. It has not been possible to convert methylisopropylcarbinol to the corresponding secondary chloride.

2. Four secondary carbinols having tertiary hydrogen atoms alpha to the carbinol group gave tertiary chlorides on treatment with hydrogen chloride at room temperature.

3. Three secondary carbinols having no branch in the alpha position reacted normally without rearrangement to give the secondary chlorides.

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[13] The yield of olefins was 30%, the higher boiling material only 2.5 g.

[14] *Cf.* deGraef, *Bull. soc. chim. Belg.*, **40**, 315 (1931).

[15] This chloride has been obtained by Levene and Mikeska, *J. Biol. Chem.*, **65**, 509 (1925), and by Maass and Sivertz, THIS JOURNAL, **47**, 2883 (1925). The iodide has been made by Umnova, *J. Russ. Phys.-Chem. Soc.*, **42**, 1530–1543.

[16] Vavon, *Compt. rend.*, **155**, 287 (1912).

[17] Whitmore and Homeyer, THIS JOURNAL, **55**, 4194 (1933).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Tertiary Butyl Chloride from Tertiary Amyl Chloride and Hydrogen Fluoride

BY J. H. SIMONS, G. H. FLEMING, FRANK C. WHITMORE AND W. E. BISSINGER

Bockemüller[1] states that alkyl chlorides, bromides and iodides are only slightly soluble in anhydrous hydrogen fluoride and that no reaction takes place when the alkyl halides are mixed with hydrogen fluoride. In the gaseous state at higher temperatures, and in the presence of a metallic fluoride catalyst, the alkyl halide will undergo double decomposition with hydrogen fluoride, yielding an alkyl fluoride. No investigations of the action of hydrogen fluoride on tertiary chlorides, bromides, or iodides, were found in the literature. The present study was started to fill this gap.

There have been obtained 10–17% yields of *t*-butyl chloride by treating *t*-amyl chloride with an equimolal quantity of anhydrous hydrogen fluoride at 0°. Besides the *t*-butyl chloride, there was also obtained a mixture probably containing hexyl, heptyl, decyl or undecyl (possibly both), and pentadecyl chlorides.

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[1] Bockemüller, Sammlung chemischer und chemisch-technischer Vortrage, 1936.

It is interesting to note the apparent ease of formation of the tertiary butyl group under the influence of certain catalysts. Gilman[2] found that *n*-amyl chloride, *n*-hexyl bromide, and *n*-octadecyl bromide, with the ethyl ester of 5-bromofuroic acid in the presence of aluminum chloride, form in each case the same product, ethyl 4-*t*-butyl-5-bromofuroate.

Experimental

The *t*-amyl chloride was prepared by stirring 20 moles (2120 g.) of commercial *t*-amyl alcohol with 6600 cc. of concentrated hydrochloric acid. The crude *t*-amyl chloride was washed with water, dried with anhydrous potassium carbonate, and distilled from potassium carbonate through a 123 × 2.5 cm. column (15 theoretical plates) packed with single turn glass helices,[3] boiling point 37–38° (150 mm.), $n^{20}\text{D}$ 1.4053.

In order to check the purity of this *t*-amyl chloride, 100 g. of it was redistilled through a 1.1 × 45 cm. column (8 theoretical plates). The first portion of distillate boiled at 84.5° (730 mm.), thus proving the absence of *t*-butyl chloride, boiling point 51°. The literature gives the boiling point of *t*-amyl chloride as 86° (760 mm.) and $n^{20}\text{D}$ 1.4054.

The anhydrous hydrogen fluoride was a commercial product received in steel cylinders.

The procedure in a typical run was as follows: 6 moles (120 g.) of hydrogen fluoride was distilled into a dry 1-liter copper flask which was packed in a salt–ice mixture; a copper tube served as the inner tube of the Liebig condenser used in this distillation. When the required amount of hydrogen fluoride had been introduced into the flask, 6 moles (636 g.) of *t*-amyl chloride was poured into the hydrogen fluoride. The copper flask was connected immediately to a 2-hole rubber stopper which was fitted with a mercury-seal copper stirrer and a reflux condenser of copper tubing. Stirring at 0° was continued for three days. A constant evolution of hydrogen chloride occurred. When this evolution ceased the reaction was considered complete. The mixture was poured on 200 g. of ice in a 2-liter separatory funnel and washed with cold 5% sodium bicarbonate solution until the lower water layer was basic to litmus. The oil was separated, washed with ice water and dried with three 15-g. portions of potassium carbonate. Finally it was distilled from 12 g. of carbonate through a 1.1 × 45 cm. column packed with glass helices, giving 70 g. of material boiling between 40 to 60°. Redistillation of this low boiling material yielded 60 g. of *t*-butyl chloride, boiling point 49–50° (735 mm.), $n^{20}\text{D}$ 1.3855. This was further identified by conversion to trimethylacetanilide and trimethylacetic acid and its anilide.

Identification of *t*-Butyl Chloride

A. Preparation of Trimethylacetanilide.—A sample (1.5 cc.) of the material of b. p. 49–50°, $n^{20}\text{D}$ 1.3855, was dissolved in 6 cc. of ethyl ether and converted to the Grignard compound in the usual manner; an ether solution of phenyl isocyanate was added until no further reaction was observed and the complex was then decomposed on ice and hydrochloric acid. The ether layer was separated, the ether removed on the steam-bath, and the solid anilide recrystallized once from petroleum ether; melting point 131°. After a second recrystallization from petroleum ether it melted at 132.5–133°; melting point of known trimethylacetanilide 132.5–133°; mixed melting point 132°.

B. Preparation of Trimethylacetic Acid and its Anilide.—In a similar manner 23 g. of the material boiling at 49–50°, $n^{20}\text{D}$ 1.3855, was dissolved in ether and converted to the Grignard compound; dry carbon dioxide gas was then bubbled into the cold mixture. The complex was decomposed on ice and hydrochloric acid and after separation of the ether layer and evaporation of the ether, the residual oil was distilled from a 25-cc. distilling flask. There was obtained 10.8 g. of trimethylacetic acid, boiling point 162–163°; melting point 28–33°.

A portion (1.5 g.) of this acid was converted to the acid chloride by refluxing with thionyl chloride. A benzene–aniline solution was added and the mixture heated on the steam-bath. Finally the benzene solution was washed with dilute acid, dilute alkali, and water, filtered, and evaporated to dryness. Recrystallized once from petroleum ether, the anilide melted at 132.5°; mixed melting point with known trimethylacetanilide 133–133.5°.

After the material boiling below 60° had been removed the pressure was reduced and the residue fractionated. The following table presents the summarized results of the distillation.

	B. p.				Exptl.	% Cl	
Fractions	°C.	Mm.	Index	Gm.	mol. wt.	Found	Remarks
1	40–60	735	1.3760–1.3865	70			*t*-Butyl chloride
2	37–41	146	1.4060	55			Unreacted *t*-amyl chloride
3–5	32–49	92	1.4062–1.4140	23			
6–9	49–53	92	1.4152–1.4175	42	123	28.1	
11–13	19–30	5.5	1.4222–1.4257	20			Hexyl and heptyl chlorides
14–16	30–32	5.0	1.4275–1.4282	25			
19–22	49–54	5.0	1.4328–1.4372	26			
23–25	54–57	5.0	1.4382–1.4400	18			Decyl or undecyl chlorides
26–28	57–63	5.0	1.4409–1.4420	25	188	17.7	
30–31	67–71	4.0	1.4440–1.4445	12			
33–35	78–91	4.0	1.4471–1.4479	16	236	11.2	Pentadecyl chloride

There was no fluorine in the fractions corresponding to the hexyl and heptyl chlorides. No tests for fluorine were made on the higher fractions.

Some preliminary investigation of this reaction had been carried out by D. E. Badertscher in 1933 in this Laboratory. A further study of this type of reaction is in progress.

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(2) Gilman, Burtner and Turck, This Journal, **57**, 909 (1935).

(3) Wilson, Parker and Laughlin, *ibid*, **55**, 2795 (1933).

Summary

t-Butyl chloride in 10–17% yields has been obtained by treating *t*-amyl chloride with anhydrous hydrogen fluoride at 0°.

In addition to the *t*-butyl chloride, there was obtained a mixture probably containing hexyl, heptyl, decyl or undecyl, and pentadecyl chlorides.

STATE COLLEGE, PENNSYLVANIA RECEIVED JULY 1, 1938

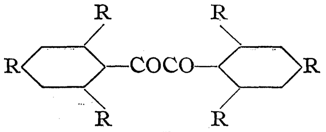
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

The Action of Methylmagnesium Halides on 2,4,6-Trisubstituted Benzoyl Chlorides

BY REYNOLD C. FUSON, J. H. VAN CAMPEN AND D. E. WOLF

The reaction of 2,4,6-trisubstituted benzoyl chlorides with methylmagnesium halides has been shown to give rise to three different types of products, depending on the nature of the substituents. In order to determine the influence of the substituents on the course of the reaction we have studied the action of methylmagnesium halides on certain benzoyl chlorides carrying alkyl groups or halogen atoms in the *ortho* positions.

In all cases the initial reaction is evidently either (1) coupling of the acid chloride to yield a benzil or (2) methylation to give the corresponding methyl ketone. For example, with 2,4,6-trimethylbenzoyl chloride and 2,4,6-triethylbenzoyl chloride both types of reactions are observed. The corresponding hexaalkylbenzils (I) and 2,4,6-trialkylacetophenones (II) are formed in nearly equal amounts.[1]



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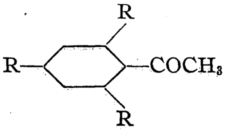
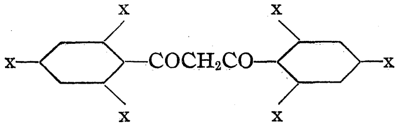


II

However, halogen atoms in the *ortho* positions suppress the coupling reaction entirely. 2,4,6-Trichlorobenzoyl chloride gives none of the benzil. The methyl ketone appears to be the primary product. It is of interest that this ketone is acylated readily, and under the conditions used is isolated chiefly as the corresponding 1,3-diketone (III, x = Cl).[2]

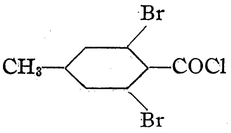


III

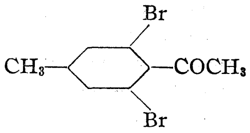
2,4,6-Tribromobenzoyl chloride reacted very sluggishly with methylmagnesium bromide or iodide, and the chief product was the 1,3-diketone, di-(2,4,6-tribromobenzoyl)-methane. The methyl ketone also was isolated in small amounts. Bromination of the diketone gave a heptabromo derivative, which could be reduced to the parent diketone by treatment with hydrogen iodide. The heptabromo compound, like the original diketone, gave a red color with an alcoholic ferric chloride solution. These facts serve to confirm the structures of the compounds in question.

Some evidence also is available to indicate that the 1,3-diketone is the result of a secondary reaction involving the methyl ketone. When the iodomagnesium enolate of the latter was treated with 2,4,6-tribromobenzoyl chloride the 1,3-diketone (III, x = Br) was formed.

One condensation was carried out with 2,6-dibromo-4-methylbenzoyl chloride (IV) and methylmagnesium iodide.



IV



V

The chloride was added slowly to a concentrated solution containing a great excess of the Grignard reagent. In this case also the reaction was exclusively of the second type; however, it stopped at the first stage giving only the methyl ketone (V). The identity of the latter was confirmed by converting it into the benzal derivative.

Experimental

A. Preparation of the Acid Chlorides

2,4,6-Trichlorobenzoyl Chloride.—This compound was prepared from 2,4,6-trichloroaniline by way of the nitrile and acid. For the synthesis of the nitrile a modification of Montagne's method[3] was employed. The nitrile was isolated by extraction and used without further purification.

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[1] Fuson and Corse, THIS JOURNAL, **60**, 2063 (1938).

[2] Ross and Fuson, *ibid.*, **59**, 1508 (1937).

[3] Montagne, *Rec. trav. chim.*, **21**, 376 (1902).

It was converted into the acid chloride by the method of Fuson, Bertetti and Ross.[4]

2,4,6-Tribromobenzoyl Chloride.—Attempts were made to prepare 2,4,6-tribromobenzonitrile using the diazotization methods of Montagne[3] and de Milt and Van Zandt.[5] However, a modification of the method of Schoutissen[6] proved to be more satisfactory. The following is an illustrative procedure for the diazotization and subsequent replacement.

One hundred grams of 2,4,6-tribromoaniline was dissolved in 300 cc. of concentrated sulfuric acid and the solution cooled to 0°. To this mixture was added an ice-cold solution of nitrosyl sulfuric acid, prepared by adding 28 g. of sodium nitrite to 300 cc. of ice-cold concentrated sulfuric acid, warming and stirring until clear. The temperature was kept below 10° while 600 cc. of 85% phosphoric acid was added dropwise, with vigorous stirring. The stirring was continued for an hour after the addition was complete. The solution was poured, with stirring, into a warm (60°) solution of 280 g. of potassium cyanide and 275 g. of copper sulfate in 600 cc. of water. After about ten hours the mixture was filtered and the nitrile was removed from the mixture of solids by extraction with ether. The nitrile was used without purification. The yield of crude product was 90–100 g.

The hydrolysis of the nitrile was carried out according to the method of Fuson, Bertetti and Ross.[4] The reaction mixture was stirred and refluxed for seven to eight hours instead of three.

Dry, crystalline 2,4,6-tribromobenzoic acid was mixed with slightly less than the molar equivalent of phosphorus pentachloride. The reaction commenced spontaneously and the mixture soon liquefied. The mixture was then heated on the steam cone for two hours. The phosphorus oxychloride was distilled under slightly reduced pressure and the acid chloride collected at 140–141° (2 mm.); 152–154° (4 mm.). The colorless distillate solidified in the receiver; m. p. 47–49°.[7] The yield was 88–92% of the theoretical.

2,6-Dibromo-4-methylbenzoyl Chloride.—2,6-Dibromo-4-methylbenzonitrile, prepared from the corresponding amine by the method of Montagne,[3] was dissolved in a mixture of sulfuric acid, acetic acid and water in the ratio 2:1:1 by volume. After being refluxed, with stirring, for eight or nine hours the reaction mixture was cooled to 0° and an excess of sodium nitrite was added in concentrated aqueous solution. The resulting acid was converted to the acid chloride by the action of phosphorus pentachloride. The melting point of the acid chloride corresponded to that reported by Buning.[8]

B. Reaction of the Acid Chlorides with Methylmagnesium Halides

2,4,6-Trichlorobenzoyl Chloride.—A number of runs according to the procedure of Ross and Fuson[2] gave yields of 32–40% of the theoretical amount of di-(2,4,6-trichlorobenzoyl)-methane. The use of a two-fold excess of 0.5 molar solution of methylmagnesium bromide solution seems to give the best results.

The structure of the diketone was confirmed by transforming it into the dibromide and reducing the latter to regain the original diketone. The reduction of the dibromide was carried out as follows.

One gram of powdered potassium iodide and 0.8 cc. of water were added to 100 cc. of a saturated solution of potassium iodide in acetone. A solution of 1 g. of di-(2,4,6-trichlorobenzoyl)-dibromomethane and 1 cc. of concentrated hydrochloric acid in 25 cc. of acetone was added dropwise, with stirring, to the iodide solution over a period of about thirty minutes. The solution was stirred for twelve hours, condensed with a stream of air to about 35 cc. and then poured into 150 cc. of water. The iodine was removed with sodium bisulfite, the solution extracted with ether, and the ethereal extract dried over anhydrous magnesium sulfate. Distillation of the ether left a solid residue which was recrystallized from methyl alcohol, giving 0.7 g. of di-(2,4,6-trichlorobenzoyl)-methane, m. p. 158–160°. The yield was 96% of the theoretical amount.

Di-(2,4,6-trichlorobenzoyl)-bromomethane.—One and five-tenths grams of di-(2,4,6-trichlorobenzoyl)-methane was dissolved in 150 cc. of glacial acetic acid, 5 cc. of bromine was added all at once, and the mixture was allowed to stand at room temperature for three to five days. The solution was poured, with stirring, into 1500 cc. of water and sodium bisulfite added to discharge the bromine color; an excess of bisulfite was carefully avoided. After standing for several hours the product was collected on a filter and dried. The crude di-(2,4,6-trichlorobenzoyl)-bromomethane weighed 1.7 g. After repeated recrystallization from low-boiling petroleum ether this material melted at 163–164°. It was very soluble in ether, chloroform, carbon tetrachloride, benzene and dioxane, and was slightly soluble in ethyl alcohol, methyl alcohol, ethyl acetate and petroleum ether. It was insoluble in dilute alkali, gave a red color immediately with alcoholic ferric chloride solution and imparted a yellow color to concentrated sulfuric acid.

One gram of this material was recovered unchanged after refluxing for three days in a solution of 5 cc. of bromine in 100 cc. of chloroform.

Anal. Calcd. for $C_{15}H_5O_2Cl_6Br$: C, 35.33; H, 0.99; mol. wt., 510. Found: C, 35.46; H, 1.09; mol. wt., 489.

2,4,6-Tribromobenzoyl Chloride.—2,4,6-Tribromobenzoyl chloride was refluxed for ninety hours at 50° with two equivalents of 0.5 molar methylmagnesium bromide or iodide and the resulting mixture decomposed with dilute hydrochloric acid. The ether was evaporated by a stream of air and the solid separated by decantation through a Büchner funnel. The solid was twice washed with ether by decantation and the aqueous solution extracted with three portions of ether. The combined ethereal extract was dried over anhydrous sodium sulfate.

The yield of this crude solid, di-(2,4,6-tribromobenzoyl)-methane, was 38% of the theoretical. After four recrystallizations from a mixture of benzene and alcohol, this compound melted at 244–245°, with decomposition.

Anal. Calcd. for $C_{15}H_6O_2Br_6$: C, 25.78; H, 0.86; Br, 68.77; mol. wt., 698. Found: C, 25.84; H, 0.89; Br, 68.79; mol. wt., 669.

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(4) Fuson, Bertetti and Ross, This Journal, **54**, 4380 (1932).

(5) De Milt and Van Zandt, *ibid.*, **58**, 2044 (1936).

(6) Schoutissen, *ibid.*, **55**, 4531 (1933).

(7) Sudborough, *J. Chem. Soc.*, **67**, 587 (1895).

(8) Buning, *Rec. trav. chim.*, **40**, 327 (1921).

The di-(2,4,6-tribromobenzoyl)-methane was soluble in chloroform, carbon tetrachloride and benzene, slightly soluble in *n*-butyl alcohol and petroleum ether, but quite insoluble in ether, alcohol, acetic acid, ethyl acetate and methyl alcohol. It was not affected by boiling for three days with a 50% solution of sodium hydroxide in 20% alcohol. The compound gave a red color in alcoholic ferric chloride solution and a yellow color with concentrated sulfuric acid. A blue-gray copper derivative was formed when a benzene solution of the compound was shaken for thirty minutes with a saturated aqueous solution of copper acetate. The copper derivative could be purified by dissolving in chloroform and reprecipitating with a small amount of alcohol.

Distillation of the ether from the ethereal extract obtained above left a dark, oily residue. By steam distillation and subsequent recrystallization from high-boiling petroleum ether 2,4,6-tribromoacetophenone was obtained, m. p. 86–90°. After recrystallization this material melted at 93°. No depression in the melting point was noted when this material was mixed with an authentic sample of 2,4,6-tribromoacetophenone prepared by diazotization of 3-amino-2,4,6-tribromoacetophenone. The yield of methyl ketone was about 16% of the theoretical.

No advantage was apparent in using chlorobenzene along with ether as a solvent and at the same time carrying out the reaction at 80–90°.[9]

2,4,6-Tribromoacetophenone.—Seventy-five cubic centimeters of 2.2 molar methylmagnesium iodide was heated on a water-bath until no more ether would distil. At this point 45 cc. of ether had been collected. The condenser was then set for refluxing and stirring begun. A solution of 5 g. of 2,4,6-tribromobenzoyl chloride in 15 cc. of anhydrous benzene was added dropwise, the rate of addition being adjusted so that forty-five minutes was required for the entire operation. Throughout the reaction the temperature was maintained at 95° by means of a water-bath. The stirring was continued for eighty minutes, the mixture cooled, and 50 cc. of anhydrous ether added. The resulting solution was poured into ice and hydrochloric acid, the ether layer separated and the aqueous layer extracted with ether. The combined ethereal extract was washed with dilute bicarbonate solution, with water and then dried over anhydrous magnesium sulfate. Distillation of the ether left a brown oil. After steam distillation of this oil and recrystallization of the distillate from high-boiling petroleum ether, 2.2 g. of a solid material was obtained; m. p. 80–86°. After recrystallization this material melted at 92°. It was shown by mixed melting point to be 2,4,6-tribromoacetophenone. The yield was 46% of the theoretical.

Di-(2,4,6-tribromobenzoyl)-methane from 2,4,6-Tribromoacetophenone and 2,4,6-Tribromobenzoyl Chloride.—Two grams of 2,4,6-tribromoacetophenone was dissolved in 25 cc. of anhydrous benzene and to this was added 3.1 cc. of 2.2 molar methylmagnesium iodide. The solution was refluxed for two hours. Two and one-tenth grams of 2,4,6-tribromobenzoyl chloride was added and the resulting mixture was refluxed for thirty hours. The mixture was poured into dilute hydrochloric acid, stirred well and the benzene layer separated and dried. Distillation of the benzene left a residue of liquid and solid. Alcohol was added and the solid collected on a filter. The di-(2,4,6-tribromobenzoyl)-methane thus obtained weighed 2.1 g. and melted at 239–241°, with decomposition. After recrystallization from benzene and alcohol the compound melted at 244–245°, with decomposition. The yield of diketone was 54% of the theoretical.

Di-(2,4,6-tribromobenzoyl)-bromomethane

1. With Bromine in Chloroform.—Eighty-five hundredths of a gram of di-(2,4,6-tribromobenzoyl)-methane was dissolved in 100 cc. of chloroform. Six cubic centimeters of bromine was added all at once and the mixture allowed to stand for three days at room temperature under the light of a 300-watt lamp. The resulting solution was washed with dilute sodium bisulfite solution, with water and then dried over anhydrous magnesium sulfate. Evaporation of the solvent and recrystallization from chloroform gave 0.7 g. of di-(2,4,6-tribromobenzoyl)-bromomethane which softened at 264° and melted, with decomposition, at 270–272°. The yield was 74% of the theoretical. After four recrystallizations from chloroform the compound softened at 264° and decomposed at 272–273°. If the tube containing the material was inserted in the bath at 260°, the compound softened at 266° and decomposed at 274–276°. The decomposition point as determined on the Maquenne block was 282°.

Anal. Calcd. for $C_{15}H_5O_2Br_7$: C, 23.20; H, 0.65. Found: C, 23.45; H, 1.01.

The solubility of this compound is very similar to that of di-(2,4,6-tribromobenzoyl)-methane. The substance gives a red color with alcoholic ferric chloride solution, the color deepening with warming, and imparts a yellow color to concentrated sulfuric acid.

2. With Sodium Hypobromite.—One gram of di-(2,4,6-tribromobenzoyl)-methane was dissolved in 20 cc. of pyridine and this solution added to 100 cc. of 10% sodium hypobromite solution. The mixture was shaken for seven days at room temperature and then extracted with two 75-cc. portions of benzene. This extract was dried over calcium chloride and the solvent distilled under reduced pressure. Recrystallization of the solid residue from chloroform gave 1 g. of di-(2,4,6-tribromobenzoyl)-bromomethane which softened at 264° and decomposed at 270–272°. The yield was 90% of the theoretical.

Reduction of Di-(2,4,6-tribromobenzoyl)-bromomethane.—One gram of this compound was reduced by the method described above for di-(2,4,6-trichlorobenzoyl)-bromomethane. Eight-tenths of a gram of di-(2,4,6-tribromobenzoyl)-methane was obtained, m. p. 233–238°.

Reaction of 2,6-Dibromo-4-methylbenzoyl Chloride with Methylmagnesium Iodide.—Thirty-two grams of the acid chloride in twice its volume of dry ether was added over a period of one hour to a boiling 5 molar solution of methylmagnesium iodide which contained a nine-fold excess of the reagent. The addition was accompanied by vigorous stirring. The reaction mixture was diluted with 800 cc. of ether and poured slowly into ice and dilute hydrochloric acid. By extraction with ether the methyl ketone was obtained as a red oil which crystallized when cooled. After five recrystallizations from 95% ethanol,

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[9] Gilman and St. John, *Rec. trav. chim.*, **49**, 222 (1930).

the solution being treated each time with Darco, the white crystalline product melted at 53–54°.

Anal. Calcd. for $C_9H_8OBr_2$: C, 37.03; H, 2.74; Br, 54.75; mol. wt., 292. Found: C, 37.41; H, 3.08; Br, 54.69; mol. wt., 286.

The Benzal Derivative of 2,6-Dibromo-4-methylacetophenone.—The identity of the methyl ketone was confirmed by condensing it with benzaldehyde. About 6 g. of the crude ketone was mixed with 20 cc. of 10% sodium hydroxide solution, 10 cc. of 95% ethyl alcohol and 10 cc. of benzaldehyde. The mixture was shaken for twenty hours at room temperature. At the end of this period there was a yellow mixture of crystals and oil at the bottom of the flask. The entire mixture was shaken with ether which was then washed with bisulfite solution. The ether solution was washed with water, dried and evaporated giving a crystalline residue. After the crystals were washed with petroleum ether and recrystallized three times from ethyl alcohol they melted at 96–97°.

Anal. Calcd. for $C_{16}H_{12}OBr_2$: C, 50.57; H, 3.16; Br, 42.06; mol. wt., 380 Found: C, 51.06; H, 3.21; Br, 42.43; mol. wt., 379.

Summary

2,4,6-Trihalobenzoyl chlorides react with methylmagnesium halides to give the corresponding di-(2,4,6-trichlorobenzoyl)-methanes. Under suitable conditions the methyl ketone, undoubtedly an intermediate in the reaction, can be isolated.

The structure of the 1,3-diketones was proved by converting them to the corresponding mono- or dibromides and then regaining the original diketone by debromination.

2,6-Dibromo-4-methylacetophenone was obtained by the interaction of 2,6-dibromo-4-methylbenzoyl chloride and an excess of methylmagnesium iodide.

URBANA, ILLINOIS RECEIVED JUNE 17, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Reformatsky Condensations Involving Vinylogs of Haloacetic Esters

BY REYNOLD C. FUSON, R. T. ARNOLD AND H. G. COOKE, JR.

The extension of the Reformatsky method to vinylogs of haloacetic esters was attempted with the hope of obtaining a method of synthesizing carotenoid chains. The general reaction sought was the following

$$XCH_2(CH{=}CH)_nCOOR \xrightarrow[Zn]{RCHO} R(CH{=}CH)_{n+1}COOR$$

Results obtained with ethyl γ-bromo- and γ-iodocrotonate show that the desired reaction takes place. The value of the method in synthetic work would appear to be conditioned by the availability of the γ-halocrotonates.

Ethyl γ-bromo- and γ-iodocrotonate react with benzaldehyde in the presence of zinc to give an oil which can be hydrolyzed to cinnamylideneacetic acid

$$XCH_2CH{=}CHCOOC_2H_5 \xrightarrow{C_6H_5CHO} C_6H_5(CH{=}CH)_2COOH$$

Cyclohexanone reacts similarly, giving the expected unsaturated ester, $C_6H_{11}(CH{=}CH)_2COOC_2H_5$.

Ethyl iodocrotonate also was condensed with *p*-chlorobenzaldehyde to give *p*-chlorocinnamylideneacetic acid. This acid was synthesized for comparison from *p*-chlorocinnamaldehyde and malonic acid.

It was of particular interest to compare the behavior of ethyl γ-iodocrotonate with that of the corresponding saturated ester, ethyl γ-iodobutyrate, to see what influence the vinylene linkage really had. The condensation reaction depends chiefly on the reactivity of the halogen atom which in turn is due presumably to the activating influence of the carbethoxy group. The transfer of this effect should be much more efficient in the vinylogs of haloacetic esters than in the corresponding saturated esters. This was found to be the case. Ethyl γ-iodobutyrate condenses with benzaldehyde in the presence of zinc to give the normal Reformatsky condensation but the reaction proceeds very slowly and the yields are almost negligible.

Experimental

The Condensation of Ethyl γ-Bromo- and γ-Iodocrotonate with Benzaldehyde.—Nineteen grams of ethyl γ-iodocrotonate[1] in 20 cc. of dry, peroxide-free butyl ether was added dropwise to a mixture of 16 g. of benzaldehyde, 30 cc. of butyl ether and 5.5 g. of zinc dust. The zinc dust was cleaned by treatment for a few seconds with dilute hydrochloric acid and subsequent washing with water, acetone and dry benzene. It was not allowed to stand in contact with the air. The mixture was refluxed, with stirring, for thirty-six hours, then decomposed with very

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(1) Braun, THIS JOURNAL, **52**, 3174 (1930).

dilute cold hydrochloric acid. Careful fractionation of the ether solution gave 2.3 g. of a viscous yellow oil; b. p. 162–165° (4 mm.).

The use of an equivalent amount of ethyl γ-bromocrotonate in the above process gave approximately 1 g. of the same high-boiling oil. Treatment of this oil with phenyl isocyanate in a closed, evacuated tube gave *sym*-diphenylurea. Oxidation with a sodium dichromate–sulfuric acid mixture converted the oil to benzoic acid.

The facts indicated that the oil was the expected hydroxy ester. Analysis showed, however, that it was impure, and it was subjected to *hydrolysis*. One cubic centimeter of the oil was added to a saturated solution of potassium hydroxide in ethyl alcohol and the mixture was allowed to stand overnight. Dilution with water followed by careful acidification with dilute sulfuric acid gave a solid which after recrystallization from benzene weighed 0.6 g. and melted at 165°. Admixture of a known sample of cinnamylideneacetic acid[2] did not depress the melting point.

The Condensation of Ethyl γ-Iodocrotonate with *p*-Chlorobenzaldehyde.—Fourteen grams of pure *p*-chlorobenzaldehyde and 6 g. of clean zinc dust were placed in a 500-cc., round-bottomed, three-necked flask containing 50 cc. of dry benzene and equipped with two efficient reflux condensers. The solution was heated to boiling and a solution of 20 g. of ethyl γ-iodocrotonate in 20 cc. of dry benzene was added dropwise. The reaction was highly exothermic, and an ice-bath was used to keep the ebullition from becoming too vigorous. After the addition was complete the mixture was refluxed for ten hours and decomposed with dilute hydrochloric acid and ice. The benzene layer gave 8.7 g. of a yellow oil; b. p. 180–185° (4 mm.). As in the case of benzaldehyde, analysis of this ester indicated that it was partially dehydrated.

***p*-Chlorocinnamylideneacetic Acid.**—One gram of the yellow oil was dissolved in 30 cc. of saturated alcoholic potassium hydroxide solution and allowed to stand overnight at room temperature. The mixture was diluted with water and acidified with dilute sulfuric acid. The precipitated *p*-chlorocinnamylideneacetic acid was recrystallized from ethanol, m. p. 251° (corr.), with decomposition.

Anal. Calcd. for $C_{11}H_9O_2Cl$: C, 63.30; H, 4.30. Found: C, 63.24; H, 4.45.

For comparison this acid was synthesized from *p*-chlorocinnamaldehyde and malonic acid by a method similar to that used by Dutt[2] for the synthesis of cinnamylideneacetic acid. To a solution of 7 g. of the aldehyde and 6 g. of the acid in 30 cc. of pyridine was added 3 cc. of piperidine, and the mixture refluxed for twenty hours. It was then poured into 250 cc. of dilute sulfuric acid and the dark gray precipitate was recrystallized first from glacial acetic acid and then repeatedly from 95% ethyl alcohol. The *p*-chlorocinnamylideneacetic acid formed in white flakes melting at 251° (corr.), with decomposition. No depression of melting point was noted when this acid was mixed with that prepared by the Reformatsky method. The methyl ester (from methyl alcohol) melted at 132° (corr.).

Anal. Calcd. for $C_{12}H_{11}O_2Cl$: C, 63.60; H, 4.90. Found: C, 64.32; H, 4.91.

The Condensation of Ethyl γ-Iodocrotonate with Cyclohexanone.—Fifteen grams of ethyl γ-iodocrotonate in 10 cc. of dry benzene was added dropwise to 50 cc. of benzene containing 12 g. of cyclohexanone and 4 g. of clean zinc dust. The mixture was refluxed for eight hours after the initial vigorous reaction had subsided and then decomposed with dilute sulfuric acid. Fractionation of the dried benzene solution produced 6.2 g. of the ethyl ester; it is a colorless oil boiling at 143–148° (8 mm.). Bromine and permanganate tests for unsaturation were positive.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.23; H, 9.48. Found: C, 74.28; H, 9.28.

Ethyl γ-Iodobutyrate.—Ethyl γ-chlorobutyrate prepared according to the method of Henry[3] was converted into the iodo ester by treatment with sodium iodide. A mixture of 127 g. of the chloro ester, 450 cc. of acetone and 127 g. of sodium iodide was shaken for three hours at 27°. Only 30 g. of sodium chloride separated. The mixture was then refluxed for two hours, filtered and the filtrate poured into 1 liter of ether. The ether solution was washed with water containing about 1% of sodium thiosulfate. Fractionation of the ether layer gave 130.6 g. or 63.5% of the theoretical amount of the iodo ester. The ester boiled at 84–85° (4 mm.).

Anal. Calcd. for $C_6H_{11}O_2I$: C, 29.75; H, 4.55. Found: C, 29.61; H, 4.61.

The Condensation of Ethyl γ-Iodobutyrate with *p*-Chlorobenzaldehyde.—To a boiling mixture of 75 cc. of benzene, 17.5 g. of *p*-chlorobenzaldehyde, and 8 g. of clean zinc was added dropwise a solution of 30 g. of ethyl γ-iodobutyrate in 30 cc. of benzene. The mixture was refluxed for twenty-four hours, cooled, decomposed with water and filtered through bone charcoal. The benzene layer yielded 10.3 g. of *p*-chlorobenzaldehyde, 4.3 g. of ethyl γ-iodobutyrate, 0.7 g. of a liquid boiling at 195–200° (3 mm.) (m. p. 122–123°) and some tarry products. The compound melting at 122–123° (from ethanol) had the composition of the expected unsaturated ester.

Anal. Calcd. for $C_{13}H_{15}O_2Cl$: C, 65.41; H, 6.29. Found: C, 65.26; H, 6.37.

Summary

The Reformatsky condensation has been extended to vinylogs of haloacetic esters. Ethyl γ-bromo- and γ-iodocrotonate have been condensed with benzaldehyde to give cinnamylideneacetic acid. *p*-Chlorocinnamylideneacetic acid has been made from *p*-chlorobenzaldehyde in a similar manner. Ethyl γ-iodobutyrate undergoes this type of condensation only with difficulty and in very low yield.

URBANA, ILLINOIS RECEIVED JUNE 18, 1938

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(2) Dutt, *J. Ind. Chem. Soc.*, **1**, 297 (1924–25).

(3) Henry, *Bull. soc. chim.*, **45**, 341 (1886).

NOTES

Structure of Lignin

By A. B. Cramer, M. J. Hunter and Harold Hibbert

The authors have been able to isolate recently, from spruce wood, by organic solvent extraction, an aromatic ketone in high yield (about 1–2% calculated on the weight of wood taken). This ketone is an oil, distilling at a bath temperature of 140–150° (0.004 mm.). On methylation it yields a well-defined white crystalline compound, formula $C_{13}H_{18}O_4$, m. p. 81–82°. The ketone structure of the latter product was proved by its additive power for the Grignard reagent and ready formation of a hydrazone. It also contains the veratryl radical since it gives veratric acid on oxidation.

Analysis of the methylated ketone.—Calcd. for $C_{13}H_{18}O_4$: C, 65.5; H, 7.6. Found: C, 65.5; H, 7.7. Total alkoxyl found (calculated as methoxyl): 38.7%. *Grignard machine analysis:* Addition, 0.85 mole per mole weight. Active hydrogen, 0.13 mole per mole weight.

The substance from which this crystalline product apparently is derived may be one of several isomers, each consisting of a guaiacyl group with a side chain of three carbon atoms containing a carbonyl and a hydroxyl group. The syntheses of the possible methylated compounds are now in progress. The extraordinary chemical reactivity of this type of parent substance would explain the previous difficulties associated with its isolation and characterization. Such a structure provides a satisfactory basis for interpreting the results obtained in the hydrogenation of methanol lignin at high temperatures and pressures [This Journal, **60,** 1467 (1938)].

The isolated ketone is accompanied by considerable quantities of what appears to be a polymerized product, an aldehyde, an acid, a neutral substance, and a carbohydrate-containing fraction. The combined yield of all of these products calculated on the weight of the wood taken amounts to a total of 5% in the case of spruce, and roughly 10% in the case of maple.

Work now in progress on oils from hard woods indicates the additional presence of derivatives containing the syringyl group and it is possible that this may be the fundamental chemical difference between soft and hard woods.

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Received July 6, 1938

The Preparation of Amyl Salicylates

By Andrew F. Freeman and H. L. Haller

A search of the literature discloses that, of the eight theoretically possible amyl salicylates, only the normal amyl[1] and the isoamyl ester[1,2] have their properties recorded. The procedure for the preparation of the latter has been given,[2] but no reference is made to the mode of formation of the former.

In the present communication methods of preparing primary normal amyl salicylate, secondary normal amyl salicylate, and tertiary amyl salicylate are described. Isoamyl salicylate from carefully purified isoamyl alcohol and salicylic acid also has been prepared, and its physical properties have been found to be identical with those recorded by Drion.[2]

The salicylates derived from the primary amyl alcohols were prepared with sulfuric acid as the esterifying agent, but when this procedure was applied to the secondary and tertiary amyl alcohols, dehydration of the alcohol occurred, and the yield of ester was negligible. It was found, however, that the secondary and tertiary esters could be obtained on condensation of salicylic acid chloride and the carbinol in the presence of a small quantity of anhydrous aluminum chloride. With the secondary carbinol this procedure gave satisfactory yields of ester, but with the tertiary carbinol the yield of ester was small.

Primary Normal Amyl Salicylate.—A commercial grade of primary amyl alcohol was purified by fractional distillation in a column of the type described by Dupont[3] and modified by Palkin.[4] The fraction employed in the esterification had the properties: b. p. 82–83.6° at 85 mm., n^{20}_D 1.4109, n^{26}_D 1.4090, d_{20} 0.8179, $[M]_D$ found 26.66, calcd. 26.815.

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(1) "International Critical Tables," Vol. I, McGraw-Hill Book Co., Inc., New York, 1926, p. 246.

(2) C. Drion, *Compt. rend.*, **39**, 122 (1854).

(3) G. Dupont, "Les Essences de Térébenthine," Paris, 1926, p. 57.

(4) S. Palkin, *U. S. Dept. Agr., Tech. Bull.*, **276** (1932); *Ind. Eng. Chem., Anal. Ed.*, **3**, 377 (1931); **7**, 436 (1935).

A mixture of salicylic acid (50 g.), primary normal amyl alcohol (200 g.), and concentrated sulfuric acid (2 cc.) was heated under a reflux condenser for about four hours. The apparatus was provided with a trap to remove the water that was formed. After the unreacted alcohol had been removed by distillation at atmospheric pressure, the residue was washed with 10% potassium carbonate and dissolved in ether, and the ether solution was dried over anhydrous sodium sulfate. The high-boiling material remaining after the removal of the ether was fractionated under reduced pressure by means of a Widmer column. The fraction that boiled at 116–121° and 1.4 mm. pressure was collected. The yield was 64 g.: $n^{27}\text{D}$ 1.5042, d_{27} 1.0552, $[M]\text{D}$ found 58.40, calcd. 58.30.

Anal.[5] Calcd. for $C_{12}H_{16}O_3$: C, 69.23; H, 7.87. Found: C, 69.15; H, 7.82.

In all these experiments some ether was formed, the amount increasing with the time of refluxing the reaction mixtures.

Secondary Normal Amyl Salicylate.—The methyl-*n*-propylcarbinol employed in this experiment was obtained by fractional distillation of a commercial grade of the carbinol in a Dupont–Palkin[4] type of still. The purified carbinol had the properties: b. p. 61.8–64.7° at 85 mm., $n^{25}\text{D}$ 1.4065, d_{25} 0.8041, $[M]\text{D}$ found 26.91, calcd. 26.815.

A mixture of 40 g. of salicylic acid, 50 cc. of thionyl chloride, and 0.08 g. of anhydrous aluminum chloride was heated under reflux in a water-bath maintained at 40–50° until the acid was entirely dissolved. The solution was then concentrated at reduced pressure to remove hydrogen chloride and excess thionyl chloride. One-half of the residue, a clear, greenish-yellow liquid, was transferred to a 125-cc. Erlenmeyer flask, and 30 cc. of methyl-*n*-propylcarbinol was added in small portions. The mixture was cooled in an ice-bath for several hours, and then, with the flask stoppered with a calcium chloride tube, allowed to stand for twenty-four hours. The solution was washed several times with ice water, then with a small quantity of dilute sodium bicarbonate, and again several times with ice water. The material was dried in ether over anhydrous sodium sulfate and, after removal of the ether, was purified by repeated distillation under reduced pressure. The yield was 9.8 g. The ester boiled at 107–110° and 4–5 mm.: $n^{25}\text{D}$ 1.5020, d_{25} 1.0470, $[M]\text{D}$ found 58.60, calcd. 58.30.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.23; H, 7.87. Found: C, 69.16; H, 7.81.

Tertiary Amyl Salicylate.—The tertiary amyl alcohol was a commercial grade which boiled at 100–102°. To the remaining half of the salicyl chloride prepared from 40 g. of salicylic acid by the procedure described above, 125 cc. of tertiary amyl alcohol was added slowly with vigorous shaking, the flask being kept cold in an ice-bath. Considerable hydrogen chloride was given off and some heat was evolved during the process. After standing in the ice-bath for several hours, the solution deposited a small quantity of crystalline material. This was removed by filtration, and the filtrate was distilled under reduced pressure. The pure ester was obtained by fractional distillation under reduced pressure. The yield was 6.5 g. It boiled at 84–86° and 3 mm. pressure: $n^{25}\text{D}$ 1.5064, d_{25} 1.0533, $[M]\text{D}$ found 58.74, calcd., 58.30.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.23; H, 7.87. Found: C, 69.12; H, 7.88.

BUREAU OF ENTOMOLOGY
AND PLANT QUARANTINE
U. S. DEPARTMENT OF AGRICULTURE
WASHINGTON, D. C.

RECEIVED JUNE 20, 1938

Reactions of Fluorinated Derivatives with Sodium, Potassium and Magnesium

BY ALBERT L. HENNE

Stable fluorinated compounds have been subjected to the action of magnesium in the hope of obtaining a Grignard reaction, and of sodium in the hope of obtaining a Wurtz reaction. In both cases the action was immediate and complete but the results were entirely different from those hoped for. The vigorous character and completeness of the reactions showed the futility of further work in the same direction and, therefore, the unexpected results are presented for publication. Some of these results (representative of what happens in other cases) were as follows.

(1) CHF_2CH_2I was dissolved in ether and allowed to drip onto clean magnesium. A reaction took place instantly. A small portion gave a faint test with Michler's ketone, indicating the formation of a Grignard compound; however, after a short period, the Grignard test was no longer positive. As the addition of CHF_2CH_2I to the magnesium was continued, a gas was evolved which was caught in bromine. It was observed that the reaction of this gas with bromine took place in the vapor phase, not the liquid, and the absorption was therefore incomplete. The gas was vinyl fluoride, as shown by the facts that the dibromide $CHFBrCH_2Br$ was the only compound found and that it was quite pure. Due to faulty experimental conditions only 50% of the vinyl fluoride was recovered as dibromide. The resulting magnesium salt was an equimolecular mixture of magnesium iodide and magnesium fluoride. Both salts are soluble in ether and in water, the fluoride as a colloid, and on account of this, a test for fluorine fails to give positive results before the magnesium fluoride has been brought from the colloidal to the crystalline stage.

(2) Attempts to cause CHF_2CH_2Br to act upon magnesium were unsuccessful.

(3) A piece of sodium or potassium reacted

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(5) We are indebted to Dr. W. G. Rose for the microcombustions.

energetically with CHF_2CH_2Br or CHF_2CH_2I. The reaction was run in ethyl ether, where it still was very vigorous and complete. Instead of acting upon the iodine atom only, the alkali metal removed one atom of fluorine and one atom of iodine, and gave a quantitative yield of sodium fluoride and sodium iodide or bromide. In doing so it behaved like magnesium or zinc.

(4) In contrast with the preceding result, fluorinated derivatives of methane (namely, CCl_2F_2, $CHClF_2$ and $CHBrF_2$) remained unaffected when passed through molten sodium.

THE MIDGLEY FOUNDATION
DEPARTMENT OF CHEMISTRY
THE OHIO STATE UNIVERSITY
COLUMBUS, OHIO
RECEIVED MAY 7, 1938

Preparation of Methylaluminum Chlorides

BY VINCENT F. HNIZDA AND CHARLES A. KRAUS

The methyl- and ethylaluminum chlorides have not been reported in the literature until recently. Walker and Willson[1] showed that methyl chloride reacts with aluminum metal when catalyzed by iodine or aluminum chloride, forming an unidentified product which "may be expressed" as Me_2AlCl plus $MeAlCl_2$. Hall and Nash[2] isolated the ethylaluminum chlorides from the products of polymerization of ethylene with a mixture of aluminum and aluminum chloride, and identified the double salt $EtAlCl_2 \cdot NaCl$. Later, Grosse[3] reported the melting and boiling points of the four methyl- and ethylaluminum chlorides.

Since none of these articles gives a satisfactory method of preparation of the compounds in question, it seems desirable to describe briefly the simple method which has been used successfully in these Laboratories since some time prior to the appearance of the articles cited. This description pertains primarily to the methyl chlorides; the ethyl chlorides and the methyl and ethyl bromides have been prepared similarly.

The desired amount of aluminum metal, preferably in an alloy such as Aluminum Company of America Alloy 12 (8% copper), is cut in clean, dry shavings or chips. These are placed in a glass or steel reaction vessel equipped with: halide inlet and product discharge lines, temperature and pressure gages, provision for heating and cooling, and a safety blow-out. The catalyst, about 0.1% of anhydrous aluminum chloride (or iodine, or the product of a previous preparation) is placed in one spot on top of the aluminum, and the reaction vessel closed. Air is pumped or flushed out, and methyl chloride gas introduced to a pressure of one atmosphere (or more, depending on the equipment used). If the reaction fails to start in one hour at room temperature, the charge is heated to 100°. Once started, the reaction is autocatalytic and highly exothermic. More methyl chloride is added, and cooling is applied, at such rates as to maintain a suitable rate of reaction and to keep the temperature of the charge below 75°. At higher temperatures, side reactions may occur with the formation of gas.

When no more methyl chloride is absorbed, the reaction is completed. The reaction of the aluminum is quantitative, while any iron or copper in the alloy remains unattacked. Side reactions are negligible. In a typical preparation, about 60 millimoles of aluminum in the form of alloy took up 88.9 millimoles of methyl chloride with the formation of only 0.9 millimole of methane; the nonvolatile residue contained no aluminum and 0.4 milliatom of chlorine; no iron or copper was detected in the distilled product.

The water-white, oily liquid is decanted or vacuum distilled, from the remaining metallic sludge, into a suitable closed container. If desired, this product can be diluted with methyl chloride to lower its viscosity and to facilitate the removal of samples from the container. Such methyl chloride solutions apparently are stable in glass or steel containers, and react slowly with copper or lead. The stability of solutions of the bromides and of the corresponding ethyl compounds is less assured, and is under investigation. In any case, a safety blow-out for the container is recommended. These aluminum compounds are, of course, highly reactive toward air, moisture, and other oxygen compounds; however, their oxidation or inflammation in air is not violent.

The product of the methyl chloride reaction is almost exactly an equimolecular mixture of dimethylaluminum chloride and methylaluminum dichloride. No evidence of either trimethylaluminum or of aluminum chloride is obtained on fractional distillation. Analysis is effected by hydrolysis of a sample with wet ether followed by dilute nitric acid, and determination of the amount of methane evolved, and of the aluminum and chloride content of the solution. In a typical preparation, this analysis gave 13.58 milliatoms of aluminum, 19.60 of chlorine, and 20.46 millimoles of methane, or a ratio of Me:Al:Cl of 1.507:1:1.443.

When the individual compounds are desired, they may be separated from their mixture by fractional vacuum distillation, or the dimethylaluminum chloride may be obtained in pure form by heating the mixture with excess sodium chloride and distilling the dimethyl compound from the monomethyl addition compound. Analysis of a typical distillate from the latter procedure gave 23.4 milliatoms of aluminum, 23.6 of chlorine, and 47.1 millimoles of methane, or a ratio of Me:Al:Cl of 2.01:1:1.01.

RESEARCH LABORATORIES
ETHYL GASOLINE CORPORATION
DETROIT, MICHIGAN

NEWPORT ROGERS LABORATORY
BROWN UNIVERSITY
PROVIDENCE, R. I.
RECEIVED AUGUST 1, 1938

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(1) W. O. Walker and K. S. Willson, *Refrig. Eng.*, **34**, 89, 126 (1937).

(2) F. C. Hall and A. W. Nash, *J. Inst. Petroleum Tech.*, **23**, 679 (1937).

(3) Abstracts, American Chemical Society, Dallas Meeting, 1938.

COMMUNICATIONS TO THE EDITOR

FORMATION OF AN ACID ANHYDRIDE BY THE ACTION OF WATER ON ORGANOMETALLIC COMPLEXES

Sir:

The formation of an acid anhydride by the addition of water to an organometallic complex has been observed in two different instances. A Grignard reagent, prepared from 4-bromo-7-isopropylhydrindene, when added to pure α-naphthoyl chloride in ether, yielded 50% of the expected ketone, 4-α-naphthoyl-7-isopropylhydrindene, together with 28% of the hydrocarbon, 4-isopropylhydrindene, and 22% of α-naphthoic anhydride. Another instance was found in the reaction between α-naphthoyl chloride and the lithium derivative from 2,7-dimethyl-4-bromohydrindene.[1] In this reaction the yield of ketone was small, but that of hydrocarbon and anhydride large. Particularly in this case, the formation of colored solutions showed the formation of complexes. A fleeting bright red color[2] gave place to a pale orange which disappeared on addition of water to give rise to the granular yellow anhydride.

The experimental procedure in both cases involved addition of the organometallic solution to α-naphthoyl chloride dissolved in absolute ether, ensuring an excess of acid chloride. To a solution of 15 g. of α-naphthoyl chloride (m. p. 21°) in absolute ether at −5° was added dropwise with stirring a Grignard reagent made from 10 g. of 4-bromo-7-isopropylhydrindene, 2 g. of magnesium and 60 cc. of ether. The solution was then refluxed for four hours. An equal volume of saturated sodium bicarbonate solution was added in order to remove the unchanged acid chloride. Upon distilling most of the ether and cooling, a yellow granular solid appeared. This proved to be α-naphthoic anhydride melting at 145°, and giving the same value upon admixture with an authentic sample. Upon distillation of the remaining material, 2 g. of 4-isopropylhydrindene, b. p. 88–90° at 1 mm., and 7.3 g. of 4-α-naphthoyl-7-isopropylhydrindene, b. p. 225–235° at 1.2 mm., were secured.

In the second instance, 0.70 g. of lithium wire was dissolved in a solution of 7 g. of 2,7-dimethyl-4-bromohydrindene[1] in 100 cc. of ether. This orange-colored solution was added over a period of three hours to 15 g. of α-naphthoyl chloride in 200 cc. of ether. The residue of lithium salt was washed with 50 cc. of ether and 100 cc. of benzene. Addition of 300 cc. of saturated sodium bicarbonate solution with stirring until the evolution of carbon dioxide had practically stopped (four hours) left a clear light red solution which was concentrated to about 50 cc. Upon standing, 7 g. of α-naphthoic anhydride, m. p. 145–146°, separated. The substance was identified by its analysis and melting point, and by hydrolysis with alcoholic sodium hydroxide to give α-naphthoic acid melting at 160–161°. From the bicarbonate solution was recovered 9 g. of α-naphthoic acid (air-dried overnight). Distillation of the filtrate from the anhydride gave 3.5 g. of 2,4-dimethylhydrindene, b. p. 100–105° at 23 mm., and 1 g. of an oil, contaminated with α-naphthoic acid, b. p. 200–235° at 2 mm., presumably 4-α-naphthoyl-2,7-dimethylhydrindene.

Further study is in progress to determine the mechanism and limits of this curious reaction.

The Baker Laboratory of Chemistry
Cornell University
Ithaca, N. Y.
William F. Bruce

Received August 8, 1938

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[1] Bruce with Fieser, This Journal, 59, 480 (1937).

[2] Professor E. P. Kohler suggested at the time that this color may have been caused by iron in the lithium; however, no ferric hydroxide is found upon solution of the lithium in water.

CRYSTALLINE DIMETHYL ACETAL OF *d*-FRUCTOSE

Sir:

Application of the method developed in this Laboratory for the preparation of glycofuranosides [Pacsu and Green, This Journal, **58,** 1823 (1936); Green and Pacsu, *ibid.*, **59,** 1205, 2569 (1937); **60,** 2056 (1938)] to fructosediethylmercaptal resulted in the unexpected formation of crystalline dimethyl acetal of *d*-fructose. The substance was obtained in practically quantitative yield on the treatment of fructosediethylmercaptal with mercuric chloride in absolute methyl alcohol at −80°, in the presence of an excess of yellow mercuric oxide; m. p. 107–108° and $[\alpha]^{20}\mathrm{D}$ −45.6° in water solution. On acetylation, it readily gave a crystalline pentaacetate, with m. p. 109° and $[\alpha]^{20}\mathrm{D}$ 0° in chloroform solution. The free acetal crystallized from *n*-propyl alcohol in beautifully developed large prisms, which were not hygroscopic and were devoid of action toward Fehling's solution. The compound was found to be stable in neutral and alkaline solutions, but it suffered rapid decomposition at room temperature in acidic media. Experiments carried out in fermentation saccharimeters showed that while yeast was capable of fermenting fructosedimethylacetal in distilled water to give carbon dioxide, methyl and ethyl alcohols in almost quantitative yield, it was without any effect on the acetal in a citric acid–disodium phosphate buffer solution of *p*H 7. The action of different invertase samples on the acetal at *p*H 4.5 and *p*H 7 was found to be completely negative, although the same samples were very active on sucrose under identical conditions.

In view of the extreme sensitiveness of the acetal toward acid, the action of yeast in an unbuffered solution might be due to the fermentation of fructose liberated from the acetal by a trace of the acid of the yeast, rather than to a genuine enzymatic effect. This problem is now being investigated. A detailed account of the work will be published shortly.

FRICK CHEMICAL LABORATORY
PRINCETON UNIVERSITY
PRINCETON, NEW JERSEY
EUGENE PACSU

RECEIVED AUGUST 11, 1938

NEW BOOKS

Modern Theories of Organic Chemistry. By H. B. WATSON, D.Sc. (Wales), F.I.C., Head of the Department of Chemistry at the City of Cardiff Technical College. Oxford University Press, 114 Fifth Avenue, New York, N. Y., 1937. vii + 218 pp. 21 figs. 16.5 × 25 cm. Price, $4.50.

"Professor G. N. Lewis's conception of the sharing of one or more electron pairs by two atoms gave a new and illuminating picture of the bonds which link carbon atoms into chains and rings, and set organic chemists the task of interpreting the reactions of carbon compounds of various types in terms of the electronic structures of the molecules. .

"In this volume an attempt is made to present the modern viewpoint in a concise and simple form, and to show how the new conceptions have followed logically from the earlier views." As is evident from its size, the book does not undertake to be complete in detail, nor to provide an exhaustive bibliography. The chapters deal with: Theories of Chemical Combination; The New Physical Methods of Investigation; Applications of the Electronic Theory in Organic Chemistry, Strengths of Acids and Bases, The Inductive Effect; Substitution Reactions; General Discussion of the Application of the Electronic Theory in Organic Chemistry; Free Radicals; Compounds of Divalent Carbon and Allied Problems; Addition to Unsaturated Compounds; Tautomeric Change; Migrations from Side-Chain to Nucleus and Other Rearrangements; The Factors Determining Reaction Velocity; A Review of Some Stereochemical Problems.

The author has an exceptionally clear and logical style. This is at its best in the introductory chapters, which can be recommended not only to students, but to every organic chemist who wishes to consider what modern physics has done for the understanding of his science. Briefly Professor Watson has put the last fifteen years into their place in chemical history, and in this placing has built a vigorous viewpoint for the present.

In the electronic interpretation of organic reactions, certain English chemists have been pioneers. Their views might originally have been more cordially received in this country if presented inductively and in terms whose meanings are well known. Professor Watson has accomplished this. He has placed the horse consistently before the cart and has shown the necessity of each concept introduced. Proceeding on this basis, he uses fewer ultimate variables than have appeared in some discussions in this field.

Chapters 6 to 10 and 12 make a less unique contribution, for in their brevity they contain little material not usually included in courses in advanced organic chemistry. Even the consideration of evidence on specific problems is far from complete. Nevertheless, the clear and discriminating presentations of some of the problems are likely to be a better introduction for students than a more exhaustive descriptive treatment.

The printing of the book is up to the usual good standard of the Oxford University Press. The publishers have done well to put the price within the reach of most students and teachers.

PAUL D. BARTLETT

The Chemistry of the Sterids. By HARRY SOBOTKA, Chemist to the Mount Sinai Hospital, New York. The Williams and Wilkins Company, Mt. Royal and Guilford Avenues, Baltimore, Maryland, 1938. xiii + 634 pp. 15 × 23.5 cm. Price, $8.50.

The word "Sterids" is a newcomer to the terminology of the organic chemist. According to the author it "is meant to comprise sterols and steroids, *i. e.*, sterol-like substances." The introduction of this new term seems rather unfortunate. It might lead to some confusion, since the term "steroid," introduced only a few years ago, refers already to the derivatives of cyclopentenophenanthrene in general.

"The Chemistry of the Sterids" is not a textbook, but a handbook; it is a combination of a "Houben–Weyl," "Landolt–Börnstein" and "Beilstein" of steroid chemistry. The author has undertaken the laborious task of selecting from almost countless papers all the facts concerning the chemistry of steroids, and presenting them in a logical and readable form.

After an introductory chapter on the history of the chemistry of "sterids," the author deals with the various methods of structural research, steric considerations, the chemical properties of naturally occurring steroids and of carcinogens, and molecular compounds. Over 400 structural formulas, which have been brought together on 46 separate pages, serve to illustrate the text.

Then follows a compilation of the physical properties of steroids. This includes much invaluable and interesting information, such as, for instance, a complete list of the known absorption spectra of steroids and references to steroid crystallography.

The bulk of the book, 336 pages, is taken up by the "Beilstein" section, "a classified catalog of sterids and their derivatives recorded before January 1, 1937." Here over 3000 substances have been arranged according to a very ingenious system which should appeal to all investigators in this field. A very fine bibliography, covering over 60 pages, has been added.

Because it is essentially a handbook, this work cannot be recommended to serve as an introductory text to a student possessing only a scant knowledge of the complexities of steroid chemistry. However, it will be welcomed as an invaluable source of information by those investigators who have more than a passing interest for this field of research. The author deserves their gratitude for this compilation, which will save them many hours of search through an endless literature.

WERNER BERGMANN

Perspectives in Biochemistry. Thirty-one Essays Presented to Sir Frederick Gowland Hopkins by Past and Present Members of his Laboratory. Edited by JOSEPH NEEDHAM and DAVID E. GREEN. Cambridge University Press: The Macmillan Company, 60 Fifth Avenue, New York, N. Y., 1937. ix + 361 pp. Illustrated. 14.5 × 22.5 cm. Price, $4.75.

Scientific writing for the most part finds its way into journals whose reputations depend increasingly upon the size of their circulation and speed of publication. The exigencies of price curtail space and individual literary style is perforce sacrificed to a crisp staccato manner, highly satisfactory to enable large numbers of people rapidly to digest the contents of an article. Excellent from this point of view, there is little room for historical perspective, for philosophical rumination, or for guarded speculation. Although journals given over to reviews take care of the first need, rumination often becomes a private feast, and speculation is left for those who, having eschewed science for journalism, can assure the eager and expectant public precisely what kind of a world this will be fifty years hence.

Among the amenities left to men of science is the pleasant habit of dedicating volumes to those they revere, especially their old teachers. But the Festschrift, or jubilee volume, has tended, with the rest of scientific writing, to be a collection of papers written by colleagues or students in the same style, and often in the same journals to which they normally contribute. The book which we are reviewing is not in this tradition. It is not a collection of reprints from scientific journals. It is a series of essays in which each author has taken time "to speculate a little on the likely paths of future thought and discovery."

The value of this volume depends upon the backgrounds and scientific insight of the contributors. All have at one time or other been students of, or associated with, Sir Frederick Gowland Hopkins. Of the thirty-one essayists many have international reputations gained from important experimental studies. Writing in this book to honor Sir Frederick they are in festive mood. Instead of dedicating to their great teacher their last paper they have sent him their most far reaching thoughts regarding the significance of their work. The result is arresting. It is good to know what R. A. Peters thinks of "Proteins and Cell-Organization." J. D. Bernal contributes "A Speculation on Muscle." Szent-Györgyi writes on "Oxidation and Fermentation," and N. K. Adam on "Molecular Forces, Orientation and Surface Films." Sir Edward Mellanby writes on "Toxamins in Food," and A. J. Clark on "Drugs and Mankind." The remainder of the thirty-one essays are no less varied in subject matter or treatment. Although this would be a break with the practice of exempting those honored from contributions, one cannot help wishing that this very catholic volume also contained an essay by Sir Frederick Gowland Hopkins on "Perspectives in Biochemistry."

EDWIN J. COHN

The Chemistry and Technology of Rubber Latex. By C. FALCONER FLINT, Ph.D., D.I.C., A.I.C., A.R.C.S., B. Sc., Imperial Chemical Industries, Ltd. Foreword by Lt. Colonel B. J. EATON. D. Van Nostrand Co., Inc., 250 Fourth Ave., New York, N. Y., 1938. xx + 715 pp. Illustrated. 16 × 24 cm. Price, $14.00.

There are few people who by actual training are so well equipped to write a book on the chemistry and technology of rubber latex as is Dr. C. Falconer Flint. For many years a staff member of the Rubber Research Institute, of Malaya and now in charge of latex research and development with the Imperial Chemical Industries, Ltd., he combines personal experience of the raw material and its technical application. Although in the preface the author states that he used G. Génin's book "Chimie et Technologie du Latex de Caoutchouc" as a framework, he has not only brought this compilation up to date but has added freely to it, which justifies the reviewer to consider Flint's book as the outstanding contribution to the science and technology of rubber latex which has been written in English.

The first parts of the book present a short historical survey of the development of rubber plantations and earlier work on latex research. Then follows a discussion of the rubber trees, the physiology and formation of latex and its production. These chapters clearly show the earmarks of the present author. The composition and properties of latex are carefully worked out contributions followed by detailed discussions of latex coagulation, preservation, and concentration. In the latter chapter the latest process of concentration by electrodecantation has not yet been included.

The chapter on compounding of latex discusses in great detail dispersing agents for latex compounds and offers a series of such materials as examples. It is interesting to note that sulfonic acid derivatives of organic compounds are not mentioned, although today their extreme efficiency is an established fact.

In the discussion on the use of sulfur we find the statement that colloidal sulfur generally consists of an aqueous suspension containing from 50–60% dry matter, the particle size being several microns. Although this is a frequent misnomer, the reviewer feels that it should not be found in a scientific treatise. Disperse sulfur is the correct term.

The section treating accelerators can safely be considered as an entirely new contribution and should prove very helpful to every latex compounder. From the point of view of an impartial reviewer, it would have been commendable had somewhat more attention been given to accelerators and other special compounding ingredients placed on the market by other manufacturers than I. C. I.

Referring to the vulcanization of latex and specifically to the Vultex process, Dr. Flint makes it clear that in his opinion, also, the addition of ultra-accelerators to latex which results in a certain degree of vulcanization upon storage cannot be considered as a patent infringement. This is in accord with a recent decision by Judge Brewster in the District Court of Massachusetts, U. S. A.

Other chapters are devoted to the technical application of latex, such as dipping, impregnation of fibers and fabrics, latex thread,[1] sponge rubber, microporous rubber, moulded rubber goods, latex bonded hair, the use of latex in the paint and varnish industry. There are also chapters on adhesives, its use as an anti-corrosive coating, as a binder in the manufacture of brake-linings and abrasives, its application in can sealing, the production of artificial leather, its use in the insulation of cables, as an ingredient for road or floor coverings, and other constructional applications.

The last chapter is concerned with the physical testing of latex rubber and the production of artificial rubber dispersions and synthetic latices.

Dr. Flint's new book deserves high praise from all those interested in latex who wish to keep currently informed on the rapid development in this field. The author has taken pains to have literature and patent references as complete as possible in such a type of book. It may be deplored that the book followed the American custom of adding the references at the end of every chapter, instead of in the form of pagewise footnotes, as this is a disadvantage to the majority of readers.

The print of the book is easy to read and well set. From a detailed survey of the numerous figures and plates, among which the reviewer could not help noticing those copied from certain publications of his own, the reproductions of this book must be considered excellent. There are practically no typographical errors. The subject index needs amendment if the book is to be of value for quick reference. However, these minor objections are by way of constructive criticism only. The book as a whole is highly recommendable.

ERNST A. HAUSER

Die Korrosion von Nichteisenmetallen und deren Legierungen. (The Corrosion of Non-Ferrous Metals and their Alloys.) Edited by Prof. Dr. Phil. OTTO KRÖHNKE, Berlin-Schlachtensee, and Prof. Dr. Phil. GEORG MASING, Göttingen. Verlag von S. Hirzel, Königstrasse 2, Leipzig C 1, Germany, 1938. xxx + 901 pp. 409 figs. 17.5 × 25 cm. Price, RM. 66.50; bound, RM. 69.

This, the second volume of a series of four [see, THIS JOURNAL, **58**, 1508 (1936)], covers the corrosion of non-ferrous metals and their alloys. The space devoted to each of the several metals is roughly proportional to its technical importance as judged by the present requirements of science and technology (in Germany). Metals having no essential "technical importance," such as building materials, are not discussed at all.

A summary of the principal contents of the several sections follows. The methods of corrosion testing and research, pp. 1–59, are discussed by P. Brenner under the headings, general testing procedure, necessary data, under natural conditions, laboratory tests, measurements of the amount of corrosion, criticisms of testing methods, review of selected tests. Copper and copper alloys pp. 60–287, by O. Dahl and W. Wunder, copper pp. 60–149, brass pp. 149–227, tin bronzes pp. 227–248, aluminum bronzes pp. 248–263, copper–nickel alloys pp. 263–275, and ternary copper alloys containing nickel pp. 275–280, copper–silicon alloys, pp. 281–283, are separately discussed in detail under the headings, corrosion in general, in liquids, and in gases. There are also brief treatments of copper–beryllium alloys, pp. 283–286, alloys of copper with magnesium, cadmium, manganese, phosphorus, and silver, pp. 286–287.

The corrosion of pure aluminum by R. Sterner-Rainer, pp. 288–318, takes up the influence of impurities, of physical state, and of different corrosion agents. A section which deals in considerable length with the corrosion of aluminum cast alloys by R. Sterner-Rainer, pp. 319–384, includes the influence of the added alloy constituent on the chemical stability, resistance toward natural corrosion agents, corrosion by chemicals, influence of corrosion including surface coatings on aluminum cast alloys on specific properties. A long section on malleable aluminum alloys by P. Brenner, pp. 385–444, discusses alloy composition, review of malleable aluminum alloys, heat treatment and cold working, corrosion and simultaneous mechanical movement, testing procedure, corrosion stability of malleable aluminum alloys, metal clad industrial materials. Magnesium and magnesium alloys by W. Schmidt and W. Schultze, pp. 445–477, discusses the influence of alloying metals, atmospheric attack, various corrosion protective measures. A lengthy discussion of lead and lead alloys by M. Werner, pp. 478–595, includes the physi-

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(1) Here the reviewer misses a reference to the manufacture of "constrolastic" thread, which in his opinion certainly constitutes one of the most interesting developments of the last years.

cal and mechanical properties of lead, general theory of corrosion stability, pure lead, lead alloys, technical lead and impurities, applicability of lead as corrosion resistant industrial material, a few special questions on the behavior of lead. A lengthy section on zinc pp. 596–670 by W. Wiederholt, discusses the electrochemical and chemical behavior of zinc in water, salt solutions and acids, in alkalies, in inorganic and organic compounds, in gases, in technical applications, and behavior of zinc alloys. Cadmium, pp. 671–685, and tin, pp. 686–721, by W. Wiederholt includes electrochemical and chemical behavior. Tungsten, molybdenum, and chromium, pp. 722–723, nickel and its alloys, and cobalt, pp. 724–764, are discussed by W. Rohn and C. Francke. They include general theory, testing procedures, nickel and its alloys in daily use and in the chemical industry, nickel and cobalt alloys with metals of the chromium group, nickel and its alloys at high temperatures, sulfur stable alloys, corrosion and aging of thermoelements. Corrosion of noble metals by L. Nowack and J. Spanner, pp. 765–827, is a long section covering introduction, physical properties, and uses of gold, gold alloys, gold as a metal coating, silver, silver alloys, silver as metal coating, platinum metals, alloys of mixed platinum metals, other alloys, platinum metals as coatings. There is a general discussion of noble metals and their alloys in the presence of various corrosive substances.

An author index of 12 pp. and a subject index of 60 pp. complete the volume. The present compilation is a valuable contribution to the literature.

MERLE RANDALL

The Chemical Analysis of Foods and Food Products. By MORRIS B. JACOBS, Ph.D., Chemist, Bureau of Food and Drugs, Department of Health, City of New York. D. Van Nostrand Company, 250 Fourth Avenue, New York, N. Y., 1938. xxii + 537 pp. 56 figs. 16 × 23.5 cm. Price, $6.00.

The general impression left after a perusal of this book is that in it the methods of food analysis have been brought thoroughly up to date, material being found which is included in no other text. Numerous methods, largely American, are described which first appeared in print as late as 1937, naturally with some danger that not all may have been sufficiently tested to be sure of their true worth. The standard methods of the A.O.A.C. have been drawn upon to a large extent.

The chapter on physical chemical methods covers an unusually wide range, considerable space being given to photoelectric colorimeters, spectrographs, electrometric determinations, surface tension apparatus, and other modern instruments, which are usually discussed only in special treatises. In the section on polarimetry it is regrettable, however, that the author did not include a discussion of the quartz wedge saccharimeter, which is much more widely used in commercial polarizations than the rotary polariscope. As a matter of fact, the "polarimeter" shown (Fig. 23), although stated to be for monochromatic light and to have a rotating analyzer, is actually a compensation saccharimeter using white light. By a curious slip the instrument is said to be capable of using a *40 dom.* tube.

Other points of marked excellence are the discussion of pasteurized milk, the chapter on jams and jellies, one of the best in the book, a chapter on chemical methods for estimating vitamins and numerous tables of the composition of foods. Especially noteworthy among the latter are useful data on the detection of adulteration in butter and olive oil and the alcohol table in the appendix, which combines in one table the data obtainable by both densimetric and refractometric methods. In the Munson and Walker method for reducing sugars the more desirable Given table is used rather than the one commonly found.

A few criticisms might be made, although they are largely matters of personal opinion and do not detract from the general excellence of the work. The discussion of the interpretation of milk analyses, if anything more than simple failure to comply with legal standards is to be shown, is practically negligible. It is rather strange, although perhaps to be expected, to see so much stress laid on the New York Board of Health lactometer instead of the more generally used Quevenne form. An anomaly certainly exists between the Ventzke normal weight of 26 grams (p. 259) and the Ventzke normal weight of 26.026 grams (p. 260), a discrepancy which, although based on the authority of the A.O.A.C., would be confusing to those not acquainted with the controversy which has raged over the Ventzke scale. Where starch is so commonly determined in various foods it would seem advisable to give some more general method than the special one for flours on page 291. Likewise, the only method given for pentosans is the very recent one of precipitation with thiobarbituric acid. The colorimetric tartaric acid method described under fruits is recommended only for use in a tartrate baking powder although no reference to the latter material is found in the index. The colorimetric method for vanillin is described in detail but no caution is given that it has been found notably unreliable with fortified vanilla extracts. The determination of glycerol in vinegar is described at great length although it has little practical value at the present time. No discussion of the range of glycerol in a normal vinegar, other than two figures in a table, is found. One wonders why a method is specified (p. 480) as for "Nitrates in Flesh Foods" when the preceding general method for nitrates is actually the A.O.A.C. method for nitrates in meats.

Other instances might be mentioned, but these are, in general, matters of relatively minor importance. The book is a distinct contribution to the literature of food analysis, the author has done a real service in assembling so much scattered recent material, and the reviewer, for one, is very glad to have the book on his shelf and within easy reach.

A. G. WOODMAN

Handbuch der Lebensmittelchemie. A. BÖMER, A. JUCKENACK and J. TILLMANS. Siebenter Band. **Alkoholische Genussmittel.** (Handbook of Food Chemistry. Vol. VII. Alcoholic Beverages.) B. BLEYER, Editor-in-Chief. Verlag von Julius Springer, Linkstrasse 22–24, Berlin W 9, Germany, 1938. xv + 828 pp. 115 figs. 17.5 × 24 cm. Price, RM. 99; bound, RM. 103.50.

Sponsored by a board of editors whose personnel includes the surviving member of the original group, A. Juckenack, and three others, J. Grossfeld, E. Bames and B. Bleyer, there has now appeared another volume, the fifth in order of completion, of the "Handbuch der Lebensmittelchemie."

Quite appropriately the subject matter of this volume is introduced by a chapter on alcoholic fermentation (31 pp.). The authors, B. Bleyer and W. Diemair, treat this topic first in its historical aspects, then from the standpoint of the morphology and the chemical composition of yeast and finally the course and products of fermentation. Following this, the book divides itself into three main parts, devoted, respectively, to beer (139 pp.), wine and other grape products (367 pp.), and distilled beverages (222 pp.). A digest of the pertinent German laws, compiled by H. Holthöfer, supplements each major chapter; those of the principal European countries and the United States in respect to alcoholic beverages have been briefly collated by E. Bames (38 pp.). A well-organized index (31 pp.) completes the book.

The whole volume appears to have been written with that suggestion of authority which can come only from the pens of those who write with the advantage of experience in their own fields. Bleyer and Diemair contribute also the chapter on beer. The subject matter begins with a discussion of the raw materials of the industry, continues with an exhaustive description of the manufacture of beer from malting to fermentation, and closes with a résumé of the properties and composition of beers. The chapter on wine represents the independent efforts of two scientists who are active in official capacities. To E. Vogt was assigned the task of discussing and describing this beverage, its various types and products, from vineyard to finished product. O. Reichard treats the subject from the twofold standpoint of analysis and official control of traffic therein. The chapter on distilled beverages also is noteworthy. It is the work of G. Büttner. The subject is presented under the following headings: technical recovery of spirits, potable spirits of all types, composition and analysis.

This volume rightfully deserves a place among its predecessors in the series, for by condensing within one set of covers a vast amount of authoritative technical and legal matter it simplifies the work of the food chemist in need either of a reference book or a ready source of information on the subject matter in question.

H. A. SCHUETTE

BOOKS RECEIVED

July 15, 1938–August 15, 1938

A. DAMIENS, Editor. "Halogènes et Composés Oxygénés du Chlore. Mémoires de MM. Scheele, Berthollet, Gay-Lussac et Thénard, H. Davy, Balard, Courtois, H. Moissan, Millon." Gauthier-Villars, Éditeur, 55 Quai des Grands-Augustins, Paris 6^e, France. 147 pp. Fr. 21.

LUCIUS JUNIUS DESHA AND LARKIN HUNDLEY FARINHOLT. "Experiments in Organic Chemistry." McGraw-Hill Book Co., Inc., 330 West 42d St., New York, N. Y. 233 pp. $1.75.

R. J. W. LE FÈVRE. "Dipole Moments. Their Measurement and Application in Chemistry." Chemical Publishing Company of New York, 148 Lafayette St., New York, N. Y. 110 pp. $1.50.

REYNOLD C. FUSON, Editor-in-Chief. "Organic Syntheses. Vol. XVIII. 1938." John Wiley and Sons, Inc., 440 Fourth Ave., New York, N. Y. 103 pp. $1.75.

ROSS AIKEN GORTNER. "Outlines of Biochemistry." Second edition. John Wiley and Sons, Inc., 440 Fourth Ave., New York, N. Y. 1017 pp. $6.00.

LÉON GUILLET, Editor. "Les Métaux Légers: Aluminium, Glucinium, Magnésium, Métaux Alcalins. Mémoires de MM. Henri Sainte-Claire Deville, Héroult, Bussy, Gay-Lussac, Thénard." Gauthier-Villars, Éditeur, 55 Quai des Grands-Augustins, Paris 6^e, France. 166 pp. Fr. 21.

JOSEPH J. JASPER. "Laboratory Methods of Physical Chemistry." Houghton-Mifflin Co., 2 Park St., Boston, Mass. 311 pp. $2.50.

HENRI LE CHATELIER, Editor. "La Dissolution. Mémoires de MM. Lavoisier, Gay-Lussac, Loewel, Gernez, Lescoeur, Raoult." Gauthier-Villars, Éditeur, 55 Quai des Grands-Augustins, Paris 6^e, France. 148 pp. Fr. 21.

R. LESPIEAU, Editor. "Determination des Poids Moléculaires. Mémoires de MM. Avogadro, Ampère, Raoult, van't Hoff, D. Berthelot." Gauthier-Villars, Éditeur, 55 Quai des Grands-Augustins, Paris 6^e, France. 165 pp. Fr. 21.

W. D. TREADWELL. "Tabellen und Vorschriften zur quantitativen Analyse." Verlag von Franz Deuticke, Helferstorferstrasse, Wien, Germany. 283 pp. RM. 9.

W. C. VOSBURGH. "Introductory Qualitative Analysis." Revised edition. The Macmillan Co., 60 Fifth Ave., New York, N. Y. 222 pp. $2.25.

ROGER J. WILLIAMS. "A Text-book of Biochemistry." D. Van Nostrand Co., Inc., 250 Fourth Ave., New York, N. Y. 525 pp. $6.00.

"Committee for the Study of Viscosity of the Academy of Sciences of Amsterdam. Second Report on Viscosity and Plasticity." Nordemann Publishing Co., Inc., 215 Fourth Ave., New York, N. Y. 287 pp. $7.50.

"Livre Jubilaire J. Böeseken." *Recueil des Travaux Chimiques des Pays-Bas*, Vol. 57, No. 6, 1938. D. B. Centen's Uitgevers-Maatschappij. N. V., Amsterdam, Holland. 348 pp. Dutch guilders 3.

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[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

The Action of Aluminum Chloride on the Diphenyl Ester of Isophthalic, Terephthalic and Naphthalic Acids

BY F. F. BLICKE AND R. A. PATELSKI[1]

Diphenyl phthalate and aluminum chloride do not yield 2-(4″-hydroxybenzoyl)-4′-hydroxybenzophenone as might be expected; phenolphthalein[2] and 1-hydroxyanthraquinone[3] are produced in this reaction.

We found that diphenyl isophthalate, heated with aluminum chloride, is transformed into 3-(4″-hydroxybenzoyl)-4′-hydroxybenzophenone. The latter compound was obtained also by interaction of isophthalyl chloride, anisole and aluminum chloride; the 3-(4″-methoxybenzoyl)-4′-methoxybenzophenone, produced in this reaction, was demethylated during the preparative process.

Weiss and Chledowski[4] stated that isophthalyl chloride and anisole react to form not only 3-(4″-methoxybenzoyl)-4′-methoxybenzophenone but also 4-(4″-methoxybenzoyl)-4″-methoxybenzophenone. They attribute the formation of the latter substance to a rearrangement produced by the aluminum chloride. Although these investigators claim that they used pure *m*-xylene from which to prepare the isophthalyl chloride, their *m*-xylene may have contained some of the para isomer.

Diphenyl terephthalate was converted by aluminum chloride into 4-(4″-hydroxybenzoyl)-4′-hydroxybenzophenone. The same benzophenone was obtained by demethylation of the reaction product, 4-(4″-methoxybenzoyl)-4′-methoxybenzophenone, produced from terephthalyl chloride and anisole.

In view of the general behavior of 1,8-disubstitution products of naphthalene it would be expected that diphenyl naphthalate would react with aluminum chloride similarly to diphenyl phthalate and that phenolnaphthalein would be produced instead of 1,8-di-(*p*-hydroxybenzoyl)-naphthalene. It was found that the phthalein was formed in this reaction in place of the diketone. Jaubert[5] had obtained this phthalein previously, in an impure state, by condensation of naphthalic anhydride and phenol. We prepared it by a modification of Jaubert's method and also by condensation of 8-(4′-hydroxybenzoyl)-1-naphthoic acid with phenol.

Experimental Part

3-(4″-Hydroxybenzoyl)-4′-hydroxybenzophenone. (a) **From Diphenyl Isophthalate and Aluminum Chloride.**—Five grams of diphenyl isophthalate,[6] 6 g. of aluminum chloride and 25 cc. of carbon disulfide were heated on a steam-bath until the carbon disulfide had been removed; the residue was then heated in an oil-bath (185–195°) for twenty-five minutes. The aluminum salt was removed with dilute hydrochloric acid and the mixture extracted with 10% sodium hydroxide solution. The product, obtained by acidification of the alkaline extract, was digested with sodium bicarbonate solution to remove carboxylic acids and the crude hydroxy ketone refluxed with 14 cc. of acetic anhydride for one hour in order to acetylate it. The diacetyl derivative of 3-(4″-hydroxybenzoyl)-4′-hydroxy-

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[1] Monsanto–Pfizer Research Associate.

[2] Csanyi, *Ber.*, **52**, 1792 (1919).

[3] Blicke and Weinkauff, THIS JOURNAL, **54**, 330 (1932).

[4] Weiss and Chledowski, *Monatsh.*, **65**, 358 (1935).

[5] Jaubert, *Ber.*, **28**, 992 (1895).

[6] Schreder [*ibid.*, **7**, 707 (1874)] reported 120° as the melting point; we found it to be 137–138°.

benzophenone was recrystallized from benzene; m. p. 189–190°.

Anal. Calcd. for $C_{24}H_{18}O_6$: C, 71.62; H, 4.51. Found: C, 71.72; H, 4.59.

Upon hydrolysis of the acetyl derivative with 10% sodium hydroxide solution and recrystallization of the 3-(4″-hydroxybenzoyl)-4′-hydroxybenzophenone several times from dilute alcohol, the latter melted at 207–209°.[7]

The dimethyl ether, obtained by methylation with dimethyl sulfate, melted at 144–146°[8] after recrystallization from alcohol.

The di-*m*-bromobenzoyl derivative was produced when 2 g. of the dihydroxybenzophenone was heated for three hours with 3.3 g. of *m*-bromobenzoyl chloride at 150–160°. After recrystallization from tetrachloroethane it melted at 234–235°.

Anal. Calcd. for $C_{34}H_{20}O_6Br_2$: Br, 23.36. Found: Br, 23.01.

(b) From Isophthalyl Chloride, Anisole and Aluminum Chloride.—Weiss and Chledowski[8] stirred a mixture of isophthalyl chloride, anisole, aluminum chloride and carbon disulfide, heated it for one hour and isolated 3-(4″-methoxybenzoyl)-4′-methoxybenzophenone. We followed their directions but heated the mixture for three hours on a steam-bath. After removal of the solvent and aluminum salt 20 g. of product, soluble in 10% sodium hydroxide solution, was obtained from 17 g. of isophthalyl chloride. The crude 3-(4″-hydroxybenzoyl)-4′-hydroxybenzophenone was refluxed for one hour with 60 g. of acetic anhydride, the crystalline diacetyl derivative (m. p. 189–190°) hydrolyzed and the benzophenone recrystallized from dilute alcohol; m. p. 207–209°.

4-(4″-Hydroxybenzoyl)-4′-hydroxybenzophenone. (a) From Diphenyl Terephthalate and Aluminum Chloride.—Diphenyl terephthalate[9] was treated with aluminum chloride in the same manner as diphenyl isophthalate. The crude hydroxy ketone obtained, after removal of carboxylic acids, was recrystallized from dilute alcohol; m. p. 297–299°. The compound contains solvent of crystallization; for analysis it was dried to constant weight at 115°.

Anal. Calcd. for $C_{20}H_{14}O_4$: C, 75.47; H, 4.40. Found: C, 75.20; H, 4.51.

The diacetyl derivative was prepared and recrystallized from acetic acid; m. p. 249–250°.

Anal. Calcd. for $C_{24}H_{18}O_6$: C, 71.62; H, 4.51. Found: C, 71.50; H, 4.54.

The di-(3-bromobenzoyl) derivative was obtained when 4-(4″-hydroxybenzoyl)-4′-hydroxybenzophenone was heated with 3-bromobenzoyl chloride. It melted at 289–291° after recrystallization from tetrachloroethane.

Anal. Calcd. for $C_{34}H_{20}O_6Br_2$: Br, 23.36. Found: Br, 23.01.

In order to prepare the dioxime 3.7 g. of the hydroxybenzophenone, 200 cc. of methyl alcohol, 5 g. of hydroxylamine hydrochloride and 10 g. of sodium hydroxide were refluxed for eight hours. The oxime was recrystallized from alcohol; m. p. 261–263°.

Anal. Calcd. for $C_{20}H_{16}O_4N_2$: N, 8.04. Found: N, 7.93.

Upon methylation with dimethyl sulfate 4-(4″-methoxybenzoyl)-4′-methoxybenzophenone was obtained; m. p. 225–227°[10] after recrystallization from toluene. Demethylation with constant boiling hydrobromic acid in acetic acid yielded the original hydroxybenzophenone.

(b) From Terephthalyl Chloride, Anisole and Aluminum Chloride.—Terephthalyl chloride[11] was allowed to react with anisole and aluminum chloride under the same conditions described above in the case of isophthalyl chloride. The hydroxybenzophenone obtained melted at 298–299°.

Phenolnaphthalein. (a) From Naphthalic Anhydride and Phenol.—A mixture of 40 g. of naphthalic anhydride, 160 g. of phenol and 100 g. of aluminum chloride was heated for seventy-two hours on a steam-bath, the product decomposed with dilute hydrochloric acid and then steam distilled to remove excess phenol. The material was digested with 10% sodium hydroxide solution, filtered and the filtrate acidified. The red precipitate was dried and dissolved in hot butyl alcohol. When the solution was cooled 5 g. of 8-(4′-hydroxybenzoyl)-1-naphthoic acid was obtained; m. p. 219–220° after several recrystallizations from alcohol.

Anal. Calcd. for $C_{18}H_{12}O_4$: C, 73.95; H, 4.14. Found: C, 73.83; H, 4.14.

The butyl alcoholic mother liquor was steam distilled and the dried, red, amorphous residue refluxed with 100 g. of acetic anhydride for four hours. The solution was concentrated, poured into water and the brown, gummy precipitate covered with alcohol. After twelve hours the mass became crystalline. The product was recrystallized several times from alcohol whereupon the colorless, crystalline diacetyl derivative of phenolnaphthalein was obtained; m. p. 198–199°.[12]

Anal. Calcd. for $C_{28}H_{20}O_6$: C, 74.31; H, 4.46. Found: C, 73.98; H, 4.49.

The diacetyl derivative was refluxed for several hours with dilute aqueous sodium hydroxide and the phthalein obtained recrystallized from dilute alcohol; m. p. 265–266°[13] with decomposition.

Anal. Calcd. for $C_{24}H_{16}O_4$: C, 78.23; H, 4.38. Found: C, 78.22; H, 4.43.

The color of an alkaline solution of phenolnaphthalein is very similar to that of an alkaline solution of phenolphthalein.

Dr. H. H. Willard found the useful *p*H range to be 8.8–10.8 and the *pK* to be 9.78.

(b) From 8-(4′-Hydroxybenzoyl)-1-naphthoic Acid.—A mixture of 5.8 g. of 8-(4′-hydroxybenzoyl)-1-naphthoic acid, 15 g. of phenol and 13.5 g. of aluminum chloride was heated at 150–160° for six hours and then treated with dilute hydrochloric acid. The phthalein was isolated in the manner described above; mixed m. p. 265–266°.

(c) From Diphenyl Naphthalate and Aluminum Chloride.—In order to obtain diphenyl naphthalate 39.6 g. of

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[7] Weiss and Chledowski [*Monatsh.*, **65**, 363 (1935)] reported 215°.

[8] Weiss and Chledowski [*ibid.*, **65**, 362 (1935)] reported 146–149°.

[9] Schreder, *Ber.*, **7**, 707 (1874).

[10] Weiss and Chledowski [*Monatsh.*, **65**, 358 (1935)] reported 236–239°.

[11] Locher, *Bull. soc. chim.*, [3] **11**, 927 (1894).

[12] Kaufmann [*Z. angew. Chem.*, **40**, 863 (1927)] reported 198–199°.

[13] Jaubert [*Ber.*, **28**, 991 (1895)] stated that the phthalein melted above 200° with charring and the evolution of phenol.

naphthalic anhydride, 80 g. of phosphorus pentachloride and 75 cc. of phosphorus oxychloride were refluxed for twenty hours in an oil-bath, the oxychloride and excess pentachloride removed under diminished pressure and the sirupy, light brown acid chloride[14] mixed, immediately, with 40 g. of phenol. After the vigorous reaction had subsided the mixture was heated for two hours at 140–150°. The product was washed with dilute alkali, with water and then recrystallized from alcohol; m. p. 150–151°.

Anal. Calcd. for $C_{24}H_{16}O_4$: C, 78.23; H, 4.38. Found: C, 78.39; H, 4.41.

A mixture of 4 g. of diphenyl naphthalate, 5 g. of aluminum chloride and 20 cc. of carbon disulfide was heated on a steam-bath until the carbon disulfide had been removed and the solid residue heated for twenty-five minutes in an oil-bath at 155–160°. The mixture was treated with dilute hydrochloric acid and the product then digested with 10% sodium hydroxide solution. The solid precipitate, obtained upon acidification of the alkaline solution, was digested with sodium bicarbonate solution and the insoluble portion recrystallized from dilute alcohol; yield of phthalein 1.6 g.; m. p. 264–266°.

Summary

It has been shown that the diphenyl ester of isophthalic acid is converted by aluminum chloride into 3-(4″-hydroxybenzoyl)-4′-hydroxybenzophenone; from diphenyl terephthalate and aluminum chloride there was obtained 4-(4″-hydroxybenzoyl)-4′-hydroxybenzophenone.

Phenolnaphthalein was prepared from diphenyl naphthalate and aluminum chloride and from the hitherto unknown 8-(4′-hydroxybenzoyl)-1-naphthoic acid and phenol.

ANN ARBOR, MICHIGAN RECEIVED JUNE 18, 1938

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[14] Mason [*J. Chem. Soc.*, **125**, 2117 (1924)] obtained this acid chloride in crystalline form and Davies and Leeper [*ibid.*, 1125 (1927)] were able to distil the material.

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Separation and Identification of Amines with 3-Nitrophthalic Anhydride

BY JOHN W. ALEXANDER AND S. M. MCELVAIN

While numerous reagents are available for the preparation of derivatives of the three classes of amines, only two, nitrous acid and aryl sulfonyl chlorides, have been used to any considerable extent as a means of separating the different types of amines from each other when they occur in a mixture. Nitrous acid has the disadvantage of destroying completely the identity of the primary amine, often with the formation of a rearranged product. Aryl sulfonyl chlorides have proved to be quite useful on account of the fact that the sulfonamides of the primary amines are generally soluble in aqueous alkali and, consequently, can be separated from the alkali-insoluble sulfonamide of the secondary amine. However, this reagent fails when primary amines of the type $C_6H_5(CH_2)_nNH_2$ are involved because the sulfonamides of these amines are alkali-insoluble.[1] Also, certain ortho-substituted amines, such as *o*-nitroaniline,[2] can be made to react with aryl sulfonyl chlorides only with considerable difficulty. Finally, recovery of the amines from the sulfonamides is inconvenient, if not difficult, in that hydrolysis of the latter types requires that the reaction be carried out in a sealed tube.

In his textbook of qualitative organic analysis, Kamm[3] mentions the use of phthalic anhydride as a means of separating the three types of amines. So far as we are aware, there is no other reference in the literature to the general use of this reagent for the separation and identification of amines.[4] In a private communication to one of us Dr. Kamm stated that he had worked on the phthalic anhydride procedure several years ago while at the University of Illinois but had had little time to use it in practical laboratory work. The use of this reagent depends upon the fact that it does not react with tertiary amines but forms phthalamic acids with both primary and secondary amines. These derivatives are separated by heat which converts the phthalamic acid of the primary amine (I) into an alkali-insoluble N-substituted phthalimide (III) but leaves the phthalamic acid derived from the secondary amine (II) unchanged, and, therefore, alkali soluble.

Attempts to utilize phthalic anhydride for the separation and identification of amines in this Laboratory revealed the following facts: (a)

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[1] Carothers, Bickford and Hurwitz, THIS JOURNAL, **49**, 2908 (1927).

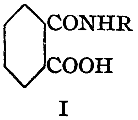
[2] *Cf.* Amundsen, *ibid.*, **59**, 1466 (1937).

[3] Kamm, "Qualitative Organic Analysis," John Wiley and Sons, Inc., New York, N. Y., 1932, p. 69.

[4] A few patents [*C. A.*, **22**, 3417 (1928); **23**, 846, 1137 (1929); **28**, 3418 (1934)] covering the separation of certain amines with phthalic anhydride have been issued. Porai-Koshitz in a paper [*C. A.*, **29**, 131 (1935)] describes a rather large scale separation of aniline, methylaniline and dimethylaniline with this reagent.

the phthalamic acids derived from the secondary amines that were studied were non-crystalline resins, (b) the temperature that was found necessary to convert the phthalamic acid of the primary amine to the N-substituted phthalimide caused some of the secondary amine derivatives to be changed into a diamide (IV) which separated as an alkali-insoluble product along with the phthalimide.[5] Succinic anhydride was found to give the desired crystalline amidic acids with the secondary amines, but these acids were converted more readily into the diamides by heat than were the corresponding derivatives from phthalic anhydride.[5b]

This paper reports the results which have been obtained with 3-nitrophthalic anhydride as a reagent for the separation and identification of amines. This anhydride has proved to be quite satisfactory as it gives crystalline derivatives with secondary amines and produces primary amine derivatives that may be converted into the phthalimides at a temperature (145°) that leaves the phthalamic acids derived from the secondary amines unchanged. With such tertiary amines as dimethylaniline, however, 3-nitrophthalic anhydride causes a violent reaction at the temperature necessary to form the phthalimide. Oxides of nitrogen are evolved and a charred mass remains as a residue. For this reason it is necessary to carry out the reaction of an amine mixture that contains such a tertiary type with 3-nitrophthalic anhydride in a solvent such as carbon tetrachloride and to separate the phthalamic acids from any tertiary amine before these acids are further heated. 3-Nitrophthalic anhydride under these conditions reacts readily and completely with *o*-substituted anilines such as *o*-nitraniline and the resulting phthalamic acids are smoothly converted by heating into the phthalimides.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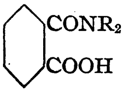
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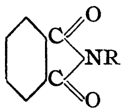
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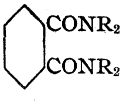
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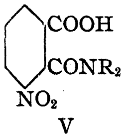
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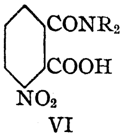
VI

It is evident that there is the possibility of forming two different nitrophthalamic acids (V and VI) by the action of 3-nitrophthalic anhydride on a secondary amine. However, in no case was more than one acid obtained from this reaction. The structure V is assigned to these derivatives on the assumption that a secondary amine would react in the same way with the anhydride as does ammonia. Chapman and Stephens[6] showed that the phthalamic acid formed from ammonia and 3-nitrophthalic anhydride could be degraded through the Hofmann reaction to 3-nitroanthranilic acid. We have confirmed this observation and have carried the characterization one step further by converting the nitroanthranilic acid to *m*-nitrobenzoic acid by the diazo reaction.

The imides that are derived from the primary amines are hydrolyzed readily by 5% sodium hydroxide solution, even at room temperature. In this alkaline solution the hydrolysis goes only as far as the phthalamic acids. These acids as well as those derived from the secondary amines, on account of their stability to alkali, may be titrated, and thereby be made to reveal the molecular weight of the amine from which they were made. The phthalamic acids, however, are quite susceptible to acid hydrolysis and readily yield the amines when warmed with 10% hydrochloric acid for a few minutes. For this reason care is necessary in precipitating the phthalamic acid from alkaline solution to avoid high local concentrations of acid.

The melting points and analyses of a number of the imides derived from primary amines and of a few phthalamic acids from secondary amines are listed in the table.

Experimental

The Separation of a Mixture of Amines with 3-Nitrophthalic Anhydride.—A 3–4 g. portion of the mixture of amines together with 8–10 g. of 3-nitrophthalic anhydride[7] is added to 25 cc. of carbon tetrachloride. This mixture is refluxed gently for fifteen minutes; it is not necessary that all of the solids go into solution in the carbon tetrachloride. After this time 30 cc. of 10% sodium hydroxide solution is added, followed by shaking and gentle heating until no solids remain. The carbon tetrachloride layer is separated, and the alkaline solution extracted with a 20-cc. portion of ether. The carbon tetrachloride and ether extract are mixed and the solvents removed by careful distillation. If no oily residue remains, no tertiary amine is present. If a residue remains, it may be purified by steam distillation.

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[5] (a) R. S. Pacl, University of Wisconsin M.S. Thesis, 1933; (b) J. W. Alexander, University of Wisconsin B.S. Thesis, 1935.

[6] Chapman and Stephens, *J. Chem. Soc.*, **127**, 1791 (1925).

[7] "Organic Syntheses," John Wiley and Sons, Inc., New York, 1931, Coll. Vol. I, p. 402.

VARIOUS N-SUBSTITUTED 3-NITROPHTHALIMIDES DERIVED FROM PRIMARY AMINES

N-Substituent	Formula	M. p., °C. (uncorr.)	Analyses, % N Found	Calcd.
Isoamyl	$C_{13}H_{14}N_2O_4$	89–90	10.40	10.69
Phenyl[a]	$C_{14}H_8N_2O_4$	137–138	10.44	10.45
Benzyl[a]	$C_{15}H_{10}N_2O_4$	142–143	9.68	9.93
m-Bromophenyl	$C_{14}H_7BrN_2O_4$	186–187	8.26	8.09
p-Bromophenyl	$C_{14}H_7BrN_2O_4$	201–202	8.09	8.09
o-Chlorophenyl	$C_{14}H_7ClN_2O_4$	135–136	9.53	9.27
m-Chlorophenyl	$C_{14}H_7ClN_2O_4$	171–173	9.11	9.27
p-Chlorophenyl	$C_{14}H_7ClN_2O_4$	198–199	9.30	9.27
o-Ethoxyphenyl	$C_{16}H_{12}N_2O_5$	163–164	8.96	8.97
p-Ethoxyphenyl	$C_{16}H_{12}N_2O_5$	172–173	8.83	8.97
o-Methoxyphenyl	$C_{15}H_{10}N_2O_5$	184–186	9.18	9.39
m-Methoxyphenyl	$C_{15}H_{10}N_2O_5$	157–158	9.26	9.39
p-Methoxyphenyl	$C_{15}H_{10}N_2O_5$	196–197	9.35	9.29
o-Nitrophenyl[a]	$C_{14}H_7N_3O_6$	170–171	13.27	13.42
m-Nitrophenyl[a]	$C_{14}H_7N_3O_6$	218–219	13.26	13.42
p-Nitrophenyl[a]	$C_{14}H_7N_3O_6$	254–255	13.28	13.42
o-Tolyl[a]	$C_{15}H_{10}N_2O_4$	149–151	9.62	9.93
m-Tolyl[a]	$C_{15}H_{10}N_2O_4$	129–130	9.75	9.93
p-Tolyl[a]	$C_{15}H_{10}N_2O_4$	155–156	9.87	9.93
α-Naphthyl	$C_{18}H_{10}N_2O_4$	222–223	9.08	8.80
β-Naphthyl	$C_{18}H_{10}N_2O_4$	211–212	9.00	8.80

[a] These compounds have been reported by Bogert and Boroschek, THIS JOURNAL, **23**, 748 (1901).

VARIOUS N,N-DISUBSTITUTED NITROPHTHALAMIC ACIDS, $C_6H_3(COOH)(CONR_1R_2)(NO_2)(1,2,3)$ DERIVED FROM SECONDARY AMINES

R_1 is	R_2 is				
Benzyl	Phenyl	$C_{21}H_{16}N_2O_5$	211–212	7.37	7.44
Butyl	Phenyl	$C_{18}H_{18}N_2O_5$	204–206	8.11	8.19
Ethyl	Phenyl	$C_{16}H_{14}N_2O_5$	203–204	8.63	8.92
Methyl	Phenyl	$C_{15}H_{12}N_2O_5$	192–194	9.28	9.33
Propyl	Phenyl	$C_{17}H_{16}N_2O_5$	222–225	8.21	8.54

To the alkaline solution of the salts of the phthalamic acids, contained in a beaker, sufficient of a 10% solution of hydrochloric acid to form the free acids is added slowly and with constant stirring. Since these acids have a tendency to form supersaturated solutions, the acid solution should be stirred vigorously until the precipitation of the phthalamic acids is complete. The precipitated solid, which may be gummy at this point, is filtered off, transferred to a small Erlenmeyer flask, and heated for thirty minutes in an oil-bath at 145°. After the first five minutes of heating, about 0.5 g. of the 3-nitrophthalic anhydride is added to the material being heated and mixed-in with a stirring rod. After heating for another twenty-five minutes, the molten reaction mixture is poured into a small mortar and allowed to solidify. Generally it is advantageous to grind the resulting hard resinous mass to a fine powder before treating it with 50 cc. of a saturated sodium bicarbonate solution to dissolve out the phthalamic acid derived from the secondary amine and any excess of 3-nitrophthalic anhydride. The reaction product which remains in the reaction flask is treated with 5 cc. of acetone and gently warmed. This amount of acetone may not dissolve all of the product remaining in the reaction flask but it loosens it sufficiently to allow it to be transferred to the sodium bicarbonate solution. The imide of the primary amine is filtered off from the bicarbonate solution and recrystallized from alcohol or an alcohol–acetone mixture. The phthalamic acid is precipitated with 10% hydrochloric acid with constant stirring as described above. This derivative may be crystallized from an alcohol–water mixture, and after drying may be titrated with standard alkali.

The primary amine may be recovered from the imide by refluxing it in 10% aqueous sodium hydroxide until all of the solid has gone into solution. This hydrolysis produces the salt of the phthalamic acid which is then hydrolyzed to the primary amine by making the alkaline solution distinctly acid with hydrochloric acid and refluxing for an additional fifteen minutes. The secondary amine may be recovered by the hydrolysis of the phthalamic acid in a similar manner with dilute hydrochloric acid.

If it is desired to prepare the N-substituted phthalimide from an individual primary amine, this readily may be accomplished by heating the amine with 3-nitrophthalic anhydride at 170° for five to ten minutes. If the preparation of a phthalamic acid derivative of an individual secondary amine is desired, it may be carried out simply by heating the secondary amine with 3-nitrophthalic anhydride at 145° for a few minutes. Higher reaction temperatures cause oxidation of the secondary amine.

Summary

A procedure for the separation of a mixture of amines with 3-nitrophthalic anhydride is described. The melting points and analyses of a number of N-substituted 3-nitrophthalimides and N,N-disubstituted nitrophthalamic acids are listed.

MADISON, WISCONSIN RECEIVED JUNE 16, 1938

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

Glycofuranosides and Thioglycofuranosides. IV. Direct Formation of Dimethyl Acetal and Preparation of α-Ethylfuranoside from *l*-Rhamnose Ethylmercaptal

BY JOHN W. GREEN[1] AND EUGENE PACSU

In the previous articles of this series[2] the preparation of glycofuranosides from the mercaptals of glucose, galactose and *l*-arabinose was described. In each case the thioethyl groups were eliminated from the sugar with the formation of a <1–4> ring linked by oxygen.

l-Rhamnose ethylmercaptal has been treated similarly with mercuric chloride in neutral alcoholic solutions. In ethyl alcohol the reaction runs in the expected manner and the product is a negatively rotating sirup. From this sirup a small yield of pure crystalline α-ethyl *l*-rhamnofuranoside was obtained. These crystals have a specific rotation of −95.5° in water solution, similar in magnitude (but necessarily opposite in sign) to the value for α-methyl-*d*-mannofuranoside.[3] The crystals melt at 54–56° and are very hygroscopic.

Similarly, from the reaction carried out in methyl alcohol solution, a negatively rotating sirup is obtained. From this sirup a small amount of crystalline material is isolated very easily, and this product is not a furanoside. The specific rotation in water solution is 10.2° and the melting point is 123–124°. The crystals are not hygroscopic. The carbon–hydrogen analysis agrees perfectly with the empirical formula of a dimethyl acetal. The small rotation is also typical of an open-chain derivative.

This is the first observed case where an acetal of a sugar has been formed without blocking some[4] or all[5] of the hydroxyl groups. It has been believed that the mechanism of the mercaptal–mercuric chloride reaction was always an initial ring closure to a thiofuranoside,[2a] then subsequent secondary changes to a glycofuranoside, a glycopyranoside or the free sugar, depending on the experimental conditions. Here is a definite case where the expected ring closure does not occur. The greater amount of the ethyl rhamnofuranoside sirup has not been obtained crystalline so it cannot be said that there is no ethyl acetal present. However, the isolation of some ethyl rhamnofuranoside shows that ring closure does occur, at least in part, when rhamnose ethylmercaptal reacts with mercuric chloride in neutral ethyl alcohol solution.

On the other hand, the greater part of the mother liquor from the dimethyl acetal has not been crystallized and so it cannot be said definitely that the acetal is the only product. The similarity in rotation of the two reaction sirups would lead to the assumption that in both cases the rhamnofuranoside is formed and in one case at least the acetal also.

The conception of the acetal as an intermediate in the glycofuranoside formation seems unlikely and the acetal is probably formed as a by-product. An intermediate product in the acetal reaction would necessarily have to be the mixed acetal, with one methoxyl and one thioethyl group. This brings up the possibility of glycofuranoside formation from the mixed acetal, which might explain why none of the sugars (except glucose) form the thiofuranosides.

The mother liquors of these two new compounds will be investigated further.

Experimental

Preparation of α-Ethyl *l*-Rhamnofuranoside.—A mixture of 10.8 g. of *l*-rhamnose ethyl mercaptal, 22 g. of mercuric chloride (2 moles), 12 g. of yellow mercuric oxide and 6 g. of drierite was shaken with 80 cc. of absolute ethyl alcohol at 25° for four hours. The mixture was filtered, the filtrate treated with 5 cc. of pyridine and kept at 0° for two hours. The pyridine–mercuric chloride was filtered and the solution evaporated to a sirup *in vacuo* at 40°. The substance was dissolved in a little cold water, the solution filtered and neutralized to phenolphthalein, with a few drops of sodium hydroxide solution, then evaporated *in vacuo* at 40°. The resulting sirup was evaporated successively from methyl alcohol and ethyl acetate solutions. The sirupy residue rotated −53° in water solution and after two months in the ice box changed to a semi-solid mass which melted at room temperature.

From 20 cc. of dry ethyl acetate solution, diluted with dry ether to a slight turbidity at 0°, 200 mg. of crystals rotating −71° in water solution was deposited. After three recrystallizations from 5 cc. of dry ether diluted

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[1] Research Assistant on Special Funds from the Rockefeller Foundation.

[2] (a) Green and Pacsu, THIS JOURNAL, **59**, 1205 (1937); (b) Green and Pacsu, *ibid.*, **59**, 2569 (1937); (c) Green and Pacsu, *ibid.*, **60**, 2056 (1938).

[3] Haworth and Porter, *J. Chem. Soc.*, 649 (1930).

[4] Wolfrom, Tanghe, George and Waisbrot, THIS JOURNAL, **60**, 132 (1938).

[5] (a) Wolfrom and Waisbrot, *ibid.*, **60**, 854 (1938); (b) Montgomery, Hann and Hudson, *ibid.*, **59**, 1124 (1937); Campbell and Link, *J. Biol. Chem.*, **122**, 635 (1938).

with petroleum ether (b. p. 30–60°), a pure product was obtained in the form of long stout needles: yield 50 mg., m. p. 54–56°, $[\alpha]^{20}\mathrm{D}$ 95.5° (0.0330 g. of substance, 3 cc. of water solution, 2-dm. semi-micro tube, 2.10° rotation to the left). The crystals were very hygroscopic and did not reduce Fehling's solution. Before analysis the substance was kept over phosphorus pentoxide in a desiccator for three days.

Anal. Calcd. for $C_8H_{16}O_5$: C, 50.0; H, 8.33. Found: C, 49.4; H, 8.6.

Preparation of *l*-Rhamnose Dimethyl Acetal.—A mixture of 5.4 g. of *l*-rhamnose ethylmercaptal, 10.8 g. of mercuric chloride (2 moles), 5 g. of yellow mercuric oxide and 3 g. of drierite was shaken in 60 cc. of absolute methyl alcohol at 25° for four hours, and worked up as in the above experiment. The sirup, rotating −35° in water solution, on evaporation from ethyl acetate solution became partly crystalline.

From a solution of 15 cc. of dry ethyl acetate in *the ice box* 300 mg. of crystals was deposited, and after one recrystallization from 15 cc. of dry ethyl acetate at 0°, 200 mg. of pure crystals was obtained: yield 5%; m. p. 123–124°; $[\alpha]^{20}\mathrm{D}$ 10.2° (0.1070 g. substance, 3 cc. of solution, 2-dm. semi-micro tube, rotation 0.73° to the right). The crystals are long fine needles, are not hygroscopic and do not reduce Fehling's solution. They are easily hydrolyzed by 0.01 *N* hydrochloric acid at 100° in a few minutes.

Anal. Calcd. for $C_8H_{18}O_6$: C, 45.7; H, 8.57. Found: C, 45.8; H, 8.5.

Summary

α-Ethyl *l*-rhamnofuranoside has been isolated in crystalline form from the reaction of ethyl mercaptal with mercuric chloride in neutral ethyl alcoholic solution. The pure crystals have a specific rotation of −95.5° in water solution and melt at 54–56°. They are hygroscopic and do not reduce Fehling's solution.

l-Rhamnose dimethyl acetal has been isolated in crystalline form by a similar reaction of the ethyl mercaptal in methyl alcohol. The pure crystals have a specific rotation of 10.2° in water solution and melt at 123–124°. This is the first observed case of direct formation of an acetal from a sugar without blocking the hydroxyl groups to prevent glycoside formation.

PRINCETON, NEW JERSEY RECEIVED JULY 13, 1938

[CONTRIBUTION FROM THE PHYSICO-CHEMICAL LABORATORY OF THE NEW YORK STATE EXPERIMENT STATION]

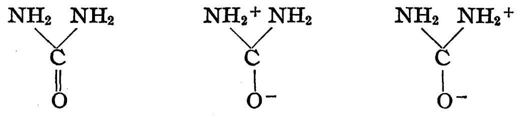
The Influence of Substances on the Optical Rotation of Gelatin. VII. Rotatory Dispersion of Gelatin in Urea Solutions[1]

BY D. C. CARPENTER AND F. E. LOVELACE

The rotatory dispersion of gelatin–sodium halide systems follows a single-term Drude equation $[\alpha]_\lambda = k/(\lambda^2 - \lambda_0^2)$ in which λ_0 is the position of an absorption band at 2200 Å. The effect of the halides of sodium on the rotatory dispersion constant of gelatin has been shown[2] to follow a linear equation with reference to salt concentration at 40°, and at 0.5° to be the result of two effects, one linear with respect to salt concentration and the other related to salt concentration by the equation

$$a/(1 - a) = e^{kC}/K^k$$

In connection with the foregoing studies of the optical behavior of protein ions in the presence of highly ionized inorganic salts, it appeared that similar studies with an optically inactive organic dipole ion would be desirable. From measurements of the dielectric constant of urea solutions[3] it has been inferred that urea exists in solution as the dipole ion ..$^+\mathrm{NH_3C(=NH)O^-}$. The dielectric constant data, however, may be accounted for by the resonance formula



as well as the zwitter ion formula. It is common knowledge that the presence of urea brings about the "denaturation" of many proteins. Only recently have the effects of urea on proteins been followed in the ultracentrifuge. Watson, Arrhenius and Williams[4] reported that the molecular weight of zein was not affected by urea. Williams and Watson[5] believe that the action of urea on egg albumin is that of dissociation, the molecular weight of the pieces being of the order of one-half that of the original protein molecule. On dialyzing out the urea from their solutions about

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(1) Approved by the Director of the New York State Experiment Station for publication as Journal Paper No. 275.

(2) Carpenter and Lovelace, THIS JOURNAL, **57**, 2342 (1935); **58**, 2438 (1936); **59**, 2213 (1937); Carpenter, *Cold Spring Harbor Symposia*, **6**, in press (1938).

(3) Devoto, *Atti soc. ital. progresso. sci.*, **19**, 2, 167 (1931).

(4) Watson, Arrhenius and Willams, *Nature*, **137**, 322 (1936).

(5) Williams and Watson, *ibid.*, **139**, 506 (1937).

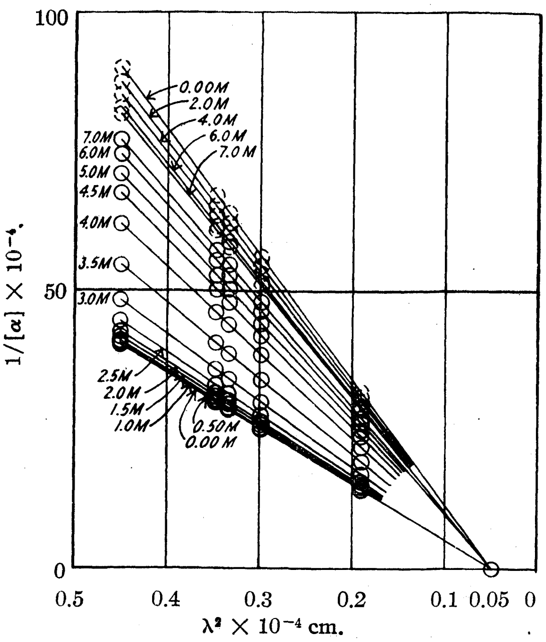

Fig. 1.—Graph of reciprocal of specific rotation *versus* wave length squared at 0.5 and 40°: ○, 40°; ○, 0.5°.

three-fourths of the egg albumin coagulated and separated out. The protein remaining in solution after dialysis had for the most part the normal molecular weight of unchanged egg albumin, although it was not entirely homogeneous. If these authors calculated the sedimentation constant of the urea-treated protein from their Fig. 2, their reported sedimentation value is too low; however, inasmuch as assumptions of greater consequence also enter into their calculations, we will not comment further on their results.

Steinhardt[6] has shown a clear-cut case of the dissociation of isoelectric horse hemoglobin into half-molecules by urea. On dialysis, part of the urea treated material re-formed molecules of the original molecular weight but a large portion aggregated into still larger particles. Steinhardt concluded that pepsin was not changed materially by urea. His data actually indicate approximately a 10% increase in the sedimentation constant (much greater than the usual experimental error) indicating partial association of pepsin rather than any dissociation. The diffusion was not measured, however, in the experiments with pepsin and the molecular weight cannot be calculated without making assumptions that are often misleading.

Dissociation and denaturation of proteins by urea are clearly different processes and take place at different rates. It appears that the former occurs rapidly and the latter more slowly. Many different environmental conditions cause changes in proteins and different observers noting such changes have spoken of them rather loosely under the term "denaturation," not necessarily meaning, for instance, that the actual change produced by heat was like that effected by light, etc. It appears that in the presence of urea some proteins are dissociated and others are not. It is chiefly when one starts to remove the urea that denaturation takes place or at least makes itself obvious. The denaturation by urea seems to reside in the reuniting of the dissociated pieces in other ways than that in which they existed in the original protein. In spite of the information about protein structure obtained from X-ray work, it is not clear what holds the parallel peptide chains together in the layer level nor what forces hold together the layer–layer levels of the molecule.

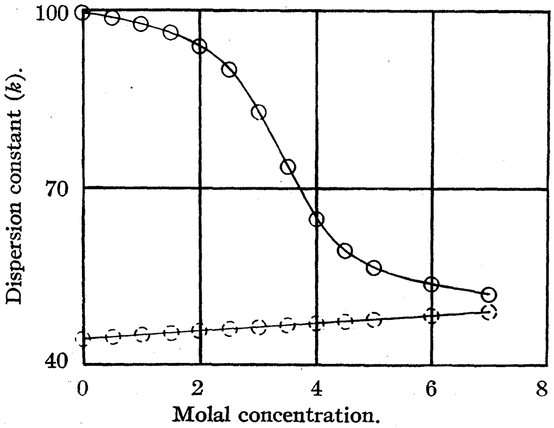

Fig. 2.—Rotatory dispersion constant of gelatin in urea solutions at 0.5 and 40°.

It is somewhat doubtful if dissociation can occur in the dimension at right angles to the main direction of the peptide chains, as dissociation of the molecule into two pieces would involve the simultaneous breakage of the peptide linkage in some forty places. Division of the molecule along the dimension parallel to the main direction of the peptide chains would cut through at least forty force fields between adjacent NH and CO groups in adjacent peptide chains. On the whole it seems more likely that cleavage of the molecule along a plane parallel to the layer levels would be accomplished by the minimum expenditure of energy. The layer–layer levels have been postulated as held together by (a)

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(6) Steinhardt, *J. Biol. Chem.*, **123**, 543 (1938).

compound formation between side-chain amino groups of the diamino acids and side-chain carboxyl groups of the dicarboxy acids[7] under which view the union necessarily would be between arginine and glutamic acid and would give a calculated layer–layer distance of 10.42 Å. or by (b) hydrogen-bond unions[8] which would give a calculated layer–layer distance of 9.94 Å. According to Astbury[9] the layer–layer distance of most proteins is about 10 Å. Egg albumin with equilateral dimensions of about 44 Å. may be expected to have four layer levels. Why urea dissociates egg albumin into half molecules instead of quarter molecules, if the cleavage is parallel to the layer level, is not apparent.

In the present paper we have studied the effect of urea on the rotatory dispersion of gelatin at 0.5 and 40° and have found that the same general formulas hold for its behavior as we have found for inorganic salts. After dialyzing out the urea from our most concentrated solutions we have found that the gelatin regained its original optical activity. This seems to be clear-cut evidence that in spite of the fact that many other proteins may suffer permanent "denaturation" in urea solutions, gelatin is not affected permanently by such treatment.

Experimental

The procedure for preparing the solutions and for the measurement of rotations, density, *p*H, etc., was the same as has been described before. The urea was recrystallized three times from hot water and melted at 132.6° (corr). It was dried by suction and stored over phosphorus pentoxide at room temperature. In preparing solutions, due to the tremendous negative heat of solution of urea, the urea was added in small quantities to the flask of gelatin solution, warming after each addition by immersing in a water-bath at 40° and shaking gently until solution took place.

The specific rotation of gelatin in various concentrations of urea solution was measured at 0.5 and 40° for five different wave lengths of light in the visible spectrum, *viz.:* red lithium line $\lambda = 6707.86$ Å.; sodium D line $\lambda = 5892.62$ Å. (optical mean); yellow mercury, $\lambda = 5780.13$ Å. (optical mean); green mercury, $\lambda = 5460.73$ Å.; and the deep blue mercury line, $\lambda = 4358.34$ Å. The light filters employed have been described. The gelatin concentration of the various solutions was 0.7641 g. per 100 g. of solution.

Discussion and Conclusions

In Tables I and II are recorded our data taken at 0.5 and 40°, respectively, for the five wave lengths employed. In Fig. 1, these data are graphed, plotting the reciprocal of the specific rotation against the square of the wave length at which the respective rotations were measured. The relationship is linear, the same as we have recorded for the effect of the various halides of sodium, which means that a single-term Drude equation expresses the results.

The straight lines in the graph for urea cut the *x*-axis at $\lambda_0 = 2200$ Å. the same as for the halides. This means that the absorption band controlling the dispersion of gelatin is located at 2200 Å. The same value for λ_0 was obtained by mathematical solution of our data as has been done before. The values of k, numerator in the Drude equation, were calculated for each urea concentration and appear in Table III and are graphed in Fig. 2. At 40° the k values bear an essentially linear relation to concentration of urea as given by the equation

$$K_{40°} = 44.517 + 0.6138\ C_{\text{urea}} \qquad (1)$$

There is a tendency for the factor preceding the concentration term to increase slightly with increasing urea concentration, but for the purposes of this paper an average of these factors may just as well be used. For the first time in our experience with the effect of added substances on the rotation of gelatin, the added substance increases the dispersion constant at 40° as its concentration is increased. For all of the substances we have examined previously the dispersion constant has decreased at all temperatures with increasing concentration of the optically inactive substance. At 0.5° the curve for the k values is made up of two simultaneously occurring effects, as has been noted previously with the sodium halides, the one a linear relationship to urea concentration for Form A

$$k_{0.5°} = 99.530 - 1.70\ C_{\text{urea}} \qquad (2)$$

and for Form B

$$k_{0.5°} = 64.00 - 1.70\ C_{\text{urea}} \qquad (2a)$$

(Forms A and B are the respective forms of

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(7) Lloyd, Marriott and Pleass, *Trans. Faraday Soc.*, **29**, 554 (1933).

(8) Mirsky and Pauling, *Proc. Nat. Acad. Sci.*, **22**, 439 (1936).

(9) Astbury and Street, *Phil. Trans. Roy. Soc.*, **A230**, 75 (1931); Astbury and Woods, *ibid.*, **A232**, 333 (1933); Astbury and Sisson, *Proc. Roy. Soc.* (London), **A150**, 533 (1935); Astbury and Lomas, *J. Chem. Soc.*, 846 (1935); Astbury, Dickinson and Bailey, *Biochem. J.*, **29**, 2351 (1935); Astbury and Atkin, *Nature*, **132**, 348 (1933).

TABLE I

SPECIFIC ROTATION OF GELATIN SOLUTIONS CONTAINING UREA AT 0.5° FOR DIFFERENT WAVE LENGTHS OF LIGHT

Soln.	Concn. of urea, molal.	Density at 25°	pH	Levo degrees λ 6707.86 Å. (a)	[α]	λ 5892.62 Å. (a)	[α]	λ 5780.13 Å. (a)	[α]	λ 5460.73 Å. (a)	[α]	λ 4358.34 Å. (a)	[α]
1	0.00	1.0026	6.04	3.83	248.04	5.14	332.87	5.38	348.41	6.15	398.28	10.86	703.30
2	.50	1.0107	6.22	3.82	245.96	5.13	330.31	5.36	345.13	6.13	394.71	10.83	697.35
3	1.00	1.0189	6.20	3.83	244.11	5.13	326.98	5.37	342.27	6.14	391.35	10.85	691.56
4	1.50	1.0269	6.21	3.79	239.64	5.09	321.84	5.33	337.02	6.09	385.08	10.75	679.73
5	2.00	1.0354	6.21	3.74	234.53	5.02	314.80	5.25	329.22	6.01	376.87	10.60	664.71
6	2.50	1.0437	6.17	3.61	224.58	4.85	301.71	5.07	315.41	5.80	360.82	10.24	637.03
7	3.00	1.0519	6.28	3.36	207.38	4.51	278.37	4.72	291.34	5.39	332.68	9.51	586.97
8	3.50	1.0604	6.38	2.99	183.08	4.02	246.15	4.20	257.12	4.81	294.53	8.48	519.25
9	4.00	1.0691	6.52	2.66	161.54	3.57	216.81	3.74	227.13	4.27	259.32	7.54	457.91
10	4.50	1.0776	6.45	2.46	148.22	3.31	199.43	3.46	208.47	3.96	238.60	6.98	420.56
11	5.00	1.0866	6.59	2.36	141.02	3.18	190.02	3.33	198.98	3.80	227.06	6.70	400.35
12	6.00	1.1037	6.62	2.28	134.12	3.06	180.01	3.20	188.25	3.66	215.31	6.46	380.02
13	7.00	1.1216	6.64	2.24	129.67	3.02	174.83	3.15	182.35	3.60	208.40	6.36	368.18

TABLE II

SPECIFIC ROTATION OF GELATIN SOLUTIONS CONTAINING UREA AT 40° FOR DIFFERENT WAVE LENGTHS OF LIGHT

Soln.	Concn. of urea, molal.	Density at 25°	pH	Levo degrees λ 6707.86 Å. (a)	[α]	λ 5892.62 Å. (a)	[α]	λ 5780.13 Å. (a)	[α]	λ 5460.73 Å. (a)	[α]	λ 4358.34 Å. (a)	[α]
1	0.00	1.0026	6.04	1.71	110.74	2.30	148.95	2.41	156.07	2.75	178.09	4.86	314.74
2	.50	1.0107	6.22	1.73	111.39	2.33	150.03	2.44	157.11	2.78	179.00	4.92	316.80
3	1.00	1.0189	6.20	1.76	112.18	2.37	151.06	2.48	158.07	2.83	180.38	5.00	318.69
4	1.50	1.0269	6.21	1.79	113.18	2.40	151.75	2.51	159.34	2.88	182.10	5.07	320.58
5	2.00	1.0354	6.21	1.82	114.13	2.44	153.01	2.55	159.91	2.92	183.11	5.15	322.95
6	2.50	1.0437	6.17	1.84	114.46	2.47	153.66	2.59	161.12	2.96	184.14	5.22	324.73
7	3.00	1.0519	6.28	1.87	115.42	2.52	155.54	2.63	162.33	3.01	185.78	5.31	327.74
8	3.50	1.0604	6.38	1.90	116.34	2.55	156.14	2.67	163.49	3.05	186.76	5.39	330.04
9	4.00	1.0691	6.52	1.93	117.21	2.59	157.29	2.71	164.58	3.10	188.26	5.47	332.20
10	4.50	1.0776	6.45	1.96	118.09	2.63	158.46	2.75	165.69	3.14	189.19	5.54	333.79
11	5.00	1.0866	6.59	1.98	118.32	2.67	159.54	2.79	166.71	3.19	190.62	5.62	335.82
12	6.00	1.1037	6.62	2.05	120.59	2.76	162.36	2.88	169.42	3.29	193.54	5.81	341.79
13	7.00	1.1216	6.64	2.11	122.17	2.84	164.41	2.96	171.35	3.39	196.24	5.98	346.18

gelatin in low urea and high urea concentrations) and a second relationship

$$C_{\text{urea}} = \frac{1}{0.89}\left[\log\left(\frac{a}{1-a}\right)\right] - \log(1/K) \quad (3)$$

where a represents the fraction of the gelatin undergoing change as shown by the change in magnitude of the dispersion constants $k_{0\cdot5}$. In Table III are given the a values for the fraction undergoing change and the calculated values obtained for log $(1/K)$. The latter agree well with one another and give a mean value of 3.373. The factor 1/0.89 preceding the $a/(1-a)$ term regulates how rapidly the change takes place from one optically active form to the other.

In its influence on the rotatory dispersion of gelatin at 0.5° urea stands about midway between sodium chloride and bromide. With all of the sodium halides, the product of the constants preceding the logarithmic $a/(1 - a)$ term multiplied by the log $(1/K)$ term, $[k \log (1/K)]$, gave a constant (2.66); however, the product of these constants for urea $(0.89 \times 3.37 = 3.00)$ does not have the same value as for the sodium halides.

TABLE III

ROTATORY DISPERSION CONSTANTS AT 0.5 AND 40°

Soln.	Concn. urea molal.	$k_{0.5°}$	a	Log (1/K)	$k_{40°}$
1	0.00	99.530	..	..	44.521
2	.50	98.681	..	..	44.801
3	1.00	97.832	..	..	45.103
4	1.50	96.220	0.0214	3.3762	45.401
5	2.00	94.107	.0570	3.3711	45.739
6	2.50	90.151	.1415	3.3796	45.975
7	3.00	83.156	.3173	3.3739	46.401
8	3.50	73.519	.5646	3.3733	46.688
9	4.00	64.826	.7853	3.3672	47.025
10	4.50	59.561	.9096	3.3734	47.323
11	5.00	56.727	.9654	3.3735	47.593
12	6.00	53.801	1.000	..	48.394
13	7.00	52.094	1.000	..	49.010

$k_{40°} = 44.521 + x_1C_{\text{urea}}$ where $x_1 = 0.6138$
$k_{0.5°} = 99.530 - x_2C_{\text{urea}}$ where $x_2 = 1.700$ (Form A)
$k_{0.5°} = 64.00 - x_2C_{\text{urea}}$ where $x_2 = 1.700$ (Form B)
mean log $(1/K) = 3.3735$
$k = 0.89$ (const. preceding $(a/(1 - a)$ term)

This indicates that general equation (3) cannot be simplified further to fit all cases although simplification of the equation for similar salts such as the alkali halides appears justified, as we have already shown.

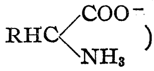
In Table IV are given the various constants obtained at the various wave lengths for the various combinations employed, calculated from the Lucas equation[10] for a system containing two optically active molecular species having unequal dispersion constants. The constancy obtained for a given combination for the five wave lengths used shows that two and only two optically active species of molecule are present, one the original gelatin molecule (probably gelatinate ion of the type  $RHC\begin{smallmatrix}COO^-\\NH_3\end{smallmatrix}$) and the other the molecule after it has undergone the change recorded by the logarithmic equation.

TABLE IV

CALCULATION OF THE LUCAS CONSTANT FOR GELATIN–UREA SYSTEMS CONTAINING TWO OPTICALLY ACTIVE COMPONENTS (0.5°)

Combination[a]	λ 6708 Å.	λ 5892 Å.	λ 5780 Å.	λ 5461 Å.	λ 4358 Å.
1–2/1–13	0.0176	0.0162	0.0198	0.0188	0.0197
1–3/1–13	.0332	.0373	.0370	.0365	.0350
1–4/1–13	.0710	.0698	.0686	.0695	.0703
1–5/1–13	.114	.114	.116	.113	.115
1–6/1–13	.198	.197	.199	.197	.198
1–7/1–13	.344	.345	.344	.346	.347
1–8/1–13	.549	.549	.550	.546	.549
1–9/1–13	.731	.734	.730	.732	.732
1–10/1–13	.843	.844	.843	.841	.844
1–11/1–13	.904	.904	.900	.902	.904
1–12/1–13	.962	.967	.966	.964	.965

[a] The numbers in this column refer to corresponding soln. no. in Table I.

In Table V we have recorded the rotation and dispersion constant at 0.5° for five different wave lengths, of gelatin which had been treated with 7.0 molal urea solution for a week at 0.5°, after which the solution was placed in collodion tubes and the urea dialyzed out. The dialyzed gelatin solution was then concentrated by freezing out part of the water as ice, was brought to the desired *p*H with dilute sodium hydroxide solution, the gelatin concentration determined, the polarizing tubes filled and the gelatin allowed to come to equilibrium during a week at 0.5°, at which temperature they were finally read in the polariscope. The average rotatory dispersion constant of the gelatin going through this cycle of treatment with urea was found to be 99.477 as compared with 99.530 for the original gelatin before treatment. The identity of these constants to one part in 2000 led us to conclude that gelatin suffers no permanent change due to treatment with urea such as is often referred to under the term "denaturation." In the case of gelatin the change is clearly reversible on removing the urea, the same as we have found repeatedly to be the case with neutral salts.

TABLE V

SPECIFIC ROTATION OF GELATIN SOLUTION AT 0.5° AFTER DIALYSIS OF UREA

Gelatin concn. 0.7858 g. per 100 g. soln.; *p*H = 6.30; *d* = 1.0027

λ	(*a*)	[α]	$k_{0.5°}$
6708	3.91	247.56	99.409
5893	5.26	333.04	99.522
5780	5.50	348.23	99.489
5461	6.29	398.25	99.481
4358	11.10	702.80	99.482
Mean			99.477

Although the same general equations express the influence of the dipole ion $^+NH_3C(=NH)O^-$ on gelatin as was found for the simple halide salts, the gelatin ion changed by urea has a dispersion constant of 64.00 at 0.5° when extrapolated to zero urea concentration as contrasted with a similar value of 46.33 for the gelatin ion when changed by the sodium halides. This total change by urea amounts to exactly two-thirds of the change produced by the sodium halides.

Summary

The rotatory dispersion of gelatin in urea solutions has been examined at 0.5 and 40° and was found to follow a single-term Drude equation.

At 40° the dispersion constants bear a linear relation to urea concentration, $k_{40°} = 44.517 + 0.6138\ C_{\text{urea}}$.

The dispersion at 0.5° is the result of two effects, one a linear relation to urea concentration for Form A of $k_{0.5°} = 99.530 - 1.70\ C_{\text{urea}}$, and for Form B of $K_{0.5°} = 64.00 - 1.70\ C_{\text{urea}}$ and the other a logarithmic function, $C_{\text{urea}} = \frac{1}{0.89}\left[\log\left(\frac{a}{1-a}\right)\right] - \log\ (1/K)$ in which log $(1/K)$ equals 3.373. Urea is intermediate in effect on the rotation of gelatin at 0.5°, lying between sodium chloride and bromide. The maximum lowering of the dispersion constant of gelatin by urea is only about two-thirds that produced by the halides of sodium.

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[10] Lucas, *Ann. phys.*, [10] **9**, 381 (1928); *Trans. Faraday Soc.*, **26**, 418 (1930).

After dialyzing out the urea from several of the most concentrated solutions, the rotatory dispersion constant returned to its original value at 0.5°, showing that gelatin had undergone no denaturation by urea.

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[CONTRIBUTION FROM THE PHYSICS LABORATORIES, THE CITY COLLEGE OF THE COLLEGE OF THE CITY OF NEW YORK]

Magneto-Optic Rotations of Paramagnetic Ions

BY SAMUEL STEINGISER AND HERBERT HYMAN

The purpose of this investigation was to observe the magneto-optic rotations of dilute solutions of complex iron salts, and to determine the partial Verdet constants. The three salts investigated were potassium ferricyanide, potassium ferrocyanide, and ferric ammonium sulfate. Ferrous ammonium sulfate was also tried, but since it absorbed most of the light in the range of the sodium lamp, accurate measurements could not be made.

Experimental

Materials and Apparatus.—All chemicals were of C. P. grade. Since, in the very dilute solutions used, a relatively large impurity would be necessary to affect the results, no further purification was attempted. The concentrations of the solutions were determined by density measurements. These were made on a chainomatic specific gravity balance, and the concentrations found from tables in the "International Critical Tables."

The source of light, for the values reported, was a General Electric Sodium Lab-Arc, $\lambda_D = 5893$ Å. (Earlier preliminary investigations were made using a mercury vapor quartz arc, but this was abandoned in favor of the more universal sodium arc.) Nicol prisms were used as polarizer and analyzer. The angle setting on the scale could be read to 0.1° and estimated to within 0.01° with the aid of a telescope and cross-hair. The Pyrex glass cell, containing the liquid under investigation, was a 21.6-cm. long tube with the ends of optically flat glass fused into the body of the cell. No cement was used on any part of the tube. It was mounted on wooden supports inside the hollow core of a large coil. The coil was 25 cm. in length, formed by winding 2-mm. diameter insulated copper wire in 17 layers of 125 turns each on a copper cylinder. The coil extended sufficiently beyond the tube to eliminate any distortion of the magnetic field due to edge effects.

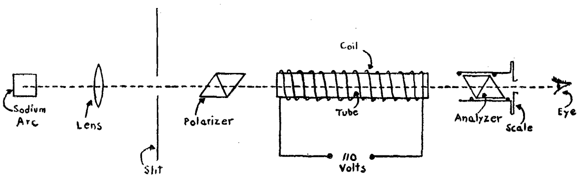

Fig. 1.—Schematic diagram of apparatus.

The apparatus was calibrated using carbon disulfide and distilled water over a range of currents as can be seen from the data. The Verdet constants for these two liquids were obtained from the "International Critical Tables." In order to facilitate calculations of the Verdet constants of the solutions under investigation, a conversion factor was found, as shown, equal to 0.0399 Verdet unit/deg./amp.

Measurements.—The values reported are the average of nine independent measurements with the field off, recorded in the tables below as N^0, nine with the field causing rotation clockwise, R^0, and finally nine with the field causing rotation counterclockwise, L^0. Altogether twenty-seven readings were taken for each solution and the average with its mean deviation calculated.

Although the partial Verdet rotations of some of the salts are in opposite directions to that of water, the actual rotations, in all cases measured, were in the same direction, due to the rather dilute solutions used. The partial Verdet constant is defined so that

$$N_1V_1 + N_2V_2 = V$$

where N_2 and N_1 are the mole fractions of the solute and solvent, respectively, V is the observed Verdet constant for the solution, and V_2 and V_1 are the partial Verdet constants of the solute and solvent. This equation is by definition exact, but in using it to determine V_2, it is necessary to make the assumption that V_1 equals the Verdet constant of pure water. While this undoubtedly is not true in concentrated solutions, it is probably true within the limit of experimental error in the solutions used in these measurements. V_2 is not necessarily the Verdet constant of the pure salt and should not be regarded as such, but is the Verdet constant of the salt in the solution of definite molality. There is considerable evidence to show that it may be regarded as constant over a considerable range of concentrations.

The agreement between the two standardizing substances is thus seen to be very good.

The factor for converting the rotation deg./amp. into Verdet units is 0.0399 Verdet unit/deg./amp.

CALIBRATION DATA

Distilled water

V = 0.01306 min./cm. oersted at 30°C.

No.	Current	Reading in deg.			Rotation in deg.			Rotation/unit current		
	I, amp.	N^0	R^0	L^0	$N^0 - R^0$	$N^0 - L^0$	$^1/_2(R^0 - L^0)$	$N^0 - R^0/I$	$N^0 - L^0/I$	$R^0 - L^0/2I$
1	14.7	49.78	45.05	54.70	4.73	4.92	4.84	0.322	0.335	0.329
2	14.6	49.52	45.05	54.45	4.47	4.93	4.70	.311	.338	.322
3	14.5	49.82	44.64	54.60	5.18	4.58	4.88	.358	.317	.337
4	14.3	49.65	44.95	54.29	4.70	4.64	4.67	.328	.323	.326
5	14.4	49.80	44.95	54.50	4.85	4.70	4.78	.336	.326	.332
6	14.3	49.45	45.00	54.10	4.45	4.55	4.50	.311	.318	.315
7	14.3	49.65	44.76	54.45	4.89	4.80	4.84	.343	.337	.328
8	14.4	49.63	45.30	54.42	4.33	4.79	4.56	.301	.333	.317
9	14.3	49.68	45.05	54.44	4.63	4.81	4.72	.324	.336	.329
							Mean	.326 ±.004	.329 ±.002	.327 ±.002

Rotation, degrees/amp. = 0.327 ± 0.002.
0.01306/0.327 = 0.0399 Verdet unit/deg./amp.

Carbon disulfide

V = 0.04151 at 30°

No.	Current	Reading in deg.			Rotation in deg.			Rotation/unit current		
	I, amp.	N^0	R^0	L^0	$N^0 - R^0$	$N^0 - L^0$	$^1/_2(R^0 - L^0)$	$N^0 - R^0/I$	$N^0 - L^0/I$	$R^0 - L^0/2I$
1	14.7	82.55	67.40	98.20	15.15	15.65	15.40	1.031	1.065	1.048
2	14.5	82.85	67.70	98.40	15.15	15.55	15.35	1.044	1.071	1.059
3	14.4	82.72	67.21	98.15	15.51	15.43	15.47	1.078	1.071	1.074
4	14.1	82.87	67.80	98.17	15.07	15.30	15.18	1.068	1.082	1.076
5	10.8	83.19	71.80	93.60	11.39	10.41	10.90	1.051	0.964	1.008
6	10.8	82.89	71.60	93.80	11.29	10.91	11.10	1.041	1.009	1.027
7	10.6	82.70	71.80	93.50	10.90	10.80	10.85	1.028	1.019	1.022
8	10.6	83.21	72.06	93.56	11.15	10.35	10.75	1.051	0.976	1.014
9	8.4	82.82	74.01	92.00	8.81	9.18	8.99	1.050	1.091	1.071
10	8.5	82.76	73.62	91.96	9.14	9.20	9.17	1.075	1.085	1.080
11	7.2	82.39	74.65	89.78	7.74	7.39	7.56	1.074	0.998	1.021
12	7.2	82.71	74.80	89.80	7.91	7.09	7.50	1.098	.984	1.042
13	5.9	82.90	76.64	89.00	6.26	6.10	6.18	1.061	1.032	1.044
14	5.9	82.41	76.25	88.38	6.16	5.97	6.07	1.042	1.012	1.028
15	5.9	82.90	76.40	88.81	6.50	5.91	6.21	1.099	1.002	1.050
16	6.0	83.05	76.18	88.75	6.87	5.70	6.28	1.160	0.950	1.045
							Mean	1.063	1.026	1.044 ±.004

Rotation, degrees/amp. = 1.044 ± 0.004.
0.04151/1.044 = 0.0398 Verdet unit/deg./amp.

FERRIC AMMONIUM SULFATE, $d^{26}{}_4$ 1.0105

No.	Current	Reading in deg.			Rotation in deg.			Rotation/unit current		
	I, amp.	N^0	R^0	L^0	$N^0 - R^0$	$N^0 - L^0$	$^1/_2(R^0 - L^0)$	$N^0 - R^0/I$	$N^0 - L^0/I$	$R^0 - L^0/2I$
1	13.3	52.28	48.37	56.81	3.91	4.53	4.22	0.294	0.341	0.317
2	13.3	52.15	48.12	56.42	4.03	4.27	4.15	.305	.322	.313
3	13.3	52.28	48.00	56.36	4.28	4.08	4.18	.321	.307	.314
4	13.3	52.24	48.22	56.38	4.02	4.14	4.08	.304	.312	.308
5	13.3	52.40	48.23	56.41	4.17	3.99	4.09	.315	.301	.309
6	13.3	52.10	47.98	56.58	4.12	4.48	4.30	.310	.336	.323
7	13.3	52.15	48.05	56.41	4.10	4.26	4.18	.309	.322	.316
8	13.2	52.18	48.48	56.39	3.70	4.21	3.96	.281	.318	.300
9	13.3	52.41	47.95	56.66	4.46	4.25	4.35	.337	.321	.328
							Mean	.308 ±.003	.320 ±.003	.314 ±.002

Molality = 0.0282, mole fraction N_2 = 0.000508, V = 0.314 × 0.0399 = 0.01253 Verdet unit, V_2 (calcd.) = −1.024 Verdet units.

POTASSIUM FERRICYANIDE, $d^{26}{}_4$ 1.0339

1	14.8	81.87	79.66	84.04	2.21	2.17	2.19	0.149	0.147	0.148
2	14.7	81.90	79.30	83.80	2.60	1.90	2.25	.177	.129	.153
3	14.5	81.75	80.10	83.81	1.65	2.06	1.91	.114	.123	.132

POTASSIUM FERRICYANIDE d^{26}_4 1.0339 (*Concluded*)

No.	Current I, amp.	Reading in deg. N^0	R^0	L^0	Rotation in deg. $N^0 - R^0$	$N^0 - L^0$	$1/2(R^0 - L^0)$	Rotation/unit current $N^0 - R^0/I$	$N^0 - L^0/I$	$R^0 - L^0/2I$
4	14.6	81.90	79.84	83.90	2.06	2.00	2.03	0.141	0.140	0.139
5	14.4	81.78	80.24	84.20	1.54	2.42	1.98	.107	.169	.138
6	14.5	81.65	79.10	83.54	2.75	1.69	2.22	.189	.113	.153
7	14.4	82.00	80.20	84.40	1.80	2.40	2.10	.125	.167	.146
8	14.4	81.80	79.70	84.02	2.10	2.22	2.16	.146	.154	.150
9	14.2	81.64	79.80	83.45	1.84	1.81	1.83	.130	.128	.129
							Mean	.142	.144	.143
								±.007	±.005	±.003

Molality = 0.173, mole fraction N_2 = 0.00312, $V = 0.143 \times 0.0399 = 0.00571$ Verdet unit, V_2 (calcd.) = −2.354 Verdet units.

POTASSIUM FERROCYANIDE, d^{26}_4 1.1124

No.	Current I, amp.	Reading in deg. N^0	R^0	L^0	Rotation in deg. $N^0 - R^0$	$N^0 - L^0$	$1/2(R^0 - L^0)$	Rotation/unit current $N^0 - R^0/I$	$N^0 - L^0/I$	$R^0 - L^0/2I$
1	14.8	52.39	47.20	57.35	5.19	4.96	5.08	0.350	0.336	0.344
2	14.9	52.46	47.18	57.60	5.28	5.14	5.21	.354	.345	.351
3	14.8	52.44	47.50	57.60	4.94	5.16	5.05	.334	.349	.341
4	14.5	52.80	47.25	57.80	5.55	5.00	5.27	.383	.345	.363
5	14.5	52.55	47.25	58.05	5.30	5.50	5.40	.365	.379	.372
6	14.4	82.38	77.10	87.38	5.28	5.00	5.14	.367	.347	.357
7	14.4	82.35	77.16	87.57	5.19	5.22	5.20	.360	.362	.361
8	14.4	82.42	77.18	87.22	5.24	4.80	5.02	.363	.334	.351
9	14.3	83.70	78.50	88.25	5.20	4.55	4.87	.363	.320	.341
							Mean	.360	.347	.353
								±.003	±.004	±.003

Molality = 0.415, mole fraction N_2 = 0.00748, $V = 0.353 \times 0.0399 = 0.01409$ Verdet unit, V_2 (calcd.) = 0.148 Verdet unit.

Discussion

Welo and Baudisch[1] have shown that, with complex ions having a central atom of a transition element, the paramagnetism can be determined from the effective atomic number. When this has the same value as an inert gas, the complex is diamagnetic, while if it differs from this by *n* units, the complex has a magnetic moment of *n* Bohr magnetons. Thus the six-covalent ferricyanides, as $K_3[Fe(CN)_6]$ with an e. a. n. $26 + 6 + 3 = 35$, give p (Weiss) = 10, and b (Bohr) = *ca.* 1, while the ferrocyanides as $K_4[Fe(CN)_6]$ (e. a. n. $26 + 6 + 4 = 36$, the atomic number of krypton) are diamagnetic. Ferric ammonium sulfate probably exists in solution as hydrated Fe^{+++} ion, which is found to be paramagnetic also.

Thus we see that potassium ferricyanide and ferric ammonium sulfate are paramagnetic and also have large negative partial Verdet constants, while potassium ferrocyanide, being diamagnetic, has a relatively low positive partial Verdet constant. There seems to be some correlation between these facts. Scherer and Cordonnier[2,3] have shown that paramagnetic cobalt ions exhibit similar negative Verdet constants over a range of temperatures and wave lengths. Since an error of even 1% in the actual rotation introduces an error of more than 20% in the determination of partial Verdet constants, a quantitative correlation is not possible as yet, but this work has shown a definite connection which may be of use in the future.

Acknowledgment and particular thanks are due to Professors Marcus and Sonkin, of the Physics Department of The City College, for their invaluable aid in this research.

Summary

The partial Verdet constants of ferric ammonium sulfate, potassium ferricyanide and potassium ferrocyanide were determined and found to be equal to −1.024, −2.354 and +0.148, at molalities 0.0282, 0.173 and 0.415, respectively. The total Verdet constant for each of these molalities was found to be 0.01253, 0.00571 and 0.01409, respectively. The diamagnetic salt, potassium ferrocyanide, shows a normal rotation, while the other salts show a large negative rotation, due to paramagnetism.

NEW YORK, N. Y.

RECEIVED JUNE 16, 1938

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[1] Welo and Baudisch, *Nature*, **116**, 606 (1925).

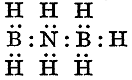
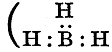
[2] Scherer and Cordonnier, *Compt. rend.*, **196**, 1724 (1933).

[3] Cordonnier, *ibid.*, **205**, 313 (1937).

[CONTRIBUTION FROM THE GEORGE HERBERT JONES CHEMICAL LABORATORY OF THE UNIVERSITY OF CHICAGO]

Hydrides of Boron. X. The Preparation and Preliminary Study of the New Compound B_2H_7N

BY H. I. SCHLESINGER, DAVID M. RITTER,[1] AND ANTON B. BURG

In the preparation of triborine triamine ($B_3N_3H_6$) from ammonia and diborane, we[2] obtained small quantities of a new volatile compound having the molecular formula B_2H_7N. The formation of this compound, for which the structural formula  $\underset{\ddot{H}}{\overset{H}{\ddot{B}}}:\underset{\ddot{H}}{\overset{H}{\ddot{N}}}:\underset{\ddot{H}}{\overset{H}{\ddot{B}}}:H$ seems most appropriate, is an important part of the evidence in favor of the hypothesis that many of the reactions of diborane are caused by its dissociation into unsaturated borine  $\left(H:\overset{H}{\ddot{B}}:H\right)$ molecules.[3] It is, therefore, of interest to describe the preparation and properties of the new compound, as well as to present further evidence concerning its structure.

Preparation.—The observation that B_2H_7N was obtained only when diborane was used in excess of that required by the formula $B_2H_6 \cdot 2NH_3$, suggested that it is formed by the action of diborane upon the "diammoniate,"[4] rather than by the direct reaction of diborane with ammonia. It therefore seemed likely that the yield of B_2H_7N would be improved considerably if diborane were passed over the "diammoniate," under conditions subject to close control.

The apparatus used for this flow method was the one which had been employed before, in the preparation of B_4H_{10} and B_5H_{11}.[5] Ammonia was condensed as a thin layer upon the walls of the first U-tube (U4A in the article referred to above) and converted to the "diammoniate" by exposing it to an excess of diborane while the tube was warmed slowly from −130° to room temperature.[6] Then a large sample of diborane was condensed in the graduated tube M, and allowed to evaporate at −80°; the gas passed through the U-tube containing the ammoniate, at a rate limited by the capillary tube C. All condensable gases and vapors were trapped in the second U-tube (at −195°), while the hydrogen passed through and registered its pressure upon a manometer in the main vacuum apparatus beyond. The proper temperature for the first U-tube was determined by warming that U-tube until the movement of the mercury in the manometer indicated a satisfactory rate of reaction.[7] After the evaporation of the last of the diborane, the major part was recovered from the material trapped in the second U-tube; in most cases it was passed through the system again, until no important quantities of hydrogen were evolved in the process. The conditions and results of four such experiments are given in Table I.

TABLE I

FLOW METHOD OF PREPARING B_2H_7N

Ammonia, cc.[a]	Total B_2H_6, cc.	No. of passages	Flow rate, cc./min.	Temp., °C.	Diborane destroyed, cc.	B_2H_7N formed, cc.	% yield (based on diborane)
105	422	1	10	100	75	14.7	19
120	730	1	5	85	83	25.0	30
173	613	2	12	85	100	29.0	29
142	877	2	30	88	108	36.0	33

[a] All gas volumes in this paper refer to standard conditions.

The product was purified by fractional condensation: it passed through a U-tube at −55°, and condensed completely at −80°.

Analysis and Molecular Weight.—Measured samples of the vapor were treated with known volumes of standard hydrochloric acid in sealed tubes. The resulting hydrolyses were completed in ten minutes at room temperature.[8] The hydrogen was collected for measurement over mercury by means of a Töpler pump with a trap at −196°; the contents of the trap and of the hydrolysis tube were then washed into a flask. The excess acid was titrated to the methyl red end-point; the difference between the quantity of acid originally used and that found by this titration represents ammonia nitrogen. Subsequent titra-

TABLE II

ANALYTICAL DATA FOR B_2H_7N

Sample	Hydrogen Quantity	Hydrogen Ratio	Boric acid Quantity	Boric acid Ratio	Ammonia Quantity	Ammonia Ratio
0.0846	0.418	4.94[a]	0.167	1.97	..	..
.0589	..	..	..	..	0.0587	1.00
.428	..	..	..	..	.406	0.95
.196	.985	5.02	..	..	..	..
.166	.848	5.10	..	..	..	..
.303	..	..	.594	1.96	..	..

[a] In this case, the sample was heated for five hours at 100° with water containing no acid.

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[1] Much of the material of this paper was taken from the dissertation presented by David M. Ritter to the Faculty of the Division of Physical Sciences of the University of Chicago, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] Schlesinger, Ritter and Burg, THIS JOURNAL, **60**, 1297 (1938).

[3] Other evidence on this subject appears in two earlier papers: Burg and Schlesinger, *ibid.*, **59**, 780 (1937); Schlesinger and Burg, *ibid.*, **60**, 290 (1938).

[4] For the structure of this compound, see Schlesinger and Burg, *ibid.*, **60**, 290 (1938).

[5] Burg and Schlesinger, *ibid.*, **55**, 4012 (1933).

[6] The preparation of the diammoniate by the slightly more tedious process of carrying on the reaction at −120° and removing the residual ammonia at −80°, led to no change of yield.

[7] It is important to employ the lowest feasible temperature, because higher temperatures lead to frothing, with the danger of clogging the capillary, and also facilitate the formation of traces of such impurities as B_4H_{10}, B_5H_{11}, and $B_3N_3H_6$.

[8] When pure water was used, the hydrolysis was far more difficult, probably because the free ammonia first liberated acted as a base to hinder the hydrolysis of the B-H links. Thus a sample which was left in contact with water in a sealed tube for two months at room temperature produced only 3.8 of the expected 5 volumes of hydrogen.

TABLE III

CORRECTED VAPOR PRESSURES OF B_2H_7N

$t°$	−27.2	−23.0	−16.2	−13.4	−9.6	−3.6	0.00	3.8	7.9	11.0	15.4	20.0	22.6	25.4	27.3	28.9
$p_{mm.}$, obsd.	5.3	7.65	12.0	14.6	18.9	26.1	32.3	39.3	49.6	57.8	72.5	90.3	102.0	117.0	126.8	135.9
$p_{mm.}$, calcd.	5.7	7.64	12.1	14.4	18.3	26.3	32.3	39.8	49.6	58.4	72.6	90.8	102.5	116.7	126.8	136.2

tion of the solution to the phenolphthalein end-point in the presence of an adequate quantity of mannite gave the amount of boric acid present. The results are given (in millimoles) in Table II.

These results agree with the formula B_2H_7N, as shown by the equation $B_2H_7N + 4H_2O + H^+ \longrightarrow 2HBO_2 + NH_4^+ + 5H_2$.

The molecular weight calculated from the observed vapor density also agreed with the formula B_2H_7N (obsd. 42.9 and 42.2; calcd. 42.6).

The melting point was determined by observations on two separately purified samples. The values, taken by means of an ammonia vapor pressure thermometer, were −66.5 and −66.4°.

The vapor pressure at various temperatures determined the equation

$$\log_{10} p_{mm.} = -(2097/T) + 1.75 \log_{10}T - 0.00642T + 6.677$$

From this equation, the molar heat of vaporization is estimated as 7300 cal., and the Trouton constant as 21.0 cal./degree mole. The normal boiling point is calculated to be 76.2°.

Decomposition and Thermal Stability.—The substance B_2H_7N can be kept for several days at room temperature without appreciable decomposition, but a sample which had been held for six hours at 45° showed an increase of vapor pressure, corresponding to about 0.2 cc. of diborane (from a 5-cc. sample). A sample left for sixteen months in a sealed bulb at room temperature, decomposed almost completely, evidently according to the equation $2B_2H_7N \longrightarrow B_2H_6 + (BH_4N)_x$; the actual results were complicated by secondary production of hydrogen, and by the probable presence of $B_3N_3H_6$ in the original sample.[9]

The 5.6-cc. sample yielded 2.4 cc. of diborane, 0.6 cc. of hydrogen, and 0.4 cc. of material having approximately the volatility of $B_3N_3H_6$. The diborane was fully identified by its vapor pressure (226 mm. at −112°) and by hydrolysis, which yielded 14.4 cc. (6.1 volumes) of hydrogen and 0.214 millimole of boric acid (2.00 equivalents per mole). The non-volatile solid was not investigated further.

The Behavior of B_2H_7N toward Trimethylamine.—A stable addition product $(CH_3)_3N \cdot B_2H_7N$, is produced by the action of trimethylamine upon B_2H_7N at −80°. Heating this product with excess trimethylamine results in the removal of a BH_3 group to produce one molecule of borine trimethylammine per mole of B_2H_7N originally used.

Thus 2.7 cc. of B_2H_7N, treated with 12.2 cc. of trimethylamine at −80°, absorbed 2.8 cc. of the latter, to give a white solid which failed to react further during two hours at room temperature. During three hours at 100°, however, there resulted 2.80 cc. of material whose vapor pressures were measured as 18.6 mm. at 69.5° and 10.6 mm. at 59.8°, in good agreement with the data recorded earlier for borine trimethylammine.[10] There resulted also 2.9 cc. of hydrogen, and a further 0.9 cc. of trimethylamine was used up. A trace (0.3 cc.) of material which seemed to be $B_3N_3H_6$, also was found among the products. The residual solid thus seemed to have the composition $BNH_2 \cdot {}^1/_2N(CH_3)_3$.

The Behavior of B_2H_7N toward Ammonia.—Like trimethylamine, ammonia adds to B_2H_7N to give a stable solid mono-ammoniate, $B_2H_7N \cdot NH_3$. By the sudden heating of this substance to 200°, a 45% yield of $B_3N_3H_6$ is obtained; this yield is somewhat higher than that obtained directly from the "diammoniate of diborane."

In a typical experiment, 5.2 cc. of B_2H_7N and 17.7 cc. of ammonia were left together for one hour at −80°. Then the excess ammonia was distilled to another part of the vacuum apparatus, while the reaction tube was being warmed to room temperature. The removed ammonia was measured as 12.6 cc., indicating that the white solid residue contained 5.1 cc. of combined ammonia. Five minutes of heating of the product at 50° caused the evolution of only 0.25 cc. of volatile material.

Another sample of the solid, composed of 9.65 cc. of B_2H_7N and 9.65 cc. of ammonia, was allowed to stand for two months at room temperature (25–30°): it produced 0.3 cc. of hydrogen and an even smaller trace of material which was trapped at −196°.

A sample composed of 4.8 cc. of B_2H_7N and 4.9 cc. of ammonia was heated for five minutes in a sealed tube at 200°. The products were 15.1 cc. of hydrogen, 1.4 cc. of $B_3N_6H_6$, 0.26 cc. of an unidentified substance slightly more volatile than $B_3N_3H_6$, and non-volatile solids. The yield of $B_3N_3H_6$ thus was slightly less than 45%.

The Behavior of $B_2H_7N \cdot NH_3$ toward Sodium in Liquid Ammonia.—When the compound $B_2H_7N \cdot NH_3$ is dissolved in liquid ammonia and

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[9] This particular sample had been obtained as a by-product in the preparation of $B_3N_3H_6$.

[10] Burg and Schlesinger, THIS JOURNAL, **59**, 785 (1937).

treated with sodium, one gram equivalent of hydrogen is liberated, per mole of B_2H_7N originally used. After completion of the reaction and removal of excess ammonia, the residue corresponds to the empirical formula $B_2H_7N \cdot NH_2Na$. The significance of these facts is discussed later.

A 5.65-cc. sample of B_2H_7N was dissolved in liquid ammonia at −77°; the solution was treated with 30 mg. of pure sodium, in the manner described in an earlier paper.[11] The resulting evolution of hydrogen was not very rapid, but it finally amounted to one gram equivalent per mole of B_2H_7N, as shown in Table IV.

TABLE IV

REACTION OF $B_2H_7N \cdot NH_3$ WITH SODIUM IN LIQUID AMMONIA

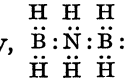
Total time, min.	Temp. during time before meas., °C.	Total H evolved, cc.	Ratio of H to B_2H_7N
16	−67	1.55	0.55
32	−55	2.45	.87
57	−60	2.90	1.03
130	−66	3.03	1.07

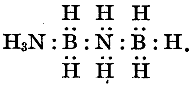
Reaction beyond that point was exceedingly slow. The major part of the ammonia was removed by distillation at −50°; a further 0.4 cc. (gas) was lost by the residue during seventy-six hours *in vacuo* at room temperature, conditions so severe that 4.0 cc. of hydrogen also was liberated. The residue was hydrolyzed completely by 3 normal hydrochloric acid; then the excess acid was distilled off and replaced by sodium hydroxide. The ammonia was determined, partly by measurement of the purified gas (9.05 cc.) and partly by titration (1.75 cc.). The total, 10.8 cc., amounts to 1.9 moles of ammonia per mole of B_2H_7N.

The slow production of somewhat more than one equivalent of hydrogen by reaction with sodium in liquid ammonia might well be due to a secondary reaction analogous to that of the "diammoniate of diborane."[4]

Discussion

Only two of the conceivable structures for the compound B_2H_7N seem worthy of serious discussion: (1) an amine of diborane, $B_2H_5NH_2$, and (2) a structure involving a B–N–B skeleton.[12] All derivatives of diborane, not immediately ammonolyzed, take up two molecules of ammonia per molecule of diborane derivative, to form stable compounds. The substance B_2H_7N, however, takes up only one molecule of ammonia; further addition, if it occurs at all, leads to very unstable addition products. This fact is sufficient to exclude further discussion of the first formulation.

The assumption of a B–N–B skeleton leads to two possible structures: (I) BH_3NHBH_3[13] and (II) $BH_2NH_2BH_3$. Formula I not only requires assumptions with regard to electronic distribution, unjustified by any of the chemical properties thus far known for the compound, but fails to explain why one and only one molecule of ammonia can be added to it. When structure II is represented electronically,  $\overset{H}{\underset{H}{B}}:\overset{H}{\underset{H}{N}}:\overset{H}{\underset{H}{B}}:H$, the addition of one molecule of ammonia (to the one "unsatisfied" boron atom) is understood readily. Compounds in which boron atoms are associated with only six bonding electrons are, of course, very common (*e. g.*, BF_3, BCl_3, BR_3, and their substitution products) and, if not ammonolyzed, take up one molecule of ammonia for each such boron atom present. They are also capable of adding trimethylamine in the same ratio, as does the compound B_2H_7N. On the other hand, compounds containing the BH_3 group tend to give borine trimethylammine, $BH_3 \cdot N(CH_3)_3$, a product which actually is obtained when the addition compound $B_2H_7N \cdot N(CH_3)_3$ is heated with an excess of the amine.

According to structure II, the addition of one mole of ammonia to B_2H_7N results in the compound  $H_3N:\overset{H}{\underset{H}{B}}:\overset{H}{\underset{H}{N}}:\overset{H}{\underset{H}{B}}:H$. This structure is analogous to that of borine ammine (H_3NBH_3) for in each an ammonia molecule is coördinatively bound to a boron atom. Although borine ammine has not been isolated, it has been shown by indirect methods[4] to react in liquid ammonia solutions with sodium to liberate one gram equivalent of hydrogen for every mole of ammonia bound in that manner. The compound $H_3NB_2H_7N$ reacts to give the same proportion of hydrogen. This cannot mean that the original ammonia addition product was an ammonium salt, for sodium would have reacted with such a salt to remove one nitrogen atom as ammonia, leaving a residue of the composition NaB_2H_6N, instead of the salt $NaNH_2 \cdot B_2H_7N$ actually obtained as a final product.

Other details of the behavior of the compound are in full agreement with formula II. Its stability is characteristic of compounds containing

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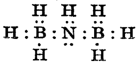
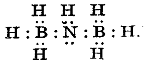
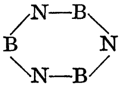
[11] Schlesinger and Burg, THIS JOURNAL, 60, 293 (1938).

[12] Other ideas are represented by the formulas $NH_4B_2H_3$, $NH_3 \cdot B_2H_4$, $NH_3 \cdot BHBH_3$, and $H^+B_2H_6N^-$. Each of these is difficult to reconcile with some of the physical and chemical properties described in this paper.

[13] According to the usual electronic formulations, two possibilities exist for structure I:  $H:\overset{H}{\underset{H}{B}}:\overset{H}{\ddot{N}}:\overset{H}{\underset{H}{B}}:H$ and  $H:\overset{H}{\underset{H}{B}}:\overset{H}{N}:\overset{H}{\underset{H}{B}}:H.$ Neither of these avoids the difficulties pointed out for the less specific formula I.

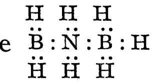
a B–N–B pattern of linking, rather than of those containing B–B bonds; the B–N–B skeleton explains why the compound, when heated, gives good yields of $B_3N_3H_6$, a substance containing the  ring; its rapid hydrolysis in acid solution to give five volumes of hydrogen suggests the existence of five B–H bonds.

Finally, attention is called to a recent paper by S. H. Bauer,[14] who, at our suggestion, investigated the electron diffraction of the vapor of this compound, and concluded that the data obtained can be explained only by the existence of a B–N–B skeleton for the molecule.

Acknowledgment.—We wish to express our thanks to the Research Corporation, for providing the liquid nitrogen used in a large part of this work.

Summary

The new volatile compound B_2H_7N (b. p. 76.2°; m. p. $-66.5°$) was prepared by the action of diborane upon its "diammoniate." The new substance is hydrolyzed easily in acid solution, to give five volumes of hydrogen, two equivalents of boric acid, and one equivalent of ammonium ion. Its thermal decomposition (slow at room temperature) produces diborane and a solid of undetermined character. It reacts with an equal gas volume of trimethylamine, to form a stable white solid; on heating with an excess of that amine, this product yields borine trimethylammine. With ammonia, B_2H_7N forms the stable solid $B_2H_7N{\cdot}NH_3$, which, on heating to 200°, gives a good yield of triborine triamine ($B_3N_3H_6$). The ammonia addition product reacts with sodium in liquid ammonia to liberate one equivalent of hydrogen; the residue after thorough removal of the solvent corresponds to the formula $NaNH_2{\cdot}B_2H_7N$.

The structure  $\overset{H}{\underset{\ddot{H}}{\ddot{B}}}:\overset{H}{\underset{\ddot{H}}{\ddot{N}}}:\overset{H}{\underset{\ddot{H}}{\ddot{B}}}:H$ is proposed for the compound, and although this specific picture is not considered definitely proved, it is shown to interpret satisfactorily all of the physical and chemical properties of the substance.

CHICAGO, ILL.

RECEIVED APRIL 11, 1938

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[14] S. H. Bauer, THIS JOURNAL, **60**, 524 (1938).

[CONTRIBUTION FROM THE BUREAU OF CHEMISTRY AND SOILS]

The Compressibilities of Hydrogen and of Four Mixtures of Hydrogen and Nitrogen at 0, 25, 50, 100, 200 and 300° and to 1000 Atmospheres

BY R. WIEBE AND V. L. GADDY

This is a continuation of work in this Laboratory on the compressibilities of hydrogen, nitrogen and their mixtures.[1] A summary of work previous to 1930 was given by Bartlett. Townend and Bhatt measured the isotherms of hydrogen at 0 and 25° to 600 atm.[2] Isothermal measurements on hydrogen between 0 and 100° and up to 1000 atm. were made by Michels, *et al.*[3] Michels and Gerver recalculated the compressibility data of Kohnstamm and Walstra on hydrogen at 15.5 and 20° between 1000 and 2000 atm.[4] Isotherms of nitrogen between 0 and 150° and at pressures from 20 to 80 atm. were determined by Michels, *et al.*[5] This latter work was continued up to 400 atm. by Otto, Michels and Wouters.[6] A further extension to 3000 atm. including a calculation of the thermodynamic properties was made by Michels, *et al.*[7] W. Edwards Deming and Lola S. Deming have calculated the thermodynamic properties of hydrogen and nitrogen.[8]

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[1] (a) Bartlett, THIS JOURNAL, **49**, 687; 1955 (1927); (b) Bartlett, *et al.*, *ibid.*, **50**, 1275 (1928); (c) **52**, 1363 (1930). Dr. Bartlett has kindly informed me that in Ref. 1b the column of figures for the compressibility of a 3:1 mixture of hydrogen and nitrogen at 99.85° was wrongly transcribed and should be as follows:

Press., atm.	Old figures	Correct
1	1.3656	1.3656
50	1.3992	1.4027
100	1.4298	1.4364
200	1.5068	1.5170
300	1.5870	1.5975
400	1.6700	1.6799
600	1.8412	1.8472
800	2.0130	2.0168
1000	2.1865	2.1865

Also in the same table, for 300 atmospheres and 0°, the figures have been transposed.

Old figure	Correct figure
1.0264	1.2064

[2] Townend and Bhatt, *Proc. Roy. Soc.* (London), **A134**, 502 (1931).

[3] Michels, Nijhoff and Gerver, *Ann. Phys.*, **12**, 562 (1932).

[4] Michels and Gerver, *ibid.*, [5] **16**, 745 (1933).

[5] Michels, Wouters and De Boer, *Physica*, **1**, 587 (1934).

[6] Otto, Michels and Wouters, *Physik. Z.*, **35**, 97 (1934).

[7] Michels, Wouters and De Boer, *Physica*, **3**, 585 597 (1936).

[8] Deming and Shupe, *Phys. Rev.*, **37**, 638 (1931), *ibid.*, **40**, 848 (1932); Deming and Deming, *ibid.*, **45**, 109 (1934).

Since in the previous investigations on hydrogen some disagreement exists among the different observers, we have repeated most of their measurements.

Apparatus and Procedure.—Figure 1 shows the low pressure part of the apparatus and the high pressure pipet. Before each run the connecting tube between pipet outlet valve M and stopcock G is open to the atmosphere through J. The 4-bulb buret A of 3000-cc. capacity is filled with mercury, stopcocks H, K and J are closed, and gas at some definite temperature and pressure is expanded from D through valve M. The whole volume is brought to atmospheric pressure by means of the oil-manometer F. Stopcock G is now closed and the gas is confined to the 4-bulb buret A. The mercury levels are now adjusted to calibration marks between the bulbs. Since usually two combinations of bulbs are possible, the one giving a pressure nearest to that of the atmosphere is selected. After opening H, manometer E is adjusted so that the mercury surface in the right arm just touches the tip of pin L. This assures a constant volume between H and L. The first two or three samples have to be discarded; after that the manometer will show the actual experimental variation, since the manometer volume is small compared with the gas volume in A. Any slight change in atmospheric pressure between closing of stopcock J and adjusting of oil-manometer F introduces only a negligible error since here again the volume of the connecting tube is small. Even a smaller volume is exposed to possible changes in room temperature. B is a coil to bring the incoming gas rapidly to the temperature of C. The large thermostat C was kept at 25 ± 0.01° while the temperature of the thermostat containing D was varied from 0 to 300°. Toluene and mercury filled regulators were used to cover the range between 0 and 200° while at 300° a thyratron control was used.[9] We used the control only for an auxiliary immersion heater; the voltage across the heating coils was that of the unregulated 110 a. c. voltage mains. It was possible to maintain the temperature within a few one-hundredths of a degree with little trouble. The true temperatures were measured with platinum resistance thermometers built according to specifications by Myers.[10] The thermometers were calibrated both at this Laboratory and at the Bureau of Standards with identical results. At 100 and 200° Crisco, or its equivalent, was used for bath liquid; while at 300° a lead–tin mixture was found satisfactory.

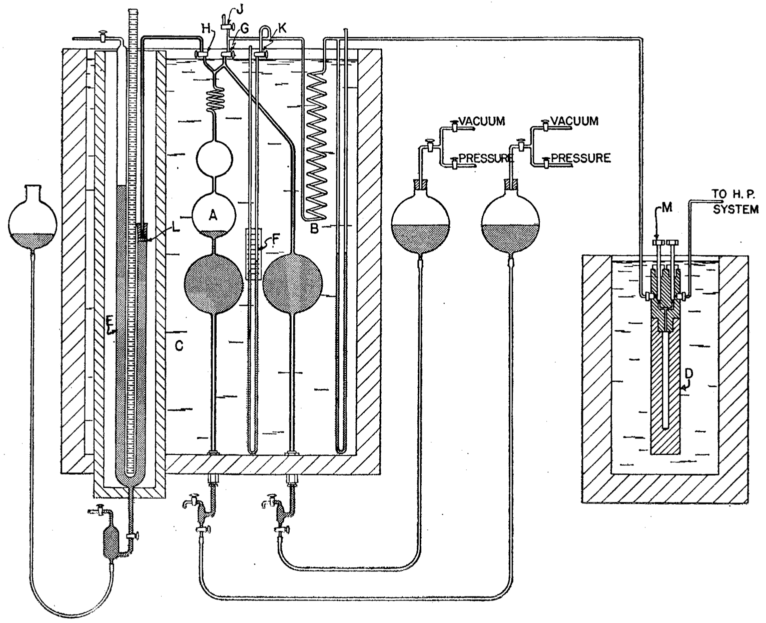

Fig. 1.

Our 200 and 1500 atmosphere piston gages were compared at 100 atm. with the National Bureau of Standards gage,[11] and it was found that only one of the pistons had developed a change of one part in 10,000 since August, 1935. The acceleration of gravity at the laboratory is taken to be 980.091 cm./sec.[2] The pressures are given in international atmospheres. The thermal conductivity and an accurate combustion method[12] were used to analyze the gas mixtures. The latter method was the more satisfactory in our case.

The high pressure volume was measured at 25 and 100° and at 100 atm. in a slightly modified steel pipet by displacing mercury by gas. The mercury was withdrawn, weighed and the volume calculated. The pressure coefficient was obtained from the work of Smith and Keyes.[13] From several determinations the compressibility of hydrogen was determined at 25 and 100°, and 100 atmospheres. These values were used as reference points throughout this work. The average coefficients of linear expansion of our steel (C 0.49%, Cr 2.48%, V 0.25%, Mn 0.68%) were determined by Dr. Peter Hidnert of the National Bureau of Standards, to whom our thanks are due. Table I gives the results obtained.

TABLE I

Temp. range, °C.	Average coefficients of linear expansion per °C. Sample heated to 300°	Sample treated with hydrogen at 300°
20–100	12.4×10^{-6}	11.4×10^{-6}
20–200	12.9×10^{-6}	12.2×10^{-6}
20–300	13.6×10^{-6}	12.9×10^{-6}

The results of Table I show a decided influence of hydrogen on steel. The sample used in determining the linear coefficient of expansion had been exposed to extreme conditions. In actual practice the thickness of the pipet walls (2.5 cm.) and the short time exposure at 300° and 1000

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(9) Zabel and Hancox, *Rev. Sci. Instruments*, **5**, 28 (1934).

(10) Myers, *Bur. Standards J. Research*, **9**, 807 (1932).

(11) Meyers and Jessup, *ibid.*, **6**, 1061 (1931).

(12) Shepherd, *ibid.*, **6**, 121 (1931).

(13) Smith and Keyes, *Proc. Am. Acad. Arts Sci.*, **69**, 313 (1934).

TABLE II

EXPERIMENTAL *pv* VALUES

P, atm.	Hydrogen	87.44 : 12.56 H_2:N_2 mixture	75.56 : 24.44 H_2:N_2 mixture	51.74 : 48.26 H_2:N_2 mixture	26.12 : 73.88 H_2:N_2 mixture	Nitrogen
0°						
25	1.0152	1.0136		1.0062	0.9999	0.9910[b]
50	1.0311	1.0293	1.0265	1.0165	1.0038	.9853[b]
100	1.0641	1.0613	1.0572	1.0416	1.0191	.9857[a]
200	1.1327	1.1311	1.1273	1.1081	1.0789	1.0363[a]
400	1.2761[a]	1.2829	1.2863	1.2837	1.2728	1.2566[a]
600	1.4221[a]	1.4411	1.4558	1.4802	1.5023	1.5251[a]
800	1.5668[a]	1.5994	1.6282	1.6820	1.7382	1.7984[a]
1000	1.7086[a]	1.7563	1.7989	1.8824	1.9727	2.0676[a]
25°						
25	1.1072	1.1063		1.1015	1.0945	
50	1.1235	1.1224	1.1202	1.1130	1.1020	1.0877[a]
100	1.1572	1.1563	1.1529	1.1425	1.1236	1.0969[a]
200	1.2271	1.2273	1.2249	1.2127	1.1894	1.1546[a]
400	1.3705	1.3794	1.3849	1.3878	1.3817	1.3699[a]
600	1.5158	1.5372	1.5542	1.5816	1.6076	1.6326[a]
800	1.6595	1.6948	1.7245	1.7822	1.8414	1.9030[a]
1000	1.8013	1.8508	1.8945	1.9817	2.0743	2.1710[a]
50°						
25	1.1993[b]			1.1949		1.1848[b]
50	1.2162[b]	1.2145	1.2134	1.2079	1.1997	1.1882[a]
100	1.2496	1.2490	1.2467	1.2394	1.2253	1.2046[a]
200	1.3203	1.3215	1.3209	1.3133	1.2959	1.2692[a]
400	1.4640	1.4745	1.4822	1.4898	1.4887	1.4825[a]
600	1.6090	1.6315	1.6505	1.6836	1.7128	1.7408[a]
800	1.7525	1.7887	1.8202	1.8829	1.9444	2.0086[a]
1000	1.8933	1.9438	1.9894	2.0818	2.1758	2.2756[a]
100°						
25	1.3827[b]			1.3812		1.3748[b]
50	1.4003	1.3996	1.4009	1.3976	1.3928	1.3853[a]
75	1.4182					
100	1.4358	1.4361	1.4377	1.4343	1.4262	1.4123[a]
200	1.5069	1.5111	1.5148	1.5142	1.5054	1.4889[a]
400	1.6513	1.6661	1.6777	1.6938	1.7021	1.7039[a]
600	1.7955	1.8231	1.8462	1.8868	1.9234	1.9569[a]
800	1.9386	1.9795	2.0159	2.0849	2.1532	2.2209[a]
1000	2.0780	2.1338	2.1844	2.2813	2.3834	2.4857[a]
200°						
50	1.7659	1.7658	1.7703	1.7702	1.7711	1.7725[c]
100	1.8018	1.8049	1.8097	1.8078	1.8134	1.8115[c]
200	1.8756	1.8822	1.8909	1.9001	1.9057	1.9119[c]
400	2.0206	2.0379	2.0593	2.0858	2.1110	2.1455[c]
600	2.1628	2.1940	2.2264	2.2793	2.3320	2.3961[c]
800	2.3043	2.3496	2.3942	2.4749	2.5590	2.6557[c]
1000	2.4568[c]	2.5027	2.5627	2.6705	2.7876	2.9212[c]
300°						
50	2.1293	2.1322	2.1323	2.1363	2.1432	2.1469[c]
100	2.1700[c]	2.1703	2.1757	2.1821	....	2.1986[c]
200	2.2393	2.2499	2.2596	2.2755	2.2914	2.3127[c]
400	2.3826	2.4079	2.4294	2.4664	2.5050	2.5506[c]
600	2.5246	2.5648	2.5978	2.6618	2.7315	2.8043[c]
800	2.6653	2.7195	2.7662	2.8581	2.9560	3.0623[c]
1000	2.8026	2.8702	2.9323	3.0554	3.1842	3.3203[c]

[a] Data from Michels, Nijhoff and Gerver, *Ann. Phys.*, **12**, 562 (1932) (Hydrogen); Michels, Wouters and De Boer, *Physica*, **3**, 585 (1936) (Nitrogen). [b] Data from Holborn and Otto, *Z. Physik*, **33**, 1 (1925). [c] Data from Bartlett, *et al.*, THIS JOURNAL, **50**, 1275 (1928).

atm. make it probable that an effect as great as that shown in the table would not occur. It was finally decided to use the equation given by Keyes[14]

$$V_t^{Fe} = V_0(1 + 3.25 \times 10^{-5}t + 2.85 \times 10^{-8}t^2 - 1.65 \times 10^{-11}t^3)$$

where V_0 is the volume at 0° and V_t the volume at temperature t. This formula gives linear coefficients for the ranges 0–200 and 0–300° which are about the averages of the two sets given in Table I. The possible error in the determination of volume incurred at 0 and 50° is probably not more than one or two parts in 10,000, since the absolute values were known at 25 and 100°. At 200 and 300° the error introduced in V_t^{Fe} using the above equation is estimated between 0.05–0.10%. This does not influence the relative precision of any one isotherm. A change in the value of the reference point will affect all the other values by the same fractional amount.

Our experimental data are shown in Table II, and also data from Bartlett, Michels, and Holborn and Otto, where we have no values of our own. Since the data of Michels for nitrogen were given at odd pressures, we have used his equations to calculate the values given in this table. Dr. Deming expects to calculate the thermodynamic properties of hydrogen–nitrogen mixtures from these data.

We want to thank Dr. E. J. Jones for assistance in setting up our thyratron temperature control and Lola S. Deming (Mrs. W. E. D.) for helping us in our calculations. We also acknowledge the help of Mr. J. R. Dilley, who assisted in the design of the high pressure equipment.

Summary

Previous work since 1930 on the compressibilities of hydrogen, nitrogen and their mixtures has been summarized. A modified Bartlett compressibility apparatus is described. The compressibilities of hydrogen and four hydrogen–nitrogen mixtures have been measured at 0, 25, 50, 100, 200 and 300° and to 1000 atmospheres.

WASHINGTON, D. C.

RECEIVED JUNE 6, 1938

[14] Keyes, Joubert and Smith, *J. Math. Phys. Mass. Inst. Tech.*, 1, 191 (1922).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK AND CO., INC.]

The Hydration of Vitamin B_1

BY W. A. BASTEDO, JR., N. R. TRENNER AND T. J. WEBB

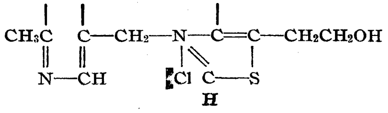
Introduction

The marked deliquescence of vitamin B_1[1] has been recognized by many investigators. The water of crystallization, however, has been given variously in the literature as one-half, one, or approximately one molecule of water (per molecule of vitamin) without regard for the conditions of humidity. The problem of preparing the one or more supposed hydrates in pure form and the measurement of their dissociation pressures was undertaken in these Laboratories. In the beginning the problem proved to be baffling on account of lack of reproducibility. This initial lack of reproducibility in the degree of hydration was attributed finally to variable minor details in the later stages of preparation of the vitamin, such, for example, as solvents used in the precipitation process, methods of removing solvent, etc. After standard procedures having regard for such details had been found, the early difficulties regarding reproducibility disappeared (at least to the extent of 0.1 g. of water per 100 g. of vitamin). The much higher reproducibility obtainable for samples under identical conditions of humidity led to the belief that the remaining difficulty lay in the inherent problem of the reproducibility of the aqueous pressures to which the samples were exposed. The fact that *slight* variations in the aqueous pressures to which the samples were exposed gave rise to appreciably variable water contents of the vitamin indicated immediately that the problem was not one of an ordinary system of hydrates.

Experimental Details and Results

In the first attack on the problem the aqueous pressure to which the samples were exposed was regulated by H_2SO_4–H_2O mixtures in evacuated desiccators at 25 ± 1°.

[1] Formula of vitamin B_1



Ninety-five per cent. sulfuric acid was found to be a complete desiccant for the vitamin. The density of the mixtures was measured with sufficient accuracy that the aqueous pressure could be found to within approximately 0.4 mm. of mercury by reference to standard measurements.[2,3] In order to check this procedure for obtaining a given aqueous pressure saturated solutions of calcium chloride and of barium chloride were used on two occasions. The results obtained with these solutions were entirely consistent with those obtained with the H_2SO_4–H_2O mixtures. Two days were sufficient for the samples (approximately 0.6 g.) to attain equilibrium with a given aqueous pressure. Weights (accurate to 0.1 mg.) were always checked on the third day, and in many cases after the lapse of one or more weeks. The water contents of the vitamin in terms of grams of water per 100 g. of anhydrous vitamin are given in Table I for various aqueous pressures (expressed in mm. of mercury). Each entry represents an average of a number of determinations—in the range of aqueous pressures above 7 mm., some of the entries represent an average of as many as ten determinations. The variations were of the order of 0.1 g. of water per 100 g. of vitamin. The large number of determinations represents an attempt to distinguish between a number of hydrates of very nearly the same water content.

Table I

Aqueous press.	Water, %	Aqueous press.	Water, %
1.2	0.46	6.8	4.31
1.4	.70	9.0	4.52
2.0	1.62	10.0	4.60
3.0	2.07	10.8	4.62
3.3	2.59	12.2	4.72
3.6	2.88	14.6	4.93
5.0	3.62	15.3	4.91
5.9	4.12	18.2	5.15

A graph of the results in Table I shows that within the estimated experimental error they can be represented by a smooth curve (Fig. 1) and give no evidence whatever of definite stoichiometric hydrates except in the extent to which there is an approach to one molecule of water per molecule of vitamin at high aqueous pressures. The region of experimental values was terminated naturally by the aqueous pressure of the saturated solution, 20.9 mm. A slight extrapolation of the experimental curve indicates that approximately one molecule of water per molecule of vitamin (in the crystalline state) would be acquired at 20.9 mm. The curve is reproducible in a hydrating as well as a dehydrating sense. The complete reversibility of the hydration and dehydration phenomena, which is often not observed in the case of continuous hydration,[4] precludes the possibility that the hydration is a slow process not attaining equilibrium. On the other hand, the absence of definite stoichiometric hydrates would seem to indicate that the forces exerted by the water molecule in the crystal play little, if any, role in the crystal lattice. The shape of the curve exhibiting the water content as a function of the aqueous pressure is strongly suggestive of a sorption process only in the range of high aqueous pressures. It is possible that the hydration phenomena observed in this case are not uncommon in the case of deliquescent organic substances of complicated structure—the assignment of definite formulas for such hydrates often being merely a matter of rounding out the results of chemical analysis.

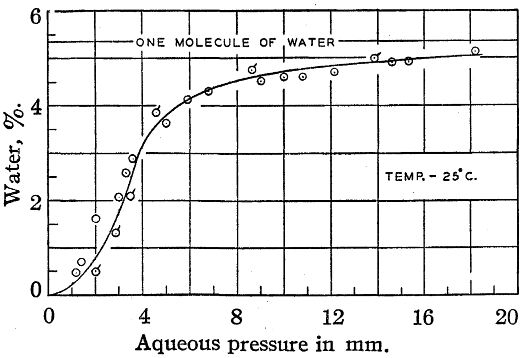


Fig. 1.—Hydration of vitamin B_1: results of gravimetric method, ⊙; volumetric method, ⊙-.

The fact that the type of result obtained above was entirely unexpected and practically without mention in standard works on the subject of salt–hydrates led to a renewed attack with an entirely different technique. A thoroughly dried sample of the vitamin was placed in an all-vacuum apparatus of the type described by Taylor and Strother[5] for sorption problems. A constant aqueous pressure was automatically preserved in the system and the decrease in the volume of water vapor measured to 0.01 cc.; the temperature of the sample of vitamin being held accurately at 25°. Corrections were applied for the dead space in the vessel containing the sample and for the adsorption on the walls of the container. The latter effect could be represented accurately by an equation of the form

$$x = kp^n$$

x being the quantity adsorbed and p the aqueous pressure. The constants k and n were found to have the values 0.0184 and 0.68, respectively,

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[2] "International Critical Tables," Vol. III, 1938, p. 56.

[3] Collins, *J. Phys. Chem.*, **37**, 1191 (1933).

[4] *Cf.* the case of Zeolites, "Inorganic Chemistry," by Ephraim, English edition, 1934, p. 756.

[5] Taylor and Strother, This Journal, **56**, 586 (1934).

if x is expressed in cc. (N. T. P.) and p in millimeters of mercury. The results obtained in this way checked those obtained by the first method, within the experimental error (estimated to be at least as great as two parts of water per 1000 of vitamin). The error in this method is as large as this in view of the fact that the samples of vitamin were necessarily very small—of the order of 2 mg. The discrepancy between the two sets of experimental results corresponds to an error of 0.004 mg. in the weighings. By this method the percentages of water in the vitamin under aqueous pressures of 14.0, 9.0, 4.57, 3.0 mm. were found to be 5.00, 4.80, 3.85, and 1.3, respectively. The results are exhibited graphically in Fig. 1. These results were considered an adequate check of the results by the first method, and it therefore seemed unnecessary to question further the continuity of this hydration phenomenon.

The second series of measurements reveals the actual speed of the hydration process as carried out (Fig. 2). It is to be noted that the time required for virtual completion of the hydration process (*e. g.*, curve C) was strictly comparable with that required for the virtual completion of the adsorption process on the glass (curve D) *i. e.*, of the order of two hours. The readings corresponding to the points representing the times labeled ∞ were taken after approximately twenty-four hours and indicate that equilibrium had been reached.

The vapor pressure of the saturated solution of vitamin B_1 was measured in the usual type of differential tensimeter, a mineral oil of specific gravity 0.894 being used as the manometric liquid. Water was used as a balancing liquid in one limb of the tensimeter and the saturated solution of the vitamin in the other. The results for several temperatures are given in Table II in terms of mm. of mercury.

TABLE II

VAPOR PRESSURE OF SATURATED SOLUTION

Temp., °C.	25	24	23	20	15	106
Press., mm.	20.9	19.6	18.5	15.4	11.4	8.0

A straight line is obtained when the logarithm of the vapor pressures is plotted against the reciprocal of the absolute temperature. The slope of this line indicates that the heat of vaporization of one mole of water from the saturated solution is 10,800 cal. (*cf.* 10,450 cal. for the molal heat of vaporization of pure water at 25°).

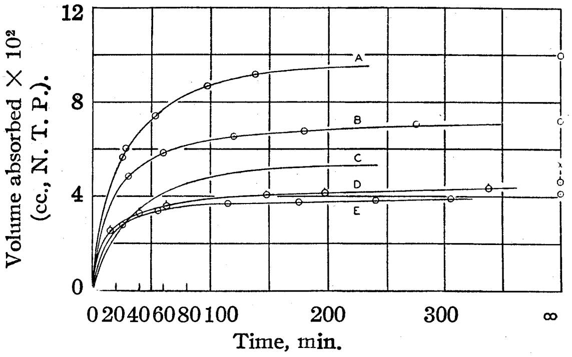


Fig. 2.—Rate of absorption of water on 2.019 mg. of vitamin B_1 at 25°: Curve A, absorption on vitamin + glass at 3.57 mm.; Curve B, absorption on vitamin + glass at 2.90 mm.; Curve C, Curve A − Curve D; Curve D, absorption on glass walls at 3.57 mm.; Curve E, absorption on vitamin + glass at 2.05 mm.

Summary

The degree of hydration of vitamin B_1 at 25° was determined gravimetrically at sixteen different aqueous pressures in the range between 1 and 19 mm. The degree of hydration was found to increase continuously from approximately 0.4% of water at 1 mm. to 5.20% at 19 mm. At the aqueous pressure of the saturated solution (20.9 mm.) the degree of hydration of solid vitamin corresponds approximately to one molecule of water of crystallization per molecule of vitamin. These determinations were checked by a volumetric method in which the volume of water vapor absorbed by the vitamin at various pressures of water vapor was measured. The vapor pressure of the saturated solution of the vitamin was measured over a temperature range in the neighborhood of room temperature.

RAHWAY, N. J. RECEIVED MAY 24, 1938

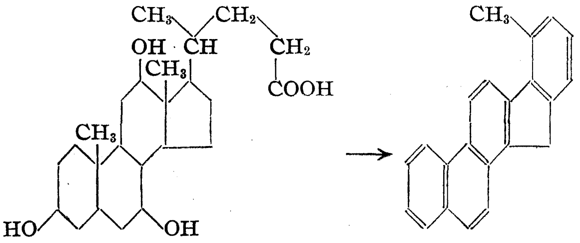
[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE]

The Strophanthidin Dehydrogenation Product $C_{21}H_{16}$

BY ERNST BERGMANN

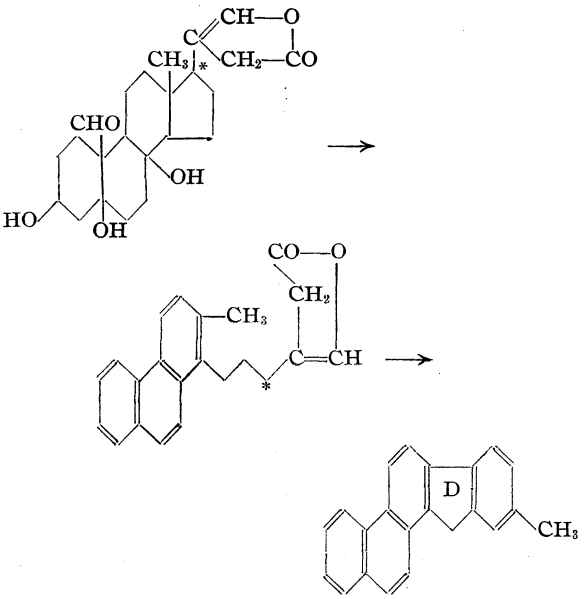
By selenium dehydrogenation of strophanthidin, Jacobs and Elderfield[1] obtained *inter al.* a hydrocarbon, m. p. 296°, to which they ascribed the formula $C_{21}H_{16}$. Their tentative suggestion that it may be 1,2-cyclopentenotriphenylene has been ruled out by synthetic work carried out in this Laboratory.[2] Further work in this direction has led to the assumption that the above hydrocarbon belongs to the 2′,1′-naphtha-1,2-fluorene derivatives, which have been obtained from cholic acid, cholesterol, ergosterol and sitosterol.[3] First of all, the absorption spectrum of the above hydrocarbon, a few milligrams of which we owe to the courtesy of Professor Jacobs, shows a definite resemblance to those of pure naphthafluorene derivatives.[4] Absorption maxima have been observed at λ 2720, 2800, 2980, 3150, and lower ones at 3200, 3400 and 3600.

With regard to the formation of the hydrocarbon from cholic acid, Bachmann, Cook, Hewett and Iball[3] have presented conclusive evidence for the scheme



but they point out that "this identification of Ruzicka's hydrocarbon throws no further light on the structure of the pentacyclic hydrocarbons of analogous structure obtained by dehydrogenation of sterols," as cholesterol does not yield 5-methyl-8-isopropyl-2′,1′-naphtha-1,2-fluorene, to be expected according to the given scheme. We may add that strophanthidin could not give rise to a pentacyclic system at all according to the scheme of the English authors, as only a three-carbon side-chain, containing one methyl group, is available.

The carbon atom lacking for the construction of the pentacyclic system can only be the quaternary methyl group at C_{13} which is used in an analogous way in the synthesis of chrysene from cholic acid[5] or oestrone.[6] There, the cyclopentane system opens and gives a six-membered ring by subsequent recyclization. Here, the new ring (D) formed is again a five-membered one, and the number of the chain atoms is increased by one, so that the possibility is given for additional six-membered ring formation:



The hydrocarbon of Jacobs and Elderfield, therefore, would be 7-methyl-2′,1′-naphtha-1,2-fluorene and have the formula $C_{22}H_{16}$ instead of $C_{21}H_{16}$; combustion analysis would not be able to differentiate between the two formulas. In fact, the hydrocarbon prepared from strophanthidin proved identical with 7-methylnaphthafluorene, prepared according to Cook and co-workers,[3] on the follow-

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[1] Jacobs and Elderfield, *J. Biol. Chem.*, **107**, 143 (1934).

[2] E. Bergmann and O. Blum-Bergmann, THIS JOURNAL, **58**, 1678 (1936); E. Bergmann and F. Bergmann, *ibid.*, **60**, 1805 (1938).

[3] Diels, Gaedke and Koerding, *Ann.*, **459**, 1 (1927); Ruzicka and co-workers, *Helv. Chim. Acta*, **16**, 216, 812 (1933); **17**, 200 (1934); Cook and co-workers, *J. Chem. Soc.*, 1727 (1934); 1319 (1935); 54 (1936).

[4] Compare Cook and co-workers;[3] Mayneord and Roe, *Proc. Roy. Soc.* (London), **158A**, 634 (1937). For comparing the spectra, I am very much indebted to Dr. Frieda Goldschmidt of this Institute.

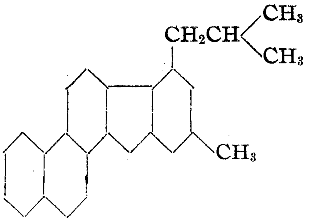
[5] Diels and Karstens, *Ann.*, **478**, 129 (1930); *cf. Ber.*, **66**, 487 (1933); Ruzicka and co-workers, *Helv. Chim. Acta*, **17**, 200 (1934). For cholesterol, see Diels, *et al.*, *Ber.*, **60**, 140 (1927); *Ann.*, **459**, 1 (1927); Raudnitz and co-workers, *Z. physiol. Chem.*, **209**, 103 (1932); *Ber.*, **66**, 879 (1933).

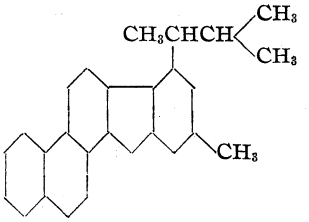
[6] Butenandt and Thompson, *ibid.*, **67**, 140 (1934).

ing evidence. They have the same m. p. 301° (on slow heating);[7] the melting point of their mixture is not depressed; the solubilities in various solvents are identical. Due to the extreme scarcity of material, it was impossible to compare derivatives of the two products; so the evidence presented is somewhat unsatisfactory, were it not for the immanent probability of the above hypothesis.

It is a curious coincidence that the naphthafluorene hydrocarbon derived from cholic acid, too, had been formulated $C_{21}H_{16}$ at first, the correct formula being $C_{22}H_{16}$ according to Cook and co-workers[3] and to Bernal and Crowfoot.[8]

In view of the reported result, the hydrocarbons obtained from cholesterol and ergosterol, respectively, have to be formulated as follows





In accordance with Ruzicka's results,[3] the two sterols would yield different naphthafluorene derivatives, and the contradictory view of Diels and co-workers[9] would be untenable. The possibilities of synthesizing 7-methyl-9-isobutyl- and 7-methyl-9-(α,β-dimethylpropyl)-naphthafluorene are being investigated in this Laboratory.

With the elucidation of the mechanism of naphthafluorene formation from steroids, all the possibilities of their aromatization seem to be clear: the methyl at C_{13} is eliminated in the formation of methylcholanthrene, picene[10] and of 5-methyl-naphthafluorene from cholic acid (see above); it is used for conversion of the cyclopentano ring into a six-membered system in the formation of chrysene[5,6] and for the formation of a new cyclopentano ring in the case of the naphthafluorene derivatives studied above; it migrates in the formation of γ-methyl-1,2-cyclopentenophenanthrene from various steroids.[11] The quaternary methyl at C_{10} is generally eliminated in dehydrogenation processes.

Summary

The polycyclic hydrocarbon obtained by dehydrogenation of strophanthidin is 7-methyl-2',1'-naphtha-1,2-fluorene and has the formula $C_{22}H_{16}$ (not $C_{21}H_{16}$). The mechanism of its formation is discussed and formulas for the analogous derivatives of cholesterol and ergosterol, respectively, are suggested.

The various aromatization mechanisms for steroids are enumerated.

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[7] Cook and co-workers give 334–336° in a bath preheated to 300°.

[8] Bernal and Crowfoot, *J. Chem. Soc.*, 93 (1935).

[9] Diels and co-workers, *Ann.*, **459**, 1 (1927); **478**, 129 (1930); *Ber.*, **66**, 1122 (1933); **67**, 113 (1934); *cf.* Ruzicka, *et al.*, *Helv. Chim. Acta*, **16**, 818 (1933); **17**, 200 (1934); **18**, 434 (1935). Recently, Diels and Stephan [*Ann.*, **527**, 279 (1937)] admit that the dehydrogenation of ergosterol does *not* give at least exclusively the same naphthafluorene derivative as the dehydrogenation of cholesterol.

[10] Compare Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, 1936, p. 159.

[11] E. Bergmann and Hillemann, *Ber.*, **66**, 1302 (1933); E. Bergmann, *Chemistry and Industry*, **54**, 175 (1935); Cohen, Cook and Hewett, *J. Chem. Soc.*, 445 (1935); E. Bergmann and F. Bergmann, *Chemistry and Industry*, **55**, 272 (1936), and unpublished results.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BRYN MAWR COLLEGE]

The Dioxanates of the Mercuric Halides

BY J. L. CRENSHAW, ARTHUR C. COPE, NORMA FINKELSTEIN AND RUTH ROGAN

The cyclic diether of ethylene glycol, 1,4-dioxane, forms addition compounds with certain types of inorganic and organic compounds. The properties of these compounds are those to be expected of rather unstable oxonium salts. Several of them lose dioxane on exposure to the air, or on heating, and some apparently are dissociated into their components in solution. However, the addition compound of dioxane with mercuric chloride, according to both Paternò and Spallino[1] and Clarke[2] is stable, and sublimes unchanged on heating. Rheinboldt and his coworkers,[3] who have prepared a large number of dioxanates of inorganic halides, state[4] that the compound with mercuric chloride decomposes at 160–165°, and that with mercuric iodide at about 90°. Curran and Wenzke[5] are of the opinion that the mercuric halides do not form coördination compounds with dioxane, their evidence being the fact that diphenyl mercury has the same dipole moment in benzene and in dioxane solution. This conclusion is questionable, in view of the fact that the magnesium halides and organomagnesium halides form dioxanates much more readily than do the dialkyl (or diaryl) magnesium compounds.[6]

We have studied the properties of the dioxanates of the mercuric halides, in an effort to explain these contradictory statements. Mercuric chloride, bromide and iodide are moderately soluble in hot dioxane, and the solutions deposit colorless crystals on cooling. On exposure to the air these crystals lose dioxane in each case, the pure mercuric halide remaining. The change is very evident in the case of mercuric iodide dioxanate, since the colorless addition compound changes to the yellow and red forms of mercuric iodide, and the loss of dioxane is apparent in all three cases under the microscope. Paternò and Spallino[1] and Clarke[2] apparently failed to notice the loss of dioxane from the mercuric chloride dioxanate, and their product which sublimed was undoubtedly the residual mercuric chloride. The dipole moments of the mercuric halides as determined in dioxane solution[5] are of doubtful significance, since the solutions probably contain, not the mercuric halides, but their dioxanates.[7]

The dioxanates of the mercuric halides have been analyzed, and their dissociation pressures determined as a measure of their stability. The vapor pressures of their saturated solutions in dioxane and the vapor pressure of pure dioxane have also been measured.

Experimental Part

Materials.—Dioxane (Carbide and Carbon Chemicals Corporation) was purified by the method described by Scatchard and Benedict[8] and refluxed over sodium for two days. After fractional distillation, followed by fractional freezing, the final product had a freezing point of 11.79°, and a boiling point (760 mm.) of 101.26°, as measured with carefully calibrated thermometers. Moisture was excluded at all times, and in the determination of the boiling point a special apparatus was used.[9] These values agree well with those already reported.[8,10]

Mercuric chloride and iodide (C. P. analyzed) were used without further purification. Since the so-called C. P. mercuric bromide which was available contained about 0.5% chloride (Cl), this salt was prepared as follows. C. P. bromine was digested with a saturated aqueous solution of sodium bromide and distilled. This bromine was converted into hydrobromic acid by treatment with red phosphorus and water. C. P. mercuric oxide was dissolved in the hydrobromic acid and the resulting bromide recrystallized several times from hot water.

Vapor Pressure Measurements.—Vapor pressure measurements were made in the apparatus shown in Fig. 1, which was connected in the usual way to a vacuum pump and manometer.[11] The apparatus was cut apart at E, and 1 or 2 g. of the mercuric salt introduced into F. After resealing a current of dry air was passed through the apparatus and the whole was warmed until the salt began to sublime. The sublimed portion was then driven along by gentle heating and out of the end B. Purified dioxane was introduced into C, along with small pieces of sodium, the apparatus was tilted to the right and the dioxane refluxed for four hours, the tube G serving as an air con-

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[1] Paternò and Spallino, *Gazz. chim. ital.*, **37**, I, 106 (1907); *Atti accad. Lincei*, **16**, V, 187 (1907).

[2] Clarke, *J. Chem. Soc.*, **101**, 1803 (1912).

[3] Rheinboldt, *et al.*, *J. prakt. Chem.*, **129**, 278 (1931); **148**, 81 (1937).

[4] Rheinboldt, *et al.*, *ibid.*, **149**, 30 (1937).

[5] Curran and Wenzke, THIS JOURNAL, **57**, 2162 (1935).

[6] Schlenk and Schlenk, *Ber.*, **62**, 920 (1929); Schlenk, *ibid.*, **64**, 735 (1931).

[7] Williams, THIS JOURNAL, **52**, 1838 (1930), has pointed out that the use of dioxane as a solvent in dipole moment studies is limited to compounds which do not form addition products with dioxane.

[8] Scatchard and Benedict, *ibid.*, **58**, 837 (1936).

[9] Brunel, Crenshaw and Tobin, *ibid.*, **43**, 561 (1921).

[10] Kraus and Vingee, *ibid.*, **56**, 511 (1934), give the freezing point as 11.78° and the boiling point as 101.24° (761 mm.).

[11] The arrangement was much the same as that described by Smith and Menzies, *ibid.*, **32**, 1412 (1910).

denser. The apparatus was then turned back to the position shown and dioxane distilled into D, where it was fractionally frozen three or four times, the unfrozen portions being poured back into C. C and D were cooled with solid carbon dioxide in acetone and the tube sealed off at H. Sufficient dioxane was then distilled into F and after cooling again the apparatus was sealed off at E. Cooling with solid carbon dioxide is of course necessary to prevent ignition or decomposition of dioxane vapor by the hot glass. Mercury was introduced through A into J to serve as a confining liquid. During all these operations the greatest care was taken to prevent the introduction of moisture, and the open ends of the apparatus were always protected by phosphorus pentoxide tubes. The filled apparatus was connected at A by means of heavy rubber tubing to the manometer and pump.[11] The lower part, up to I, was placed in a well-stirred bath of water or oil which was electrically heated, and provided with windows through which the mercury in J could be observed. The traps in the bulbs F, I and K form a necessary part of the apparatus. The trap in F prevented any of the mercuric halide from being carried over and fouling the mercury in J; that in I prevented any loss of mercury; and that in K kept any condensed dioxane from running back on the mercury.

The amounts of halide and dioxane introduced into F were so chosen that all the halide could be brought into solution by warming with a free flame, and on cooling no crystals would appear above the transition point. It was thus possible, in measuring the vapor pressure of the saturated solutions of the dioxanates, to be sure that no undioxanated salt was present. To ensure saturation at all temperatures the bath was adjusted to the highest temperature to be used. The solution in F was boiled vigorously under reduced pressure until a reproducible vapor pressure was obtained. Readings at lower temperatures were then taken.

The dissociation pressures of the dioxanates were measured after all the liquid in F had been boiled away and partial decomposition of the crystals had taken place. The vapor pressure of pure dioxane was also measured in the same apparatus. It was introduced in the manner already described.

Temperatures were read to one hundredth (0.01°) of a degree on calibrated thermometers. In some cases there were considerable stem corrections and though these were checked by using thermometers with overlapping ranges we do not believe the readings are accurate to much better than ±0.05°.

Pressures were read to one-tenth of a millimeter (0.1 mm.) by means of a cathetometer. A calibrated glass scale and mercury manometer were used. All pressures are given in millimeters of mercury, corrected to 0°, 45° latitude and sea level.

Table I contains the vapor pressures of each system studied, calculated for round temperatures by means of the least square equations, which are also given. The number of observations used in calculating each equation is given as well as the probable error. The equations should not, of course, be used outside of the range indicated in each case. In calculating absolute temperatures, 273.2 was added to the centigrade readings.[12]

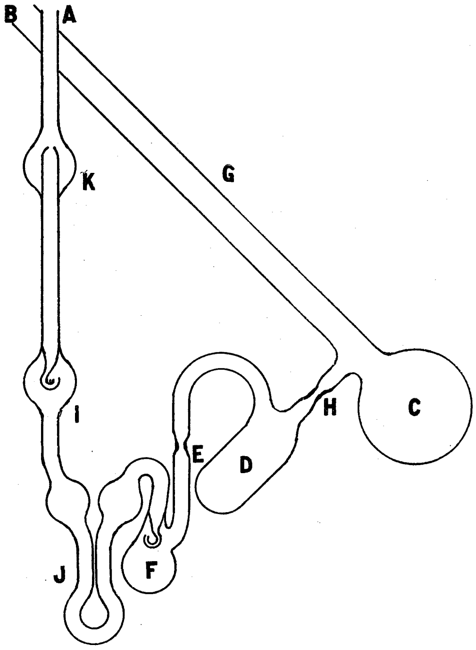

Fig. 1.

The experimental data are plotted in Fig. 2. The curves are graphs of the equations given, and are numbered to correspond with the numbers of the equations in Table I. The curves for the saturated solutions of the chloride and iodide have been omitted since they almost coincide with that for the bromide.

Discussion of Results

The vapor pressure of dioxane has been measured by several investigators. The most recent work is that of Hovorka, Schaeffer and Dreisbach,[13] whose data cover the range from 10 to 80°. Since dioxane is very hygroscopic we thought it advisable to determine its vapor pressure in our apparatus from which we think we have been able to exclude water vapor very effectively. We have extended the measurements above the boiling point and so are able to check our vapor pressure equation by means of boiling point determinations. Several determinations made at different barometric pressures in an apparatus from which moisture was excluded gave the same value for the normal boiling point (760 mm.), 101.26 ± 0.01°. This value also was obtained when metallic sodium was present in the dioxane so that we believe it is safe to assume that water was absent. The equation for pure dioxane (number 1, Table I) gives a calcu-

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[12] Birge, *Rev. Modern Phys.*, **1**, 1 (1929).

[13] Hovorka, Schaeffer and Dreisbach, THIS JOURNAL, **58**, 2264 (1936).

TABLE I

EQUATIONS AND VAPOR PRESSURES (MM.) AT ROUND TEMPERATURES

No. of obsns.	Temperature, °C. 20	25	30	40	50	60	70	80	90	100	105	Prob. error in % P
	Dioxane–pure liquid: (1) $\log P = -2316.26/T - 2.77251 \log T + 16.2007$											0.37
21	28.9	37.4	47.9	76.8	119.3	179.9	264.2	378.8	531.2	730.3	850.2	
	Satd. soln. of $HgCl_2$ dioxanate: (2) $\log P = -1748.04/T + 1.39892 \log T + 3.96062$											1.00
12	28.2	36.3	46.5	74.3	115.5	175.2						
	Solid $HgCl_2$ dioxanate (3) $\log P = -2676.42/T + 0.737604 \log T + 8.36180$											0.92
12	11.3	16.3	23.2	45.4	85.5	154.9	(Trans. point solid, 67.3°)					
	Satd. soln. of $HgBr_2$ dioxanate[a]: (4) $\log P = -2384.81/T - 3.62617 \log T + 18.5391$											1.11
17	28.8	37.0	47.3	74.9	115.0	171.4	248.9	352.8	489.2	664.7	769.4	
	Solid $HgBr_2$ dioxanate (5) $\log P = -3158.99/T + 2.96571 \log T + 2.80748$											1.60
23	0.2	0.4	0.6	1.3	3.0	6.4	13.3	26.3	50.4	93.4	125.8	
	Satd. soln. HgI_2 dioxanate: (6) $\log P = -2263.96/T - 2.78651 \log T + 16.0546$											0.55
18	28.9	36.9	47.0	74.4	114.1	170.0	247.0	350.5				
	Solid HgI_2 dioxanate (7) $\log P = -3023.86/T + 11.0344$											1.25
23	5.3	7.8	11.5	24.0	47.7	91.0	167.3	297.2	(Trans. point solid, 173.1°)			

[a] Additional values for $HgBr_2$ dioxanate were obtained as follows:

Temperature, °C.	110	120	130	
Satd. soln., mm.	886.6	...	...	
Solid, mm.	168.1	294.0	491.1	(Trans. point solid, 87.7°)

lated boiling point of 101.30° at 760 mm. Considering the probable error of our equation, the agreement is as good as could be expected. Boiling points at various barometric pressures and our equation both give 23.3 mm./degree for the slope of the vapor pressure–temperature curve at the normal boiling point. If the boiling points are taken as correct the values for the vapor pressure calculated from the equation are about 0.9 mm. low in the neighborhood of the boiling point. Our calculated vapor pressures are higher at low temperatures and lower at high temperatures than those previously reported.[13]

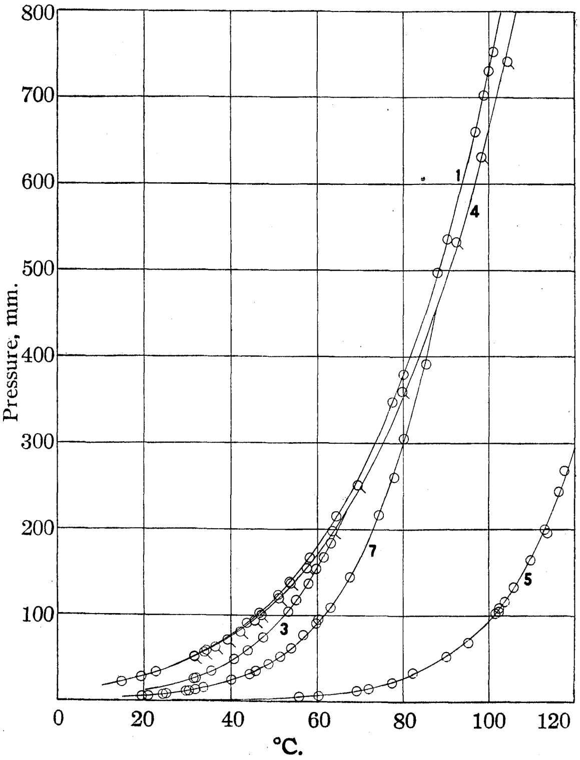

Fig. 2.—1, Dioxane; 3, $HgCl_2$·dioxanate; 4, saturated solution·$HgBr_2$ dioxanate; 5, $HgBr_2$·dioxanate; 7, HgI_2·dioxanate.

As may be seen from Fig. 2, the dioxanates of mercuric chloride and iodide have transition points which easily can be determined experimentally. The equations for the vapor pressures of the saturated solutions are for those in which the dioxanates are the solid phase. The temperatures at which the vapor pressures of these saturated solutions are equal to the dissociation pressures of the dioxanates are shown in Fig. 2. More exact values were obtained by a simultaneous solution of the equations for the saturated solution and the dissociation pressure. These calculations give 67.3° for the transition point of mercuric chloride dioxanate, and 87.7° for that of the iodide. The point for the iodide was checked by slowly heating a sealed tube containing an excess of dioxanate crystals in their saturated solution in dioxane, and observing the temperature at which the red color of mercuric iodide appeared. The point so obtained agreed with that given above to a few tenths of a degree. This method was not satisfactory for the dioxanates of the chloride and bromide as no color change occurred. The transition points of the chloride and iodide were checked also by observing the temperature at which an absorption of heat occurred when the crystals were slowly heated. The results were not very accurate since the heat absorption took place over an interval of a degree or two. This may have been due to the difficulty of stirring the crystals adequately. The transition points already given were within the range of heat absorption, provided moisture was excluded.

The behavior of mercuric bromide dioxanate seems rather surprising. As is shown in Fig. 2, its dissociation pressure, instead of being intermediate between that of the chloride and the iodide, is much lower than that of either. Under our experimental conditions it was not possible to determine the transition point of this salt. A rough estimate may be made by a simultaneous solution of the fourth and fifth equations in Table I. This gives a transition temperature of 173° at a pressure of about five atmospheres. Independent evidence of the relatively great stability of mercuric bromide dioxanate was obtained by comparing the rates at which the dioxanates of the three halides lost dioxane at room temperatures. The samples were put into open weighing bottles which were laid on their sides and protected from drafts. After four hours the losses in percentage of dioxane present were: mercuric chloride, 44%; mercuric bromide, 0.78%; mercuric iodide, 52%. This obviously crude method does not give a correct indication of the relative stability of the chloride and iodide, but it does show that the bromide is much the most stable of the three.

Rheinboldt[4] has analyzed the dioxanates of many salts and gives values which indicate that the mercuric halides combine with dioxane in the molecular ratio of 1 to 1. Since it is difficult to obtain these crystals in a pure state by the method he used, we have repeated the analyses. Crystals of the dioxanates were brought to constant weight in a stream of dry air which contained dioxane vapor at a partial pressure greater than the decomposition pressure but less than the vapor pressure of the saturated solution. The dioxane of crystallization was then removed by a current of pure dry air and the loss in weight determined. The results obtained together with those calculated on the assumption that one molecule of halide combines with one of dioxane are given in Table II.

TABLE II

COMPOSITION OF THE DIOXANATES

Dioxanate	Dioxane Obsd.	Dioxane Calcd.
$HgCl_2 \cdot C_4H_8O_2$	24.46	24.49
$HgBr_2 \cdot C_4H_8O_2$	19.65	19.63
$HgI_2 \cdot C_4H_8O_2$	16.26	16.23

From the vapor pressure measurements, the free energies of formation of the dioxanates from the solid salts and liquid dioxane (ΔF°_{298}) and the heats of formation ($-\Delta H_{298}$) have been calculated for 25° and are given in Table III.

TABLE III

FREE ENERGIES AND HEATS OF FORMATION AT 25° (CALORIES)

Compound	ΔF°_{298}	$-\Delta H_{298}$
$HgCl_2 \cdot C_4H_8O_2$	−490	3725
$HgBr_2 \cdot C_4H_8O_2$	−2750	7253
$HgI_2 \cdot C_4H_8O_2$	−925	4880

From equation 1, Table I, the molal heat of vaporization of pure dioxane is calculated to be 8960 cal. at 25°. The heat of vaporization for temperatures between 10 and 110° is given by the equation $\Delta H = 10{,}600 - 5.51T$.

Surface tension measurements[13] indicate that dioxane is a non-associated liquid and it should therefore give a normal value for the entropy of vaporization. At the boiling point we obtain 22.8 cal. per degree, which is somewhat larger than the value to be expected from Trouton's rule. Hildebrand's[14] modification of the rule gives 27.7 cal. per degree at 45.8°, at which temperature the molar concentration of the vapor is 0.005. This is very close to the value to be expected for normal liquids and is evidence that our values for ΔH are not greatly in error.

Summary

1. The vapor pressures of pure dioxane and of saturated solutions of dioxanates of the mercuric halides in dioxane have been measured.

2. The dissociation pressures of the dioxanates of the mercuric halides have been measured and their transition points determined.

3. Free energies and heats of formation of the dioxanates from the solid salts and liquid dioxane have been calculated.

4. The dioxanate of mercuric bromide has been found to be much more stable than the dioxanates of mercuric chloride and iodide.

BRYN MAWR, PENNA.

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[14] Hildebrand, THIS JOURNAL, **37**, 970 (1915).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WISCONSIN]

β-Aminoethylsulfuric Acid, an Irregular Ampholyte[1]

BY DEAN B. ROLLINS AND H. N. CALDERWOOD[2]

Although an enormous amount of work[3] has been done on amphoteric substances, and the compounds studied have been of many varieties,[4] the literature contains no mention of β-aminoethylsulfuric acid as an ampholyte other than the assignment to it of an inner salt structure by its discoverer,[5] who found that neither acids nor alkalies formed salts with it.

Incidental to work along other lines, we had occasion to investigate some of the properties of β-aminoethylsulfuric acid and were impressed by its desirability as a subject for study by those interested in ampholytes. The compound is very stable and easily purified by recrystallization from dilute ethanol. In common with the aliphatic amino acids,[6] it has an absence of a true melting point, insolubility in ethanol, great solubility in water, a definite end-point by the formol titration and an anomalous end-point by direct titration with alkali, but it differs from them by the presence of an ester linkage and a sulfate group in the molecule. Although its composition is very similar to that of taurine, it differs from it in having an ester linked sulfate group instead of the sulfonic group. By its faintly acid reaction with litmus it shows a closer similarity to the aliphatic amino acids than to taurine.

Since other demands prevent our continuing the study of this compound, we desire to bring it to the attention of investigators in the field of ampholytes, and offer our findings, together with our simple method for obtaining theoretical yields of β-aminoethylsulfuric acid, an improvement over the method which superseded Gabriel's.[7,8]

Experimental

Reagents.—Monoethanolamine, 99.4% purity, from the Carbon and Carbide Chemicals Corporation; sulfuric acid, C. P. grade, 88.3%.

β-Aminoethylsulfuric Acid Preparation, Preferred Method.—To 8.9 g. (0.8 mole) of acid cooled in a freezing mixture and stirred vigorously by a motor, there was added dropwise, in the course of ten minutes or more, 4.9 g. (0.8 mole) of cooled monoethanolamine. Too rapid addition, or addition of the reactants in the reverse order, produced a violent reaction. After all the amine had been added there was put into the mixture 0.9 g. (0.08 mole) of acid, the entire mixture was heated in an oil-bath to 130°, and while being stirred was held at this temperature for one hour. At the end of this time the mixture was cooled and 40 ml. of absolute ethanol added with stirring. The precipitate was collected on an asbestos or fritted glass filter and washed with four 5 ml. portions of absolute ethanol; yield 9.9 g. Evaporation of the acid filtrate, preferably under reduced pressure, and the addition of two volumes of absolute ethanol to the cooled residue gave an additional 1.5 g., total yield 11.4 g. or 100%.

Alternate Method.—An equimolal mixture of acid and amine was prepared as above, 2.4 g. (0.27 mole) of acid was added, and the mixture allowed to stand at room temperature for seventy-two hours. Treatment of the reaction mixture with absolute ethanol, as in the preferred method, gave a total yield of 11.6 g. of coarse crystalline aggregates containing some occluded acid.

Purification.—The crude product was recrystallized by solution in hot water (15 g. in 30 ml.), the cooled solution poured into 90 ml. of absolute ethanol, and the mixture cooled to 0°; recovery 94.5%. In a melting point tube this purified material started to sinter at 230° and decomposed at 255° with incomplete fusion. Analyses of the crude and the purified product are given in Table I. All nitrogen determinations were semi-micro Dumas and sulfur was determined by both wet and dry oxidation. After three additional recrystallizations, using five volumes of absolute ethanol per volume of aqueous solution, the refined product began to sinter at 275° and became brown at 280° without melting. Its aqueous solution showed only a faintly acid reaction to litmus; and gave not the slightest turbidity with barium chloride even after standing for ten hours at room temperature. Neither acids, alkalies, nor salts precipitated the compound from even its concentrated aqueous solutions. Microscopic examination of the refined product revealed but one crystalline form, identical with that described by Gabriel.[5] The purified compound did not give insoluble derivatives with any of the reagents used for the detection of amino groups.

TABLE I

ANALYSIS OF CRUDE AND PURIFIED PRODUCTS

	Crude		Purified		Calcd.
Material	I	II	I	II	$C_2H_6NO_4S$
Sample, g.	0.07025	0.07753	0.07117	0.07054	
Nitrogen, %	9.96	9.94	10.13	10.05	9.93
Sample, g.	0.2710	0.2652	0.2745	0.2714	
Sulfur, %					22.68
Wet			22.40	22.48	
Dry	22.34	22.37			

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[1] Original manuscript received October 4, 1937.

[2] Present address: 3105 Cross Street, Madison, Wisconsin.

[3] See "Symposium on the Dielectric Properties of Matter," *Chem. Rev.*, **19**, 163 (1936), especially the papers by Wyman and by Cohn, for excellent bibliographies on the subject.

[4] Bjerrum, *Z. physik. Chem.*, **104**, 147 (1923), gives a good review of the substances studied.

[5] Gabriel, *Ber.*, **21**, 2667 (1888).

[6] Sidgwick, "Organic Chemistry of Nitrogen," new edition, revised and rewritten by J. W. T. Taylor and Wilson Baker, Oxford University Press, New York, 1937, Chap. IV, pp. 105 *et seq.*

[7] Gabriel, *Ber.*, **21**, 1056 (1888).

[8] Frankel and Cornelius, *ibid.*, **51**, 1666 (1918).

Determination of the Molecular Weight.—Direct titration with alkali, phenolphthalein indicator, gave two end-points: the first, which persisted upon the addition of more base until the second was reached, being a faint pink and giving large and irregular values for the molecular weight; the second end-point, much deeper in color, gave values agreeing closely with the theoretical. In order to secure concordant results with the formol titration it was necessary to add at least one equivalent or more (a large excess caused no change in the final results) of the aldehyde, prior to the addition of any alkali. Under these conditions the observed and the theoretical values were in good agreement. The calculated and the observed molecular weights as determined by titration were corroborated by cryoscopic measurements of aqueous solutions of the compound. These molecular weight data have been assembled in Table II.

TABLE II

DETERMINATIONS OF THE MOLECULAR WEIGHT OF β-AMINOETHYLSULFURIC ACID

Method		I	II
Titration direct alkali	First end-point	620	588
	Second end-point	141.3	142.0
Titration, "formol"		141.2	142.5
Cryoscopic, water solution		140.5	141.5
Theoretical		141	

Hydrolysis.—An aqueous solution of the refined substance treated with barium chloride and set aside for ten hours at room temperature did not form enough barium sulfate to produce even a slight turbidity. Heating this mixture on a steam-bath for fifteen hours produced a precipitate of barium sulfate which was far below the theoretical amount. When the solution was made strongly acid, methyl orange indicator, with hydrochloric acid, treatment with barium chloride and heating for fifteen hours on the steam-bath produced so little barium sulfate as to cause only a slight turbidity. The solutions of the refined material remaining after direct alkali titration, when made acid to phenolphthalein with hydrochloric acid, showed only a slight turbidity after the addition of barium chloride. Hydrolysis with stoichiometric amounts of barium hydroxide produced very little barium sulfate at room temperature, and the reaction was not completed even after digestion for several days on a steam-bath.

The quantitative experiments reported in Table III were made as follows: the sample (0.27 to 0.29 g.) was dissolved in 10 ml. of water, the reagent solution added, and the mixture refluxed on the steam-bath. The extent of the hydrolysis was calculated from the weight of barium sulfate obtained. In the experiments with barium chloride the hydrolyzed solutions were diluted with hot water, made acid to methyl orange with hydrochloric acid, and digested overnight on the steam-bath. The weight of barium sulfate was determined in the usual manner. In the experiments with potassium hydroxide the addition of 10 ml. of ethanol was necessary to prevent frothing during hydrolysis. After hydrolysis the solutions were distilled with steam to remove the ethanol and the volatile amines. To the steam distillation residue, diluted with hot water and made acid to methyl orange with hydrochloric acid, two moles of barium chloride were added and the amount of barium sulfate was determined by the method described above.

TABLE III

HYDROLYSIS OF β-AMINOETHYLSULFURIC ACID

Name	Concn., %	Reagents Moles in excess	Hours refluxed	% Hydrolyzed Crude	Refined
$BaCl_2$	10	1	5.0	0.035	0.067
$BaCl_2$	10	1	15.0	.039	.070
KOH	25	21	3.5	...	75.56
KOH	25	54	5.0	...	75.27

Acknowledgment.—We greatly appreciate the assistance of Mr. Elmer E. Schiebe in making all of the sulfur and sulfate determinations reported in this paper.

Discussion

Although β-aminoethylsulfuric acid possesses the characteristic properties of a "zwitterion," and our determinations of its neutralization and cryoscopic values indicate that in aqueous solution the compound exists in the simplest possible state of molecular aggregation, the acid reaction with litmus points to actual ionization, even though so slight as not to appear in the cryoscopic measurements. From the above it might be assumed that the compound is an acyclic ampholyte, the irregularities being caused by the activating effect of the sulfate group,[9] and one might expect the compound to have a large electric moment. By the same reasoning, the two strong polar groups of the compound, by preventing ionization at the ester linkage[9] (pp. 166–167, 262–265) might be the cause of the latter's great resistance to hydrolysis demonstrated both in our work and elsewhere.[10] Dielectric constant and X-ray studies might help to decide these questions.[11]

On the other hand, the absence of insoluble derivatives with amino group reagents, the great resistance of the ester linkage to hydrolysis, the slight acid reaction in solution, together with the occurrence of but one crystalline form, might be considered evidence of ring–chain isomerism, with the cyclic form predominant, an opinion favored by the long molecule (a six atom chain) and in agreement with some of the current views on amino acids.[12]

It would be interesting to see further work done upon β-aminoethylsulfuric acid in order to obtain a better knowledge of its structure.

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(9) Waters–Lowry, "Physical Aspects of Organic Chemistry," D. Van Nostrand Co., Inc., New York, N. Y., 1936, Chap. VIII, pp. 159–194.

(10) Wenker, THIS JOURNAL, **57**, 2328 (1935).

(11) Wyman and McMeekin, *ibid.*, **55**, 908 (1933).

(12) Sidgwick,[4] p. 106; Wyman and McMeekin, *ibid.*, **55**, 912 (1933).

Summary

1. We have improved the Frankel and Cornelius method for preparing β-aminoethylsulfuric acid from monoethanolamine and sulfuric acid so that the theoretical yields may be obtained readily.

2. The crude product is purified easily, since water is the only other reaction product.

3. Although copiously soluble in water, the compound is not precipitated, even from its concentrated solutions, by acids, alkalies, or salts.

4. In aqueous solution the compound exists in the simplest possible state of molecular aggregation.

5. The compound displays many of the properties common to the aliphatic amino acids.

6. The ester linkage of the compound is very resistant to hydrolysis, thus allowing it to be used in solution with substances that catalyze hydrolytic reactions.

7. The compound is worthy of further study as an ampholyte.

MADISON, WISCONSIN RECEIVED JULY 7, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NEW YORK UNIVERSITY COLLEGE OF MEDICINE]

Complex Formation between Carboxylic Acids and Divalent Metal Cations

BY R. KEITH CANNAN AND ANDRE KIBRICK

This paper contains a comparison of the hydrogen electrode titration curves of a number of mono- and dicarboxylic acids in 0.2 *M* potassium chloride and in various $KCl–MCl_2$ solutions of the same ionic strength. M represents Mg, Ca, Sr, Ba or Zn. The work was instigated by recent observations of Greenwald[1] on the effect of calcium chloride on the *p*H of a variety of carboxylic acid buffer solutions. Its immediate purpose was to provide information as to the relative activity coefficients of certain salts of physiological importance but observations were extended to a number of related cations and acids. The ionic strength at which observations were made is comparable to that of mammalian body fluids.

The results indicate the existence of notable specific effects which are consistently related not only to the nature of the cation but to the molecular structure of the acid. These effects have been reduced to mass action constants for the formation of binary compounds between the carboxylate anions and each cation. Within the range of concentrations studied, and within the plausible errors of the method, we find that the formation of binary compounds suffices for a fairly satisfactory quantitative description of the observations. Were association to more complex compounds to occur to any important extent, we should expect the specific effects which have been observed to be a function of the total concentration of organic acid. We have found no clear indication of this for concentrations of acid ranging from 0.002 to 0.05 *M* (Tables III and VII).

In our use of the law of mass action to describe the effects observed, we are committed to no particular views as to the nature of the forces involved. It is generally acknowledged that mass action constants may be expected to describe, with fair precision, certain specific electrostatic effects, whose existence is ignored in the approximations which are involved in the working equations of interionic attraction theory. Where electrostatic forces of ions are involved the definition of what constitutes a reversibly dissociable compound is difficult. The mass action constants are submitted merely as convenient descriptions of relative activity coefficients.

We appreciate the fact that the use of the hydrogen electrode introduces indeterminate errors due to the presence of a liquid junction (L. J.) potential. The observations comprise two types of hydrogen electrode potentials: (a) those of the organic acid buffer in $KCl–MCl_2$ solutions; and (b) those of dilute solutions of hydrochloric acid in corresponding $KCl–MCl_2$ solutions. The latter were employed to calculate γ_{H^+} for the corresponding solutions containing the carboxylic acid. Into both of these potential measurements L. J. potentials enter as a source of error. In the majority of the calculations, however, γ_{H^+} appears only as a small correction term. Its precise value is unimportant. In the few systems in which it is an important term (those of rather low

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[1] I. Greenwald, *J. Biol. Chem.*, **124**, 437 (1938).

pH), the association constants derived with its aid are in satisfactory agreement with those calculated from observations at much higher pH, where its significance is small. Apart from the question of γ_{H^+}, indeterminate L. J. potentials enter into all the observations. We believe that the evidence is good that the method which we have adopted for the calibration of the reference electrode[2] eliminates the greater part of the potential at a broad junction between saturated potassium chloride and dilute electrolyte solutions containing few H^+ or OH^- ions. However this may be, our calculations depend, not upon the absolute potentials of any one solution, but upon changes in potential as MCl_2 is substituted for potassium chloride at constant ionic strength. The calculated association constants are based on changes in potential varying between 5 and 80 mv. The simultaneous changes in L. J. potentials must be very small compared with these. Using Henderson's equation to indicate their order of magnitude, we calculate differences, in extreme cases, of only 0.4 mv. It is fair to conclude that the calculated mass action constants provide a fairly satisfactory measure of relative activity coefficients.

Apart from the question of L. J. potentials, the calculations require the assumptions (a) that carboxylate anions do not associate to a significant extent with Na^+ or K^+, (b) that in solutions containing MCl_2, no significant concentration of MCl^+ exists. The former assumption conforms to prevailing views of the state of the alkali salts of organic acids in dilute solutions such as those used in this investigation. The absence of $CaCl^+$ and $BaCl^+$ receives support from the activity coefficients of calcium and barium chlorides published by Scatchard and Tefft.[3] The observations of these authors on zinc chloride at $\mu = 0.20$ may be taken, however, to indicate significant concentrations of $ZnCl^+$ in our solutions. This we have ignored. The essential effect of the presence of this complex on the calculated constants would be to increase them all in the proportion $(Zn^{++}) + (ZnCl^+)/(Zn^{++})$.

Experimental

Measured volumes of standard solutions of the acid and of sodium hydroxide were mixed. Amounts of M KCl and of 0.33 M MCl_2 were added to give the desired cation mixtures, and the whole was diluted to $\mu = 0.2$ (calculated from KCl–MCl_2 only). In this way the concentration of divalent cation was varied while approximate constancy of μ was maintained. The concentration of monocarboxylic acids was usually 0.02 M and of dicarboxylic acids 0.01 M. The ionic strength would increase with the degree of neutralization and decrease with the extent of complex formation. For a 0.01 M dicarboxylic acid the range of μ under these influences would be 0.23 to 0.17. Actual calculations of μ for representative reaction systems, using the association constants found, showed that μ seldom fell outside of the range 0.19–0.21. It is improbable that activity coefficients would be seriously affected by such variation.

The pH of each reaction mixture was measured in a rocking hydrogen electrode (Clark) using a saturated calomel electrode and a saturated salt bridge. The reference electrode was calibrated by means of 0.1 M acetic acid–0.1 M sodium acetate to which a pH of 4.66 was assigned.[2] The liquid junction potential was taken to be −2.4 mv. This was calculated from Henderson's equation.[4] The potential of the junction, saturated potassium chloride–reaction mixture, was taken to be −1.3 mv. in all cases. Calculations for the junctions with 0.2 M potassium chloride and with 0.067 M magnesium, calcium or barium chlorides gave values varying from 1.1 to 1.5 mv.

A series of determinations were made of the pH of 0.01 and 0.002 M hydrochloric acid in salt mixtures representative of those used in the reaction mixtures. The values of $-\log \gamma_{H^+}$ calculated from these ranged from 0.090 to 0.110. Since the precise value of $[H^+]$ is important only in a few systems of low pH, we have been content to take $-\log \gamma_{H^+} = 0.100$ for all systems.

The recorded potentials were found immediately after preparation of reaction mixtures and were accurately reproducible over many hours. The reproducibility of the potential of duplicate reaction mixtures was about 0.2 mv.

Monocarboxylic Acids.—The following relations may be stated for an organic acid, HA, at a chosen ionic strength[5]

$$\begin{aligned}
&(a)\quad (T_A) = (HA) + (A^-) + (MA^+)\\
&(b)\quad (T_m) = (M^{++}) + (MA^+)\\
&(c)\quad (Na^+) + (H^+) = (A^-) + (MA^+)\\
&(d)\quad K_1 = [H^+](A^-)/(HA)\\
&(e)\quad C_1 = (MA^+)/(A^-)(M^{++})
\end{aligned}$$

(T_A), (T_m) and (Na^+) are known from the composition of the reaction mixtures. $[H^+]$ is calculated from $pH = -\log [H^+]$, and (H^+) is obtained with the aid of γ_{H^+}. In systems containing no MCl_2, (A^-) is, then, calculated from (c), (HA) from (a) and K_1 from (d). In the presence of MCl_2, (HA) is obtained from (a) − (c), (A^-) from (d), (MA^+) from (a) or (c), (M^{++}) from (b) and C_1 from (e).

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(2) E. A. Guggenheim and T. D. Schindler, *J. Phys. Chem.*, **38**, 533 (1933).

(3) G. Scatchard and R. F. Tefft, THIS JOURNAL, **52**, 2272 (1930).

(4) In this equation concentrations were employed in place of activities. The latest values for the transference numbers of potassium chloride were used [MacInnes and Dole, THIS JOURNAL, **53**, 1357 (1931)].

(5) Square brackets indicate activities and parentheses, concentrations.

In the special case where (T_m) is so much larger than (T_A) that we may put $(M^{++}) = (T_m)$, the dissociation curve of the acid suffers a parallel displacement on the pH ordinate from its position when MCl_2 is not present. The new curve will be that of an acid with an apparent dissociation constant

$$K_1' = [(A^-) + (MA^+)][H^+]/(HA) = K_1[C_1(T_m) + 1]$$

Dicarboxylic Acids.—The assumption of binary compound formation implies the formation of MA^+ from A^- and of MA from $A^=$. The pertinent relations are

(a′) $(T_A) = (HA) + (A^-) + (A^=) + (MA^+) + (MA)$
(b′) $(T_m) = (M^{++}) + (MA^+) + (MA)$
(c′) $(Na^+) + (H^+) = (A^-) + 2(A^=) + (MA^+) + 2(MA)$
(d′) $K_1 = (A^-)[H^+]/(HA)$
(e′) $K_2 = (A^=)[H^+]/(A^-)$
(f′) $C_1 = (MA^+)/(A^-)(M^{++})$
(g′) $C_2 = (MA)/(A^=)(M^{++})$

There are not sufficient equations for the calculation of either the dissociation or the association constants from a single observation. Under appropriately restricted conditions, however, we may make approximations to each of them in turn and then attempt to adjust the preliminary values so as to conform simultaneously to all observations. Provided the latter cover a sufficient range of (T_m) and a range of pH corresponding to a wide variation in $(A^-)/(A^=)$, successive approximations to a pair of constants may be made with confidence. In the absence of MCl_2, observations at low pH may be used to calculate a preliminary value for K_1, since $(A^=)$ will be very small. Corresponding observations at high pH will give an approximation to K_2. These constants are then adjusted to observations at intermediate values of pH until the best fit is attained. This is the common practice in deriving dissociation constants of polyvalent acids or bases from their dissociation curves.

The same procedure may now be applied to determine C_1 and C_2 from observations on solutions containing MCl_2, using the above values for K_1 and K_2. Where $(T_m)/(T_A)$ is large, the curve will be that of a dicarboxylic acid with apparent constants $K_1' = K_1[C_1(T_m) + 1]$ and

$$K_2' = K_2\frac{C_2(T_m) + 1}{C_1(T_m) + 1}$$

From observations at appropriate extremes of pH, preliminary values of K_1' and K_2' and, hence, of C_1 and C_2 may be obtained. In the refinement of the values of the latter, we have found it convenient to introduce the quantity

$$K_4 = (MA)[H^+]/(MA)^+ = K_2C_2/C_1$$

and to impose the successive approximations on this. Combining equations (a′) to (g′) and introducing K_4 we have derived

$$\alpha = \frac{((Na^+) + [H^+])/(T_A - x/w}{(2K_4 + [H^+])/(K_4 + [H^+]) - x/w} \quad (1)$$

and

$$C_2 = \frac{\alpha}{1 - \alpha}\cdot\frac{K_4w}{K_1K_2(K_4 + [H^+])}\cdot\frac{1}{(T_m) - \alpha(T_A)} \quad (2)$$

where α is the fraction of the total acid combined with the cation

$$x = 2K_1K_2 + K_1[H^+]$$

and

$$w = K_1K_2 + K_1[H^+] + [H^+]^2$$

The preliminary values of C_1 and C_2 fix a tentative value for K_4 and this allows calculations of α and of C_2 from (1) and (2), respectively. K_4 is subjected to minor adjustments until consistent values for C_2 emerge from observations over the whole experimental range of (T_m) and of pH.

Results

Monocarboxylic Acids.—The results are so extensive that only a few representative experiments can be given in detail. In Table I the

TABLE I

ACETIC ACID, T_a = 0.0200

	$(Na^+) \times 10^3$	0.200 *M* KCl	0.0636 *M* $ZnCl_2$	0.0664 *M* $MgCl_2$	0.0668 *M* $CaCl_2$	0.0670 *M* $SrCl_2$	0.0662 *M* $BaCl_2$
		*p*H					
A	6.264	...	4.096	4.212	4.219	4.237	4.240
B	8.352	4.496	4.280	4.413	4.401	4.421	4.430
C	10.44	4.675	...	...	...	...	...
D	12.53	4.864	4.663	4.782	4.780	4.797	4.800
E	14.62	5.076	4.876	4.990	4.993	...	...
F	16.70	5.347	5.149	5.262	5.265	5.260	5.279
G	18.79	5.842	...	5.761	5.761	...	...
			α				
A			0.123	0.061	0.058	0.046	0.045
B			.168	.075	.085	.070	.058
C			...	...	...	...	...
D			.236	.112	.114	.090	.083
E			.270	.133	.127	...	...
F			.308	.150	.146	.140	.112
G			...	.138	.143	...	...
		$K_1 \times 10^5$	C_1				
A		...	10.7	3.67	3.41	2.58	2.52
B		2.31	11.0	3.81	3.91	2.43	2.49
C		2.32	...	...	...	...	...
D		2.30	10.2	3.38	3.45	2.58	2.38
E		2.29	10.1	3.47	3.27	...	...
F		2.29	10.1	3.45	3.30	3.11	2.43
G		2.24	...	2.70	2.81	...	...
Mean		2.29	10.4	3.4	3.4	2.7	2.4
Logarithm		−4.640	1.02	0.53	0.53	0.43	0.38

data of an experiment on acetic acid are recorded. Table II relates to a similar experiment with glycolic acid. These two tables illustrate the constancy of C_1 despite a 4- to 5-fold variation in anion concentration. The effect of MCl_2 on the unsubstituted acids was very small and the calculated values of C_1 are correspondingly irregular.

TABLE II

GLYCOLIC ACID, $T_a = 0.01996\ M$

	$(Na^+) \times 10^3$	0.200 *M* KCl	0.0636 *M* $ZnCl_2$	0.0664 *M* $MgCl_2$	0.0668 *M* $CaCl_2$	0.0670 *M* $SrCl_2$	0.0662 *M* $BaCl_2$
		*p*H					
A	4.176	3.231	2.671	3.090	3.019	3.105	3.134
B	8.352	3.598	2.948	3.425	3.359	3.457	3.493
C	12.53	3.949	3.275	3.775	3.708	3.809	3.845
D	16.70	4.428	3.748	4.256	4.190	4.289	4.320
			α				
A			0.284	0.084	0.122	0.076	0.059
B			.402	.154	.200	.129	.100
C			.537	.215	.284	.184	.143
D			.683	.282	.363	.237	.191
		$K_1 \times 10^4$	C_1				
A		1.92	82.2	7.35	12.7	6.3	4.60
B		1.94	82.2	8.46	12.9	6.46	4.58
C		1.95	81.8	8.24	13.0	6.43	4.59
D		1.95	82.8	8.28	12.8	6.30	4.73
Mean		1.94	82.2	8.1	12.8	6.4	4.6
Logarithm		−3.712	1.91	0.91	1.11	0.81	0.66

TABLE III

GLYCOLIC ACID AND ACETIC ACID, EFFECT OF VARYING T_a AND T_m

T_m	T_a	$(Na^+) \times 10^3$	*p*H	α	Log C_1
		Acetic acid—$ZnCl_2$			
0.0318	0.0200	12.53	4.753	0.145	1.02
		14.62	4.963	.168	1.02
		16.70	5.228	.204	1.06
.0636	.0500	10.44	3.856	.083	1.03
		20.88	4.284	.162	1.06
		Glycolic acid—$ZnCl_2$			
0.0636	0.00499	2.61	3.273	0.560	1.89
.0318			3.427	.419	1.85
.0191			3.538	.316	1.84
.0127			3.600	.267	1.87
.00636			3.700	.158	1.84
.0636	.02994	15.66	3.077	.455	1.95
	.01996	10.44	3.097	.470	1.92
	.00998	5.22	3.154	.504	1.89
	.00499	2.61	3.273	.560	1.89
		Glycolic acid—$CaCl_2$			
0.0668	0.00499	2.61	3.604	0.263	1.09
.0318			3.698	.161	1.08
.0191			3.745	.103	1.01
.0127			3.779	.058	0.94
.0668	.02994	15.66	3.516	.244	1.14
	.01996	10.44	3.527	.243	1.12
	.00998	5.22	3.557	.249	1.10

When T_m was reduced below 0.03 the displacements of *p*H were too small to justify calculations. With the hydroxy acids, on the other hand, a five-fold variation of T_m and T_a was possible (Table III). The variations in C_1 are well within the possible effects of the accompanying variations in μ and the liquid junction potentials. The constants for the eight monocarboxylic acids are assembled in Table IV.

TABLE IV

LOG C_1 FOR MONOCARBOXYLIC ACIDS (μ = *circa* 0.2)

Acid	Zn	Mg	Ca	Sr	Ba	pK_1
Acetic	1.03	0.51	0.53	0.43	0.39	4.640
Propionic	1.01	.54	.50	.43	.34	4.703
Butyric	1.00	.53	.51	.36	.31	4.742
β-Hydroxybutyric	1.06	.60	.60	.47	.43	4.390
Glycolic	1.92	.92	1.11	.80	.66	3.712
Lactic	1.86	.93	1.07	.70	.55	3.739
Glyceric	1.80	.86	1.18	.89	.80	3.517
Gluconic	1.70	.70	1.21	1.00	.95	3.556

Association Constants of Davies[6] for CaA^+ (μ = 0)

Acetic	0.0
β-Hydroxybutyric	.82
Glycolic	1.58
Lactic	1.47

The more significant conclusions are:

1. The three unsubstituted acids and the β-hydroxy acid give almost identical constants for a particular cation.

2. The constants of the four α-hydroxy acids are also very similar in magnitude but are much greater than those of the unsubstituted acids. A hydroxyl in other positions has little effect although the results with glyceric and gluconic acids suggest a slight enhancement of association with the alkaline earth cations and a slight depression with Zn^{++} and Mg^{++}.

3. The relative tendencies of the cations to associate with any one anion is in the order Zn$\gg$Ca$>$Sr$>$Ba. The position of Mg is irregular. In the series of the alkaline earth cations, the effect of the size of the cation is manifest. No simple relation is apparent between K_1 and C_1 but it is worthy of remark that the α-hydroxyl which so notably enhances association of the carboxylate ion with these divalent cations, as strongly reduces its association with the hydrogen ion.

In a very recent publication, Davies[6] has reported the dissociation constants of a number of calcium carboxylates which he has calculated from conductivities or from solubility data. They refer to μ = 0. The logarithms of their

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[6] C. W. Davies, *J. Chem. Soc.*, 277 (1938).

reciprocals are included in Table IV. For comparison, our values must be increased by an activity coefficient term which will approximate $-\log \gamma_{Ca^{++}}$. If we assign to the latter the reasonable value of 0.35 at $\mu = 0.2$, we find fairly satisfactory agreement between the two sets of constants. The one exception is the case of acetic acid. When the constant is as small as it would appear to be with the unsubstituted acids, the calculations, both from conductivities and from potentiometric data, are very uncertain.

Dicarboxylic Acids.—The values derived for K_1 and K_2 of the various acids agree fairly well with values in the literature where comparisons on the basis of μ are possible. Their absolute magnitude is unimportant to our argument provided they define our data for potassium chloride systems with precision. This they do to the extent that, in no case, was the difference between (Na^+), calculated from *p*H and x/w, and (Na^+), derived from the composition of a mixture, greater than 0.005 equivalent. Details of the potassium chloride experiments are omitted.

The results for MCl_2 with one unsubstituted and with one hydroxy acid are illustrated in Tables V, VI and VII. The mean values of C_2 (as log C_2) of the six dicarboxylic acids studied are assembled in Table VIII together with the values for pK_4 which finally were adopted and those of log C_1 calculated from pK_4. In some cases the range of observations was limited by the insolubility of the particular complexes. With oxalic

Table V

Malonic Acid $T_a = 0.01$

	(Na^+) × 10^3	Zn 0.0636 *M*	Mg 0.0664 *M*	Ca 0.0668 *M*	Sr 0.0670 *M*	Ba 0.0662 *M*
		*p*H				
A	0	2.436	2.464	2.473	2.476	2.471
B	4.176	2.723	2.798	2.809	2.809	2.813
C	8.352	3.085	3.319	3.393	3.403	3.401
D	12.532	3.540	4.122	4.415	4.540	4.541
E	16.700	4.105	4.829	5.154	5.284	5.294
		α				
A		0.125	0.072	0.071	0.063	0.076
B		.174	.101	.094	.093	.085
C		.284	.178	.136	.134	.147
D		.470	.353	.303	.240	.256
E		.739	.623	.504	.407	.412
		Log C_2				
A		2.85	1.92	1.48	1.26	1.31
B		2.79	1.88	1.43	1.16	1.18
C		2.80	1.94	1.41	1.25	1.26
D		2.80	1.93	1.51	1.24	1.26
E		2.83	1.96	1.52	1.27	1.27

Table VI

Malic Acid $T_a = 0.009605$

	(Na^+), × 10^3	0.0636 *M* Zn	0.0664 *M* Mg	0.0668 *M* Ca	0.0670 *M* Sr	0.0662 *M* Ba
		*p*H				
A	0	2.491	2.669	2.634	2.677	2.684
B	4.052	2.786	...	3.041	...	...
	4.176	...	3.121	...	3.126	3.143
C	8.241	3.119	...	3.500	...	...
	8.352	...	3.586	...	3.625	3.651
D	12.16	3.486	...	3.982	...	...
	12.53	...	4.097	...	4.161	4.212
E	16.48	4.037	4.699	4.640	...	...
	16.70	...	...	...	4.834	4.900
		α				
A		0.290	0.086	0.128	0.078	0.067
B		.411	.130	.205	.132	.116
C		.591	.246	.352	.242	.215
D		.747	.400	.504	.404	.355
E		.912	.581	.685	.569	.496
		Log C_2				
A		2.85	1.60	1.83	1.45	1.33
B		2.82	1.54	1.75	1.39	1.25
C		2.84	1.57	1.79	1.40	1.29
D		2.85	1.58	1.80	1.48	1.35
E		2.97	1.60	1.82	1.51	1.36

Table VII

Malonic Acid, Effect of Varying T_a and T_m

T_m	T_a	(Na^+) × 10^3	*p*H	α	Log C_2
		$ZnCl_2$			
0.0654	0.01	16.70	4.105	0.739	2.83
.0327		16.70	4.430	.666	2.74
.01308		8.352	3.325	.094	2.74
.01308		12.53	4.093	.267	2.70
.01308		16.70	4.832	.562	2.78
		$MgCl_2$			
0.0664	0.01	16.70	4.829	0.623	1.96
.0332	.01	16.70	5.079	.487	1.89
.01328	.01	16.70	5.336	.269	1.78
.00664	.01	16.70	5.438	.164	1.90
.0664	.05	20.62	2.581	.060	1.78
		41.25	3.225	.127	1.84
		61.87	4.151	.298	1.90
		82.50	4.936	.521	1.91
		$CaCl_2$			
0.0664	0.01	16.70	5.154	0.504	1.52
.0332			5.326	.333	1.45
.01336			5.451	.165	1.43
		$SrCl_2$			
0.0670	0.01	16.70	5.284	0.407	1.27
.0335			5.406	.248	1.21
.0134			5.489	.117	1.17
		$BaCl_2$			
0.0662	0.01	16.70	5.294	0.412	1.27
.0331			5.409	.247	1.21
.01324			5.492	.109	1.16

TABLE VIII

DICARBOXYLIC ACIDS—SUMMARY OF RESULTS

			Log C_2					
Acid	pK_1	pK_2	Zn	Mg	Ca	Sr	Ba	Mg (Simms) $\mu = 0.07$
Oxalic	1.14 ?	3.85		2.55				2.65
Malonic	2.69	5.24	2.78	1.91	1.46	1.25	1.23	2.06
Succinic	4.07	5.28	1.78	1.20	1.20	1.06	1.03	0.98
Glutaric	4.21	5.06	1.60	1.08	1.06	...	...	...
Azelaic	4.40	5.15	...	...	...	...	...	.72
Malic	3.26	4.68	2.80	1.55	1.80	1.45	1.30	...
r-Tartaric	2.88	3.94	2.68	1.36	1.80	1.65	1.62	...
Oxalic Acid (Money and Davies[9]) $\mu = 0$			4.89	3.43	3.00	2.54	2.33	

	pK_4					Log C_1				
	Zn	Mg	Ca	Sr	Ba	Zn	Mg	Ca	Sr	Ba
Oxalic		1.8 ?					0.5 ?			
Malonic	3.3	3.8	4.25	4.4	4.45	0.84	.47	0.47	0.41	0.44
Succinic	4.4	4.6	4.6	4.7	4.7	.90	.52	.52	.48	.45
Glutaric	4.3	4.5	4.5	...	...	.84	.52	.50	...	...
Malic	3.45	3.9	3.9	3.95	4.0	1.57	.77	1.02	.72	.67
r-Tartaric	2.7	3.5	3.25	3.2	3.2	1.44	.92	1.11	.91	.88

acid, observations with Mg^{++} alone were possible. With tartaric acid and Ca^{++} they were limited to $T_m = 0.013$ or less. In a few other systems, a salt separated some hours after completion of observation. In these cases, the possibility of anomalous potentials due to precipitation at the electrode must be entertained. We have accepted potential observations only when they were stable for five minutes after cessation of rocking and only if they were reproducible after renewed rocking.

The values of K_4 and C_1 for oxalic acid are highly tentative because it was not possible to make accurate calculations from observations at the low *p*H range in which C_1 dominates the extent of association. The recorded value of C_2 for oxalic acid is, however, independent of K_4, provided (as seems most probable) the latter is not much greater than 2. In general, there is less satisfactory agreement between individual values of C_2 for dibasic acids than was found for C_1 with the monobasic acids. This is inherent in the calculation which makes C_1 and C_2 very sensitive to the precise values of K_1, K_2 and K_4. We have not attempted to approximate pK_4 more closely than 0.05.

The following conclusions are submitted:

1. The unsubstituted dicarboxylic acids give values for C_1 very close to those of the unsubstituted monocarboxylic acids; *i. e.*, a COOH group is without important influence on association at a neighboring carboxylate ion.

2. Similarly, the hydroxy dicarboxylic acids give values for C_1 close to those of α-hydroxy monocarboxylic acids.

3. C_2 for a particular cation diminishes, first rapidly and then slowly, with increasing separation of the carboxyl groups in the dianion.

4. C_2 is increased as greatly by a single α-hydroxyl group as by two.

5. The cation series $Zn \gg Ca > Sr > Ba$ is found for C_2, Mg being, again, irregular in position.

6. For a particular anion, C_2 is always much greater than C_1, but no simple relation obtains. If complex formation actually involves the formation of a coördinate link, then the question of ring strain enters. Possibly the relative values of C_2/C_1 for a series of anions and a particular cation reflect this factor.

The values found for C_1 are small compared with C_2. It may seem a precarious undertaking to attempt their evaluation from systems in which C_2 also operates. To ignore C_1, however, is to ignore the behavior of the monocarboxylic acids. Without it, constant values for C_2 are not obtained. For example, in a series of malonic acid–zinc chloride mixtures quoted in Table V, the values of log C_2 were 2.85, 2.79, 2.80, 2.80, 2.83. The corresponding values, when C_1 is assumed to be very small, are 3.26, 3.00, 2.82, 2.72, 2.62.

Simms[7] has reported extensive potentiometric data on the titration of various acids in magnesium chloride solutions. Greenwald[8] recently has shown that the specific effects observed may be reduced to mass action constants comparable

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(7) H. S. Simms, *J. Phys. Chem.*, **32**, 1121 (1928).

(8) I. Greenwald, *ibid.*, in press (1938).

(9) R. W. Money and C. W. Davies, *Trans. Faraday Soc.*, **28**, 609 (1932).

with our C_2. Greenwald's constants for oxalic acid and malonic acid are included in the last column of Table VIII together with those which we have calculated from Simms' observations on succinic and azelaic acids. For these calculations we used the method of the present paper. Simms' constants must be reduced slightly to translate them from $\mu = 0.07$ to 0.20. The activity correction is $-\log \gamma_{Ca^{++}}\gamma_{a^{=}}$. A reduction of log C_2 by 0.1 is entirely reasonable. If that is done, the agreement is good, except for succinic acid.

Money and Davies[9] have determined constants for oxalic acid and a series of cations from the conductivities of the salts (Table VIII). To convert these to $\mu = 0.2$ a reduction of log C_2 by 0.6 – 0.8 is consistent with available data on the activity coefficients of divalent ions. Agreement with our value for oxalic–Mg is then good and the relative behavior of the series of cations is in harmony with our observations on the other acids.

Summary

1. The hydrogen electrode titration curves of a number of mono- and bivalent carboxylic acids have been compared in varying KCl–MCl_2 mixtures of constant ionic strength ($\mu = 0.2$). (M represents Mg, Ca, Sr, Ba or Mg.)

2. The specific effects which have been observed have been reduced to mass action constants for the formation of binary compounds between the cations and the carboxylate anions.

NEW YORK, N. Y.

RECEIVED JUNE 8, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ST. LOUIS UNIVERSITY SCHOOL OF MEDICINE]

A Study of Some Reactions between Dry Inorganic Salts. IV. Reactions below the Fusion Point[1]

BY HAROLD L. LINK AND LYMAN J. WOOD

Recently all of the possible reactions that might occur between dry alkali halides above the fusion temperature have been studied by Thomas and Wood.[2] Of the possible 60 reactions that might occur between pairs of alkali halides not having a common ion, it was found that 57 of the reactions proceeded (in the fused state) to completion in such a direction that the average cube edge of the stable pair was less than the average cube edge of the reciprocal pair. In these 57 cases, without exception, the larger cation united with the larger anion and the smaller cation with the smaller anion. In each of these 57 cases, also without exception, the sum of the heats of formation of the stable pair was greater than that of the reciprocal pair, *i. e.*, ΔH was minus. In the remaining three cases equilibrium was indicated as represented in the following reactions

$$KBr + RbCl \rightleftharpoons KCl + RbBr \text{ (Reaction 10)}$$
$$KI + RbBr \rightleftharpoons KBr + RbI \text{ (Reaction 14)}$$
$$RbBr + CsCl \rightleftharpoons RbCl + CsBr \text{ (Reaction 16)}$$

The present report concerns studies of reactions that have been made under the fusion point and is limited to double decompositions involving only Na^+, K^+, Rb^+, Cs^+, Cl^-, Br^-, and I^- (see reactions 1–18, Table I). The variation of the speed of reaction with time at a fixed temperature has been studied and also the variation of the speed with temperature for a fixed time. In five cases what appear to be equilibrium mixtures have been obtained and these mixtures have been studied in some detail.

Materials and Experimental Procedure

The salts used were Analytical Reagents with the exception of cesium chloride and bromide, which were prepared from the nitrate according to the method of Wells.[3] The salts were fused and ground to a fine powder and kept in a desiccator until wanted. After heating the various salt pairs at temperatures and for lengths of time indicated in the proper place, all mixtures were examined by the method of X-ray crystal analysis as previously described.[2a]

It is, in general, more difficult to obtain good films from salt mixtures which have been heated under the fusion point rather than above the

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[1] Read at the Rochester meeting of the American Chemical Society, September, 1937. This communication is for the most part from a thesis presented by H. L. Link for the degree of Master of Science.

[2] (a) E. B. Thomas and Lyman J. Wood, THIS JOURNAL, **56**, 92 (1934); (b) *ibid.*, **57**, 822 (1935); (c) *ibid.*, **58**, 1341 (1936).

[3] H. L. Wells, *Am. J. Sci.*, [3] **46**, 186 (1893).

fusion point. In many cases the material being examined does not appear to be in the proper crystalline form. The crystals are perhaps too small or are strained and for these and, no doubt, other reasons yield patterns consisting of a limited number of lines that are in many cases difficult to read. In addition to these difficulties, quantitative results from equilibrium studies are difficult to obtain because the formation of solid solutions is not as common as above the fusion point. It is often possible, however, to draw definite conclusions from surprisingly few data.

Results

In Table I are listed the results obtained for reactions 1 to 18 at 400° when the heating was continued for thirty-six hours. What previously has been called the stable pair (indicated in Table I by the letter a) was heated in each case and the resulting mixtures were analyzed (by means of the X-ray beam) for evidence of reversal toward the reciprocal pair (indicated in the table by the letter b). As was to be expected from previous work above the fusion point most of the stable pairs showed little or no evidence of any tendency toward reversal. Reactions 3, 5, 8, 9, 11, 14, and 16 showed unmistakable evidence of some reversal. The results obtained from heating the reciprocal pairs are shown in column b. All of the reactions with the exception of 10 and 14 proceeded partially or completely toward the stable pair. Reaction 10 possibly did also since it seems likely that reaction would have preceded the formation of a solid solution. The formation of this solid solution at 400° was not expected since it was known that neither the mixture KBr–KCl nor the mixture RbCl–KCl forms a solid solution at 400°. The cube edge obtained is only 0.001 Å. different from that of either component of the reciprocal pair but the interference diagram obtained can scarcely be the patterns of potassium bromide and rubidium chloride superimposed on each other since in this case interference lines with odd ordered indices would have been obtained such as 111 and 311 and no such lines were obtained. The situation was made even more interesting by reason of the fact that the stable pair, when heated at 400°, produced only patterns of potassium chloride and rubidium bromide. It is, of course, quite possible that a solid solution of compounds that are just being formed may occur more readily than will be the case for a mixture of these same compounds after they have already been formed.

The results in Table I indicate that reactions 3, 5, 8, 9, 11 and 16 should also reach an equilibrium if heated long enough at 400°.

Several of the reactions were examined at higher temperatures. When the reciprocal pair of reaction 14 (KI–RbBr) was heated at 480° for thirty-six hours there was evidence of considerable reaction whereas at 400° no evidence of reaction was found. The lowest fusion temperature of this mixture was found to be about 608°. When the reciprocal pair for reaction 2 was heated at 480° for thirty-six hours the extent of the reaction was found to be 62% as calculated from the resulting solid solution of rubidium

TABLE I

SHOWING THE RESULTS OBTAINED BY HEATING VARIOUS SALT PAIRS AT 400° FOR 36 HOURS

Reaction			Accepted cube edge a[a]	X-Ray Observations			
				Reciprocal pair—b a[a]	Remarks	Stable pair—a a[a]	Remarks
1	a.	NaCl	5.628	5.629	Partial reaction	[b]	No reversal
		KBr	6.570	6.561			
	b.	NaBr	5.94	5.947			
		KCl	6.280	6.288			
2	a.	NaCl	5.628	5.628	Partial reaction	5.631	No reversal
		RbBr	6.86	6.868		6.860	
	b.	NaBr	5.94	5.946			
		RbCl	6.570	6.582			
3	a.	NaCl	5.628		Partial reaction	5.628	Partial reversal
		CsBr	4.29			4.265	
	b.	NaBr	5.94	5.971			
		CsCl	4.110	4.182			
4	a.	NaCl	5.628	5.628	Partial reaction	[b]	Little or no reversal
		KI	7.052	7.032			
	b.	NaI	6.46	6.46			
		KCl	6.280				

TABLE I (*Concluded*)

Reaction			Accepted cube edge a[a]	X-Ray Observations			
				Reciprocal pair—b		Stable pair—a	
				a[a]	Remarks	a[a]	Remarks
5	a.	NaCl	5.628	5.622	Almost complete reaction	5.626	Partial reversal
		RbI	7.325	7.320		7.327	
	b.	NaI	6.46	[b]			
		RbCl	6.570	[b]		6.575	
6	a.	NaCl	5.628	5.637	Complete reaction	5.628	No reversal
		CsI	4.562	4.564		4.558	
	b.	NaI	6.46				
		CsCl	4.110				
7	a.	NaBr	5.94	5.937	Almost complete reaction	5.937	A very little reversal
		KI	7.052	6.998		6.995	
	b.	NaI	6.46				
		KBr	6.570				
8	a.	NaBr	5.94	[b]	Partial reaction	[b]	Some reversal
		RbI	7.325	[b]		7.257	
	b.	NaI	6.46				
		RbBr	6.86				
9	a.	NaBr	5.94	6.001	Partial reaction	[b]	Some reversal
		CsI	4.562	4.515		4.508	
	b.	NaI	6.46				
		CsBr	4.29				
10	a.	KCl	6.280	6.571	Solid soln. of the four ions	6.281	No reversal
		RbBr	6.86			6.857	
	b.	KBr	6.570				
		RbCl	6.570				
11	a.	KCl	6.280		Partial reaction	[b]	Partial reversal
		CsBr	4.29			4.273	
	b.	KBr	6.570	[b]			
		CsCl	4.110	4.134			
12	a.	KCl	6.280		Partial reaction	[b]	No reversal
		RbI	7.325	7.212		7.315	
	b.	KI	7.052				
		RbCl	6.570	6.570			
13	a.	KCl	6.280	[b]	Complete reaction		Little or no reversal
		CsI	4.562	4.555		4.544	
	b.	KI	7.052				
		CsCl	4.110				
14	a.	KBr	6.570		No reaction	[b]	Partial reversal
		RbI	7.325				
	b.	KI	7.052	7.047			
		RbBr	6.86	6.868		[b]	
15	a.	KBr	6.570	[b]	Partial reaction	[b]	No reversal
		CsI	4.562	4.525		4.560	
	b.	KI	7.052				
		CsBr	4.29				
16	a.	RbCl	6.570		Partial reaction	6.874	Partial reversal
		CsBr	4.29			4.234	
	b.	RbBr	6.86	6.858			
		CsCl	4.110	4.154			
17	a.	RbCl	6.570	[b]	Partial reaction	[b]	Little or no reversal
		CsI	4.562	4.561		4.543	
	b.	RbI	7.325	[b]			
		CsCl	4.110	[b]			
18	a.	RbBr	6.86	[b]	Very little reaction	[b]	Little or no reversal
		CsI	4.562			4.556	
	b.	RbI	7.325				
		CsBr	4.29	4.292			

[a] Cube edge in Å.

[b] Pattern observed by direct comparison with standard lines. No accurate value of the cube edge could be obtained.

TABLE II

SHOWING THE RESULTS OF SOLID SOLUTION STUDIES ON SOME ALKALI HALIDE PAIRS WHEN HEATED FOR THIRTY-SIX HOURS UNDER THE FUSION TEMPERATURE

50 : 50	Cube edge of observed phases						
Mole, %	a	400°	Remarks	480°	Remarks	Fused[a]	Remarks
NaCl	5.628	5.628	No solid solution		Completely soluble	5.811	Limited solubility
NaBr	5.940	5.940		5.789		5.628	
KCl	6.280	6.280	No solid solution		Completely soluble		Completely soluble
KBr	6.570	6.570		6.425		6.423	
KCl	6.280	6.272	No solid solution				Completely soluble
RbCl	6.570	6.562				6.418	
KI	7.052	7.058	No solid solution	One phase	Complete soly. indicated		Completely soluble
RbI	7.325	7.318				7.185	
RbCl	6.570			One phase	Complete soly. indicated	6.708	Completely soluble
RbBr	6.860						
CsCl	4.110		Completely				Completely soluble
CsBr	4.290	4.209	soluble			4.202	
CsBr	4.290	4.294	No solid solution			4.426	Completely soluble
CsI	4.562	[b]					
NaBr	5.940	5.937	Limited soly. of			5.971	Limited solubility
NaI	6.460	6.379	NaBr in NaI			6.419	
RbBr	6.86	[b]	Limited solubility			7.092	Completely soluble
RbI	7.325	[b]					
KBr	6.570	6.599	Limited solubility			6.641	Limited solubility
KI	7.052	6.959				6.962	

[a] Values obtained by Thomas and Wood.[2a,b] [b] No accurate value for the cube edge could be obtained.

bromide and residual rubidium chloride. This solid solution did not form at 400° but there was considerable reaction, perhaps 50% or more as nearly as could be judged by relative intensities of the rubidium bromide and rubidium chloride patterns. The lowest fusion temperature of this mixture was 503°. When the reciprocal pair of reaction one was heated at 500° the reaction appeared to be complete since patterns for pure potassium bromide and sodium chloride were obtained. If there had been any residual sodium bromide or potassium chloride solid solutions would have resulted at this temperature. At 400° the extent of the reaction was much less, four patterns corresponding to the four pure substances being clearly observed. The lowest fusion temperature of this mixture was about 603°. It is not possible to make any quantitative statement concerning the relation between the temperature and the rate of reaction which must depend upon several factors. In general, however, it has been found that if the temperature is much more than 100° below the fusion temperature the rate of reaction is very slow.

In the case of the number one reaction previous calculation of the free energy at 25° has shown that the reaction should proceed spontaneously from reciprocal to stable pair at room temperature. This was tested by subjecting the reciprocal pair, at room temperature, to a pressure of 3500 atmospheres per square inch for ten minutes. The pressure was applied by means of a huge hydraulic press kindly made available by The Reverend Basile J. Luyet of the Department of Biology of St. Louis University. Before mixing the sodium bromide and potassium chloride they were passed through a 200-mesh sieve and dried over sulfuric acid for several days. The reaction was found to proceed from reciprocal to stable pair to the extent of about 50%. This had to be judged from the relative intensities of the patterns for the pure components since solid solutions were not formed.

Reaction 7 has been studied at 510° (a few degrees under the fusion temperature) for various lengths of time and the results are shown in Table III.

TABLE III

SHOWING THE RESULTS OBTAINED BY HEATING A 50-50 MOLAR MIXTURE OF NaI AND KBr (REACTION 7) AT 510°

Time of heating, hours	0.5	2.0	15.0	30.0
Extent of reaction	20	35	80	90

Reaction 4 was examined in the same way except that the temperature was 488° (a few degrees under the fusion temperature) instead of 510°. Very similar results were obtained. The extent of the reaction had to be judged in both cases by relative intensities of the patterns since there was only a very small amount of solid solubility.

Equilibrium Studies

The principal interest in the reactions that did not go to completion in either direction centered in the compositions of the reaction mixtures since they were possibly equilibrium mixtures or might become such upon proper treatment. In the case of one of these reactions that does not go to completion in either direction and in case of which no solid solutions are formed (under the given conditions) it is frequently possible to demonstrate, by means of the X-ray analysis, that the four pure components are present (reaction 1, Table I) but the extent of the reaction can only be estimated from the intensities of the various interference lines. On the other hand, if solid solutions are formed, it is sometimes possible to determine the extent of the reaction from the interference patterns.

Because of the formation of suitable solid solutions, reaction 11 has been studied in considerable detail (Table II). It is clear from Table I that the reaction does not go to completion in either direction when either the reciprocal or stable pair is heated at 400° for thirty-six hours. Two interference patterns were obtained in each case, one body centered and the other face centered. From the body centered patterns were calculated cube edge values of 4.134 and 4.273 corresponding to the patterns obtained, respectively, from the reciprocal and stable pairs. These two cube edge values are each intermediate between the cube edge values of cesium chloride and bromide. Since it is known, from Table II, that a 50 mole per cent. mixture of cesium chloride and bromide, when heated at 400°, dissolves completely in each other, forming a solid solution, the intermediate cube edge values are explained very easily. The face centered pattern in each case was quite light by comparison with the body centered pattern which is exactly what would be expected for a mixture of potassium salts and cesium salts. While it was not possible to obtain satisfactory cube edge values in either case, there was no doubt about the nature of the patterns. Several of the lines appeared to indicate values intermediate between potassium chloride and bromide, which would be contrary to the solid solution data of Table II. This situation is not quite comparable to the one described in Table II, however, since in the former case both compounds were heated in the presence of each other, while in this case one of the compounds is formed in the presence of the other.

The solid solution of cesium chloride and bromide gave excellent interference patterns and can be used for calculating the extent of the reaction if it can be shown that all of the cesium chloride and bromide are contained in this solution and that the solution, furthermore, contains none of the potassium chloride nor bromide, *i. e.*, it must be shown that ternary solutions are not present.

TABLE IV

SHOWING CsCl–CsBr SOLID SOLUTION CUBE EDGES RESULTING FROM A STUDY OF REACTION 11

Mole ratio of reacting mix.	Heat treatment T,°C.	Heat treatment Hrs.	Solid soln. cube edge	Mole ratio of resultant mix. CsCl : CsBr
1 KBr:1 CsCl	400	38	4.134	0.87 :0.13
	480	36	4.247	.24 : .76
	480	72	4.253	.211: .789
1 KCl:1 CsBr	400	38	4.273	.09 : .91
	480	36	4.258	.18 : .82
	480	72	4.253	.211: .789
1 KCl:2 CsBr	480	72	4.263	.150: .850
2 KCl:1 CsBr	480	72	4.241	.272: .728

Although the existence of such ternary solutions seemed highly improbable because cesium chloride and bromide are body centered and the cube edges are small and potassium chloride and bromide are face centered and the cube edges are large, the possibility of such ternary solutions was eliminated when the results for reaction 11 were obtained at 480° instead of 400° (Table IV). Considering the last mixture described in Table IV, it is to be seen that the composition of the starting mixture is 2KCl:1CsBr. Because of the larger amount of potassium chloride with respect to cesium bromide it was possible to obtain a satisfactory cube edge of the KCl–KBr solid solution which is known to form at this temperature (Table II). If the CsCl–CsBr solid solution be a binary solution and all of the cesium chloride and bromide in the resultant mixture be contained in this solution, then the two moles of potassium chloride and the one mole of cesium bromide of the original mixture have reacted with each other according to the equation

$$0.272\,\mathrm{KBr} + 0.272\,\mathrm{CsCl} \rightleftarrows 1.728\,\mathrm{KCl} + 0.728\,\mathrm{CsBr}$$

and the cube edge of the KCl–KBr solid solution should be

$$\frac{0.272}{2}\,6.57 + \frac{1.728}{2}\,6.28 = 6.320\ \text{Å}.$$

whereas the value obtained from the inter-

TABLE V

SHOWING THE EXTENT OF REACTION 11 OCCURRING FROM EACH SIDE AT 400 and 480°

Temp., °C.	Time, hrs.	Case	Mole ratio of reacting mixture	Composition of resulting mixture
400	38	A	1 CsCl:1 KBr	$0.87\ \mathrm{CsCl} + 0.87\ \mathrm{KBr} \longrightarrow 0.13\ \mathrm{CsBr} + 0.13\ \mathrm{KCl}$
400	38	B	1 CsBr:1 KCl	$.91\ \mathrm{CsBr} + .91\ \mathrm{KCl} \longrightarrow .09\ \mathrm{CsCl} + .09\ \mathrm{KBr}$
480	36	C	1 CsCl:1 KBr	$.24\ \mathrm{CsCl} + .24\ \mathrm{KBr} \longrightarrow .76\ \mathrm{CsBr} + .76\ \mathrm{KCl}$
480	36	D	1 CsBr:1 KCl	$.82\ \mathrm{CsBr} + .82\ \mathrm{KCl} \longrightarrow .18\ \mathrm{CsCl} + .18\ \mathrm{KBr}$
480	72	E	1 CsBr:1 KCl	$.789\ \mathrm{CsBr} + .789\ \mathrm{KCl} \rightleftarrows .211\ \mathrm{CsCl} + .211\ \mathrm{KBr}$
480	72	F	1 CsCl:1 KBr	$.211\ \mathrm{CsCl} + .211\ \mathrm{KBr} \rightleftarrows .789\ \mathrm{CsBr} + .789\ \mathrm{KCl}$
480	72	G	2 CsBr:1 KCl	$.300\ \mathrm{CsCl} + .300\ \mathrm{KBr} \rightleftarrows 1.700\ \mathrm{CsBr} + .700\ \mathrm{KCl}$
480	72	H	1 CsBr:2 KCl	$.272\ \mathrm{CsCl} + .272\ \mathrm{KBr} \rightleftarrows 0.728\ \mathrm{CsBr} + 1.728\ \mathrm{KCl}$

ference pattern was 6.322 Å. The very excellent agreement between the values indicates clearly that at 480° two binary solid solutions are formed which together contain all of the mixture. In view of this excellent agreement the authors have used only the CsCl–CsBr solid solution for calculating the resultant mixtures for this reaction, the results of which are shown in Table V.

The cube edges of the CsCl–CsBr solid solutions obtained for reaction 11 are shown in Table IV and the extent of the reaction for each direction is shown in Table V. It is clear that at 480° equilibrium is approached quite closely in thirty-six hours. By drawing a composition–temperature diagram from the data in Table IV it was estimated that the composition of the equilibrium mixture at 490° should be KBr 21%, CsCl 21%, KCl 79%, CsBr 79%. A reheating of a mixture of potassium chloride and cesium bromide (stable pair) in a 1:1 mole ratio at 480° for seventy-two hours produced a CsCl–CsBr solid solution having a cube edge of 4.253 Å. (av. of two closely agreeing results) and the reciprocal pair heated in the same way produced likewise a cube edge of 4.253 Å. (cases E and F, Table V). That equilibrium has been reached can scarcely be doubted.

Cases G and H of Table V are very interesting. The shift in the reaction is in the direction that would be expected from mass action considerations. Furthermore, the amount of the shift is in almost exact quantitative agreement with what might be expected. In case G the shift to the left is just slightly too much and in case H the shift is just slightly too little. Reactions 3 and 16 are now being investigated in an effort to determine whether or not a similar effect can be discovered in these cases also.

Summary

1. Eighteen double decomposition reactions occurring between the sodium, potassium, rubidium and cesium halides (chloride, bromide, iodide) were investigated between 400 and 500° (below the fusion point) and the resultant mixtures examined by the method of X-ray crystal analysis.

2. When the reciprocal pairs (large cation–small anion and small cation–large anion combinations) were heated at 400° for thirty-six hours, reaction proceeded to some extent toward the stable pairs in 16 of the 18 cases.

3. When the stable pairs were heated at 400° for thirty-six hours, reaction proceeded to some extent toward the reciprocal pair in 7 cases.

4. One reaction was subjected to a pressure of 3500 atmospheres per square inch for ten minutes and it was found to proceed partially toward the stable pair.

ST. LOUIS, MO. RECEIVED OCTOBER 11, 1937

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY]

Interpretation of Diffusion Data for Some Strong Electrolytes

BY PIERRE VAN RYSSELBERGHE

I. Introduction

In the theory[1] consisting of combining Fick's law of diffusion with the thermodynamic idea that the driving force per unit mass of solute is equal to the gradient of the Gibbs chemical potential, one finds that the coefficient of diffusion D of a binary electrolyte is given by the formula

$$D = 2RT\frac{\Omega}{C}(1 + C\partial \log f/\partial C)10^3 \qquad (1)$$

in which R is the gas constant, T the absolute temperature, Ω/C the mobility or velocity due to unit force, C the concentration in moles per liter, f the mean activity coefficient of the ions. At infinite dilution Ω/C reduces to the classical Nernst expression which, for a uni-univalent electrolyte, is

$$10^{20}\lim_{C=0} \Omega/C = 1.074\frac{\Lambda^0_+\Lambda^0_-}{\Lambda^0_+ + \Lambda^0_-} \quad \text{(c. g. s. units)} \qquad (2)$$

where the limiting equivalent conductivities Λ^0_+ and Λ^0_- are expressed in reciprocal ohms. As explained by Onsager and Fuoss[1] the factor $1 + C\partial \log f/\partial C$ allows "for the interionic attraction reducing the thermodynamic tendency of the ions to separate by diffusion." For the factor Ω/C Onsager and Fuoss[1] give a theory in which they "compute the effect of interaction on the mobility of the migrating ions." The result of this theory for a uni-univalent electrolyte at 18° is

$$10^{20}\Omega/C = 1.074\frac{\Lambda_+\Lambda^0_-}{\Lambda^0_+ + \Lambda^0_-} - 9.60\left(\frac{\Lambda^0_+ - \Lambda^0_-}{\Lambda^0_+ + \Lambda^0_-}\right)^2 \frac{\sqrt{2C}}{1 + \mathrm{A}\sqrt{2C}} + 15.6\ C\varphi(A\sqrt{2C}) \qquad (3)$$

in which A is a specific constant for the electrolyte and $\varphi(A\sqrt{2C})$ is a function defined by

$$\varphi(x) = e^{2x}Ei(2x)/(1 + x)^2 \qquad (4)$$

with

$$Ei(y) = \int_y^\infty e^{-t}\frac{dt}{t} = -0.5772 - \log y + y - \frac{y^2}{2.2!} + \frac{y^3}{3.3!} - \cdots \qquad (5)$$

For salts such as potassium chloride and potassium nitrate, which are both considered in the present paper, the difference $\Lambda^0_+ - \Lambda^0_-$ is small and Ω/C varies with concentration only on account of the last term in formula (3). For sodium chloride, however, the second term on the right-hand side of this formula is not negligible. As indicated on Fig. 7 of the paper of Onsager and Fuoss,[1] their theory predicts an increase of Ω/C with concentration for both potassium and sodium chloride, but these authors have not shown that, when Ω/C is calculated from the experimental values of D according to formula (1), one finds that, for sodium chloride, this mobility Ω/C decreases steadily as concentration rises, while for potassium chloride an increase of Ω/C of the order required by the theory appears only at concentrations higher than 2 molar. They mention, however, that "at higher concentrations, we meet with quite appreciable deviations, particularly in the case of sodium chloride, and our theory of Ω/C is definitely not adequate." They also state that viscosity and hydration are the probable causes for the deviations. Whether the limiting law for Ω/C is verified or not is doubtful on account of the lack of accurate diffusion data at very low concentrations. A comparison between experimental and calculated coefficients of diffusion such as that presented by Onsager and Fuoss[1] on Fig. 8 of their paper can hardly be considered as a conclusive test of the theory. In the present paper we compare theoretical and "experimental" values of Ω/C after elimination of the thermodynamic factor $2RT\ (1 + C\ \partial \log f/\partial C)$ from the measured values of D. To the two cases considered by Onsager and Fuoss (potassium and sodium chloride at 18°) we are adding potassium chloride at 25° and potassium nitrate at 18°. Diffusion data for potassium chloride at 25° recently have been published by McBain and Dawson.[2] The dependence on concentration of these new data is of the same type as that exhibited by Clack's data[3] at 18°, a fact which entitles us to reject most of the previous data for potassium chloride (see

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[1] Onsager and Fuoss, *J. Phys. Chem.*, **36**, 2689 (1932). The first complete proof that the affinity of diffusion is measured by the gradient of the Gibbs chemical potential is due to Defay [Compt. rend. du 2$^{\text{me}}$ Congrès National des Sciences, Brussels, 1935, p. 317] whose reasoning is based upon DeDonder's theory of affinity [see DeDonder and Van Rysselberghe, "Thermodynamic Theory of Affinity, a Book of Principles," Stanford University Press, 1936.]

[2] McBain and Dawson, *Proc. Roy. Soc.* (London), **148A**, 32 (1935). It should be noted that the legend of the vertical coördinate axis of Fig. 3 of this paper was given erroneously as "cm.^{2}/sec. × 10^5" instead of "cm.^{2}/day."

[3] Clack, *Proc. Phys. Soc.* (London), **36**, 313 (1924).

Fig. 1 of McBain and Dawson[2]). For potassium nitrate we use Clack's diffusion coefficients[3] and Robinson's activity data.[4] The latter were not available at the time of the publication of the paper of Onsager and Fuoss.[1] Following these authors, who used Harned's activity data[5] for 25°, we likewise use Robinson's data for 25° in order to study diffusion coefficients at 18°, hence neglecting the small difference due to heats of dilution. We also present a quantitative investigation of the effect of viscosity on diffusion.

II. Comparison between Measured and Calculated Diffusion Mobilities

1. Potassium Chloride.—At 25° we have[5,6]

$$\log f = -\frac{0.820\sqrt{2C}}{1 + 0.76\sqrt{2C}} + 0.0394 \times 2C$$

and hence

$$1 + C\partial \log f/\partial C = 1 - \frac{0.410\sqrt{2C}}{(1 + 0.76\sqrt{2C})^2} + 0.0788\ C$$

At infinite dilution we have, according to the data of MacInnes, Shedlovsky and Longsworth[7] at 25° and other standard data

$$10^{20}\Omega/C = 34.84 \text{ and } 2RT = 4.842 \times 10^{10} \text{ at } 18°$$
$$10^{20}\Omega/C = 40.22 \text{ and } 2RT = 4.958 \times 10^{10} \text{ at } 25°$$

Experimental values of Ω/C are then deduced from the measured coefficients of diffusion by means of formula (1). *Theoretical* values of Ω/C are given by the following equations, the second term on the right-hand side of formula (3) being neglected

$$10^{20}\Omega/C = 34.84 + 15.6\ C\varphi(0.76\sqrt{2C}) \text{ at } 18°$$
$$10^{20}\Omega/C = 40.22 + 18.6\ C\varphi(0.76\sqrt{2C}) \text{ at } 25°$$

In the tables we give: in column 1 the concentration C of the salt in moles per liter; in column 2 the measured coefficient of diffusion D in cm²./sec. × 10⁵; in column 3 the difference Δ_m between the experimental values of $10^{20}\Omega/C$ and the value at infinite dilution (c.g.s. units); in column 4 the difference Δ_c between the Onsager–Fuoss values of $10^{20}\ \Omega/C$ and the value at infinite dilution; in column 5 the differences Δ_I calculated by means of the formula

$$\Delta_I = (1/\eta - 1) \lim_{C=0} \Omega/C\ 10^{20} \qquad (6)$$

in which η is the viscosity of the solution referred to water; in column 6 the differences Δ_{II} calculated by means of the formula

$$\Delta_{II} = \frac{1}{\eta}\left[\lim_{C=0} \Omega/C\ 10^{20} + \Delta_c\right] - \lim_{C=0} \Omega/C\ 10^{20} \qquad (7)$$

The difference defined by formula (6) corresponds to the hypothesis that the mobility Ω/C might be given by the simple formula

$$\Omega/C = \frac{1}{\eta} \lim_{C=0} \Omega/C \qquad (8)$$

The difference defined by formula (7) corresponds to the hypothesis that the mobility Ω/C might be given by the formula

$$\Omega/C = \frac{1}{\eta}(\Omega/C)_c \qquad (9)$$

in which $(\Omega/C)_c$ is the mobility calculated in the Onsager–Fuoss theory.

The results obtained for potassium chloride at 18 and at 25° are reported in Tables I and II, respectively. They are also represented graphically on Figs. 1 and 2.

TABLE I

DIFFUSION OF POTASSIUM CHLORIDE IN AQUEOUS SOLUTION AT 18°

1 C	2 D	3 Δ_m	4 Δ_c	5 Δ_I	6 Δ_{II}
0	1.69	0	0	0	0
0.05	1.55	+0.76	+0.46	+0.03	+0.49
.1	1.52	+ .18	+ .66	+ .07	+0.73
.2	1.50	− .29	+ .87	+ .14	+1.01
.4	1.50	− .41	+1.06	+ .30	+1.39
.6	1.53	− .18	+1.16	+ .45	+1.64
.8	1.55	− .25	+1.20	+ .57	+1.79
1.0	1.58	− .30	+1.22	+ .64	+1.88
1.5	1.65	− .26	+1.29	+ .71	+2.03
2.0	1.74	+ .09	+1.43	+ .64	+2.10
2.5	1.83	+ .50	+1.70	+ .43	+2.14
3.0	1.93	+1.05	+1.96	+ .09	+2.05
3.5	2.03	+1.50	+2.30	− .38	+1.89
4.0	2.13	+1.99	+2.62	−1.05	+1.49

TABLE II

DIFFUSION OF POTASSIUM CHLORIDE IN AQUEOUS SOLUTION AT 25°

1 C	2 D	3 Δ_m	4 Δ_c	5 Δ_I	6 Δ_{II}
0	1.99	0	0	0	0
0.1	1.89	+1.92	+0.79	+0.04	+0.83
.2	1.88	+2.00	+1.04	+ .05	+1.09
.5	1.83	−0.47	+1.33	+ .12	+1.45
1.0	1.86	− .50	+1.45	+ .20	+1.65
1.5	1.99	+ .47	+1.54	+ .12	+1.66
2.0	2.31	+5.04	+1.70	− .12	+1.58

(4) Robinson, THIS JOURNAL, **57**, 1165 (1935).

(5) Harned, *ibid.*, **51**, 416 (1929).

(6) Onsager and Fuoss[1] write (see formulas 4.13.22) $B = 0.071$ for KCl, $B = 0.129$ for NaCl, while we get from Harned's data $B = 0.0171 \times \log 10 = 0.0394$ for KCl and $B = 0.032 \times \log 10 = 0.0739$ for NaCl. Other misprints are 10^{10} instead of the correct 10^{13} in formula (4.13.19), $\varphi(0.76\sqrt{m})$ instead of the correct $\varphi(0.76\sqrt{2m})$ and 10^{22} instead of the correct 10^{20} in the two formulas at the bottom of page 2768.

(7) MacInnes, Shedlovsky and Longsworth, THIS JOURNAL, **54**, 2758 (1932).

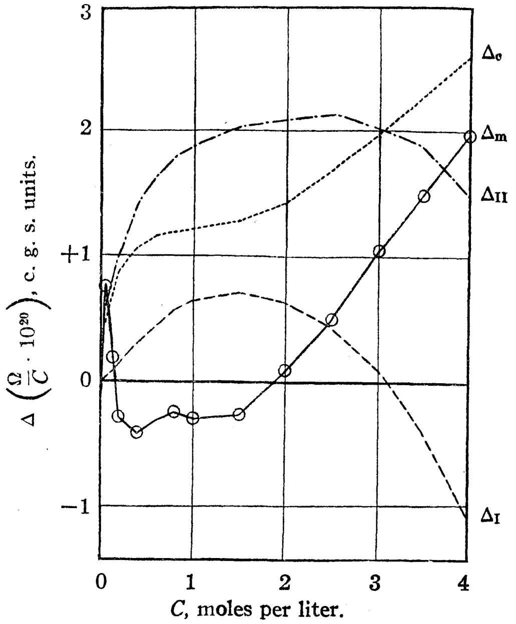

Fig. 1.—Diffusion of KCl at 18°. At infinite dilution $\Omega/C = 34.84 \times 10^{-20}$.

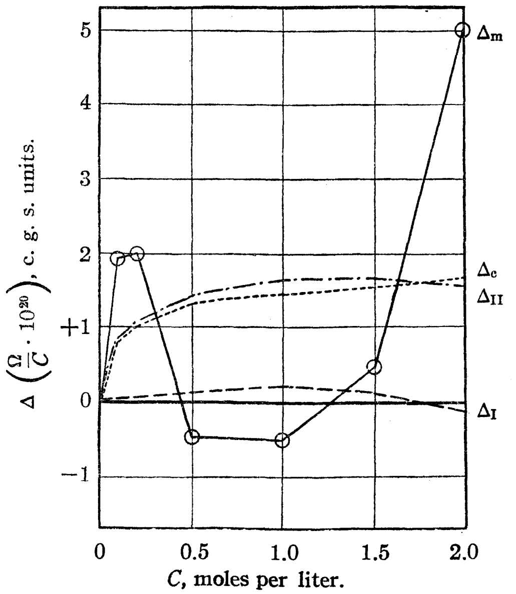

Fig. 2.—Diffusion of KCl at 25°. At infinite dilution $\Omega/C = 40.22 \times 10^{-20}$.

2. Sodium Chloride.—At 25° we have[5,6]

$$\log f = -\frac{0.820\sqrt{2C}}{1 + 0.84\sqrt{2C}} + 0.0739 \times 2C$$

and hence

$$1 + C\partial \log f/\partial C = 1 - \frac{0.410\sqrt{2C}}{(1 + 0.84\sqrt{2C})^2} + 0.1478\, C$$

At infinite dilution we have, for 18°

$$10^{20}\,\Omega/C = 28.01 \text{ with } 2RT = 4.842 \times 10^{10}$$

Formula (1) yields *experimental* values of Ω/C and *theoretical* values are given by the equation

$$10^{20}\,\Omega/C = 28.01 + 15.6\, C\varphi(0.84\sqrt{2C}) - 0.39\,\frac{\sqrt{2C}}{1 + 0.84\sqrt{2C}}$$

TABLE III

DIFFUSION OF SODIUM CHLORIDE IN AQUEOUS SOLUTION AT 18°

1 C	2 D	3 Δ_m	4 Δ_c	5 Δ_I	6 Δ_{II}
0	1.35	0	0	0	0
0.05	1.26	+0.10	+0.33	−0.11	+0.22
.1	1.24	− .10	+ .46	− .24	+ .22
.2	1.22	− .58	+ .59	− .39	+ .19
.4	1.20	−1.64	+ .70	− .82	− .14
.6	1.21	−2.16	+ .76	−1.33	− .61
.8	1.22	−2.70	+ .76	−1.62	−1.00
1.0	1.23	−3.27	+ .75	−2.17	−1.48
1.5	1.26	−4.42	+0.79	−3.33	−2.63
2.0	1.29	−5.46	+1.05	−4.67	−3.79
2.5	1.33	−6.17	+1.33	−5.95	−4.91
3.0	1.36	−6.96	+1.65	−7.42	−6.20
3.5	1.39	−7.66	+1.98	−8.82	−7.47
4.0	1.43	−8.17	+2.29	−10.17	−8.71
4.5	1.46	−8.72	+2.61	−11.53	−10.00
5.0	1.49	−9.26	+2.93	−12.71	−11.11

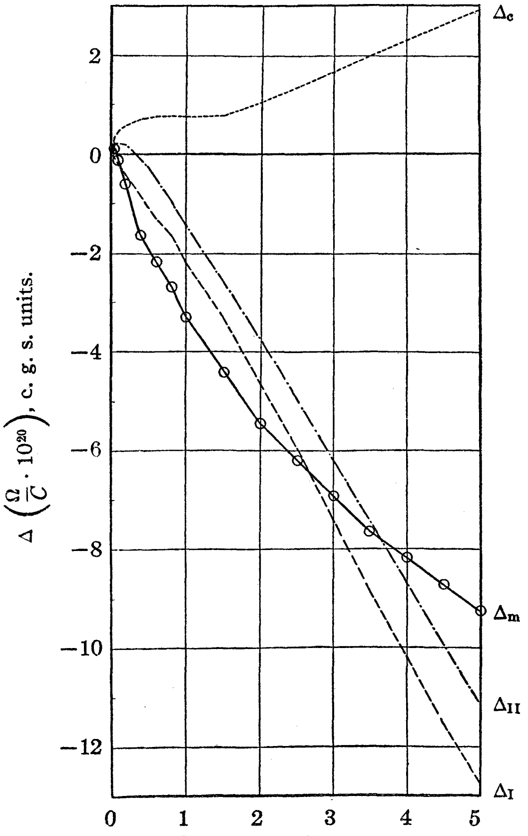

Fig. 3.—Diffusion of NaCl at 18°. At infinite dilution $\Omega/C = 28.01 \times 10^{-20}$.

Differences Δ_{I} and Δ_{II} have also been calculated according to formulas (6) and (7). The results are reported in Table III and represented graphically on Fig 3.

3. **Potassium Nitrate.**—Activity coefficients of potassium nitrate in aqueous solutions up to 3.5 molal have been measured by Robinson.[4] It is difficult to describe these data by means of a formula of the Hückel type with two parameters A and B

$$\log_{10} f = -0.356 \frac{\sqrt{2C}}{1 + A\sqrt{2C}} + B \times 2C$$

The activity coefficient of potassium nitrate decreases steadily as concentration rises and at low concentrations the application of a formula without the linear term $2BC$ would require impossibly small values of the parameter A. In order to calculate the function φ (κa) of the Onsager–Fuoss theory for this salt we have followed a suggestion due to Guggenheim[8] and have adopted for $A\sqrt{2}$ the value *one*. One readily sees that we could have used this same value of $A\sqrt{2}$ for both potassium and sodium chloride without modifying more than by a negligible amount the calculated values of Ω/C. The factor $1 + C\partial \log f/\partial C$ has been obtained graphically from Robinson's experimental curve for f (after the usual conversion of activity coefficients γ into the corresponding f's and of molalities into concentrations). We get experimental values of Ω/C from formula (1) and theoretical values are given by the equation

$$10^{20}\ \frac{\Omega}{C} = 34.00 + 15.6\ C\varphi(\sqrt{C})$$

for 18°, the second term on the right-hand side of formula (3) being neglected. Differences Δ_{I} and Δ_{II} also have been calculated according to formulas (6) and (7). The results are reported in Table IV and represented graphically on Fig. 4.

TABLE IV

DIFFUSION OF POTASSIUM NITRATE IN AQUEOUS SOLUTION AT 18°

1 C	2 D	3 Δ_m	4 Δ_c	5 Δ_{I}	6 Δ_{II}
0	1.53	0	0	0	0
0.05	1.45	−0.18	+0.62	+0.11	+0.72
.1	1.43	+ .24	+ .72	+ .20	+0.93
.2	1.39	+ .72	+ .96	+ .45	+1.42
.4	1.34	+1.53	+1.17	+ .76	+1.96
.6	1.30	+2.33	+1.29	+1.02	+2.34
.8	1.27	+3.55	+1.37	+1.16	+2.57
1.0	1.24	+4.80	+1.40	+1.30	+2.76
1.5	1.19	+7.36	+1.43	+1.30	+2.79
2.0	1.15	+11.64	+1.47	+0.83	+2.34
2.5	1.17	+18.14	+1.71	+0.28	+2.00

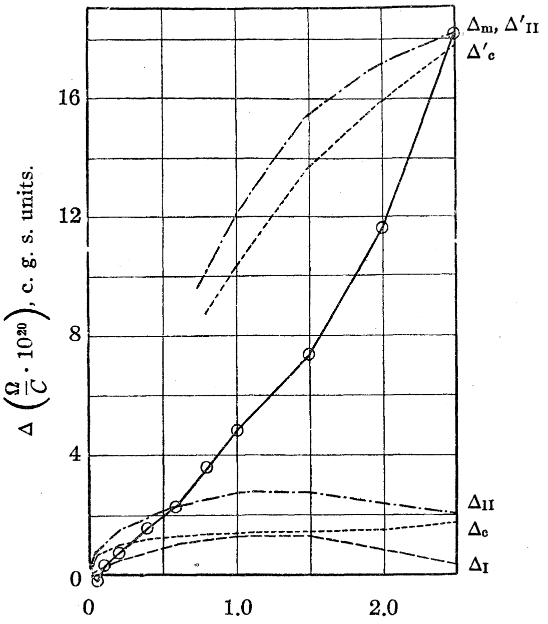

Fig. 4.—Diffusion of KNO_3 at 18°. At infinite dilution $\Omega/C = 34.00 \times 10^{-20}$.

III. Discussion

Close inspection of the tables will make the following points clear.

1. With potassium chloride Ω/C varies very slightly with concentration. Although the calculated increments Δ_c are of the right order of magnitude at high concentrations the behavior of Δ_m is not reproduced correctly at low concentrations. Consideration of the increments Δ_{I} and Δ_{II} shows that viscosity corrections are not sufficient to explain the experimental Δ_m, whether the corrections are applied to the limiting value of Ω/C or to the Onsager–Fuoss value corresponding to each particular concentration. The diffusion coefficient D of potassium chloride is seen to depend mostly on the activity factor $1 + C\,\partial \log f/\partial C$.

2. With concentrated sodium chloride Ω/C differs by as much as 30% from its limiting value in a direction *opposite in sign* to that predicted by the Onsager–Fuoss theory. The simple viscosity correction applied to the limiting value of Ω/C reproduces the experimental Δ_m's correctly both in sign and order of magnitude. When the viscosity correction is applied to the Onsager–

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[8] Guggenheim, *Phil. Mag.*, [7] **19**, 588 (1935).

Fuoss values of Ω/C a slight improvement is obtained in the agreement at high concentrations, but at low concentrations the differences Δ_I are more nearly correct. Such a situation greatly reduces the significance of the Onsager–Fuoss theory of diffusion.

3. With potassium nitrate the experimental increments Δ_m are unexpectedly large; in concentrated solutions they are nearly ten times as large as the Δ_c's calculated from the Onsager–Fuoss theory. The increments Δ_I and Δ_II are in the right direction, Δ_m coinciding exactly with Δ_c at a concentration of 0.6 molar. In view of the arbitrary choice of the parameter A ($A\sqrt{2C} = \kappa a = \sqrt{C}$ or $a = 3$ Å.) we have repeated the calculation of Δ_c with a value of a such that Δ_II is identical with Δ_m at $C = 2.5$ moles/liter. We found $a = 0.6$ Å., $A\sqrt{2C} = \kappa a = 0.2\sqrt{C}$. Such a value of a yields the Δ_c' and Δ_II' values reported in Table V and represented on Fig. 4. At concentrations smaller than 0.8 the values calculated with $\kappa a = \sqrt{C}$ given in Table IV are themselves larger than the corresponding Δ_m's showing that it is impossible to interpret the mobility of potassium nitrate in terms of a constant value of the ionic diameter a. This difficulty is similar to that encountered in the interpretation of activity data for this salt.

TABLE V

DIFFUSION OF POTASSIUM NITRATE IN CONCENTRATED AQUEOUS SOLUTIONS AT 18°

1 C	2 Δ_c'	3 Δ_II'	4 Δ_m
0.8	8.74	10.19	3.55
1.0	10.30	12.00	4.80
1.5	13.69	15.52	7.36
2.0	15.91	17.14	11.64
2.5	17.72	18.14	18.14

In all cases studied in this paper the variation with concentration of the thermodynamic factor $1 + C\partial \log f/\partial C$ is found to be at least as important as the variation of the mobility factor Ω/C. The importance of the thermodynamic factor is particularly striking in the case of salts exhibiting a minimum in the activity coefficient curve. Such salts also exhibit a minimum in the curve for the coefficient of diffusion, as is borne out by potassium and sodium chloride studied in this paper and also by magnesium chloride and magnesium nitrate for which diffusion coefficients have been reported recently by Öholm.[9] With cadmium and magnesium sulfates the diffusion coefficients also exhibit minima, as has been observed by Davies,[10] while the activity coefficients decrease steadily as concentration rises, finally reaching practically constant values.

The remarks made in the present discussion apply to strong electrolytes. It is interesting to examine, at least approximately, the behavior of a typical non-electrolyte such as sucrose. The coefficient of diffusion is given by the formula

$$D = RT\frac{\Omega}{C}(1 + C\partial \log f/\partial C)10^3 \qquad (10)$$

The variation of Ω/C with concentration is much larger than in the case of electrolytes and cannot be accounted for quantitatively by means of the simple viscosity correction as is shown in Table VI obtained by means of various data in the "I. C. T." and Landolt–Börnstein–Roth "Tables."

TABLE VI

DIFFUSION OF SUCROSE IN AQUEOUS SOLUTIONS AT 20°

C, moles/liter	D, cm.^{2}/day	$\frac{\Omega}{C} \times 10^{20}$ c.g.s.	$\frac{1}{\eta}\,\mathrm{lin}\,\frac{\Omega}{C} \times 10^{20}$
0	0.380	8.97	8.97
0.25	.368	8.15	6.35
0.50	.353	7.45	4.90
2.00	.272	4.76	0.08

The results indicate that the agreement between measured and calculated Ω/C might be satisfactory in very dilute solutions for which, unfortunately, good experimental data are lacking. Let us note that in the various attempts at applying the Stokes–Einstein law of diffusion to molecular solutions[11] better results might have been obtained by introducing the thermodynamic factor $1 + C\,\partial \log f/\partial C$. We would have

$$D = \frac{RT}{N}\frac{1}{6\pi\eta r}(1 + C\partial \log f/\partial C) \qquad (11)$$

in which N is Avogadro's number, and r the radius of the solute molecules. Comparison with formula (10) gives

$$\frac{\Omega}{C} = \frac{10^3}{N6\pi\eta r} \qquad (12)$$

IV. Summary

1. The diffusion mobilities of potassium chloride, sodium chloride and potassium nitrate in aqueous solution are calculated from the experimental diffusion coefficients and the thermodynamic factors $1 + C\,\partial \log f/\partial C$.

2. The diffusion mobilities are compared with theoretical values obtained in three different man-

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[9] Öholm, *Finska Kemistamfundets Medd.*, **45**, 71 (1936).

[10] Davies, *Phil. Mag.*, [7] **15**, 489 (1933).

[11] See for instance Taylor, "Treatise on Physical Chemistry," D. Van Nostrand Co., Inc., New York, N. Y., 1931, Vol. II, 2d. ed., pp. 1026–1028.

ners: (a) by means of the Onsager–Fuoss theory of diffusion; (b) by applying the simple viscosity correction to the mobility at infinite dilution; (c) by applying the viscosity correction to the Onsager–Fuoss mobilities.

3. It is shown that the viscosity correction is at least as important as the Onsager–Fuoss interionic effects and that, with sodium chloride, the correct sign for the variation of the mobility cannot be obtained without the viscosity correction.

4. Remarks are made concerning the minima in the diffusion and activity coefficient curves and concerning the diffusion of sucrose. A modified form of the Stokes–Einstein law of diffusion is proposed.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

Hydrogen as Carrier Gas for the Catalytic Dehydrogenation of Borneol to Camphor

BY B. E. CHRISTENSEN, E. C. GILBERT AND MAX BOCEK

In connection with another investigation it became necessary to convert borneol quantitatively into camphor. Since oxidation or dehydrogenation in the vapor phase appeared to have many advantages over other methods available, attack upon the problem was made from this aspect.

Although there are numerous references (largely patents) to the vapor phase dehydrogenation of borneol to camphor, the majority deal with the use of copper in some form as the catalyst.[1] Examination of these references, however, reveals data of highly conflicting and contradictory nature, one reporting 100% conversion,[1a] while others[1e] found only traces, and one of the latest[1i] states that reduced copper is a poor catalyst from the standpoint of yield.

In the hope of clearing some of the contradictory points and establishing conditions under which the method might be used reliably, extensive experiments have been carried out in this Laboratory with different catalysts and carrier (diluent) gases. In this paper the results obtained with reduced copper are reported.

Preliminary tests were made with many forms of this catalyst. Using a spongy form obtained by the reduction of fused cupric oxide, conversions of 96–100% were observed at 360°, confirming to some extent the work of Aloy and Brustier.[1a] Repeated tests under these conditions indicated, however, that the high catalytic efficiencies could not be maintained over any period of time and that the color of the copper gradually changed with use. This discoloration could not be restored by further reduction with hydrogen.

Since it was believed that either undesired decomposition products of borneol (due to the high concentration of borneol) or oxidation of the catalyst by traces of oxygen were responsible for the discoloration and diminishing catalytic activity, experiments were next attempted using carrier gases. Others have shown that borneol vapor diluted with benzene gave yields around 86%[1h] while another process using carbon dioxide[1d] (no data given) has been patented.

Although hydrogen is a product of the reaction and in excess logically should retard its progress, this gas would prevent oxidation of the catalyst while also serving as a diluent for the borneol vapor. Attempts made to use hydrogen as the carrier gas met with immediate success, making it possible to maintain the catalyst at high efficiency through many runs, and, under the optimum conditions, apparently minimizing side reactions, so that the product was uniformly of high quality.

Experimental

A borneol reservoir was maintained at any desired temperature by an air-bath. From this, borneol vapor was passed over the catalyst either by its own vapor pressure or by a stream of diluent or carrier gas. Approximately 2–3 g. samples of borneol were generally used. The temperature of the catalyst was controlled by an electric furnace and was measured by a thermocouple. The volume of carrier gas was measured by a calibrated flow-meter.

The catalyst in every run reported in this part of the work consisted of spongy copper prepared by the reduction of fused copper oxide with hydrogen at 200°. The volume

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(1) (a) Aloy and Brustier, *Bull. soc. chim.*, **9**, 733 (1911); (b) Aloy and Brustier, *J. pharm. chim.*, **10**, 42 (1914); (c) French Patent 353,919; *C. A.*, **1**, 383 (1907); (d) British Patent 17,573, Aug. 31, 1906; *C. A.*, **1**, 2320 (1907); (e) Ikeda, *Sci. Papers Inst. Phys. Chem. Research* (*Tokyo*), **7**, 1 (1927); (f) Masumoto, *Mem. Coll. Sci. Kyoto Imp. Univ.*, **9A**, 219 (1925); (g) Japanese Patent 99,469, Feb. 9, 1933; *C. A.*, **28**, 2373 (1934); (h) Shoruigin and Makarov-Zemlyanski, *Zhur. Prikladnoi Khim.*, **4**, 68 (1931); (i) Sivov, Korotaeva and Kochneva, *J. Chem. Ind.* (*Moscow*), **3**, 52 (1933); *C. A.*, **28**, 138 (1934).

of catalyst was 23 cc., contained in a tube of 1-cm. diameter. Catalysts which lost their activity were reactivated easily by repeated oxidation by air at 500°, followed by the regular reduction at 200°. The use of a catalyst prepared by the reduction of copper nitrate on porous plate gave very poor results. (Porous plate was later found to be quite active alone, yielding liquid products.)

In all more than one hundred runs were made, and since the standard method of estimating camphor is time consuming,[2] the percentage conversion in a given run was estimated by comparing the melting point of the product with a known borneol–camphor melting point curve. Confidence was had in this procedure because repeated comparison of estimations from the melting points with those obtained by the gravimetric method gave quantitative agreement, within the limit of accuracy of either method.[2] Certainly, therefore, in those instances where a high yield is indicated by the melting point method the estimation is trustworthy. No attempt was made to identify products other than camphor which may conceivably have been present in runs carried out far from the optimum conditions.

Results

Attempts to duplicate the quantitative conversion reported by Aloy and Brustier[1a] using only borneol vapor resulted in a rapid decrease in the catalyst efficiency (about 30% per run).

Hydrogen as Carrier Gas.—The exploratory tests with hydrogen having shown excellent promise, experiments were carried out to determine the optimum conditions for its use. To study the effect of temperature, runs were made at 20° intervals. The results are shown in Table I.

Table I

Effect of Temperature, Using Hydrogen as Carrier

Temp. of borneol reservoir 135–140°. Product in all cases uniformly white and solid. Each run given a number, the missing runs being omitted from the table in the interest of brevity. Space velocity 880.

Run	Catalyst temp., °C.	M. p. product, °C.	Est. % camphor in product
1	280	187.5	65
3	320	180.0	96
11	480	180.0	96
13	520	183.5	86

It is important to note that above 420° Aloy and Brustier obtained considerable amounts of liquids identified as terpenes. With the present precedure the products are still solid at a reaction temperature of 520°, though the camphor percentage has dropped somewhat. Furthermore, life tests at 300° in the presence of hydrogen showed the same percentage conversion in the *tenth* run as in the first (95–96%). In no case did hydrogen seem to reverse the process or reduce the yield as might have been predicted.

In order to determine the effect of time of contact, runs were made under otherwise optimum conditions with various space velocities of hydrogen gas. It was observed that maximum efficiencies were maintained with space velocity as high as 2000. Above this value the efficiencies slowly diminished.

Carbon Dioxide as Carrier Gas.—Although the use of carbon dioxide is mentioned in some patents[1d] no data were found in the literature. In order to determine whether the beneficial effect of hydrogen on this reaction is specific or due merely to its action as a diluent, a series of runs was made with carbon dioxide. The effect of catalyst temperature, space velocity, and length of catalyst life were studied in over twenty runs. The effect of temperature is shown in Table II.

Table II

Effect of Temperature Using Carbon Dioxide as Carrier

Temperature of borneol reservoir 140°. Space velocity 800.

Run	Catalyst temp., °C.	M. p. product, °C.	Est. % camphor in product
1	270	203	1
2	320	179	100
5	380	179	100
9	480	185	78

No particular significance is attached to the fact that some of the yields are apparently 100% as compared to 96% for hydrogen because of the method of estimation. The catalyst soon lost its activity, the efficiency dropping to 73% on the fourth run at 400° and to 65% on the seventh run at 340°. The use of carbon dioxide is less advantageous in other respects because it is slower and less efficient also in carrying over the borneol vapor.

Other Catalysts.—Preliminary experiments using hydrogen as a carrier gas for this reaction with other catalysts (notably reduced cobalt and nickel) have given excellent results. Although the effective temperature range is lower and narrower (200–250°) and there is more tendency to form terpenes, experiments conducted in this Laboratory have given very high yields of camphor. Cobalt seems to be superior in many respects to copper.

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(2) U. S. Pharmacopoeia, Vol. XI, p. 353; Hampshire and Page, *Quart. J. Pharm. Pharmacology*, **7**, 558 (1934); Goldstein and Reindollar, *J. Am. Pharm. Assoc.*, **XXVI**, 887 (1937).

Summary

1. Results have been given to show that hydrogen is highly efficient as a carrier gas for the dehydrogenation of borneol vapor over reduced copper, particularly in respect to catalyst life and purity of product.

2. Optimum conditions with respect to temperature and time have been established for the reaction thus conducted.

3. Results have been given to show that carbon dioxide is in most respects inferior to hydrogen as a carrier.

4. Preliminary experiments have been reported which indicate that reduced cobalt and nickel are excellent catalysts for the dehydrogenation of borneol when used in the presence of hydrogen.

CORVALLIS, OREGON RECEIVED MARCH 30, 1938

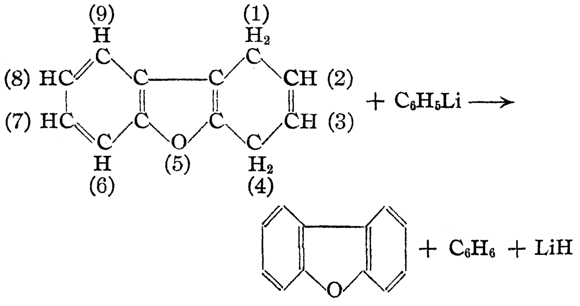
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Dehydrogenation by Organometallic Compounds

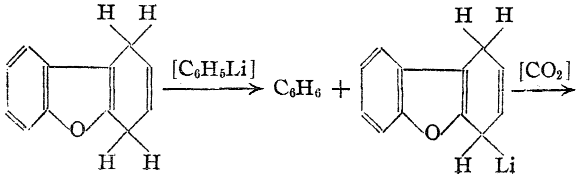
BY HENRY GILMAN AND CHESTER W. BRADLEY

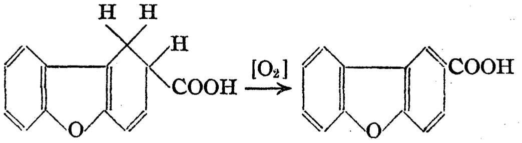
Introduction

In attempting to metalate 1,4-dihydrodibenzofuran in ether solution by means of phenyllithium, dibenzofuran instead of the expected metalation product was the chief compound isolated. The brown color produced at the inception of reaction indicated the formation of a metalation product. This color slowly disappeared on refluxing and a white precipitate, subsequently shown to be lithium hydride, formed. The isolation of dibenzofuran, lithium hydride and benzene indicated that the following transformation had taken place.



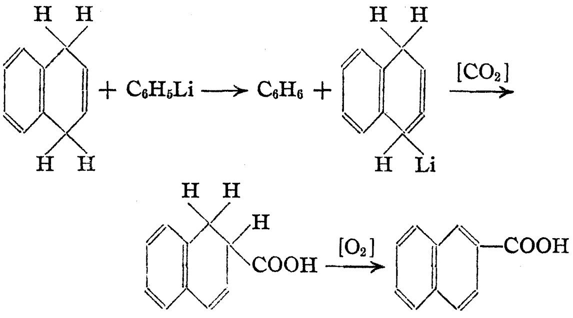
The intermediate metalation product was characterized subsequently (after allowing the reaction to proceed for a shorter time and at a lower temperature) by carbonation, to yield 1,2-dihydrodibenzofuran-2-carboxylic acid. The position of the carboxyl group was established by oxidizing the dihydro acid to the known dibenzofuran-2-carboxylic acid.





Dehydrogenation of 1,4-dihydrodibenzofuran also was effected by *n*-butyllithium and *n*-butylsodium. It was shown subsequently that the related 1,4-dihydrodibenzothiophene is dehydrogenated to dibenzothiophene by organolithium and organopotassium compounds.[1]

A related series of reactions was then observed with 1,4-dihydronaphthalene. Here, also, moderate conditions made it possible to characterize the intermediate metalation compound.



Carbonation of the intermediate organometallic compounds derived from 1,4-dihydrodibenzofuran, 1,4-dihydrodibenzothiophene and 1,4-dihydronaphthalene probably involves an allylic rearrangement. An illustration of a related rearrangement with organosodium compounds is the work of Schlenk and Bergmann.[2] These authors obtained the same acid by carbonating the organosodium compounds obtained from the

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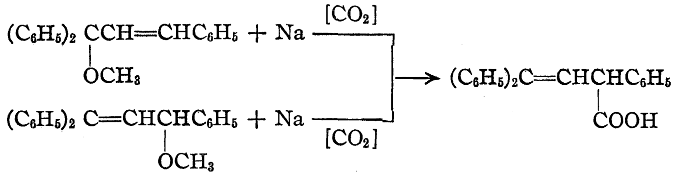
(1) Gilman and Jacoby, *J. Org. Chem.*, **3**, in press (1938).

(2) Schlenk and Bergmann, *Ann.*, **479**, 78 (1930).

methyl ethers of diphenylstyrylcarbinol and β,β-diphenylvinylphenylcarbinol, respectively.



$$\left.\begin{array}{l}(C_6H_5)_2\underset{\displaystyle OCH_3}{C}CH{=}CHC_6H_5 + Na \xrightarrow{[CO_2]} \\ (C_6H_5)_2C{=}CH\underset{\displaystyle OCH_3}{C}HC_6H_5 + Na \xrightarrow[{[CO_2]}]{} \end{array}\right] \longrightarrow (C_6H_5)_2C{=}CH\underset{\displaystyle COOH}{C}HC_6H_5$$

The illustrations just given are of lateral types. Related allylic rearrangements also take place with lateral-nuclear types as in 2-furylmethylsodium[3a] and benzyllithium.[3b] Rearrangements of these kinds now appear to be reactions common to practically all types of reactive and moderately reactive organometallic compounds,[4] but they have been most closely examined with organomagnesium compounds.[5]

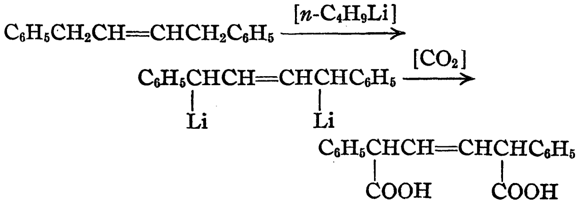
If an allylic rearrangement is the correct interpretation for the mechanism of reaction, it is interesting to inquire why the carboxyl group in the dihydrodibenzofuran- and dihydrodibenzothiophenecarboxylic acids is attached to the 2-position and not to the 3-position. Both dihydro types have active methylene groups in the 1- and in the 4-positions. Replacement of hydrogen in the 1-methylene group followed by rearrangement should give a 3-carboxylic acid, whereas replacement in the 4-methylene group should give the 2-carboxylic acid. It may be significant that metalation of the parent types, dibenzofuran and dibenzothiophene, by organoalkali compounds invariably involves the 4-position. Furthermore, metalations of ethers (like anisole and diphenyl ether) invariably involves the position ortho to the ether linkage.

Dehydrogenation by organometallic compounds is not restricted to cyclic compounds. It has been shown that *n*-butyllithium dehydrogenates 1,4-diphenylbutene-2 to give 1,4-diphenylbutadiene-1,3.

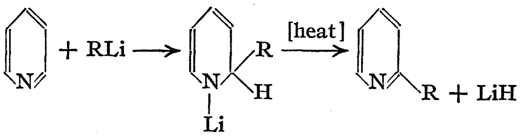
$$C_6H_5CH_2CH{=}CHCH_2C_6H_5 + n\text{-}C_4H_9Li \longrightarrow C_6H_5CH{=}CHCH{=}CHC_6H_5$$

Carbonation of the reaction mixture also yielded 1,4-diphenyl-2-butene-1,4-dicarboxylic acid. This dibasic acid probably was formed as a consequence of dimetalation of the reactive methylene groups in 1,4-diphenylbutene-2.

The loss of alkali hydrides from organometallic compounds at temperatures not exceeding the boiling point of ether rarely has been observed. However, the N-lithium derivatives of some reduced nitrogen heterocycles, formed by addition and not substitution reactions, lose lithium hydride at temperatures as low as 70–100°. The following reaction illustrates a transformation described by Ziegler and Zeiser.[6]



$$C_6H_5CH_2CH{=}CHCH_2C_6H_5 \xrightarrow{[n\text{-}C_4H_9Li]} \underset{\displaystyle Li}{C_6H_5CH}CH{=}CH\underset{\displaystyle Li}{CHC_6H_5} \xrightarrow{[CO_2]} \underset{\displaystyle COOH}{C_6H_5CH}CH{=}CH\underset{\displaystyle COOH}{CHC_6H_5}$$



A related reaction takes place with other nitrogen heterocycles, but generally at more elevated temperatures. Also, ethylsodium decomposes slowly at room temperature and quite rapidly at 100° to give sodium hydride, ethane and ethylene.[7] Pyrolysis of ethylmagnesium bromide at 175° gives magnesium hydride and ethylene.[8]

Experimental Part

1,4-Dihydrodibenzofuran.—To a solution of 12.0 g. (0.54 g. atom) of sodium in 400 cc. of liquid ammonia was added 30 g. (0.18 mole) of *finely divided* dibenzofuran over a period of twenty to thirty minutes and the stirring continued for thirty minutes.

Ammonium chloride was then added slowly in slight excess, and the product was finally distilled under reduced pressure (b. p. 110° (5 mm.)). The yield was 82%, after recrystallization from methanol and petroleum ether (b. p. 60–68°), m. p. 42°.

Anal. Calcd. for $C_{12}H_{10}O$: C, 84.65; H, 5.93. Found: C, 84.40; H, 5.87.

Dehydrogenation of 1,4-Dihydrodibenzofuran by Phenyllithium.—A filtered ether solution of phenyllithium (0.125 mole) was run into an ether solution of 17 g. (0.01 mole) of 1,4-dihydrodibenzofuran. The mixture immediately turned brownish and the color intensified slowly. In about two hours a white precipitate became noticeable, and at the end of fifteen hours of refluxing all of the brown color disappeared and there was a considerable accumulation of white precipitate.

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(3) (a) Gilman and Breuer, THIS JOURNAL, **56**, 1123 (1934); (b) Gilman and Breuer, *ibid.*, **56**, 1127 (1934).

(4) Studies by Joseph F. Nelson.

(5) General references are contained in the following articles: Gilman and Kirby, THIS JOURNAL, **54**, 345 (1932), and Austin and Johnson, *ibid.*, **54**, 647 (1932).

(6) Ziegler and Zeiser, *Ber.*, **63**, 1847 (1930); *Ann.*, **485**, 174 (1931). See also Bergstrom, THIS JOURNAL, **52**, 2845 (1930).

(7) Carothers and Coffman, *ibid.*, **51**, 588 (1929).

(8) Jolibois, *Compt. rend.*, **155**, 353 (1912); Clapp and Woodward, THIS JOURNAL, **60**, 1019 (1938).

The ether solution was filtered from the precipitate, and the filtrate distilled to yield 1.5 g. (19%) of benzene (identified as the *m*-dinitrobenzene derivative). Distillation of the residue gave dibenzofuran; 88% yield of crude material or 70% yield of compound highly purified by crystallization.

The white precipitate was analyzed by decomposing with water and measuring the hydrogen evolved and also titrating the lithium hydroxide formed. The hydrogen and lithium hydroxide were formed in equivalent quantities from a sample. The hydrogen was analyzed by combustion methods.

In another experiment in which refluxing was continued for only one and one-quarter hours before carbonation, some brownish colored material was present at the end of that time. However, the quantity of intermediate metalation product must have been small for the yield of dibenzofuran was 86% and only a trace of acidic material was isolated.

Apropos the ready loss of lithium hydride, it was noted that refluxing and extended time of reaction are not necessary. From an experiment allowed to run but ten minutes and with no refluxing, the yield of dibenzofuran was 70% and the yield of dihydrodibenzofurancarboxylic acid was 27%.

In another experiment in which an excess of phenyllithium was used there was obtained a 66% yield of dibenzofuran and a 5% yield of dibenzofuran-4-carboxylic acid. This acid undoubtedly was due to metalation of the dibenzofuran by the excess of phenyllithium.

Metalation of 1,4-Dihydrodibenzofuran.—Five-hundredths mole of dihydrodibenzofuran and an equivalent quantity of phenyllithium were allowed to react for thirty-five minutes at −15°, after which time carbonation was effected by an ether–solid carbon dioxide mixture. From the ether extract there was recovered a 59% yield of the dihydrodibenzofuran. No dibenzofuran was isolated.

Acidification of the alkali extract yielded 3.6 g. (34%) of dihydrodibenzofurancarboxylic acid which melted at 278–279° after recrystallization from ethanol.

Anal. Calcd. for $C_{13}H_{10}O_3$; C, 72.75; H, 4.70; neut. equiv., 217. Found: C, 72.58; H, 4.84; neut. equiv., 220.

The dihydrodibenzofurancarboxylic acid was oxidized by two different procedures to dibenzofuran-2-carboxylic acid. First, the dihydro acid was heated with an equal weight of sulfur at 250° for three-fourths of an hour to give a 66% yield of dibenzofuran-2-carboxylic acid. Second, a glacial acetic acid solution of the dihydro acid and an equivalent quantity of bromine were refluxed for fifteen minutes to give a 90% yield of dibenzofuran-2-carboxylic acid. The acid obtained by these two oxidation procedures was identified by (1) direct comparison with an authentic specimen and (2) conversion to methyl dibenzofuran-2-carboxylate which was also compared with an authentic specimen.

Dehydrogenation of 1,4-Dihydrodibenzofuran by *n*-Butylsodium and *n*-Butyllithium.—*n*-Butylsodium was prepared by adding 2.5 g. (0.11 g. atom) of sodium to 8.5 g. (0.0271 mole) of di-*n*-butylmercury in 200 cc. of petroleum ether (b. p. 60–68°). The reaction was allowed to proceed for one hour and then 9.2 g. (0.054 mole) of dihydrodibenzofuran in 25 cc. of petroleum ether was added. Slight warming was observed, and a muddy brown suspension appeared immediately. After three hours of refluxing, the mixture became gray in color.

The supernatant liquid was decanted through a filter, and the residue washed once with petroleum ether. From the petroleum ether was obtained 3.7 g. of dibenzofuran.

The solid residue was suspended in petroleum ether and carbonated. Extraction with 5% sodium hydroxide followed by acidification of the extract yielded 2.5 g. (21.5%) of dibenzofuran-4-carboxylic acid. The petroleum ether fraction yielded an additional 2.4 g. of dibenzofuran which made the total yield of this product 66%.

From a reaction between dihydrodibenzofuran and *n*-butyllithium there was obtained an 84% yield of dibenzofuran.

Dehydrogenation of 1,4-Dihydronaphthalene.—The 1,4-dihydronaphthalene was prepared in accordance with the directions of Bamberger and Lodter[9] and purified by the method of Sand.[10]

Dehydrogenation was carried out with phenyllithium in a manner identical with that used with dihydrodibenzofuran. Reaction was slower, as evidenced by the slow development of the brown color and the noticeable formation of a precipitate in about four hours. After sixteen hours of refluxing the brown color had faded considerably and much white precipitate was present. The reaction mixture was then carbonated and the products worked up. Starting with 4 g. of dihydronaphthalene, the yield of naphthalene was 85%.

In another experiment, the precipitate was filtered before carbonation and shown to be lithium hydride.

Metalation of 1,4-Dihydronaphthalene.—Five grams of 1,4-dihydronaphthalene was metalated at −15° with an equivalent amount of *n*-butyllithium. After stirring for seven hours the reaction mixture was carbonated.

The products isolated were a 64% recovery of dihydronaphthalene and 1.7 g. or a 26% yield of 1,2-dihydro-2-naphthoic acid melting at 105–106°. This dihydro acid was oxidized to β-naphthoic acid in accordance with the procedure of Baeyer.[11] Identification was completed by the method of mixed melting points.

Dehydrogenation of 1,4-Diphenylbutene-2.—A filtered solution of *n*-butyllithium, prepared from 0.014 mole of *n*-butyl bromide, was added to an ether solution of 2.1 g. (0.01 mole) of 1,4-diphenylbutene-2 (prepared in accordance with the directions of Freund and Immerwahr[12]). The mixture turned yellow at first, then brown in about ten minutes, and brilliant red in thirty minutes. The maximum color intensity seemed to have been reached in about two hours. The solution was refluxed for nine hours and was then filtered into an ether–solid carbon dioxide mixture.

From the ether fraction obtained after carbonation there was isolated a 12% yield of 1,4-diphenylbutadiene-1,3 (mixed melting point). In a check experiment the yield was 15%.

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(9) Bamberger and Lodter, *Ann.*, **288**, 75 (1895).

(10) Sand, *Ber.*, **36**, 3705 (1905).

(11) Baeyer, *Ann.*, **266**, 202 (1891).

(12) Freund and Immerwahr, *Ber.*, **23**, 2857 (1890); see also Straus, *Ann.*, **342**, 253 (1905).

The aqueous solution gave 0.30 g. or a 12% yield of acid melting at 219–220°. This acid was shown to be 1,4-diphenyl-2-butene-1,4-dicarboxylic acid.[13]

Summary

It has been shown that the more reactive organometallic compounds dehydrogenate some partially reduced nuclear and open-chained compounds smoothly and under very mild conditions. Illustrations are the conversion of 1,4-dihydronaphthalene to naphthalene, 1,4-diphenylbutene-2 to 1,4-diphenylbutadiene-1,3, and 1,4-dihydrodibenzofuran to dibenzofuran.

Intermediate compounds have been isolated and a mechanism considered.

AMES, IOWA RECEIVED JULY 14, 1938

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[13] Schlenk and Bergmann, *Ann.*, **463**, 100 (1928).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Relative Reactivities of Organometallic Compounds. XIX. Hydrogenolysis of RM Compounds

BY HENRY GILMAN, ARTHUR L. JACOBY AND HELEN LUDEMAN

Introduction

The smooth and ready dehydrogenation by organometallic compounds described in the preceding[1] paper suggested that the more reactive organometallic compounds might undergo easy hydrogenolysis. This has been found to be the case. Actually, some of the organoalkali compounds are cleaved by hydrogen under extremely mild conditions: room temperature, atmospheric pressure and in the absence of any catalyst. Apparently there is no report of any other class of organic compounds reacting with hydrogen under such mild conditions. Not only do some organometallic compounds undergo easier reduction than any other type of organic compound, but they also appear to be oxidized at least as readily as any other class.

Relative Rates of Hydrogenolysis of RM Compounds Having Different Metals.—The varying rates of hydrogenolysis of organoalkali and other reactive organometallic compounds suggested the possibility of a correlation with the relative reactivities of organometallic compounds established with other reactants. Earlier studies by others pointed to such a relationship. Ipatieff and Rasuwajeff[2a] showed that under elevated pressures (60 atmospheres), elevated temperatures (225 and 350°) and in the absence of catalysts, the rate of hydrogenolysis of the triphenyl derivatives of phosphorus, arsenic, antimony and bismuth increased in the order: P, As, Sb, Bi. Then Zartman and Adkins,[3] in an examination of the hydrogenation of some more reactive RM compounds, found that the order of increasing ease of hydrogenation of R_3Sb, R_4Pb, R_2Zn and R_2Mg compounds was: Sb, Pb, Zn, Mg. These authors used not only elevated temperatures and pressures but also a nickel catalyst. Two reactions were noted, depending on the kind of RM compound used

$$R_2M + H_2 \longrightarrow R{\cdot}R + M$$
$$R_2M + H_2 \longrightarrow 2RH + MH_2$$

For example, tetraphenyllead gave biphenyl and lead, both a catalyst and hydrogen being necessary, and diphenylmagnesium gave benzene and magnesium hydride. Ipatieff and co-workers[2b] observed the following reaction with tetraalkyl- and tetraaryllead compounds in the absence of a catalyst, but in a glass and not a copper reaction vessel.

$$R_4Pb + 2H_2 \longrightarrow 4RH + Pb$$

We have found that the order of increasing ease of hydrogenolysis of some very reactive organometallic compounds is: Ca, Li, Na, K, Rb, Cs. This order together with the orders established by Ipatieff and by Adkins follows almost exactly the order of increasing chemical reactivity of the organometallic compounds as established in other reactions. It is interesting to note that here, as in the recent study[4] on the relative reactivities of organoalkali compounds, there is only a small difference between the relative reactivities of organopotassium and organorubidium compounds.

The preponderant reaction which takes place with organoalkali compounds is

$$RM + H_2 \longrightarrow RH + MH$$

The rate of hydrogenolysis varies somewhat with the medium, as illustrated in Fig. 1. The

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[1] Gilman and Bradley, THIS JOURNAL, **60**, 2333 (1938).

[2] (a) Ipatieff and Razuwajeff, *Ber.*, **63**, 1110 (1930); (b) Ipatieff, Razuwajeff and Bogdanov, *ibid.*, **63**, 335 (1930).

[3] Zartman and Adkins, THIS JOURNAL, **54**, 3398 (1932).

[4] Gilman and Young, *J. Org. Chem.*, **1**, 315 (1936).

curves indicate that the rate-controlling factor in petroleum ether suspension may be the rate of diffusion of hydrogen through the petroleum ether; and with benzene, a first-order reaction in which the concentration of hydrogen is constant. Obviously, the high reactivity of organoalkali compounds made it desirable to work with suspensions in benzene and petroleum ether.

Relative Rates of Hydrogenolysis of RLi Compounds Having Different Radicals.—Under corresponding conditions, and in benzene, the times in hours required for the hydrogenolysis of some organolithium compounds were: phenyl (32.2 hours), methyl (38.5), α-naphthyl (40), n-butyl (61), n-heptyl (66), n-lauryl (91), p-tolyl (150). This order follows somewhat the tendency of corresponding organoalkali compounds to metalate systems like dibenzofuran and dibenzothiophene.[5]

Effect of Catalysts on Rates of Hydrogenolysis.—It seemed of interest to examine the effect of some catalysts on the rates of hydrogenolysis. For this purpose, platinum and palladium were selected because of their general accelerating effect on organic reductions. Neither catalyst appeared to have any significant effect on the rate of hydrogenolysis of phenyllithium and phenylsodium.

Experimental Part

The organoalkali compounds were prepared in accordance with general procedures, details of which have been given in earlier publications from this Laboratory. Phenylpotassium was prepared by stirring for forty-eight hours 75 cc. of dry benzene, 4.0 g. (0.10 g. atom) of cut potassium and 6.9 g. (0.22 mole) of di-n-butylmercury. The reaction started promptly with the appearance of a precipitate of phenylpotassium, but with very little noticeable warming. Related reactions were used for the syntheses of phenylrubidium and phenylcesium.

Depending upon the particular organometallic compound, comparative runs were made at atmospheric pressure; at pressures slightly above atmospheric pressure (about 785 mm.); and at 100 lb. (7 atm.) pressure in a shaking machine. The rate of hydrogenolysis was determined by disappearance of the color test,[6] or by noting the time for absorption of 90% of the hydrogen. The latter procedure was used rather than the time for complete absorption because the reaction was observed to be erratic toward the end and variations were then noted with individual experiments. Rates determined by disappearance of the color test were confirmed by carbonation; no acid was obtained in those cases where no color test was observed.

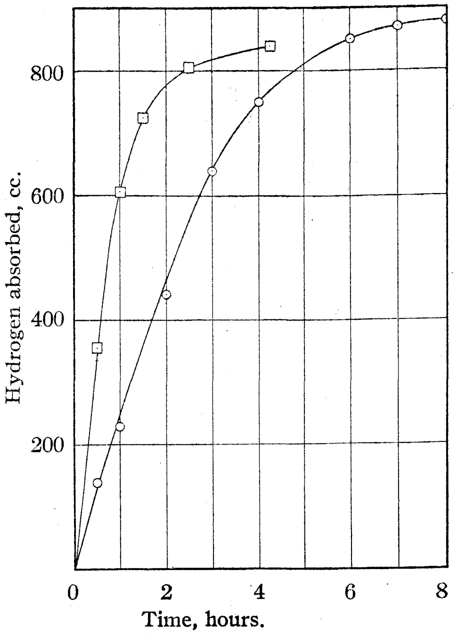

Fig. 1.—Rates of hydrogenolysis of phenylsodium: ⊡, benzene as medium; ⊙, petroleum ether (b. p. 115–130°).

In some experiments, the lithium hydride was analyzed by hydrolysis, the evolved hydrogen being measured, and the lithium hydroxide being titrated with standard acid. The results of two analytical experiments showed: 0.00072 mole of hydrogen and 0.00078 equivalent of lithium hydroxide; and, 0.00027 mole of hydrogen and 0.00024 equivalent of lithium hydroxide. The benzene formed by hydrogenolysis was isolated in yields upward of 60% and characterized as m-dinitrobenzene.

TABLE I

REDUCTION RATES IN BENZENE SUSPENSION

Organometallic compound	Av. time (hours) for complete redn. at 100 lb.	Av. time (hours) for 90% redn. at pres. sl. above atm.
C_6H_5CaI	Incomplete, 150	..
C_6H_5Li	32.2	..
C_6H_5Na	0.5	1.9
C_6H_5K	..	0.54
C_6H_5Rb	..	.42
C_6H_5Cs	..	.2

Typical of results obtained for 90% reduction at pressures a few millimeters above atmospheric pressure are phenylsodium, one and eight-tenths and two hours, respectively; and phenylpotassium, one-half and fifty-eight hundredth hours, respectively. Also, in the series of RLi compounds having different R groups, phenyllithium was reduced completely at 100 lb. (7 atm.) pressure in thirty-one hours, thirty-one and one-half hours and thirty-four hours, respectively.

Summary

The more reactive organoalkali compounds are

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(5) Gilman and Jacoby, *J. Org. Chem.*, **3**, in press (1938). Also, unpublished studies by R. L. Bebb.

(6) Gilman and Schulze, THIS JOURNAL, **47**, 2002 (1925).

reduced more easily than any reported type of organic compound. Reduction is effected at room temperature, atmospheric pressure and in the absence of any catalyst. The reaction is $RK + H_2 \longrightarrow RH + KH$.

The order of increasing ease of hydrogenolysis of the phenyl derivatives is: Ca, Li, Na, K, Rb, Cs. This series follows essentially the series of relative reactivities as established by other reactants.

The rates of hydrogenolysis appear to be unaffected by the presence of platinum and palladium.

The rates of hydrogenolysis have been established for a series of RLi compounds having different R groups.

AMES, IOWA RECEIVED JULY 14, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Urethans as Local Anesthetics. IV. Alkyl N-(*p*-Aminobenzyl)-carbamates

BY R. L. SHRINER AND JAMES M. CROSS

A study of the local anesthetic action of *p*-aminophenyl urethans (Formula I) showed that their anesthetic potency was high but that they were very irritating whether applied topically or intracutaneously.[1] It seemed possible that the irritation might be due to the *p*-phenylenediamine grouping present as a portion of the molecule since other derivatives of this compound have been found to cause irritation.[2]

In molecules of the type of alkyl N-(*p*-aminobenzyl)-carbamates (II) the urethan grouping is separated from the benzene ring by a methylene

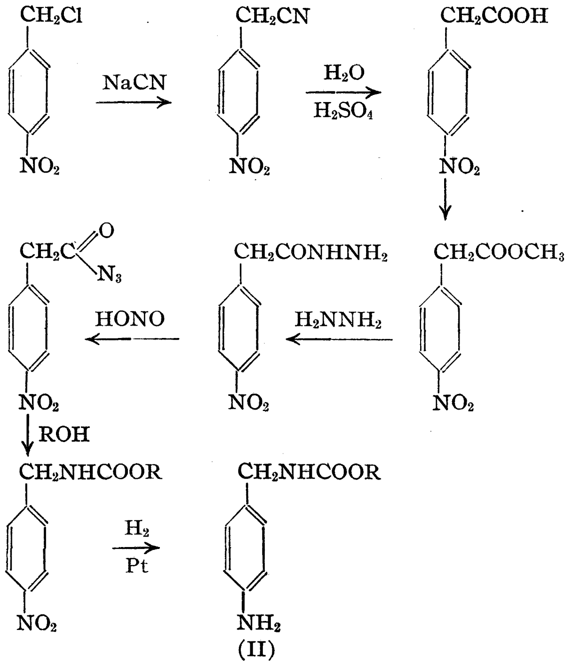
I $H_2NC_6H_4NHCOOR$
II $H_2NC_6H_4CH_2NHCOOR$
III $H_2NC_6H_4COO(CH_2)_xNR_2$

group and the *p*-phenylenediamine group is no longer present. The structure of urethans of type II is related to compounds of the novocaine type (III) in that each contains a *p*-aminophenyl radical attached to a carbon atom. Since the alkyl *p*-aminobenzoates are not especially irritating, it was considered of interest to synthesize the urethans of type II in order to determine whether this structure would be non-irritating to the tissues but still retain the superiority in topical and injection anesthetic potency of the urethans of type I over those of the *p*-aminobenzoates of type III.

The urethans were synthesized by means of the reactions summarized in Chart I.

Although the final compounds are new, each of the individual steps in the above synthesis represents well-known reactions which were adapted to the present compounds with slight modifications which are given in the experimental part.

CHART I



Through the courtesy of the Lilly Research Laboratories the pharmacological action of 1% aqueous solutions of the hydrochlorides of this series of urethans was determined. The data obtained are summarized in Table I.

The pharmacological data in Table I show that these urethans cause some local anesthesia when injected intracutaneously but that they are not especially active when applied topically. All of these urethans were irritating both to the skin and eyes and this fact probably accounts for the somewhat erratic results. These urethans are

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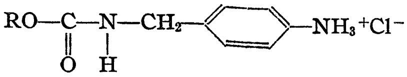
[1] Horne, Cox and Shriner, THIS JOURNAL, **55**, 3435 (1933).

[2] Hanzlik, *J. Ind. Hyg.*, **4**, 386, 448 (1923); Erdmann and Bakken, *Arch. Exptl. Path. Pharm.*, **53**, 402 (1905).

TABLE I

PHARMACOLOGICAL ACTION OF ALKYL N-(*p*-AMINOBENZYL)-CARBAMATE HYDROCHLORIDES



Alkyl group R—	Toxicity (mice) mg./kg.	Anesthesia Skin (min.)	Eyes (min.)
Normal			
CH_3—	1000	30	None
CH_3CH_2—	340	25	None
$CH_3CH_2CH_2$—	250	21	None
$CH_3CH_2CH_2CH_2$—	140	38	6
$CH_3(CH_2)_4$—	125	11(?)	10
$CH_3(CH_2)_5$—	60	40	46
$CH_3(CH_2)_6$—	30	None	None
$CH_3(CH_2)_7$—	50	36	None
Iso			
$(CH_3)_2CHCH_2$—	175	23	None
$(CH_3)_2CHCH_2CH_2$—	100	10	None
$CH_3CH_2(CH_3)CHCH_2$—	90	45	22
Secondary			
$(CH_3)_2CH$—	400	28	None
$CH_3CH_2(CH_3)CH$—	230	23	None
$CH_3CH_2CH_2(CH_3)CH$—	200	21	None
$CH_3(CH_2)_5(CH_3)CH$—	35	None	None
$(CH_3CH_2)_2CH$—	125	120	None

not as potent local anesthetics as the *p*-aminophenylurethans previously described.

Experimental

Methyl *p*-Nitrophenylacetate.—Forty grams of *p*-nitrophenylacetic acid, prepared by the hydrolysis of *p*-nitrophenylacetonitrile,[3] was dissolved in 120 g. of absolute methanol and dry hydrogen chloride passed into the solution for two hours. The solution was refluxed for two hours and the excess methanol removed by distillation. The residue was extracted with warm ligroin and the resulting solution cooled in an ice-bath. The ester separated in the form of colorless needles which melted at 54°. The yield was 83.5%. This procedure is a modification of the one used by Curtius,[4] who obtained a 42% yield.

***p*-Nitrophenylacethydrazide.**—A mixture of 34 g. of the ester with 50 g. of 42% hydrazine hydrate solution was heated on a steam-bath for thirty minutes. At first a red coloration developed which gradually disappeared and the mixture solidified to a hard yellow cake. The product was washed with water and recrystallized from absolute ethanol. Thirty-three grams (97%) of needles was obtained melting at 167° which agreed with the value given by Curtius.[4]

***p*-Nitrophenylacetazide.**—Twelve grams of the hydrazide was dissolved in two liters of warm water and 8 cc. of concentrated hydrochloric acid added. This solution was cooled to 20° and 5 g. of sodium nitrite sifted in with vigorous mechanical stirring. The insoluble azide floated on the surface and was separated by filtration. Nine preparations using the above quantities and conditions gave an average yield of 10.6 g. (83.5%). The azide melted at 45° with decomposition. The azide decomposes upon standing and hence always was used within a few hours after it was prepared.

Alkyl N-(*p*-Nitrobenzyl)-carbamates.—A solution of 10 g. of the azide in 400 cc. of each of the anhydrous alcohols was refluxed for three to four hours, at the end of which time the evolution of nitrogen had ceased. The excess alcohol was removed by distillation and the residue chilled. In most cases the urethan solidified and was recrystallized from ligroin. Four of the urethans were oils (see Table II) which could not be crystallized satisfactorily and which decomposed upon attempted distillation *in vacuo*. The oils were washed with water and dried. The analyses of the oils indicated that they were not quite pure but they were sufficiently so for the next step. The data on the alkyl

TABLE II

ALKYL N-(*p*-NITROBENZOYL)-CARBAMATES

Alkyl group	Yield, %	M.p., °C. (corr.)	Mol. formula	N Analyses, %	
				Calcd.	Found
Methyl	68	104–105	$C_9H_{10}O_4N_2$	13.33	13.53
Ethyl	63	115–116	$C_{10}H_{12}O_4N_2$	Ref. 4	
n-Propyl	97	89–90	$C_{11}H_{14}O_4N_2$	11.76	11.95
Isopropyl	76	107–108	$C_{11}H_{14}O_4N_2$	11.76	11.75
n-Butyl	66	62–63	$C_{12}H_{16}O_4N_2$	11.11	11.06
Isobutyl	70	59–60	$C_{12}H_{16}O_4N_2$	11.11	10.94
2-Butyl	61	62–63	$C_{12}H_{16}O_4N_2$	11.11	11.24
n-Amyl	52	49–50	$C_{13}H_{18}O_4N_2$	10.52	10.77
Isoamyl	70	Oil	$C_{13}H_{18}O_4N_2$	10.52	10.03
2-Pentyl	70	50–51	$C_{13}H_{18}O_4N_2$	10.52	10.49
3-Pentyl	55	50–51	$C_{13}H_{18}O_4N_2$	10.52	10.72
2-Methyl-1-butyl	70	Oil	$C_{13}H_{18}O_4N_2$	10.52	10.10
n-Hexyl	61	Oil	$C_{14}H_{20}O_4N_2$	10.00	10.92
n-Heptyl	63	Oil	$C_{15}H_{22}O_4N_2$	9.52	9.29
1-Octyl	63	48–50	$C_{16}H_{24}O_4N_2$	9.09	9.00
2-Octyl	56	64–65	$C_{16}H_{24}O_4N_2$	9.09	8.94

TABLE III

ALKYL N-(*p*-AMINOBENZYL)-CARBAMATE HYDROCHLORIDES

Alkyl group	Decomposition temp.,[a] °C.	Mol. formula	Cl Analyses, %	
			Calcd.	Found
Methyl	177–178	$C_9H_{13}O_2N_2Cl$	16.39	16.50
Ethyl	160–161	$C_{10}H_{15}O_2N_2Cl$	15.41	15.05
n-Propyl	153–155	$C_{11}H_{17}O_2N_2Cl$	14.51	14.90
Isopropyl	177–178	$C_{11}H_{17}O_2N_2Cl$	14.51	14.60
n-Butyl	156–158	$C_{12}H_{19}O_2N_2Cl$	13.84	13.84
Isobutyl	160–162	$C_{12}H_{19}O_2N_2Cl$	13.84	13.76
2-Butyl	153–154	$C_{12}H_{19}O_2N_2Cl$	13.84	14.05
n-Amyl	152–154	$C_{13}H_{21}O_2N_2Cl$	13.03	12.84
Isoamyl	157–159	$C_{13}H_{21}O_2N_2Cl$	13.03	13.20
2-Pentyl	140–146	$C_{13}H_{21}O_2N_2Cl$	13.03	13.70
3-Pentyl	149–150	$C_{13}H_{21}O_2N_2Cl$	13.03	13.15
2-Methyl-1-butyl	152–153	$C_{13}H_{21}O_2N_2Cl$	13.03	13.30
n-Hexyl	157–158	$C_{14}H_{23}O_2N_2Cl$	12.37	12.33
n-Heptyl	157–158	$C_{15}H_{25}O_2N_2Cl$	11.81	12.01
1-Octyl	159–161	$C_{16}H_{27}O_2N_2Cl$	11.29	11.39
2-Octyl	147–148	$C_{16}H_{27}O_2N_2Cl$	11.29	11.47

[a] In all cases these salts darkened 5 to 10° below the decomposition temperature.

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[3] Robertson, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1932, p. 398.

[4] Curtius, *J. prakt. Chem.*, **197**, 521 (1913).

N-(p-nitrobenzyl)-carbamates are summarized in Table II.

Alkyl N-(p-Aminobenzyl)-carbamates.—A solution of 5 g. of the alkyl N-(p-nitrobenzyl)-carbamate in 100 cc. of absolute ethanol was shaken with 0.2 g. of platinum oxide-platinum black and hydrogen at 3 atm. pressure. The reductions were complete in three to ten minutes. The platinum was removed by filtration and the filtrate saturated with dry hydrogen chloride. An equal volume of absolute ether was added to facilitate the separation of the hydrochloride. The hydrochloride salts were removed by filtration. The yields varied from 50 to 90%, most of the loss being due to the difficulties in causing complete separation of the hydrochlorides. Evaporation of the alcohol-ether mother liquor gave colored impure products which could not be obtained in a colorless condition by recrystallization. The data are summarized in Table III.

Summary

A series of alkyl N-(p-nitrobenzyl)-carbamates was prepared by the action of the alcohols from methyl to octyl on the azide of p-nitrophenylacetic acid. Catalytic reduction of these nitro compounds and subsequent treatment with hydrogen chloride produced the corresponding hydrochlorides of alkyl N-(p-aminobenzyl)-carbamates. Solutions of these hydrochlorides produced intracutaneous anesthesia but only a few caused surface anesthesia. All were quite irritating to the tissues.

URBANA, ILLINOIS RECEIVED JULY 15, 1938

[CONTRIBUTION OF THE G & A LABORATORIES, INC., SAVANNAH, GEORGIA]

Reactions Involved in the Sulfonation of Heat Treated Abietic Acid

BY TORSTEN HASSELSTROM AND JOHN D. MCPHERSON

Recent work of Fieser and Campbell[1] on dehydroabietic acid together with the investigations of Fleck and Palkin[2] and Littman[3] has produced evidence that α-pyroabietic acid heretofore regarded as an isomeric abietic acid is actually a mixture of dehydroabietic acid and hydrogenated abietic acids produced through the reactions of dehydrogenation and disproportionation of abietic acid.

In a previous communication[4] we reported that the sulfonation of heat treated abietic acid yields a crystalline sulfonic acid and as a by-product a lactone belonging to the tetrahydroabietic acid series of compounds. We have obtained evidence that the sulfonic acid[5] has the composition of $C_{20}H_{28}O_5S \cdot 3H_2O$ and hence may be established as a dehydroabietic acid sulfonate. This identity is established further by the preparation of the dimethyl ester, diethyl ester and diamide of this sulfonic acid. Since the lactone is saponified only with difficulty and easily regenerated,[4] it is apparently a γ-lactone formed from a $\Delta^{9,10}$-dihydroabietic acid as a result of hydration due to the sulfuric acid employed. Hence it is likely that the corresponding hydroxytetrahydroabietic acid has the hydroxyl in position 10. It is worthy of note that the addition of two atoms of hydrogen to abietic acid by catalytic means produces an easily lactonized dihydroabietic acid.[6] This lactone formation in the abietic acid series points to the fact that on saturation of one double bond of the original abietic acid, the remaining double bond moves to a position more favorable for hydration and lactonization.

The results obtained by us on the sulfonation of heat treated abietic acid do not agree with those previously recorded in the literature. On sulfonation of α-pyroabietic acid Fanica[7] obtained a crystalline monosulfonic acid for which the formula $C_{20}H_{30}O_5S$ was designated. He also reports as a residue a non-crystalline sulfur containing material.

Our findings that the sulfonation of heat treated rosin yields a dehydroabietic acid sulfonate and a lactone belonging to the tetrahydroabietic series of compounds are additional proof that the dehydrogenation and disproportionation of abietic acid occur on heat treatment.

Experimental

Dehydroabietic Acid Sulfonate.—The sulfonic acid was prepared from partially refined pseudopimaric acid according to Hasselstrom.[5a] It was recrystallized from water, glacial acetic acid and water; m. p. 223–224° (dec.). It was dried at 100° under vacuum.

Anal. Calcd. for $C_{20}H_{28}O_5S \cdot 3H_2O$: C, 55.29; H, 7.83;

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[1] Fieser and Campbell, THIS JOURNAL, **60**, 159 (1938).

[2] Fleck and Palkin, *ibid.*, **60**, 921 (1938).

[3] Littman, *ibid.*, **60**, 1419 (1938).

[4] Hasselstrom, Brennan and McPherson, *ibid.*, **60**, 67 (1938).

[5] (a) Hasselstrom, U. S. Patent 2,121,032 (1938); (b) Hasselstrom, U. S. Patent 2,121,033 (1938).

[6] (a) Ruzicka and Meyer, *Helv. Chim. Acta*, **5**, 333 (1922); (b) Ruzicka, Waldman, Meier and Hösli, *ibid.*, **16**, 139 (1933).

[7] (a) Fanica, *Bull. inst. pin.*, **44**, 151 (1933); (b) *ibid.*, **45**, 181 (1933); (c) Greth, *Z. angew. Chem.*, **47**, 927 (1934).

mol. wt., 434. Found: C, 55.33; H, 8.15;[8] mol. wt. (by titration for a dibasic acid), 433.

When dried at 150° for six hours, it lost 3 molecules H_2O. Calcd. for $C_{20}H_{28}O_5S$: mol. wt., 381. Found: mol. wt. (by titration for a dibasic acid), 381, 379.5.

Dimethyl Ester of Dehydroabietic Acid Sulfonate.—Five grams of dehydroabietic acid sulfonate was neutralized to phenolphthalein with a dilute aqueous solution of sodium hydroxide and the whole was evaporated to dryness. The pale yellowish powdered residue was dried for two hours at 125° and then boiled for ten minutes with 30 g. of dimethyl sulfate. After cooling, the clear dark solution was poured into ice water and then the mixture boiled for about one hour. The separated solid was removed, washed with a hot dilute sodium bicarbonate solution and then with water; yield, about 3 g. of crude dimethyl ester. It was recrystallized from acetone and methanol, the white silky needles melting at 176.7–177.7° (corr.).

Anal. Calcd. for $C_{22}H_{32}O_5S$: C, 64.69; H, 7.86. Found: C, 64.87; H, 8.04.

Diethyl Ester of Dehydroabietic Acid Sulfonate.—This was obtained in the same manner as the dimethyl ester, from 5 g. of dehydroabietic acid sulfonate and 30 g. of diethyl sulfate. It was recrystallized from acetone and methanol, the white silky needles melting at 150.4–151.4° (corr.).

Anal. Calcd. for $C_{24}H_{36}O_5S$: C, 66.00; H, 8.32. Found: C, 66.18; H, 8.35.

Diamide of Dehydroabietic Acid Sulfonate.—Five grams of dehydroabietic acid sulfonate was mixed with about 15 g. of phosphorus pentachloride and heated for about one hour on the water-bath under reflux. After cooling, the liquid was poured drop by drop into strong aqueous ammonia cooled with ice. The precipitated solid material was removed and extracted with boiling water until free from sulfonic acid. The diamide was then crystallized from ethanol, the transparent prismatic plates melting at 254–255.5° (corr.) (with slight dec.).

Anal. Calcd. for $C_{20}H_{30}O_3N_2S$: C, 63.43; H, 7.99. Found: C, 63.22; H, 8.09.

Summary

1. A dehydroabietic acid sulfonic acid is formed on sulfonation of heat treated abietic acid. This was confirmed further by the preparation of the dimethyl ester, diethyl ester and the diamide of the sulfonic acid.

2. The fact that a dehydroabietic acid sulfonate and a lactone belonging to the tetrahydroabietic acid series are formed on sulfonation of heat treated abietic acid are additional evidence that dehydrogenation and disproportionation of abietic acid occurs on heat treatment.

SAVANNAH, GA.

RECEIVED JULY 11, 1938

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[8] All analyses by Mr. S. Gottlieb, Columbia University.

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSICAL CHEMISTRY, HARVARD MEDICAL SCHOOL, AND THE BIOLOGICAL LABORATORIES, HARVARD UNIVERSITY]

Alicyclic Amino Acids

BY J. P. GREENSTEIN AND J. WYMAN, JR.

I

A great amount of data is now available on the dielectric constants of solutions of various amino acids, peptides, betaines and related molecules, which exist as dipolar ions. Although an exact theory of the relation of dielectric constant to molecular properties is still lacking in the case of polar liquids, the picture which emerges from such data is fairly simple and convincing.[1] There is no question that the large positive dielectric increments of all these compounds are due to their very large moments as dipolar ions. But beyond this a correlation of these increments with the properties of the molecules, as well as other empirical considerations, has led to the conclusion that in the case of polar liquids there is an approximately linear relation between dielectric constant and volume polarization, a conclusion which has been justified to some degree by recent theoretical investigations of Onsager[2] and of Van Vleck.[3] On this basis the dielectric increments of highly polar molecules like dipolar ions should be very nearly proportional to their molar polarizations, or, in view of that part of Debye's theory relating polarization to moment, to the square of their moments. This interpretation of the dielectric increments has made it possible to assign relative values to the moments of molecules, and, in connection with further inductions from data on pure liquids, even to estimate absolute values which are not far different from those estimated on an entirely different basis. Its application in detail to the large body of data on dipolar ions containing one positive and one negative charge separated by an aliphatic chain shows that in these molecules the mean square distance between the charges is proportional to the length of the intervening chain.

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[1] J. Wyman, *Chem. Rev.*, **19**, 213 (1936).

[2] Onsager, THIS JOURNAL, **58**, 1486 (1936).

[3] Van Vleck, *J. Chem. Phys.*, **5**, 556 (1937).

This agrees with what would be expected on the basis of free rotation in the chain according to statistical considerations of Eyring[4] and Werner Kuhn,[5] and the whole picture falls together in a very consistent way.

All the aliphatic dipolar ions so far studied have been straight chain compounds as regards the structure separating the charged groups, although in many cases the molecules contain cyclic radicals of one type or another, as for example histidine or phenylglycine. In the present study we have investigated the behavior of a series of compounds in which the charged amino and carboxyl groups are attached to a six-membered aliphatic ring, namely, the 2-, 3- and 4-aminocyclohexane-carboxylic acids. In these alicyclic amino acids the situation in regard to free rotation is quite different and offers a problem of some interest in itself as well as in relation to that of rotation in the straight chain compounds.

II

The cyclohexane amino acids may be prepared by two different procedures. The first is the method of Einhorn, which consists in boiling a solution of *o*-,[6] *m*-,[7] or *p*-[8] aminobenzoic acid with sodium in amyl alcohol. In the present study, only the 2-acid was so prepared. The second method is the catalytic hydrogenation of the aminobenzoic acids, using the Adams platinum oxide catalyst. In the present investigation the hydrogenation was carried out both in aqueous suspension and in hydrochloric acid solution. The meta and para homologs were reduced smoothly to the cyclohexane forms by the catalytic procedure; the ortho acid, on the other hand, in spite of repeated crystallizations, could not be hydrogenated completely.[9] In Table I are listed the melting points of the homologous aminocyclohexane acids prepared by these methods. Details of the procedure used in the preparations are given.

TABLE I

MELTING POINTS OF THE ACIDS ACCORDING TO THE METHODS OF PREPARATION

Carboxylic acids	Melting points, °C. Na in $C_5H_{11}OH$	Pt in HCl	Pt in H_2O
2-Aminocyclohexane	273[10]	. . .	. . .
3-Aminocyclohexane	268[10]	264[a]	278[a]
4-Aminocyclohexane	303[10]	285[a]	303[10] 260[a]

[a] Results by the present authors.

4-Aminocyclohexane-carboxylic Acid.—Fourteen grams of thrice-crystallized *p*-aminobenzoic acid was dissolved in 200 cc. of warm 1 *N* hydrochloric acid. The yellowish solution was filtered into the hydrogenation vessel and shaken in the presence of hydrogen with a suspension of 4.3 g. of the Adams platinum oxide catalyst. There was very little lag in forming the black, and within three and a half hours absorption ceased when about nine liters of hydrogen gas had been consumed. At 27° and 761 mm. pressure, the amount of acid used required about eight liters of hydrogen. The difference of one liter was due to the conversion of and adsorption by the catalyst. The latter coagulated toward the end of the reaction.

The filtered, water-white solution was made up to 500 cc. and an aliquot tested for the presence of ammonia with Nessler's reagent. It was found that 0.303 g. of ammonia was present in the entire solution, indicating that about 5 g. of the starting material had become deaminated. There was a strong odor of valerianic acid in the solution, and it is probable that some di-(cyclohexyl-4-carboxy)-amine may also have been formed. No attempt was made, however, to isolate these possible by-products.

The solution was treated with a slight excess of silver sulfate, filtered and gassed with hydrogen sulfide. The filtrate from the silver sulfide, freed by aeration from hydrogen sulfide, was treated with a considerable excess of baryta, filtered and condensed *in vacuo* to remove ammonia. The residual solution was then treated carefully with dilute sulfuric acid until barium was removed quantitatively. The filtrate was then evaporated *in vacuo* until crystals appeared, transferred to a flask and treated with a large amount of absolute ethanol and dry ether. A fine white precipitate appeared. It was filtered off and washed. After drying, it weighed 6.5 g. The substance, possessing no definite crystal form, was non-hygroscopic and was crystallized three times from acetone–water mixtures.

The molecule separates with 0.5 molecule of crystal water which is removed readily on drying at 100° *in vacuo*. It is extremely soluble in water; the solution is neutral to litmus.

Anal. Calcd. for $C_7H_{13}O_2N \cdot 0.5H_2O$ (152): N, 9.2. Found: N, 9.2.

The 4-acid was again prepared by suspending 8.1 g. of *p*-aminobenzoic acid in 100 cc. of water and shaking with about 3 g. of platinum oxide catalyst in the presence of hydrogen. The uptake of gas was quite rapid. The material went into complete solution within the first hour. After three hours the reaction was at an end. The filtered solution gave a strong test for ammonia. It was evapo-

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(4) Eyring, *Phys. Rev.*, [2] **39**, 746 (1932).

(5) Kuhn, *Z. physik. Chem.*, **175A**, 1 (1935).

(6) Einhorn and Meyenberg, *Ber.*, **27**, 2466 (1894).

(7) Bauer and Einhorn, *Ann.*, **319**, 329 (1901).

(8) Einhorn and Meyenberg, *Ber.*, **27**, 2829 (1894).

(9) Heckel and Adams, THIS JOURNAL, **47**, 1712 (1925), had reduced under pressure certain of the alkyl-substituted amino phenols. In view of our inability completely to hydrogenate anthranilic acid, it is interesting to note that Heckel and Adams found it impossible to hydrogenate *o*-aminophenol; with *o*-dialkyl aminophenol only a partial reduction could be achieved.

(10) Houben and Pfau, *Ber.*, **49**, 2294 (1916). These investigators used the Willstätter catalyst in a suspension of *p*-aminobenzoic acid in water. The rate of hydrogenation was extremely slow.

rated to crystals *in vacuo*, taken up with water and the material precipitated with acetone. The amino acid was then warmed twice with 85–90% alcohol to remove the ammonia and then crystallized twice out of water–acetone as long, feathery needles. The properties of the molecule were similar to those above; yield 3.2 g.

Anal. Calcd. for $C_7H_{13}O_2N \cdot 0.5H_2O$ (152): N, 9.2. Found: N, 9.1.

3-Aminocyclohexane-carboxylic Acid.—Fourteen grams of thrice-crystallized *m*-aminobenzoic acid was treated by the catalytic hydrogenation procedure in hydrochloric acid solution exactly as the case of the 4-compound. Complete reduction again was achieved in three and a half hours. However, ammonia determinations indicated the presence of only 150 mg. of ammonia in the solution, pointing to the deamination of about 2.5 g. of the original acid. The meta acid is, therefore, a good deal more stable toward the hydrogenation procedure than the para homolog.

The saturated 3-amino acid was isolated as in the case of the 4-acid. The yield of white, non-hygroscopic material was 8.3 g. This is extremely soluble in water and its solution is neutral to litmus. It separates with 0.5 molecule of crystal water which is removed readily on drying.

When the compound is crystallized out of concentrated aqueous solution by the addition of much acetone, it separates first as an oil. On cooling, beautiful long needles are formed, which, when dry, easily pick up a charge and are hard to handle, in this respect differing from the 1- and 4-compounds. After three such crystallizations, the substance melts at the constant value of 264°.

Anal. Calcd. for $C_7H_{13}O_2N \cdot 0.5H_2O$ (152): N, 9.2. Found: N, 9.2.

The 3-acid also was made by hydrogenating a suspension of 11.5 g. of *m*-aminobenzoic acid in water in the presence of 3 g. of platinum oxide. Solution was complete in less than an hour and the reaction was over in five hours. The saturated amino acid was recovered in the usual manner and boiled twice with 85–90% alcohol to remove ammonia. After several crystallizations from water–acetone the material was obtained as a mass of fine needles. The properties are like those of the compound prepared from hydrochloric acid solution.

Anal. Calcd. for $C_7H_{13}O_2N \cdot 0.5H_2O$ (152): N, 9.2. Found: N, 9.0.

2-Aminocyclohexanecarboxylic Acid.—Twenty grams of four-times crystallized anthranilic acid was dissolved in 250 cc. of 1 *N* hydrochloric acid and the hydrogenation carried out as in the previous cases. The uptake of gas began very slowly and ceased after about one-third of the theoretical amount of hydrogen had been absorbed. An ammonia determination on the solution revealed that practically all of the reduction achieved had been accompanied by deamination.

The substance, therefore, was prepared according to the method of Einhorn and Meyenberg[6] and possessed all the properties described by these authors; m. p. 273° with decomposition.

Anal. Calcd. for $C_7H_{13}O_2N$ (143): N, 9.8. Found: N, 9.6.

Throughout the remainder of the paper we designate the 3- and 4- acids with α or β according to whether they were hydrogenated in aqueous suspension or in solution in hydrochloric acid. The 2-acid, which was prepared in only one way, namely, by the amyl alcohol treatment, requires no special designation.

III

Measurements of dielectric constant were made by a resonance method previously described.[11] The results, expressed in terms of δ, the dielectric increment (the increase of dielectric constant per mole of solute per liter of solution at 25°), are given in Table II. The frequency varied between about 5.35×10^7 ($\lambda = 5.6$ m.) and 5.1×10^7 ($\lambda = 5.9$ m.). The sharpness of the settings and the accuracy of the results varied with the conductivity of the solutions as determined by very small traces of conducting impurities from which it is well-nigh impossible to free such soluble compounds by crystallization. In dealing with dilute solutions, as in the present case, errors in dielectric constant are much magnified in the values of the dielectric increments. The errors in the values of the increments given in Table II are estimated from the consistency of the dielectric constant measurements. In every case measurements were made at at least three different concentrations within the range indicated in the table. This table also contains values of the apparent molal volumes based on density measurements made with a pycnometer over a range of concentrations usually two or three times greater than that for the dielectric constant measurements. In addition to these, there are listed in the last two columns values of the two acidity constants (expressed as pK_1 and pK_2) calculated from titration data obtained on aqueous solutions with a hydrogen electrode.

Compound	δ	Concn. range, moles per liter	V	pK_1	pK_2
2	24.4 ± 0.6	0.04–0.10	108.3 ± 0.2	3.4	10.1
3α	59 ± 1	.05– .15	106.2 ± .1	4.2	10.5
3β	62 ± 4	.04– .11	103.9 ± .2	4.2	10.5
4α	62 ± 0.6	.04– .17	106.8 ± .3	4.3	10.5
4β	61 ± 2	.05– .13	103.6 ± .1	4.35	10.5

IV

It is generally accepted that cyclohexane exists in two different forms, commonly referred to as the chair and the boat, with each of which there is associated approximately the same energy, and which occur consequently with approximately the same frequency. When, as in the case of the cyclohexane amino acids, two different groups are substituted for two hydrogens attached to different carbon atoms of the ring, whether in the

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[11] Wyman, *Phys. Rev.*, **35**, 623 (1930).

1,2-, 1,3- or 1,4-positions, there are, geometrically, 24 possible ways in which the substitution can be made in the case of the chair form and 24 also in the case of the boat form, although, for reasons of symmetry, not all of these configurations are distinguishable. We will consider the latter form first. From a geometrical point of view, without regard to steric hindrance or the mutual energy of the substituted groups, this form is capable of free rotation whereby certain configurations can pass over into certain others without a deformation of valence angles. On this basis the 24 configurations fall into two classes of 12 members each, members of the same class being derivable from one another by free rotation. One class embraces what may be called the *cis* configurations, the other the *trans* configurations. For any *cis* configuration there exists a corresponding *trans* configuration obtainable from it by interchanging one and only one of the substituted groups with the hydrogen attached to the same carbon atom.

We will consider now the chair form. In this case the geometry is such that there is no possibility of free rotation. For each of the 24 possible configurations of this form there is a corresponding boat configuration, from which it arises when the ring passes through the state of strain required to convert it from the boat to the chair form. For this reason the chair configurations also fall into two classes, *cis* and *trans*, of twelve members each, members of the *cis* class having each a corresponding *cis* configuration, members of the *trans* class each a corresponding *trans* configuration, in the boat form. If, as the evidence of organic chemistry suggests, there is a constant transition back and forth between chair and boat forms then, owing to the free rotation in the boat form (neglecting steric hindrance and interaction of substituents), there also must be a constant transition between the various configurations of the chair form, and any such disubstituted cyclohexane as we are considering should exist either in a *cis* or a *trans* condition. The ring, despite its flexibility and all the free rotation associated with it, acts like a double bond to separate *cis* from *trans* configurations.

In the picture just presented no account is taken of steric hindrance, electrostatic effects, or van der Waals forces involving the substituents. Such factors certainly must influence the frequencies of occurrence of the various configurations, perhaps even so far as to rule out certain configurations entirely. Whenever energy differences between different configurations are of the order of kT (*i. e.*, 4×10^{-14} erg per molecule or 0.6 kcal. per mole at 25°), then we may expect free rotation to be greatly diminished or even completely suppressed and the molecule to be stabilized in the configuration of least energy. This seems to be the case with the 1,4-*trans*-dihalogenated cyclohexanes studied by Hassel[12,13] which have zero moments in benzene. In this case, where the moment is given by the vector sum of the two dipoles associated with the halogens, the electrostatic energy depends in a complicated way on the orientation of the dipoles with reference to the line joining them and on the cube of the distance separating them. In the case of dipolar ions like the cyclohexane amino acids, the electrostatic energy term is simply $e^2/\epsilon r$, in which e is the elementary charge, r the distance between the centers of charge of the positively and negatively ionized groups and ϵ the effective dielectric constant. For a given value of ϵ, the electrostatic energy of a dipolar ion is larger than that of a molecule containing two dipoles separated by the same distance except for very small values of r (*e. g.*, always less than 1 Å. when the moments of the dipoles do not exceed 3.3 D). However, in the case of solutions in water or other highly polar media, in which dipolar ions have been studied, the effective dielectric constant is probably very much greater than in the case of solutions in benzene. If we take ϵ as 80, the value for water, the electrostatic energy for $r = 3$ Å. is close to -8×10^{-14} erg, and is equal to $-KT$ at $r = 6.2$ Å. It increases with r and gives rise to an attraction between the charged groups, which tend to approach one another until the effect is overbalanced by repulsive forces due to the interference and the interaction of these groups, *e. g.*, the NH_3 and COO^- groups in the case of the alicyclic amino acids. It is impracticable to attempt to estimate quantitatively the magnitude of the potentials due to the various factors, at least for the amino acids, but it may be recalled that heats of combustion give a value of about 20×10^{-14} erg for the potential energy due to the repulsion of two methyl groups separated by 2.9 Å., in nonpolar molecules.[14] There is this difference between the amino acids and the dihalogenated

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(12) Hassel, *Z. Elektrochem.*, **37**, 540 (1931).

(13) Hassel, *Z. physik. Chem.*, **B15**, 472 (1932).

(14) H. A. Stuart, "Molekülstruktur," Verlag von Julius Springer, Berlin, 1934, p. 101.

TABLE II

		cis			*trans*	
Substance	d^2		Frequency	d^2		Frequency
1,2-Boat	10.45		8	18.47		4
	7.78		4	15.78		4
				10.45		4
	Av. 9.56			Av. 14.90		
Chair	10.45		12	18.47		6
				10.45		6
	Av. 10.45	Av. 10.01		Av. 14.46	Av. 14.68	
1,3-Boat	29.02		2	27.19		2
	27.23		2	26.19		2
	26.19		2	23.38		2
	15.15		2	23.17		2
	13.19		2	21.22		2
	6.70		2	23.17		2
	Av. 19.58			Av. 24.05		
Chair	29.02		6	23.38		6
	6.70		6	20.34		6
	Av. 17.86	Av. 18.72		Av. 21.86	Av. 22.96	
1,4-Boat	36.90		2	30.61		4
	36.25		4	27.57		4
	13.93		4	19.46		2
	2.34		2	14.45		2
	Av. 23.27			Av. 25.05		
Chair	25.34		6	38.97		6
	22.40		6	24.70		6
	Av. 23.87	Av. 23.57		Av. 31.84	Av. 28.44	

cyclohexanes, that in the latter the electrostatic forces between the dipoles lead to a repulsion whenever the halogens are close together.

In Table II are listed the different values of the square of the distance between the plus and minus charges which occur in the three cyclohexane amino acid dipolar ions. Certain distances occur in more than one configuration, and the number of configurations in which each distance occurs is given in the columns headed "frequency." These distances are calculated on a purely geometrical basis, without regard to interaction or interference of the NH_3^+ and COO^- groups, on the basis of the following assumptions: that all the valence angles of the carbon atoms of the ring are the same as the tetrahedral angle; that the distance between these atoms is 1.52 Å.; that the locus of positive charge of the NH_3^+ group is at the center of the nitrogen atom; that the distance between this nitrogen atom and the associated carbon atom of the ring is 1.40 Å.; that the locus of negative charge of the COO^- group is midway between the two oxygen atoms and on the line of the valence bond between the carbon atom and the associated carbon atom of the ring at a distance of 2.14 Å. from the center of the latter. It seems clear from a consideration of these figures that there is no stabilization of the dipolar ions in the configuration of least energy, as appears to be the case in the 1,4-*trans*-dihalogenated cyclohexanes. If this were so, the dielectric increment, which is a measure of the electric moment, should not be less for the 1,2-form than for the other two forms, as is actually the case, since the charged groups certainly can approach quite as close (geometrically, closer) in the case of the 1,3- and 1,4-forms as in the case of the 1,2-form, and the mutual energy of the groups must depend only on their distance.

Notwithstanding the arbitrariness and artificiality of the procedure of neglecting the interaction of the groups, it is of interest to consider the average values of the squares of the distances listed in Table II, which are also included in the table. These may be compared with mean square values for the distances between the charges in straight chain amino acids also calculated on a purely geometrical basis, making use of the same assumptions about valence angles and so on, without regard to interference, by integrating over all the possible configurations. Such values have been calculated for the α,[15] β, γ, and δ acids, and are, respectively: 8.53, 13.12, 17.71, 21.96. They increase very nearly linearly with the number of

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[15] In the case of an α acid, no averaging is required since the distance between the NH_3^+ and COO^- groups is fixed.

carbons between the amino and carboxyl groups, and the values 25.2 and 30.0 for the ϵ and ζ acids may be extrapolated with considerable assurance.[16] In Fig. 1 these values are plotted against the observed values of the dielectric increment. In the same figure are plotted the dielectric increments of the cyclohexane amino acids against the mean square distances (given in Table II) for both *cis* and *trans* forms. On the whole the two sets of data are consistent and suggest that free rotation occurs to the same degree in the cyclic compounds as in the straight chain forms. The identity of the increments of the 1,3- and 1,4-alicyclic acids suggests that the former occurs in what we have called the *trans*, the latter in what we have called the *cis*, form. It also appears that the 1,2-acid probably occurs in the *cis* form. The identity of the dielectric increments of the 1,3-α and -β preparations as well as of the 1,4-α and -β preparations suggests that these are not different. The differences of melting point between α and β preparations are probably not significant, and in any case represent a temperature range of decomposition rather than a true melting point, as in the case of amino acids generally.

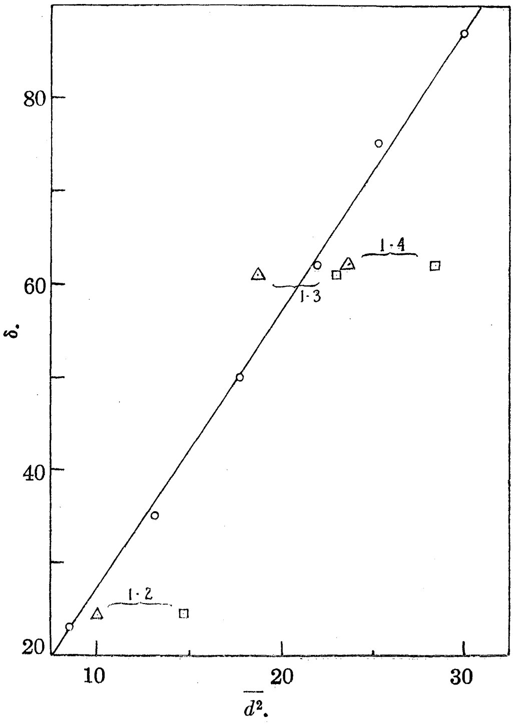

Fig. 1.—○, Aliphatic amino acids; △, *cis* alicyclic amino acids; ☐, *trans* alicyclic amino acids.

It should be emphasized that the procedure of correlating dielectric increments with the mean square distances calculated so arbitrarily on a geometrical basis was adopted solely as a basis for comparing the straight chain and alicyclic amino acids. The mean square values involved cannot be expected to be realized with any degree of exactness in either set of compounds. The smallest values of the distance between the NH_3^+ and COO^- groups involved in these averages are certainly too small to be physically possible, and the largest values are statistically improbable in view of the energy relations. Kuhn[5] by taking account of the coulomb forces in a statistical treatment of the case of straight chain amino acids has obtained much lower values for the mean square distances, *e. g.*, for an α-acid, 3.88; for a β-acid, 5.54; for a δ-acid 9.3; for a ζ-acid, 16.4. Nevertheless, we may expect that the effect of any interactions between the groups will be essentially the same and cause essentially the same deviations from the geometrically calculated mean square distances in both series of amino acids, and the argument for the same degree of free rotation in both types of amino acid is not seriously affected.

It is to be observed that the apparent specific volumes of the 1,3- and 1,4-acids, which have the same dielectric increments (moments) are equal and less than that of the 1,2-isomer, indicating a greater electrostriction associated with a greater moment. The relatively small differences of volume between the α- and β-preparations are probably not significant, and may well be due to slight differences of water content. It also is to be noted that the acidity constants (pK_1 and pK_2) are both very nearly the same and much like those of a δ-aliphatic amino acid ($pK_1 = 4.21$, $pK_2 = 10.69$), which has a dielectric increment of 63, about the same as that of the 1,3- and 1,4-alicyclic acids. The dissociation constants of the 1,2-acid are between those of α- and β-straight chain amino acids. This bears out the view that the effect of one charged substituent on another depends on the mean square distance between them.

Summary

A comparison of the dielectric increments of 1,2-, 1,3- and 1,4-aminocyclohexane-carboxylic acids with those of aliphatic amino acids in

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[16] An attempt to correlate the effect of one substituent on another in aliphatic acids from the values of the square of the distance between them, and based on a completely extended configuration, yielded an approximately linear relation—Greenstein, THIS JOURNAL, 58, 1314 (1936).

aqueous solution leads to the view that there is free rotation to much the same degree in both series of compounds. The correlation between dielectric increments, apparent molal volumes and acidity constants is pointed out for these alicyclic amino acids.

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Recombination of Hydrogen Atoms. III

BY I. AMDUR

It is generally conceded that the combination of hydrogen atoms to form molecules proceeds according to a trimolecular mechanism. The presence and extent of first or second order wall reactions, as well as the efficiencies of hydrogen atoms and hydrogen molecules as third bodies, have been the subject of much controversy and speculation. Agreement among various investigators is definitely lacking. Smallwood,[1] for example, contends that it is possible to eliminate any wall reaction and that the essential recombination mechanism involves only triple collisions of hydrogen atoms, whereas Steiner[2] finally concludes that there is a small first order wall reaction, but that hydrogen molecules are the most efficient third bodies. In contradiction to this, Amdur[3] found that the assumption of a homogeneous reaction involving only triple collisions of hydrogen atoms was adequate to account for the experimental data for the relative rate of recombination of atomic hydrogen and atomic deuterium over a narrow range of composition and pressure. And yet, some time previously, Smallwood[4] and Amdur and Robinson[5] had decided that for any extended range of variables it was necessary to include a wall reaction as well as both types of triple collisions. In all the cases cited the investigators used high concentrations of atomic hydrogen (95 to 10%) produced in a discharge tube at total pressures of the order of 1 mm. Other experimenters[6] working at total pressures of the order of 10 mm. with small concentrations of atomic hydrogen (less than 1%) produced by photosensitization of mercury saturated hydrogen, report results as varied as those noted above.

In the opinion of the author, there are several reasons for these discrepancies even after one has taken into account the widely different experimental methods and range of variables. One reason is a tendency, in the treatment of experimental data, to oversimplify the formal rate equation containing the desired velocity constants. To include the proper diffusion terms in the equation involved for the recombination of hydrogen atoms in a dynamic system, for example, involves much laborious calculation and necessitates data of considerable accuracy and consistency. However, the omission of these diffusion terms, whose magnitude is small, is capable of effecting tremendous variations in the rate constants or even of yielding negative values when the constants are simultaneously solved for. The same situation results from the use of values for the fraction or partial pressure of atomic hydrogen which are of low accuracy. Finally, if the range of data is not sufficiently wide, a mechanism may be sponsored which may be quite inadequate to account for experimental results over a larger range of variables. In this connection it should be noted that several mechanisms may fit the experimental data equally well. This point has been overlooked, in some cases, possibly, due to personal prejudice regarding the correct mechanism to be assumed for the reaction.

It is the purpose of this paper to avoid, as much as possible, any arbitrary decisions by treating objectively a very large number of experimental points covering the widest possible range of composition and pressure attainable with the present experimental method. This objective treatment consists, first, of least squaring all the data to fit a family of curves for the various pumping speeds and using least square methods to calculate rate constants taking all experimental points into account; second, of rigorously deriving the rate expressions, taking into account all factors involved

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(1) Smallwood, THIS JOURNAL, **56**, 1542 (1934).

(2) Steiner, *Trans. Faraday Soc.*, **31**, 623 (1935).

(3) Amdur, THIS JOURNAL, **57**, 856 (1935).

(4) Smallwood, *ibid.*, **51**, 1985 (1929).

(5) Amdur and Robinson, *ibid.*, **55**, 1395 (1933).

(6) (a) Senftleben and Riechemeier, *Ann. Physik*, **6**, 105 (1930); (b) Farkas and Sachsse, *Z. physik. Chem.*, **B27**, 111 (1934); (c) Senftleben and Hein, *Ann. Physik*, **22**, 1 (1935).

in a dynamic system as well as all possible mechanisms of recombination, and, finally, of using the calculated rate constants to obtain *calculated* values to compare with the *measured* fraction of atomic hydrogen. Any decision as to mechanism will be based on the agreement between these calculated and measured values.

Experimental

Apparatus.—The essential parts of the apparatus are shown in Fig. 1. Molecular hydrogen from an H-shaped electrolytic generator was expanded through the capillary A into the Wood discharge tube B where the atomic hydrogen was produced by a glow discharge. Mixtures of molecular and atomic hydrogen were pumped along the recombination tube C by means of two parallel four-jet mercury pumps backed by a Langmuir diffusion pump and a Hypervac oil pump. The fraction of atomic hydrogen at any point along the recombination tube was computed from the amount of energy liberated on a catalyst-calorimeter D by the recombination of the atoms. This calorimeter consisted of two concentric platinum tubes $1^3/_4''$ (4.44 cm.) long with diameters 0.312″ (7.92 mm.) and 0.219″ (5.56 mm.). A platinum ring was gold soldered in one end, producing a double-walled tube having an annular space of 0.046″ (1.17 mm.). A copper tube $1^1/_2''$ (3.81 cm.) long with diameter and wall thickness to permit a snug fit into the annulus between the platinum tubes was then wound with approximately 20 inches (50.8 cm.) of 0.002″ (0.05 mm.) pure platinum wire which served as a resistance thermometer and heater. Insulation was effected by cutting a double thread into the outside wall of the copper tube and baking a thin layer of enamel glaze into the threads, after which the resistance wire was wound in these grooves and made fast by a top coating of baked enamel. The unit was then inserted into the platinum sheath and the leads led out from the top through small platinum tubes. Lead glass was melted into the top opening of the annulus securing and insulating the platinum tubes. To render the calorimeter less liable to damage, the fine platinum leads were gold soldered to the platinum tubes encasing them, and all electrical connections were made to these tubes. In the recombination tube, the calorimeter was supported by a thin, flexible, four-wire rubber-covered cable connected to the windlass E which permitted movement of the calorimeter in vacuum. The drum of the windlass was calibrated to permit determination of the calorimeter position in the recombination tube by means of a dial attached to the ground joint of the windlass. That greater accuracy might be obtained in estimating the energy liberated on the calorimeter, the recombination tube was surrounded by an oil thermostat at 30.000 ± 0.005°. The McLeod gage arrangement shown in the diagram permitted a simultaneous reading of the pressure at four points along the recombination tube when a steady state had been reached with respect to the calorimeter.

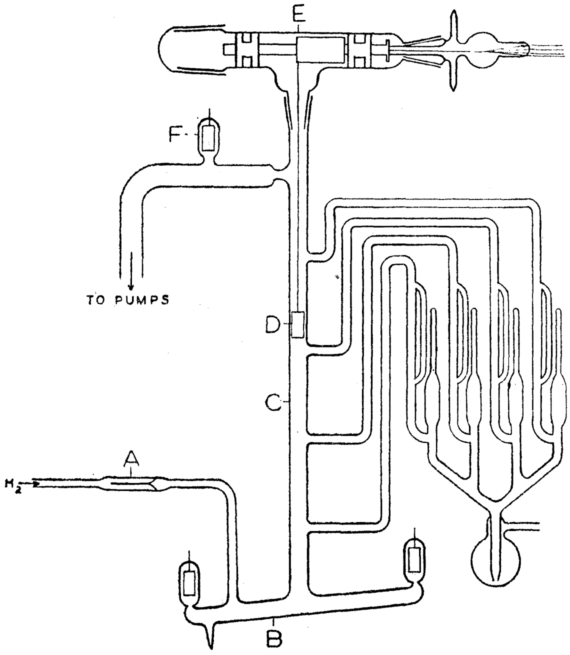

Fig. 1.

Procedure.—All glass parts of the apparatus through which atomic hydrogen flowed were cleaned carefully with cleaning solution and aqua regia, rinsed repeatedly with distilled water and pumped dry. The walls of the recombination and discharge tubes were then coated with sirupy phosphoric acid to minimize wall reaction and the system evacuated until the vapor pressure of water was less than 0.001 mm. The catalyst was then raised and hydrogen pumped through the system to permit a clean-up of the recombination tube by means of the third electrode F. After this treatment, the catalyst was lowered to the bottom of the recombination tube and the discharge turned on and maintained until the catalyst-calorimeter had reached a steady state temperature, as shown by the resistance of the internal platinum wire. The mercury in the McLeod gages was then permitted to rise from a position just below the shutoffs to the height necessary for reading the pressures. The discharge was then shut off, and the proper heating current passed through the catalyst-calorimeter to produce the same resistance change as that previously caused by the recombination of the atoms. From the known current and resistance at this second steady state the energy input to the catalyst-calorimeter was obtained, and since all conditions, with the exception of the presence of hydrogen atoms, were the same in the second part of the run as in the first, this energy input was equal to the energy per second previously produced by the recombination of the atoms. In view of the fact that the heat of dissociation of molecular hydrogen was known (102,800 calories per mole), it was merely necessary to know the number of moles of molecular hydrogen flowing through the apparatus per second in order to determine the fraction of atomic hydrogen. This was obtained directly from the electrolytic current required to produce hydrogen at the same rate at which it was being withdrawn by pumping as shown by equal heights of the electrolytic liquid (30% potassium hydroxide containing a small amount of barium hydroxide) in the limbs of the H-shaped generator. For a given position of the catalyst-calorimeter runs were made at seven different pumping speeds by using different combinations of diffusion pumps and by pumping with the Hypervac through 2-cm. tubing as well as through capillary by-passes. Runs were made in this manner for all pumping speeds at 10-cm. intervals along the recombination tube.

All electrical quantities were measured with a Type K potentiometer using precision standard resistances to determine currents. The McLeod gages were read with a cathetometer. It was possible to return the catalyst to a given position and check within 0.5% a previous determination made several weeks earlier under the same conditions of flow and pumping speed.

Preliminary Treatment of Data.—Since there were but four pressure taps along the recombination tube, there were a great many positions of the catalyst-calorimeter between any two of these taps for which the appropriate pressures were obtained by interpolation. To secure these interpolated values, for a given pumping speed, the drop in pressure, $\Delta P_{\text{a-b}}$, between taps a and b was determined for all runs in which the calorimeter was at tap b or above, and, similarly, the pressure drop, $\Delta P_{\text{b-c}}$, between taps b and c was obtained in all runs where the catalyst was at or above tap c. This was repeated for all pumping speeds. It was found that for all pump combinations, except the first two at low pressures, the pressure distribution along the recombination tube was a linear function of distance. Deviations from linearity were less than 0.5%, the approximate error in the measurement of pressures at the taps. In the case of pump combinations I and II, $\Delta P_{\text{c-c}}$ was greater than $\Delta P_{\text{a-b}}$ by 0.009 and 0.008 mm., respectively. For these combinations, it was assumed that $\Delta P_{\text{c-d}}$ exceeded $\Delta P_{\text{b-c}}$ by like amounts. Since the distance between taps was known, it was possible to obtain $\Delta P/\Delta x$ values for all pump combinations and, in the case of combinations I and II, for different positions along the recombination tube. Using these $\Delta P/\Delta x$ values the pressure existing at the calorimeter when it was *between* any two taps was found by interpolation. Examination of the pressure data showed that the pressure distribution below the calorimeter was independent of the position of the calorimeter in the recombination tube. For this reason it is felt that the accuracy of the interpolated pressures is not less than that of the pressures recorded at the four taps.

The values of the pressure, P, thus obtained were valid only for the particular rate of flow of molecular hydrogen (as recorded by the ammeter of the electrolytic circuit) existing during the particular run. In order to simplify treatment of the data, all pressures were corrected to a single average rate of flow. If I is the electrolytic current giving the number of moles of hydrogen flowing per second in a given run, and I', the corresponding current for the desired average rate of flow, $(I' - I)/I'$ is the fractional deviation of the actual rate of flow from the mean. The nature of the ΔP values showed that there was viscous or Poiseuille flow in the recombination tube. The end of the recombination tube near the pumps being at essentially zero pressure, the pressure in the section of the tube containing the pressure taps should vary as the square root of the number of moles of hydrogen flowing per second, or the fractional pressure change should be $^1/_2(I' - I)/I'$. In this manner all pressures were corrected to a single rate of flow. To obtain new α values consistent with the new P values, a curve of α against P for each pumping speed was drawn from the original data. Values of $\mathrm{d}\alpha/\mathrm{d}P$ were obtained graphically from these curves. The correction applied to α, therefore, was $\mathrm{d}\alpha/\mathrm{d}P\delta P$ where δP was the correction to the original pressure. On the average, δP was about 1% of the original pressure, and $\delta\alpha$, about 1% of the original α value.

As measurements of α were made at a single calorimeter position for all pumping combinations before proceeding to a new position, it was necessary to take into account possible changes in pumping speed with time. In some cases, for example, some α determinations with the same pump combination were made two months apart. Inasmuch as it had been ascertained that the ΔP values between taps for all the pump combinations did not vary with time, the correction of pressures to constant pumping speed for each pump combination was simply made by passing a curve with the proper slope through the P values (corrected to a single rate of flow) existing at the catalyst. In the case of pump combinations I and II this meant graphically fitting the P values (at the corresponding values of x) to a curve whose first and second derivatives were fixed. For all other combinations a single $\Delta P/\Delta x$ value for the entire length of the recombination tube was used, corresponding to a constant first derivative. After making the proper constant pumping speed corrections to the pressure, it was again necessary to calculate the corresponding corrections to α. These were determined as explained in connection

TABLE I

Internal diameter of recombination tube = 0.994 cm. Common rate of flow of H_2 = n_0 = 1.117 × 10^{-5} mole/sec.

	I		II		III		IV		V		VI		VII	
x	P	α	P	α	P	α	P	α	P	α	P	α	P	α
34.1	0.438	0.693	0.477	0.638	0.612	0.482	0.703	0.376	0.739	0.353	0.856	0.278	1.044	0.200
44.1	.425	.601	.465	.550	.602	.423	.694	.314	.731	.300	.849	.213	1.039	.142
54.1	.411	.609	.452	.522	.592	.335	.684	.241	.723	.222	.842	.172	1.035	.1132
64.1	.397	.566	.439	.478	.582	.280	.675	.202	.715	.178	.835	.139	1.030	.091
74.1	.381	.485	.424	.417	.572	.232	.666	.176	.707	.151	.828	.114	1.025	.0719
84.1	.364	.471	...	...	.562	.194	.657	.148	.699	.135	.821	.0948	1.020	.0617
94.1	.348	.461	.394	.389	.552	.196	.648	.146	.691	.128	.814	.0891	1.016	.0573
104.1	.332	.455	.379	.388	.542	.198	.639	.141	.683	.125	.807	.0858	1.011	.0529
114.1	.313	.442	.362	.360	.532	.170	.630	.121	.675	.110	.800	.0753	1.006	.0472
124.1	.295	.442	.345	.364	.522	.176	.620	.112	.667	.108	.793	.0736	1.002	.0456
134.1	.276	.454	.328	.368	.512	.162	.611	.112	.659	.104	.786	.0659	0.997	.0410

with the reduction to a single rate of flow. The constant pumping speed pressure corrections averaged slightly over 1% showing that the pumps retained their speed characteristics remarkably well. The corresponding average change in α was less than 1%.

The application of the above-mentioned corrections for each of the seven pump combinations yielded a set of α, x and P values applicable to a single rate of flow and constant pumping speed. It should be emphasized that the *average total correction to the original data was only about 2%* and in only three runs out of 83 did the total correction reach 5%. Since the individual corrections were known to at least 5%, the final values of α and P, in addition to being self-consistent, are as accurate as the original measured values.

Results

Analytical Representation of Data.—The experimental results, corrected to constant rate of flow and constant pumping speed, are given in Table I. The Roman numerals represent pump combinations; x, the distance in cm. from the bottom of the calorimeter to the discharge tube; P, the pressure in mm. existing at x, and α, the fraction of atomic hydrogen. All measurements were taken at 30.000 ± 0.005°.

In order to use all the experimental data in solving for reaction velocity constants it is necessary to have extremely self-consistent values for $d\alpha/dx$ as a function of x. To obtain these, the x, α values of Table I were fitted to an empirical family of seven curves by the method of least squares. An examination of the α values of Table I shows several slightly erratic variations. Since all values were reproducible, such variations were probably due to slight gradual changes in the catalytic activity of the recombination tube. The effect of fitting the data to a family of curves is to smooth out such fluctuations in the same manner for all pump combinations.

As a result of many attempts, the type equation best representing all x, α values was found to be

$$x = a(-\log_{10} \alpha) + b(-\log_{10}\alpha)^c \qquad (1)$$

Although much calculation is involved, it is possible to solve for a, b and c in equation (1) using the method of least squares. The process involves successive approximations and can be used to calculate a, b and c to any desired accuracy. Table II summarizes the results of Table I in terms of the values of a, b and c necessary to represent the α and x values for each pump combination. The percentage deviation column gives the magnitude of the average absolute percentage deviation of the α values as given by equation (1) from the experimental values of Table I. Since equation (1) is not explicit in α, calculated α-values were obtained from the curves which resulted from plotting x's calculated from given α's using equation (1). Figure 2 shows how the points of Table I scatter with respect to the smooth curves derived from the constants of Table II.

TABLE II

ANALYTICAL REPRESENTATION OF EXPERIMENTAL α,x VALUES

	a	b	c	Deviation, %
I	226.2851	78.6940 × 10^5	11.67250	3.0
II	175.1821	201.1848 × 10^2	7.40127	2.5
III	112.3282	434.3611	9.61006	3.9
IV	81.1155	69.4310	5.78891	3.1
V	79.3988	62.1211	8.73140	5.1
VI	63.1952	21.6183	6.28395	2.9
VII	49.3034	8.1251	6.46043	2.7

The variation of pressure with distance for each pump combination was also expressed in analytical form by quadratic equations for pump combinations I and II and by linear equations for all other pump combinations. The general equation in this case is

$$P = P_0 - Ax - Bx^2 \qquad (2)$$

where P_0 is the pressure at the discharge tube and where B is zero for all pump combinations except I and II. Table III summarizes the representation of pressure as a function of distance. The values of P_0, A and B are such as to give the pressure, P, in dynes/sq. cm.

TABLE III

ANALYTICAL REPRESENTATION OF EXPERIMENTAL P,x VALUES

	P_0	A	B
I	639.9	1.492	0.00802
II	688.0	1.396	.00702
III	860.6	1.332	.0
IV	977.8	1.221	.0
V	1020.7	1.066	.0
VI	1170.8	0.932	.0
VII	1412.1	.628	.0

The maximum deviation of P values calculated from equation (2) using the above constants, from the experimental values of Table I is less than 0.5%.

Derivation of Rate Expressions.—In order to derive rigorous rate expressions applicable to a dynamic system, it is necessary to take into account loss of atoms (a) by both heterogeneous and homogeneous recombination, (b) by the streaming of gas along the recombination tube and (c) by diffusion resulting from concentration gradients.

If it is assumed that recombination at the wall may result from collision of atoms in the gas phase with atoms adsorbed on the wall and also from the collision of two atoms from the gas phase at the wall, the rate of removal of atoms by recombination at a point x along the recombination tube is

$$-\left(\frac{\mathrm{d}\,[\mathrm{H}]}{\mathrm{d}t}\right)_{x(\mathrm{a})} = k_1[\mathrm{H}] + k_2[\mathrm{H}]^2 + k_3[\mathrm{H}]^2[\mathrm{H}_2] + k_4[\mathrm{H}]^3 \qquad (3)$$

where k_1 and k_2 are the wall reaction rate constants, k_3, the rate constant for the recombination of hydrogen atoms by triple collisions with molecules and k_4, the corresponding rate constant for the case of hydrogen atoms as third bodies. [H] and [H_2] are the concentrations of atoms and molecules in moles per cc.

The removal of atoms by the streaming of gas is given by the equation of continuity

$$-\left(\frac{\mathrm{d}[\mathrm{H}]}{\mathrm{d}t}\right)_{x(\mathrm{b})} = \frac{\mathrm{d}(V_x[\mathrm{H}])}{\mathrm{d}x} \qquad (4)$$

where V_x is the linear velocity of the gas stream in centimeters per second at x. For a rigorous derivation it is necessary to take account of the fact that V_x is affected by diffusion which, in addition to the pumps, causes a transport of mass along the recombination tube. The considerations are as follows.

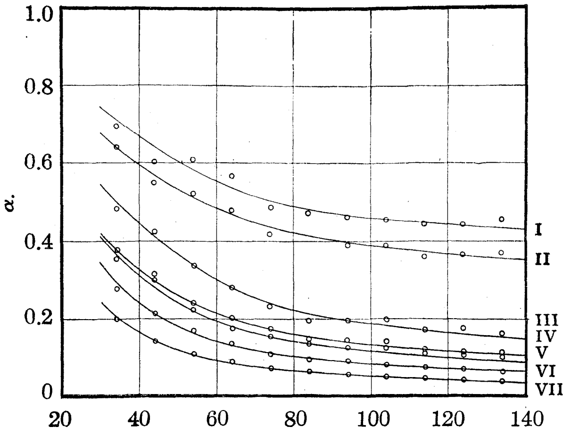

Fig. 2.

The mass of gas per cm.^{2} transferred per second by flow is

$$V_x\rho = V_x(M[\mathrm{H}] + 2M[\mathrm{H}_2]) \qquad (5)$$

where ρ is the density of the gas mixture and M the atomic weight of hydrogen. The mass of gas per cm.^{2} transferred per second by diffusion is

$$-D_{12}\frac{\mathrm{d}\rho}{\mathrm{d}x} = -D_{12}\left(M\frac{\mathrm{d}[\mathrm{H}]}{\mathrm{d}x} + 2M\frac{\mathrm{d}[\mathrm{H}_2]}{\mathrm{d}x}\right) \qquad (6)$$

where D_{12} is the diffusion coefficient for the mixture of atoms and molecules at the conditions existing at x. Since the mass of gas per cm.^{2} admitted per second to the apparatus is $2Mn_0/\pi r^2$

$$V_x(M[\mathrm{H}] + 2M[\mathrm{H}_2]) - D_{12}\left(M\frac{\mathrm{d}[\mathrm{H}]}{\mathrm{d}x} + 2M\frac{\mathrm{d}[\mathrm{H}_2]}{\mathrm{d}x}\right) = \frac{2Mn_0}{\pi r^2} \qquad (7)$$

so that

$$V_x = \frac{2n_0/\pi r^2 + D_{12}\left(\frac{\mathrm{d}[\mathrm{H}]}{\mathrm{d}x} + 2\frac{\mathrm{d}[\mathrm{H}_2]}{\mathrm{d}x}\right)}{([\mathrm{H}] + 2[\mathrm{H}_2])} \qquad (8)$$

Equation (4) thus becomes

$$-\left(\frac{\mathrm{d}[\mathrm{H}]}{\mathrm{d}t}\right)_{x(\mathrm{b})} = \frac{\mathrm{d}}{\mathrm{d}x}\left\{\frac{\frac{2n_0}{\pi r_2} + D_{12}\left(\frac{\mathrm{d}[\mathrm{H}]}{\mathrm{d}x} + 2\frac{\mathrm{d}[\mathrm{H}_2]}{\mathrm{d}x}\right)}{([\mathrm{H}] + 2[\mathrm{H}_2])}[\mathrm{H}]\right\} \qquad (9)$$

In addition to diffusion of atoms and molecules altering the linear velocity, atoms are removed from the point x by diffusion according to the equation

$$-\left(\frac{\mathrm{d}[\mathrm{H}]}{\mathrm{d}t}\right)_{x(\mathrm{c})} = -D_{12}\ \mathrm{div.\ grad.}\ [\mathrm{H}] \qquad (10)$$

Since the construction of the calorimeter was such as to give the average value of α across the cross section of the recombination tube at x, the concentration of atomic hydrogen at x in a plane perpendicular to the axis of the recombination tube may be considered constant. Equation (10), therefore, reduces to

$$-\left(\frac{\mathrm{d}[\mathrm{H}]}{\mathrm{d}t}\right)_{x(\mathrm{c})} = -D_{12}\frac{\mathrm{d}^2[\mathrm{H}]}{\mathrm{d}x^2} \qquad (11)$$

At the steady state

$$\left(\frac{\mathrm{d}[\mathrm{H}]}{\mathrm{d}t}\right)_{x(\mathrm{a})} + \left(\frac{\mathrm{d}[\mathrm{H}]}{\mathrm{d}t}\right)_{x(\mathrm{b})} + \left(\frac{\mathrm{d}[\mathrm{H}]}{\mathrm{d}t}\right)_{x(\mathrm{c})} = \left(\frac{\mathrm{d}[\mathrm{H}]}{\mathrm{d}t}\right)_{x} = 0$$

so that the rigorous general rate expression obtained by adding equations (3), (9) and (11) is

$$D_{12}\frac{\mathrm{d}^2[\mathrm{H}]}{\mathrm{d}x^2} - \frac{\mathrm{d}}{\mathrm{d}x}\left\{\frac{2n_0/\pi r^2 + D_{12}\left(\frac{\mathrm{d}[\mathrm{H}]}{\mathrm{d}x} + 2\frac{\mathrm{d}[\mathrm{H}_2]}{\mathrm{d}x}\right)}{([\mathrm{H}] + 2[\mathrm{H}_2])}[\mathrm{H}]\right\} - k_1[\mathrm{H}] - k_2[\mathrm{H}]^2 - k_3[\mathrm{H}]^2[\mathrm{H}_2] - k_4[\mathrm{H}]^3 = 0 \qquad (12)$$

There are numerous special cases which are of interest in connection with equation (12). For example, if the wall reaction is assumed to be second order $k_1 = 0$, while if it is assumed to be first order $k_2 = 0$. In the present case, all such mechanisms which include a third order rate constant (k_3, k_4) will be considered and appropriate rate constants calculated. Decisions regarding the suitability of any mechanism will depend upon how well such rate constants reproduce the α-values calculated with the constants of Table II.

Evaluation of Rate Constants.—Before solving for combinations of k_1, k_2, k_3 and k_4, it is necessary to express the various terms as functions of the measured variables α, x and P and the calculated derivatives $\mathrm{d}\alpha/\mathrm{d}x$, $\mathrm{d}^2\alpha/\mathrm{d}x^2$, $\mathrm{d}P/\mathrm{d}x$, $\mathrm{d}^2P/\mathrm{d}x^2$. From considerations involving viscosity data it was found[7] that the diffusion coefficient for mixtures of atomic and molecular hydrogen could be represented by the relation

$$D_{12} = \frac{374.9T^{3/2}(1.0364 - 0.0303\,\alpha)}{P(1 + 31.9/T)} \qquad (13)$$

Starting with

$$[\mathrm{H}] = \frac{P}{RT}\frac{2\alpha}{1 + \alpha} \qquad (14)$$

and considering both α and P functions of x, the first and second derivatives of [H] are found to be

$$\frac{\mathrm{d}[\mathrm{H}]}{\mathrm{d}x} = \frac{2}{RT}\frac{P}{(1 + \alpha)^2}\frac{\mathrm{d}\alpha}{\mathrm{d}x} + \frac{2}{RT}\frac{\alpha}{1 + \alpha}\frac{\mathrm{d}P}{\mathrm{d}x} \qquad (15)$$

and

$$\frac{\mathrm{d}^2[\mathrm{H}]}{\mathrm{d}x^2} = \frac{2}{RT(1 + \alpha)}\left[\frac{2}{(1 + \alpha)}\frac{\mathrm{d}\alpha}{\mathrm{d}x}\frac{\mathrm{d}P}{\mathrm{d}x} - \frac{2P}{(1 + \alpha)^2}\left(\frac{\mathrm{d}\alpha}{\mathrm{d}x}\right)^2 + \frac{P}{(1 + \alpha)}\frac{\mathrm{d}^2\alpha}{\mathrm{d}x^2} + \alpha\frac{\mathrm{d}^2P}{\mathrm{d}x^2}\right] \qquad (16)$$

Since

$$[\mathrm{H}_2] = \frac{P}{RT}\frac{1 - \alpha}{1 + \alpha} \qquad (17)$$

the total concentration of atoms and molecules is

$$[\mathrm{H}] + [\mathrm{H}_2] = P/RT \qquad (18)$$

from which it follows that

$$\frac{\mathrm{d}[\mathrm{H}_2]}{\mathrm{d}x} = \frac{1}{RT}\frac{\mathrm{d}P}{\mathrm{d}x} - \frac{\mathrm{d}[\mathrm{H}]}{\mathrm{d}x} \qquad (19)$$

By using the above relations the following identity is obtained

$$\frac{\mathrm{d}}{\mathrm{d}x}\left\{\frac{2n_0/\pi r^2 + D_{12}\left(\frac{\mathrm{d}[\mathrm{H}]}{\mathrm{d}x} + 2\frac{\mathrm{d}[\mathrm{H}_2]}{\mathrm{d}x}\right)}{([\mathrm{H}] + 2[\mathrm{H}_2])}[\mathrm{H}]\right\} = \frac{2n_0}{\pi r^2}\frac{\mathrm{d}\alpha}{\mathrm{d}x} + \frac{2}{RT(1 + \alpha)}\frac{374.9T^{3/2}(1.0364 - 0.0303\,\alpha)}{P(1 + 31.9/T)}\left[\frac{1}{1 + \alpha}\frac{\mathrm{d}\alpha}{\mathrm{d}x}\frac{\mathrm{d}P}{\mathrm{d}x} - \frac{(1 - \alpha)P}{(1 + \alpha)^2}\left(\frac{\mathrm{d}\alpha}{\mathrm{d}x}\right)^2 + \alpha\frac{\mathrm{d}^2P}{\mathrm{d}x^2} - \frac{\alpha}{P}\left(\frac{\mathrm{d}P}{\mathrm{d}x}\right)^2 - \frac{\alpha}{1 + \alpha}\frac{P\mathrm{d}^2\alpha}{\mathrm{d}x^2}\right] \qquad (20)$$

The remaining terms of the rate equations are obtained directly from equations (14) and (17).

The substitution of numerical values into the rate expressions was carried out in the following manner. At each pump combination a series of α-values at increments of 0.025 were taken, starting near the highest measured value and ending near the lowest measured value. The corresponding x's were then calculated from equation (1) using the appropriate constants from Table II, and the desired values of P computed from equation (2) using Table III. General expressions for $\mathrm{d}\alpha/\mathrm{d}x$ and $\mathrm{d}^2\alpha/\mathrm{d}x^2$ were obtained by direct differentiation of equation (1) resulting in

$$\frac{\mathrm{d}\alpha}{\mathrm{d}x} = {\frac{2.3026\,\alpha}{-a - bc\,(-\log_{10}\alpha)}}^{c-1} \qquad (21)$$

and

$$\frac{\mathrm{d}^2\alpha}{\mathrm{d}x^2} = \frac{1}{\alpha}\left(\frac{\mathrm{d}\alpha}{\mathrm{d}x}\right)^2\left[1 - \frac{1}{\alpha}\frac{bc\,(c - 1)(-\log_{10}\alpha)^{c-2}}{2.3026}\frac{\mathrm{d}\alpha}{\mathrm{d}x}\right] \qquad (22)$$

The required numerical values for these derivatives were obtained by using the constants of Table II. In like manner $\mathrm{d}P/\mathrm{d}x$ and $\mathrm{d}^2P/\mathrm{d}x^2$ values were obtained by differentiation of equation (2) and the use of Table III.

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(7) Amdur, *J. Chem. Phys.*, **4**, 339 (1936).

After substitution of numerical values it is possible to solve simultaneously for all the reaction velocity constants in any one rate equation.[8] In the present case, using the method of least squares, all experimental data (represented by 83 measured α-values) were used to solve for the reaction velocity constants in each rate equation. This corresponded to the use of 71 rounded α-values in solving for each set of constants. The results of these solutions are summarized in Table IV, where the rate constants are in the following units: k_1, sec.$^{-1}$; k_2, cc.^{1} mole^{-1} sec.$^{-1}$; k_3 and k_4, cc.^{2} mole^{-2} sec.$^{-1}$. The nature of the mechanism is deduced from the constants regarded as having zero value.

TABLE IV

REACTION VELOCITY CONSTANTS FOR POSTULATED MECHANISMS

Mechanism	k_1	$k_2 \times 10^{-8}$	$k_3 \times 10^{-16}$	$k_4 \times 10^{-16}$
A	0.69	2.33	1.00	1.70
B	0	3.234	1.004	1.419
C	1.956	0	1.038	2.578
D	0	0	1.212	3.063
E	0	6.028	0	0.745
F	0	5.810	0.925	0
G	4.231	0	0	2.770
H	8.425	0	1.233	0
I	0	0	0	4.160
J	0	0	3.634	0

The method of calculating α-values using the above constants can be illustrated by considering a specific mechanism, A. Using the numerical values of the constants for each of the 71 rounded experimental points (7 pump combinations) the quantities $k_1[\mathrm{H}]$, $k_2[\mathrm{H}]^2$, $k_3[\mathrm{H}]^2[\mathrm{H}_2]$ and $k_4[\mathrm{H}]^3$ are evaluated. From the sum of these terms the quantity $D_{12}\dfrac{\mathrm{d}^2[\mathrm{H}]}{\mathrm{d}x^2}$ is subtracted leaving a numerical quantity Z, where

$$Z = -\frac{2n_0}{\pi r^2}\frac{\mathrm{d}\alpha}{\mathrm{d}x} - \Phi$$

Φ is identified from equations (12) and (20) as

$$\frac{2}{RT(1+\alpha)}\,\frac{374.9T^{3/2}\,(1.0364 - 0.0303\,\alpha)}{(1 + 31.9/T)}\left[\frac{1}{1+\alpha}\frac{\mathrm{d}\alpha}{\mathrm{d}x}\frac{\mathrm{d}P}{\mathrm{d}x} - \frac{(1-\alpha)P}{(1+\alpha)^2}\left(\frac{\mathrm{d}\alpha}{\mathrm{d}x}\right)^2 + \alpha\frac{\mathrm{d}^2P}{\mathrm{d}x^2} - \frac{\alpha}{P}\left(\frac{\mathrm{d}P}{\mathrm{d}x}\right)^2 - \frac{\alpha}{1+\alpha}\frac{P\mathrm{d}^2\alpha}{\mathrm{d}x^2}\right]$$

If the appropriate Φ values are now added to each of the 71 Z values and the resulting sums $(Z + \Phi)$ multiplied by $-\pi r^2/2n_0$, the result is 71 calculated $\mathrm{d}\alpha/\mathrm{d}x$ points. A number of $\mathrm{d}\alpha/\mathrm{d}x$ points are derived from smoothed experimental points using equation (21) and plots made of $\alpha_{\text{exptl.}}$ *vs* $\mathrm{d}\alpha/\mathrm{d}x_{\text{exptl.}}$ for each pump combination. From these plots the 71 α's corresponding to the 71 calculated $\mathrm{d}\alpha/\mathrm{d}x$'s are read.

The results of the above procedure for the ten mechanisms of Table IV are summarized in Table V for all pump combinations. The numbers are the average absolute percentage deviations of the α's calculated from numerical rate constants from the corresponding smoothed experimental points. For all mechanisms, the individual deviations in each pump combination scattered well between positive and negative values.

TABLE V

PERCENTAGE DEVIATION OF α-VALUES

Mechanism	I	II	III	IV	V	VI	VII
A	3.2	3.4	6.2	3.2	5.9	4.0	5.6
B	3.2	3.4	6.2	3.2	5.9	4.0	5.6
C	3.2	3.4	7.1	3.6	6.7	5.2	7.2
D	3.6	2.6	8.6	3.6	7.2	4.6	5.6
E	10.3	9.6	6.8	4.4	8.9	8.0	12.0
F	3.2	4.6	5.5	5.2	6.3	4.6	8.0
G	9.8	9.4	8.0	5.2	8.9	9.2	13.6
H	7.3	9.4	13.2	13.2	12.2	15.4	21.6
I	8.2	8.0	12.9	9.6	11.8	15.4	24.8
J	16.4	17.6	21.5	10.8	8.4	21.4	46.3

Discussion

In interpreting Table V it should be noted that the average experimental value of α for pump combination VII is almost five times smaller than that for pump combination I, so that equal percentage deviations correspond to different actual deviations. This is apparent from the curves of Fig. 2. Thus a 1% average absolute deviation is equivalent to the following changes in the rounded α-values:

I	II	III	IV	V	VI	VII
0.0056	0.0050	0.0032	0.0025	0.0024	0.0018	0.0012

An inspection of Table V reveals that five of the mechanisms (E, G, H, I and J) fail to reproduce the experimental data over the entire range. Thus recombination does not take place homogeneously as the result of triple collisions involving only atoms (mechanism I) as suggested by Smallwood,[1] nor as the result of triple collisions involving only molecules as third bodies (mechanism J). The proposal of Steiner[2] that

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(8) In the case of equation (12) it was found that the smoothed experimental data and derivatives lacked the necessary self-consistency to permit simultaneous solution for k_1, k_2, k_3 and k_4. A change of but 0.05% in the constant terms of the final least square equations was sufficient to produce four positive constants instead of the usual three positive and one negative. The values given in Table IV for this particular mechanism, therefore, were obtained by trial and error substitution in the four final least square simultaneous equations and reproduce these equations to better than 0.2%.

recombination occurs as the result of a first order wall reaction and a homogeneous reaction involving only molecules as third bodies (mechanism H) is ruled out. Similarly, the assumption of a first order wall reaction with a three atom homogeneous reaction (mechanism G) or a second order wall reaction with a three atom homogeneous reaction (mechanism E) fails to provide the proper mechanism.

The other five mechanisms (A, B, C, D and F) show percentage deviations not much larger than those of the experimental and analytically smoothed α's (Table II), and are therefore all regarded as possible mechanisms. On the basis of the deviations in Table V, it is not possible to advocate one of these mechanisms in preference to the others. Thus the elimination of a first order wall reaction (mechanism B) produces α-values which are identical with those derived assuming both types of heterogeneous and homogeneous reaction (mechanism A). The elimination of a second order wall reaction (mechanism C) or the assumption of completely homogeneous reaction involving both types of third bodies (mechanism D) also reproduces the data almost as well as the other postulated mechanisms. Only one of the five mechanisms (mechanism F) does not require both atoms and molecules as third bodies. Although there is no reason to exclude the possibility of a mechanism involving a second order wall reaction and only molecules as third bodies, it should be pointed out that the difference in k_3 values for mechanisms D and F is but 31% so that the second order wall reaction of mechanism F is numerically equivalent, within a factor of 1.31, to the three atom homogeneous reaction of mechanism D.

A final decision as to which of the five mechanisms is correct can be made only when independent evidence eliminates four of the mechanisms as being incorrect. For example, if it could be shown experimentally that there is no wall reaction, mechanism D would be the correct solution; or if it could be shown that the wall reaction must be *only* first order, mechanism C would be correct. Independent accurate evaluations of k_4 might also be used as a means of choosing the one correct mechanism.

The author wishes to emphasize that the correct mechanism in all probability will not be some average mechanism derived from mechanisms A, B, C, D and F but a specific one of these five with the numerical rate constants as given in Table IV.

Objection has been raised to the present experimental method on the basis that the sudden recombination of atoms at the catalyst causes diffusion of atoms toward the catalyst and consequent high values of α. In order to determine the magnitude of this effect accurately, it is necessary to integrate equation (12). Since this cannot be done readily it is only possible to present evidence showing that the effect is negligible.

The diffusion produced by the catalyst is equivalent to increasing suddenly the linear velocity of the gas stream and thus shortening the time of recombination. This acceleration is greatest at the catalyst and dies off very rapidly for high linear velocities. The disturbance produced by the catalyst will be most marked when the catalyst is near the discharge for two reasons. First, the high concentration of atomic hydrogen will result in a greater diffusion when the concentration is suddenly reduced to zero at the catalyst. Second, the rate of recombination near the discharge tube is very rapid (as shown by the curves of Fig. 2) so that a given effective increase in velocity results in less recombination than that resulting from the same increase in velocity occurring far up in the recombination tube. Catalyst measurements such as those made in pump combinations IV, V, VI and VII at α-values from 0.125 to 0.05 should, therefore, be correct to a high degree of accuracy with respect to disturbance produced by the catalyst. If, now, the catalyst measurements at higher values of α produced high numerical results, rate constants calculated using all α-values should be smaller than those obtained from only low α-values. Consequently, rate constants which reproduced high values of α measured near the discharge tube should fail to reproduce low values of α measured far up in the recombination tube. That this is not the case is observed from the percentage deviation of the α-values in Table II for the possible mechanisms A, B, C, D and F. Pump combinations I, II and III contain many high values of α as compared with combinations IV, V, VI and VII where low α-values predominate. Actually, an examination of the individual percentage deviations from which the averages of Table V were computed shows that for very low values of α at high values of x, the α's computed from rate constants are slightly *higher* than the experimental values instead of lower. In fact, it is these wrong direction deviations which cause the average absolute percentage deviations of Table V for the five possible mechanisms to be slightly greater than the smoothing deviations of Table II.

Summary

Using a dynamic system, the fraction of atomic hydrogen has been measured as a function of distance along the recombination tube for seven pumping speeds at pressures ranging from 0.276 to 1.044 mm. The measured fraction of atomic hydrogen varied from 0.0410 to 0.693.

The experimental data have been fitted to a family of empirical curves by the method of least squares. The resulting smoothed variables as well as calculated derivatives have been used to solve for rate constants in rigorous equations applicable to a dynamic system.

Ten mechanisms involving recombination by triple collisions have been postulated and appropriate rate constants calculated using all the smoothed experimental data to obtain unique numerical values for the rate constants in each mechanism.

On the basis of the ability of the calculated rate constants to reproduce the smoothed experimental values for the fraction of atomic hydrogen, five of the postulated mechanisms have been eliminated.

It has been pointed out that, on the basis of reproducibility, it is not possible to advocate any specific one of the remaining five acceptable mechanisms but that future definite information regarding the presence and nature of a wall reaction could determine which one of the five possible sets of rate constants should be used to describe the recombination of hydrogen atoms.

CAMBRIDGE, MASS. RECEIVED MARCH 11, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FRESNO STATE COLLEGE]

Electrical Factors in the Adsorption of Polar Molecules at the Surface of Solutions

BY ROBERT DUBOIS AND ERIC E. TODD

In an earlier paper McBain and DuBois[1] reported extensive measurements of adsorption at the air–solution interface which were made as experimental tests of the Gibbs adsorption equation

$$\Gamma_{2(1)} = -\frac{d\sigma}{RT\, d\ln a_2} = -\frac{d\sigma}{RT\, d\ln c_2} \qquad (1)$$

where $\Gamma_{2(1)}$ is the absolute excess of solute (component 2) adsorbed in 1 sq. cm. of the surface of a binary solution, σ is the surface tension of the solution, and a_2, c_2 are, respectively, the activity and the molar concentration of the solute in the bulk solution. ($\Gamma_{2(1)}$ is defined in the Gibbs manner[2] so that $\Gamma_1 = 0$.) The adsorption of various solutes on the surfaces of moving bubbles was measured and found to be much larger than the values calculated by means of the above equation. These results confirmed the earlier measurements of McBain and Davies[3] made with similar apparatus and are in line with the excessive adsorption found by other workers using dynamic methods of measurement.

As a result of this apparent failure of the Gibbs equation to account for the experimental values, it has been suggested by several writers that an electrical term should be added to the equation to take account of the known electrification of the bubbles and drops upon which the adsorption takes place. The validity of such suggestions will be discussed later; their implication is that the excess of the observed adsorption over the calculated value is of electrical origin. As part of a general investigation of the factors responsible for the excessive adsorption on moving bubbles, the present authors have undertaken to test the electrical explanation by measuring the effect of enhanced electrification of the bubbles on the observed adsorption.

Meaning of the Term "Electrification."—The term "electrification of bubbles and drops" may refer to any of the following:

(1) *Electrokinetic double layer*, the electrical double layer which always exists at the surface of any bubble or drop in contact with water or an aqueous solution and whose parts may be tangentially displaced under the influence of an external electric field. The charge which is thus made evident by cataphoretic migration originates in the dissociation of a surface layer, either a part of the

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[1] McBain and DuBois, THIS JOURNAL, **51**, 3534 (1929).

[2] Gibbs, "Collected Works," Longmans, Green and Co., New York, N. Y., 1928, Vol. I, p. 234.

[3] McBain and Davies, THIS JOURNAL, **49**, 2230 (1927).

primitive particle (*e. g.*, oleic acid droplets in water) or adsorbed thereon (adsorption of sodium oleate on oil drops, fatty acids on air bubbles).

(2) *Oriented dipole layer*, composed of adsorbed polar molecules arranged with more or less complete vertical orientation in the surface. Changes in the number and orientation of these adsorbed molecules are evidenced by changes in surface tension and by variations in the interfacial potential first observed by Kenrick[4] and later more extensively studied by Frumkin,[5] and others. The distinction between the "electrokinetic" and the "oriented dipole" double layers has been discussed recently by Chalmers and Pasquill.[6] The elements of the latter kind of double layer are of course fixed in the molecules themselves and are not displaceable in an external electrical field.

(3) *Space charge in the interior of a gas bubble.* It has been known for many years that a gas may become electrically charged by having liquid sprayed into it or by bubbling it through a liquid. For example, Lord Kelvin[7] bubbled air, hydrogen, and other gases through water and aqueous solutions of various (organic and inorganic) substances and found that in all cases the gas became electrically charged. Similar observations were made by Coehn and Mozer[8] with solutions of organic compounds.

The first two of these electrical states cannot be altered by the experimenter except by changing the concentration of the solute or by the addition of other solutes whose adsorption would necessitate additional terms in the adsorption equation. Moreover, any electrical contribution to the surface energy which is due to adsorption of the solute and whose magnitude is determined by the bulk concentration of the solution, is implicitly included in the Gibbsian equations. This may be seen if we write equation (1) in the more general form

$$d\sigma = -\Gamma_1 d\mu_1 - \Gamma_2 d\mu_2 \quad (2)$$

or

$$\Gamma_{2(1)} = -d\sigma/d\mu_2 \quad (3)$$

and note that μ_2, the chemical potential of component 2 (the solute), is definable by the equation

$$\mu_2 = \left(\frac{\partial E}{\partial n_2}\right)_{S,V,n} \quad (4)$$

Here E, the total energy of the system, represents the sum of the energies of all portions thereof, including the surface layer, and includes every kind of energy possessed by any part of the system. (S, V, n represent constancy of the variables entropy, volume and number of moles of all components other than 2.)

The third electrical condition, space charge in the gas, can be varied without changing the composition of the solution, and we planned, therefore, to investigate the effect on the adsorption of organic molecules on the surface of moving bubbles which might be brought about by alterations in the electrification of the gas.

Experimental

The apparatus and method of measurement used in this work were practically identical with those employed by McBain and DuBois and have been described in detail in their paper.[1] The electrical bubble counter there mentioned was modified by replacing the vacuum tube circuits with a photoelectric cell and suitable relays actuated by the passage of the bubbles through a beam of light. All the experiments to be described were made with solutions of *p*-toluidine in boiled-out distilled water at a fixed concentration of 2.0 g. of *p*-toluidine per kg. of water. The toluidine was the best obtainable from Kahlbaum and was further purified by sublimation after mixing with solid potassium hydroxide. The "Gibbs value" for the adsorption of *p*-toluidine at the concentration given is 7.1×10^{-8} g./sq. cm. (ref. 1, page 3546). The experimental values obtained from measurements with moving bubbles are generally about twice this value.

Effect of Discharging Gas.—We were interested first in determining whether any charge could be detected in the gas escaping from the collapsed bubbles. For this purpose we interposed in the gas stream at the outlet of the adsorption tube a Kelvin electric filter.[9] This was made by packing clean brass filings in a 6-in. (15-cm.) length of 1/2-in. (1.27-cm.) tin pipe and supporting this pipe inside a metal shield tube by means of insulated glass tubes set in brass end caps. The filter was connected to the ungrounded side of a 1 mfd. condenser. While a stream of gas bubbles was passing through the apparatus, the condenser was allowed to accumulate charge for various periods of time (up to ten minutes) and was then shorted to ground through a sensitive galvanometer. Although no evidence of charge was observed with the ordinary rate of bubbling, unusually vigorous bubbling caused a small galvanometer deflection. Evidently a small charge must have been present in the ordinary gas stream. Now the nitrogen gas used to create bubbles in the adsorption tube passes first through two long saturators filled with the same solution and must already possess a charge when it reaches the adsorption tube. We decided, therefore, to discharge the gas just before entering the bubbling nozzle and observe the effect, if any, on the measured adsorption.

A three-way stopcock was placed in the gas line just before the adsorption tube so that the nitrogen could either

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[4] Kenrick, *Z. physik. Chem.*, **19**, 625 (1896).

[5] Frumkin, *ibid.*, **111**, 190 (1924).

[6] Chalmers and Pasquill, *Phil. Mag.*, [7] **23**, 88 (1937).

[7] Kelvin, Maclean and Galt, *Proc. Roy. Soc.* (London), **A67**, 335 (1895).

[8] Coehn and Mozer, *Ann. Physik*, [4] **43**, 1048 (1914).

[9] Kelvin, Maclean and Galt, *Proc. Roy. Soc.* (London), **A61**, 483 (1897); *Trans. Roy. Soc.* (London), **A191**, 187 (1898).

be passed through a grounded Kelvin filter interposed at this point or allowed to by-pass the filter and enter the tube directly. A number of adsorption measurements were made in succession, both with and without discharging the gas, and without any other change in the experimental conditions. No variation in the adsorption values could be observed other than those usually found in duplicate determinations.

In the face of the negative results on discharging the gas, we decided to enhance the electrical effect, if there was one, by forced charging of the gas stream before it entered the adsorption tube.

Spark Discharge.—We first tried the effect of a spark discharge between platinum wires sealed into the inlet to the adsorption tube. Several experiments were conducted in the usual manner until constant results were obtained. Connection was then made to an induction coil without disturbing the bubble rate or the overflow rate. A marked change immediately became apparent in the adsorption tube. The bubbles, which had previously maintained a steady stream, began to bunch and coalesce. As shown by the interferometer readings, the adsorption appeared to drop considerably, and with succeeding experiments even became negative. However, when the sparking was interrupted and additional adsorption measurements were made, the effect was found to persist, since the adsorption values rose only very slowly and the bubbles continued to bunch. Because of its persistence after sparking ceased we concluded that the effect observed was not electrical but was due to the chemical action of some product or products formed in the discharge.

Ionization by Alpha Particles.—In order to avoid the chemical effects caused by electrical discharge we produced ionization in the nitrogen gas by means of alpha particles. A few milligrams of ionium bromide was placed on the bottom of a small flask interposed in the gas line between the last saturator and the adsorption tube. Since about 0.4 cc. of nitrogen gas per second passed directly over several milligrams of ionium emitting 8×10^5 alpha particles per mg. per sec., each capable of producing 1.4×10^5 ions in a range of 2.85 cm., it is evident that an enormous number of ions would be present in the gas as it passed on to the bubbling nozzle. Preliminary tests with a Kelvin filter placed between the ionization chamber and the nozzle demonstrated that a charge did exist in the gas stream. No evidence of charge could be detected in the gas leaving the adsorption tube, indicating, as would be expected, that the initial charge had disappeared because of ion recombination and adsorption on the bubble surfaces during the twelve seconds required for the bubbles to pass along the 156 cm. tube.

In order to test the effect of the ionization of the gas on the adsorption of *p*-toluidine on the bubble surfaces, a number of adsorption measurements were first made in the usual way without charging the nitrogen (gas by-passed around the ionization chamber). Then, without any other alteration in the experimental conditions, the gas was diverted through the flask containing ionium salt before entering the bubbling nozzle and additional measurements of adsorption were made. Table I gives the results of two such experiments.

TABLE I

ADSORPTION EXPERIMENTS WITH RADIOACTIVE IONIZATION OF NITROGEN

	Experiment 1				Experiment 2			
Measurement	1a	1b	1c	1d	2a	2b	2c	2d
Ionization?	No	No	No	Yes	No	No	Yes	Yes
Duration, min.	11.4	17.2	13.7	9.0	18.3	16.7	17.9	14.0
Adsorption Γ (g./sq. cm. $\times 10^8$)	12.0	12.8	14.3	16.1	12.9	13.8	..	14.0

In the first experiment some difficulty was experienced in keeping bubble rate and flow of liquid properly adjusted to ensure passage of unbroken films up the short vertical drainage section of the adsorption tube. The variations in the adsorption values are therefore not more than we would expect from such a run and they do not in themselves give any indication of an effect of bubble charge on the adsorption. In experiment 2c the weight of collapsed film liquid was lost and Γ could not be calculated. The interferometer reading on this film liquid, however, indicates a value of Γ about the same as those obtained in the other experiments.

It is apparent that ionization of the nitrogen gas has had only a slight effect, if any, on the measured adsorption of *p*-toluidine. We are therefore led to the conclusion that the excessive adsorption of *p*-toluidine on moving bubbles is not due to any volume or surface electrification of the bubbles produced by their passage through the solution. This conclusion can probably be extended generally to other substances showing excessive adsorption (excessive as compared to the predicted "Gibbs" values).

Discussion

Calculation of the Effect of Surface Charge on Adsorption of Polar Molecules at the Surface of a Solution.—We shall now consider from a theoretical point of view what effect on the measured adsorption should be expected in experiments such as those described above. The ionization produced in the gas bubbles by collision of gas molecules with alpha particles consists of approximately equal numbers of positive and negative gaseous ions. Since the collisions of these ions with the bubble surface are proportional to their respective concentrations in the gas phase, approximately the same number of positive and negative ions will strike the surface in unit time. The life of any ion at the surface will depend on the nature of this surface.

In the case of *p*-toluidine solutions of the concentration used the values obtained for the adsorption of the solute (both observed values and those calculated from surface tension data) as well as the surface potential measurements of Frumkin[10] indicate that the surface being struck

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(10) Frumkin, Donde and Kulvarskaya, *Z. physik. Chem.*, **123**, 321 (1926).

consists of at least one complete layer of close-packed, vertically oriented *p*-toluidine molecules. The positive sign of the surface potential observed by Frumkin shows that the positive side of the dipole layer is directed toward the gas phase. This means that all ions striking the surface come under the influence of the local field of the positive ends of the adsorbed dipoles. The life of a negative ion in this surface is therefore probably much longer than that of a positive ion; in other words, adsorption of negative ions preponderates over that of positive ions, and the surface possesses a net negative charge. In this way a considerable electric field could be produced at the surface. In fact, if only one millionth of the surface were thus covered with adsorbed ions (10^9 ions/sq. cm.), the corresponding field strength, considered as a time average, would be

$$E = \frac{4\pi\sigma}{D} = \frac{4 \times 3.1 \times 10^9 \times 4.8 \times 10^{-10} \times 300}{80} = 22 \text{ volts/cm.} \qquad (5)$$

or somewhat more, if we use a smaller value for the dielectric constant of the surface layer. The maximum value of E, corresponding to a surface completely covered with ions of one sign, is about 22×10^6 volts/cm., or 73,000 e. s. u./cm.

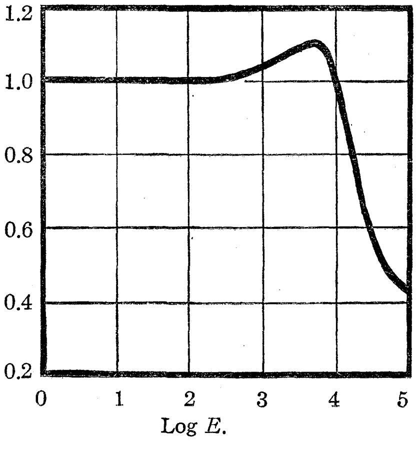

Fig. 1.—Effect of electric field on adsorption of *p*-toluidine.

The effect of an electric field on the adsorption of organic molecules has been discussed for the gas–solid interface,[11] the gas–solution interface,[12-14] and the mercury–solution interface.[15,16] None of these discussions is quite applicable to the present problem, and for our purpose we shall use a somewhat different procedure from any of these.

The potential energy of a solute molecule of dipole moment μ_s, oriented with its axis in the direction of an electric field of intensity E, is $-\mu_s E$. When one solute molecule is brought from the bulk solution into the surface layer, there are displaced v_s/v_w molecules of water (v_s and v_w represent the volumes occupied by individual molecules of solute and water). The water molecules (with dipole moment μ_w) originally in the surface layer were subject to the orienting influence of the external field, and their average moment in the direction of the field is given by

$$\bar{\mu}_w = \mu_w \times L(x) \qquad (6)$$

where $L(x)$ is the Langevin function cotgh $x - 1/x$ and $x = \mu_w E/kT$. Therefore the net work done against the external field E in bringing a solute molecule from the interior of the solution (where $E = 0$) to a vertically oriented position in the surface (where E ranges from 0 to 75,000 e. s. u./cm.) is

$$W = -\mu_s E + \frac{v_s}{v_w}\bar{\mu}_w E = -\mu_s E + \frac{v_s}{v_w}\mu_w E L(x) \qquad (7)$$

The Langevin function can be expanded in series

$$L(x) = \frac{x}{3} - \frac{x^3}{45} + \ldots$$

and all terms but the first can be neglected for small values of x. That is, for all values of x up to about 1.3, corresponding to a temperature of 27° and a surface 40% covered with ions of one sign ($E = 30{,}000$ e. s. u./cm.), the net work of adsorption of one solute molecule is

$$W = -\mu_s E + \frac{v_s}{v_w}\frac{(\mu_w E)^2}{3kT} \qquad (8)$$

At sufficiently large values of E it is necessary to take into account the induced moments $\alpha_s E$ and $\alpha_w E$ of both solute and solvent molecules in the surface layer and the corresponding contributions $-\alpha_s E^2$ and $-\alpha_w E^2$ to the energies of these molecules in the electric field (α_s and α_w represent the polarizabilities of the two kinds of molecules). We shall therefore add two more terms to equation 8 and obtain the more accurate expression for the electrical adsorption work

$$W = -\mu_s E + \frac{v_s}{v_w}\frac{(\mu_w E)^2}{3kT} - \alpha_s E^2 + \frac{v_s}{v_w}\alpha_w E^2 \qquad (9)$$

The polarizabilities can be calculated from the respective molar refractions by use of the relation

$$R = \frac{4\pi N\alpha}{3}$$

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(11) Blüh and Stark, *Z. Physik*, **43**, 575 (1927).

(12) Bradley, *Phil. Mag.*, [7] **7**, 142 (1929).

(13) Wagner, *Physik. Z.*, **25**, 474 (1924).

(14) Belton, *Trans. Faraday Soc.*, **33**, 653, 1449 (1937).

(15) Frumkin, *Z. Physik*, **35**, 792 (1926).

(16) Butler, *Proc. Roy. Soc.* (London), **A122**, 399 (1929).

If now we let Γ_0 denote the number of solute molecules adsorbed per sq. cm. in the absence of an external field, then Γ, the number of molecules adsorbed in the presence of the field, is obtained by the aid of the Boltzmann distribution law. That is

$$\Gamma = \Gamma_0 e^{-W/kT} \qquad (10)$$

where W is given by equation 9. The values of Γ/Γ_0 have been calculated for various field strengths by means of this equation; the results are given in Table II and in graphical form in Fig. 1. The following numerical values have been used for the constants of equation 9.

	p-Toluidine	Water
Dipole moment	1.65×10^{-18} e. s. u.[17]	1.85×10^{-18} e. s. u.[17]
Molar refraction	34 cc.[18]	3.6 cc.[19]
Polarizability	1.34×10^{-23} e. s. u.	1.42×10^{-24} e. s. u.
Molecular volume	192×10^{-24} cc.[20]	30×10^{-24} cc.[21]

TABLE II

EFFECT OF ELECTRIC FIELD ON THE ADSORPTION OF *p*-TOLUIDINE (TEMPERATURE 27°)

Field strength E e. s. u./cm.)	% Surface covered by adsorbed gaseous ions	Electrical adsorption work W (ergs/molecule)	Effect on adsorption Γ/Γ_0
1		-1.65×10^{-18}	1.000
10		-1.65×10^{-17}	1.000
100		-1.63×10^{-16}	1.004
755	1	-1.15×10^{-15}	1.025
1000		-1.47×10^{-15}	1.036
2000		-2.60×10^{-15}	1.065
4750	6	-3.90×10^{-15}	1.100
7550	10	-2.64×10^{-15}	1.066
10000		$+0.87 \times 10^{-15}$	0.980
75500	100	$+7.70 \times 10^{-14}$	.440[22]

Differentiation of equation 10 with respect to E shows that the function Γ/Γ_0 has a maximum at $E = 4750$ e. s. u./cm. and we see therefore that although the local electric field at the surface of the solution has a positive effect on the adsorption of *p*-toluidine (except at very large values of E), the increase is never more than 10%. While the above treatment of discrete charges of adsorbed gaseous ions as a continuous surface charge is admittedly somewhat simplified, the method gives an approximate average effect of such charges on the adsorption of a polar solute.

The experiments described above were completed in the chemical laboratories of Stanford University and the authors wish to thank Prof. J. W. McBain for much helpful advice. Acknowledgment is also made of the grant of a du Pont Fellowship to one of us (E. E. T.).

Summary

1. Attention is called to the fact that the adsorption of solutes at the air–solution interface, when measured by dynamic methods (moving bubbles, etc.), is generally found to be several times greater than the values calculated from surface tension data by means of the Gibbs adsorption equations.

2. In order to test the suggestion that the excessive observed adsorption is due to electrification of the moving surfaces, the authors have attempted to alter the adsorption of *p*-toluidine on moving bubbles by forced charging of the gas.

3. Marked decrease in the apparent adsorption was observed when the gas was subjected to spark discharge and to silent discharge before entering the adsorption apparatus. Because of its persistence after discharge ceased the effect was believed to be of chemical origin.

4. Ionization of the bubbling gas by exposure to ionium salt was found to have no effect on the measured adsorption.

5. The effect of a surface charge on the adsorption of polar molecules is discussed theoretically. Calculations show that the adsorption of *p*-toluidine on gas bubbles should be only slightly increased by electrification of the surface and at extreme charge densities should be somewhat decreased.

6. It is concluded that electrification of gas bubbles in contact with solutions of organic solutes is not responsible for the marked discrepancy between the observed adsorption and the calculated "Gibbs" adsorption.

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(17) C. P. Smyth, "Dielectric Constant and Molecular Structure," Chemical Catalog Co., New York, N. Y., 1931, pp. 67, 203.

(18) Obtained by adding the individual bond refractions[17] (p. 152).

(19) Fajans, *Naturwissenschaften*, **9**, 734 (1921).

(20) Obtained by multiplying an estimated length of 8 Å. by 24 Å.^{2}, the limiting area for condensed films of para-substituted benzene compounds found by Adam, *Proc. Roy. Soc.* (London), *A*103, 676 (1923).

(21) Obtained from the molar volume 18 cc., divided by 6×10^{23}.

(22) For E = 75,500 e. s. u./cm. we have included the first *two* terms in the expansion of the Langevin function (equation 7) used to calculate W.

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 655]

The Electron Diffraction Investigation of Sulfur Monochloride, Sulfur Dichloride, Sulfur Trioxide, Thionyl Chloride, Sulfuryl Chloride, Vanadium Oxytrichloride, and Chromyl Chloride

BY K. J. PALMER

Despite the rapid development of the electron diffraction method of studying the structure of molecules, comparatively few inorganic compounds have been investigated by this means. The stress which has been laid on organic molecules is due in part to the large number of organic compounds which have appreciable vapor pressures at, or near, room temperature, as compared with the number of inorganic compounds in this category, and in part to the fact that the organic chemist has in general been more interested in stereochemistry than the inorganic chemist, and has built up a large amount of purely chemical evidence supporting definite configurations.

From a purely structural point of view, inorganic molecules are nevertheless of great interest. Especially is it desirable to determine whether or not the empirical relations connecting bond distance with bond type, which have proved so useful in the discussion of interatomic distances in organic compounds, are applicable to inorganic molecules as well. The investigations reported in this paper were carried out with these considerations in mind.

Preparation of Materials

Sulfur Dichloride.—The sulfur dichloride used was prepared by passing dry chlorine into sulfur monochloride until the color of the liquid became deep red. This liquid was then distilled carefully in an all-glass apparatus, and only a small fraction boiling at 59° at atmospheric pressure was retained. This product was redistilled twice, the middle fraction only being retained. There was no evidence of decomposition during the distillation.

Sulfur Monochloride.—Sulfur monochloride was prepared by passing chlorine over hot sulfur. The product was purified by distillation over activated bone charcoal and sulfur. The final product was light yellow and boiled at 135–136°.

Thionyl Chloride.—Eastman thionyl chloride was purified by fractional distillation under reduced pressure.

Sulfur Trioxide.—Kahlbaum C. P. sulfur trioxide was used without further purification.

Sulfuryl Chloride.—Sulfuryl chloride was prepared by passing a mixture of sulfur dioxide and chlorine over camphor. The product was purified by distillation.

Chromyl Chloride.—Chromyl chloride was prepared by heating potassium dichromate, potassium chloride, and concentrated sulfuric acid. The blood-red liquid was purified by distillation.

Vanadium Oxytrichloride.—Vanadium oxytrichloride was prepared by passing hydrogen over heated V_2O_5 until it was completely reduced to V_2O_3. The water which was generated by the reaction was carefully driven off, and chlorine was then introduced. The generated vanadium oxytrichloride was condensed in a trap cooled by a mixture of ice and salt. This product was purified by repeated distillation.

Experimental Method

The method of obtaining and interpreting the photographs already has been described in the literature.[1] All radial distribution curves were calculated using C $(= s_0^2Ie^{-as_0^2})$ in place of I as recently suggested.[2] Because the vapor pressure of some of the compounds investigated is very low at room temperature it was necessary to use a high temperature nozzle.[3] This design of nozzle was found to be particularly advantageous in these cases because of the hygroscopic nature of the compounds.

Sulfur Dichloride.—The photographs show six well-defined rings. The second and fourth maxima appear to have shelves on the outer edge, the shelf on the fourth maximum being more pronounced than that on the second. The third and fifth minima (second and fourth on the reproduced curves) appear to be broad and less deep than the fourth.

Values of s_0 [= 4π sin /2/λ], I (the visually estimated intensities) and C $(=s_0^2Ie^{-as_0^2})$ are given in Table I. The radial distribution curve is reproduced as curve A in Fig. 1. The two well-defined peaks at 1.98 and 3.06 Å. correspond to the S–Cl and Cl–Cl distances, respectively. The Cl–S–Cl angle is 101°10′. Intensity curves calculated for S–Cl = 1.98 Å. and Cl–S–Cl angle equal to 101°10′, 109°28′, 125°, and 180° are reproduced as curves A, B, C, and D, respectively, in Fig. 2. Curve E is the intensity curve for chlorine, which has been included because of the

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[1] L. O. Brockway, *Rev. Modern Phys.*, **8**, 231 (1936).

[2] V. Schomaker and C. Degard, to be published in THIS JOURNAL.

[3] L. O. Brockway and K. J. Palmer, THIS JOURNAL, **59**, 2181 (1937).

possibility of the sulfur dichloride decomposing to give sulfur monochloride and chlorine. This curve can be eliminated because the photographs do not appear to have the regular structure required. Curve D is also in disagreement with the photographs, in that all of the peaks have shelves on the outer edge, and the fourth minimum is not deeper than the third and fifth as is required by the photographs. In curve C the intensity relations of the minima are again wrong, and in addition the third maximum appears to be broad and flat, whereas the photographs show it to be quite sharp. Curve B can be eliminated because the shelf on the fourth maximum is on the inner edge instead of the outer edge, as required by the photographs, and also the third, fourth, and fifth minima have the wrong intensity relationship.

TABLE I

SULFUR DICHLORIDE

Max.	Min.	I	C	s_0	s^a	s/s_0
1		10	3	4.545	4.15	(0.913)
	2			5.724	5.55	(.970)
2		8	5	6.910	6.92	1.001
	3			8.934	8.65	0.968
3		6	5	10.424	10.48	1.005
	4			11.790	11.87	1.007
4		3	2	13.178	13.24	1.005
	5			14.999	15.30	1.020
5		2	1	16.397	16.76	1.022
	6			17.851	18.12	1.015
6		1	1	19.227	19.52	1.015
					Average	1.006
					Average deviation	0.011

S–Cl = (1.98)(1.006) = 1.99 ± 0.03 Å.

Cl–Cl = (3.06)(1.006) = 3.08 ± 0.04 Å.

[a] Calculated for the model with S–Cl = 1.98 Å. and Cl–Cl = 3.06 Å.

On the other hand, curve A (101°10′ model) agrees very well with the photographs. The outside shelves on the second and fourth maxima are present, and the fourth minimum is deeper and narrower than either the third or fifth. Since this model agrees also with the results of the radial distribution curve, it is accepted as correct. The quantitative comparison given in the last column of Table I leads to an S–Cl distance

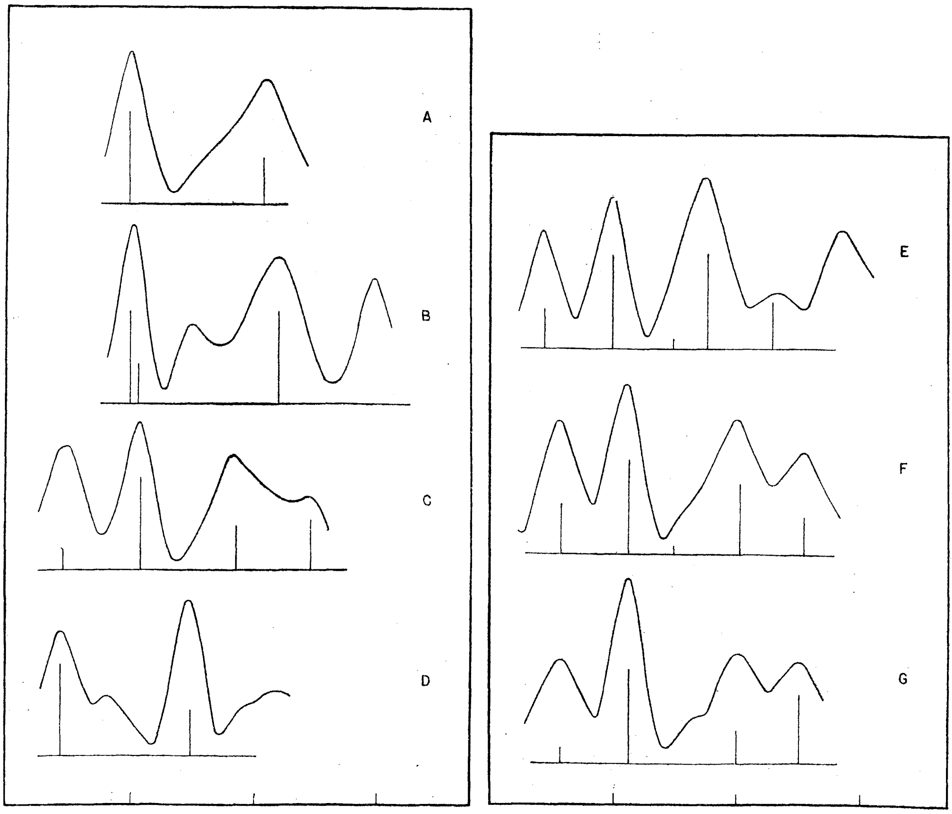

Fig. 1-A. Fig. 1-B.

Fig. 1.—Radial distribution curves for (A) sulfur dichloride, (B) sulfur monochloride, (C) thionyl chloride, (D) sulfur trioxide, (E) sulfuryl chloride, (F) chromyl chloride, and (G) vanadium oxytrichloride.

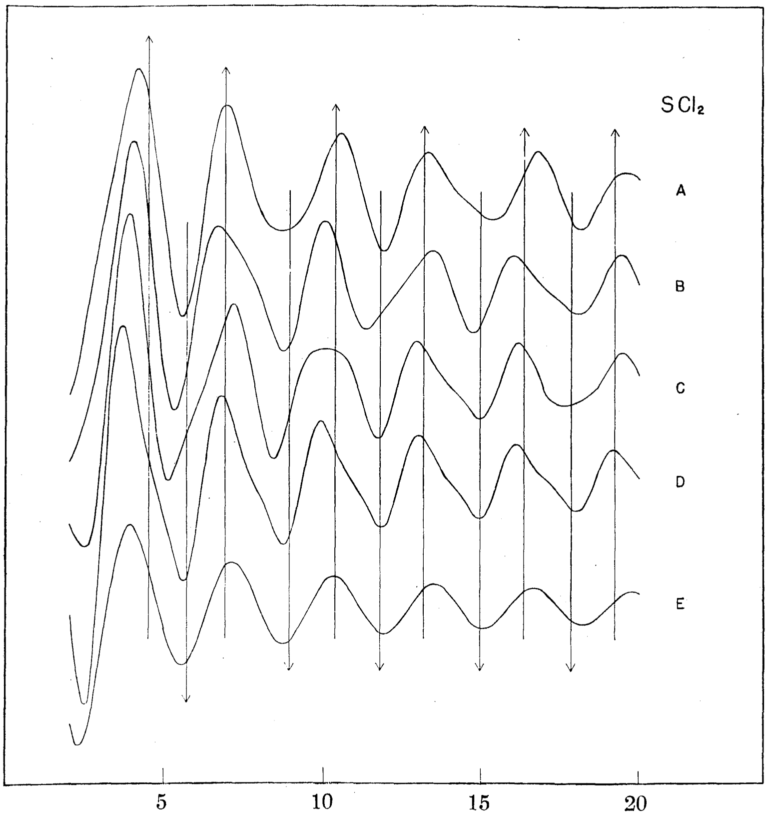

Fig. 2.—Theoretical intensity curves for sulfur dichloride.

of 1.995 Å. The final values are therefore taken as S–Cl = 1.99 ± 0.03 Å. and the angle Cl–S–Cl = 101 ± 4°.

Sulfur Monochloride.—The sample of sulfur monochloride was transferred to the high temperature nozzle inside a moisture-proof box. When the nozzle was opened after the exposures were made there was no trace of sulfur and the remaining sample was still light yellow in color.

The photographs of sulfur monochloride show eight maxima, seven of which were measured accurately. The first maximum appears to be symmetrical, the second has a very decided outer shelf which is called the third maximum in the tables, the fourth is symmetrical, the fifth very broad, the sixth sharp, and the seventh is not very prominent. The values of s_0, I, and C are given in Table II. The radial distribution curve, calculated using the values of C, is reproduced as curve B in Fig. 1. The peaks at 2.01, 3.18, and 3.96 Å. are interpreted as the sum of the S–Cl and S–S, the long S–Cl, and the Cl–Cl distances, respectively. The small peak at 2.47 Å. is not given any significance.

The radial distribution curve immediately excludes the structure in which there are two chlorine atoms attached to one sulfur atom, because under these circumstances the radial distribution curve would exhibit only two peaks of about equal height (the outer peak being due to the long S–Cl and Cl–Cl distances), or perhaps three peaks, the outer two lying very close together.[4] Of these two outer peaks that representing the long S–Cl distance should be approximately twice as intense as that representing the Cl–Cl distance. Both the heights and the positions of the peaks are, however, compatible with the model in which one chlorine atom is attached to each sulfur atom. For this reason intensity curves were calculated only for models compatible with this latter configuration.

Assuming the value 1.99 Å. for the S–Cl distance (this value being found in both SCl_2 and SO_2Cl_2), and considering the peak at 2.01 Å. to be the weighted mean of the two S–Cl and the one S–S distance, it is then possible to calculate an

TABLE II

SULFUR MONOCHLORIDE

Max.	Min.	I	C	s_0	s^a	s/s_0
1		10	3	4.632	4.00	(0.864)
	2			5.603	5.48	(.978)
2		8	4	6.548	6.72	1.026
	3			....	...	...
3		3	2	8.239	8.10	0.983
	4			9.162	9.00	.982
4		7	6	10.216	10.18	.996
	5			11.456	11.52	1.005
5		5	5	13.237	13.10	0.990
	6			15.069	15.20	1.009
6		5	4	16.201	16.32	1.007
	7			....	...	...
7		3	2	19.383	19.70	1.016
					Average	1.002
					Average deviation	0.012

Final values: S–Cl = 1.99 ± 0.03 Å.
S–S = 2.05 ± 0.03 Å.
Cl–S–S∠ = 103 ± 2°

[a] Calculated for the model with S–S = 2.05 Å., S–Cl = 1.99 Å. and Cl–Cl = 3.95 Å.

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(4) Refer to curve C, Fig. 1, for thionyl chloride.

S–S distance. The value found is 2.05 Å.[5] Using the values 1.99 Å. for the S–Cl distance, 2.05 Å. for S–S, 3.18 Å. for the long S–Cl and assuming the value 3.96 Å. for the Cl–Cl distance, the S–S–Cl angle is calculated to be 103°35′ and the angle between the Cl_1–S–S and Cl_2–S–S planes 97°7′.

In calculating intensity curves the S–Cl and S–S distances and the Cl–S–S angle were given the values 1.99 Å., 2.05 Å., and 103°35′, respectively. This is justifiable because the well resolved inner peaks on the radial distribution curve are probably reliable to within 1%. Curves A, B, and C for Fig. 3 were calculated for models in which the angle between the two Cl–S–S planes is 97°7′, 180° (*trans*), and 0° (*cis*), respectively. Model C can be eliminated because there is no shelf on the outside of the second maximum, this shelf being a very distinctive feature of the photographs. Curves A and B agree qualitatively with the photographs. The similarity of these two intensity curves, both as regards intensity and position of the maxima and minima, makes the reliability of the radial distribution peak at 3.96 Å. very doubtful, since the distribution curve is calculated with the aid of just the s_0 values and the visually estimated intensities.

No intensity curves were calculated for models in which there was either free or restricted rotation for the reason that there is no feature of the curve which appears to be sensitive to the Cl–Cl separation, and it is consequently impossible at the present time to determine accurately the nature or height of the potential hump restricting free rotation.

The static *trans* model can be eliminated, however, from other considerations. Five Raman frequencies have been reported,[6] whereas only three frequencies of the *trans* model are Raman active. It is evident therefore that the molecule can have only one static configuration, namely, the so-called "right angled" structure, or the chlorine atoms can be oscillating or rotating with respect to one another. It is unfortunate that more reliability cannot be placed upon the radial distribution peak at 3.96 Å. because its position and sharpness would then immediately eliminate all but the static "right angled" structure. The quantitative comparison of s to s_0 for curve A is given in Table II.

Y. Morino and S. Mizushima[6] recently have measured the dipole moment of sulfur monochloride, reporting the value of 1 Debye unit. They have also measured the Raman spectrum in dilute hexane solution and have concluded from their results that the "right angled" static structure is the correct one. It can be said in support of this view that the electron diffraction results are compatible with this configuration.

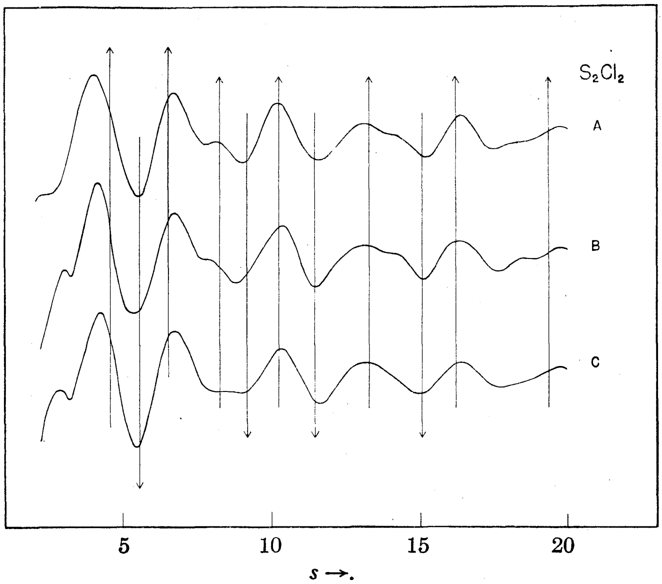

Fig. 3.—Theoretical intensity curves for sulfur monochloride.

Ackermann and Mayer[7] have investigated the molecular structure of sulfur monochloride by the diffraction of comparatively slow (about 6 kv.) electrons. They concluded that there is one chlorine atom attached to each sulfur atom and claimed to obtain best agreement when they assumed S–Cl = 1.98 Å., S–S = 2.04 Å., and Cl–S–S angle = 105°. They also state that the intensity curve calculated for free rotation gave best agreement with their photographs. An intensity curve calculated assuming free rotation is almost identical with curve A, Fig. 3, and consequently their results are in good agreement with those obtained in this investigation.

Thionyl Chloride.—The photographs of thionyl chloride show seven measurable rings, having the visually estimated intensities shown under I, Table III. The third minimum (second on curves) appears to be very deep, the fourth com-

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[5] This value is in good agreement with that found in H_2S_2 by Beach and Stevenson (private communication).

[6] Y. Morino and S. Mizushima, *Sci. Papers I. P. C. R.*, **32**, 220 (1937).

[7] Ackermann and Mayer, *J. Chem. Phys.*, **4**, 377 (1936).

TABLE III

THIONYL CHLORIDE

Max.	Min.	I	C	s_0	s^a	s/s_0	s^b	s/s_0
1		10	4	4.78	3.98	(0.833)	4.08	(0.854)
	2			5.79	5.18	(.894)	5.29	(.914)
2		8	6	6.91	7.05	1.020	6.80	.984
	3			8.30	8.32	1.002	8.38	1.010
3		9	11	9.78	9.79	1.001	9.69	0.991
	4			11.67	11.60	0.994	...	...
4		4	6	13.07	13.12	1.004	13.32	1.019
	5			14.69	14.46	0.984	14.58	0.993
5		2	3	16.07	16.08	1.001	15.75	.980
	6			17.43	17.33	0.994	17.38	.997
6		3	4	18.66	18.58	.996	18.77	1.006
	7			...	...	...	...	...
7		1	1	22.10	22.17	1.003	22.45	1.016
					Average	0.999		1.000
					Average deviation	0.007		0.012

Final values: S–O = 1.45 ± 0.02 Å. O–S–Cl ∠ = 106 ± 1°
S–Cl = 2.07 ± 0.03 Å. Cl–S–Cl ∠ = 114 ± 2°
Cl–O = 2.84 ± 0.03 Å.
Cl–Cl = 3.47 ± 0.03 Å.

[a] Calculated for the model with S–O = 1.44 Å., S–Cl = 2.07 Å., Cl–O = 2.84 Å., and Cl–Cl = 3.50 Å. [b] Calculated for the model with S–O = 1.44 Å., S–Cl = 2.07 Å., Cl–O = 2.84 Å., and Cl–Cl = 3.40 Å.

paratively shallow and broad, the fifth fairly sharp but of even less depth than the fourth, the sixth deep and well defined, and the seventh broad and not as deep as the sixth. The fifth maximum appears to be less intense than either the fourth or sixth. The values of s_0, I, and C are given in Table III. The radial distribution curve calculated from these values is shown as curve C in Fig. 1. The peaks at 1.46, 2.07, 2.84, and 3.42 Å. are interpreted as the S–O, S–Cl, Cl–O, and Cl–Cl distances, respectively. The value 2.07 Å. for the S–Cl distance seemed to be a little large, and to make sure that an impurity was not the cause of the apparent anomaly, electron diffraction photographs were taken of a new sample of thionyl chloride. When these were measured, it was found that the s_0 values from the two sets of photographs were in very good agreement, indicating that the large S–Cl distance is probably real.

Intensity curves were calculated for the following models: planar, with S–O = 1.44 Å., S–Cl = 2.07 Å., and a Cl–S–Cl angle of 110, 113, 116, and 120°; pyramidal, with S–O = 1.44 Å., S–Cl = 2.07 Å., Cl–O = 2.84 Å. and Cl–S–Cl angle equal to 106, 110, 115, and 120°. These last four curves are shown as curves A, B, C, and D, respectively, in Fig. 4. None of the intensity curves for planar models has been reproduced because they are all in very definite disagreement with the photographs. Curve D can be eliminated because the intensity relationship between the first three maxima is wrong; also, the intensity of the fifth maximum should be less than that of either the fourth or sixth. Curve C is in good qualitative agreement with the appearance of the photographs. Curve B is also in good agreement except for the appearance of the shelf on the inside of the fourth maximum, and the equality in depth of the fifth and sixth minima. The model finally selected is a weighted average of these two. Curve A is less satisfactory than B because the shelf on the fourth maximum has become too prominent and the intensity relationships of the fourth, fifth, and sixth maxima, which are about right in curves B and C, are unsatisfactory.

The quantitative comparison for models B and C is given in the last column of Table III. The final values selected, taking into account both the results of the radial distribution curve and the quantitative comparisons, are S–O = 1.45 ± 0.02 Å., S–Cl = 2.07 ± 0.03 Å., Cl–O = 2.84 ± 0.03 Å., and Cl–S–Cl angle = 114 ± 2°. This leads to an O–S–Cl angle of 106°17′. The same value for the O–S–Cl angle has been observed in sulfuryl chloride.

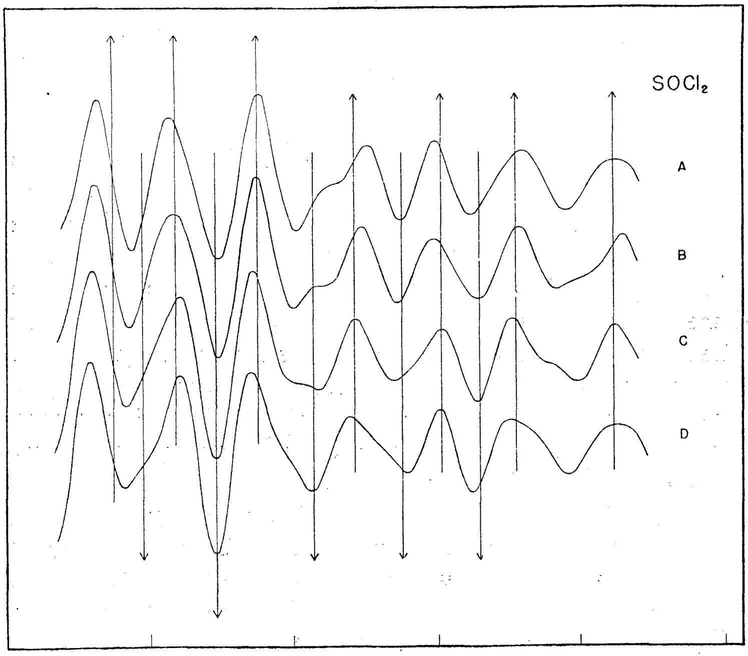

Fig. 4.—Theoretical intensity curves for thionyl chloride.

Sulfur Trioxide.—The sample of sulfur trioxide was distilled under vacuum into the sample holder, phosphorus pentoxide being used as the lubricant on the stopcock. The best photographs showed six rings, the second of which appears to be quite broad, the intensity falling off gradually on the inside and somewhat more abruptly on the outside. The third ring has a distinct outer shelf, the other rings being more or less regular in appearance. The average values of the visual measurements of the maxima and minima, as well as the estimated intensities I and the values of C are given in Table IV.

The radial distribution curve is reproduced in Fig. 1, curve D. The two well-defined peaks at 1.43 and 2.45 Å. are interpreted as the S–O and O–O distances, respectively. These values lead to an O–S–O angle of 117°50′. Theoretical intensity curves calculated for models having an S–O distance equal to 1.43 Å. and an O–S–O angle of 120°, 117°50′, 116°, and 110° are shown as curves A, B, C, and D, respectively, in Fig. 5. Curve D is not acceptable because the shelf on the second maximum is on the outside, rather than the inside, and also because the third maximum does not possess a distinct enough outer shelf.

The rather flat top of the second peak with the subsequent steep slope on the inside exhibited by curve C, and the inner shelf on the fifth maximum are also in disagreement with the photographs. Curves A and B are very similar, except for the slight change in the nature of the inside shelf of the second maximum, and are both in good qualitative agreement with the photographs. The intensity of this peak reaches its maximum value at about the same point in both curves A and B, but falls off on the inside at approximately a constant rate in A, while for B the rate is at first less than for A and then becomes greater. This change in the rate of falling off of the intensity in curve B would, if exhibited by the photographs, probably give the impression of a definite edge to the shelf, whereas no such edge would be expected if the intensity followed curve A. As no edge can be discerned on the photographs, model A is to be favored over model B.

The ratios s/s_0 for curves A and B are given in Table IV. The final values selected for the parameters are S–O = 1.43 ± 0.02 Å. and O–S–O angle 120 ⩽ 2°. This leads to an O–O distance of 2.48 ± 0.03 Å.

The dielectric constant of sulfur trioxide vapor recently has been measured[8] over a considerable temperature range, and it was shown that the plot of the polarization against the reciprocal of the absolute temperature gives a horizontal straight line, indicating that the dipole moment is zero in agreement with the planar model.

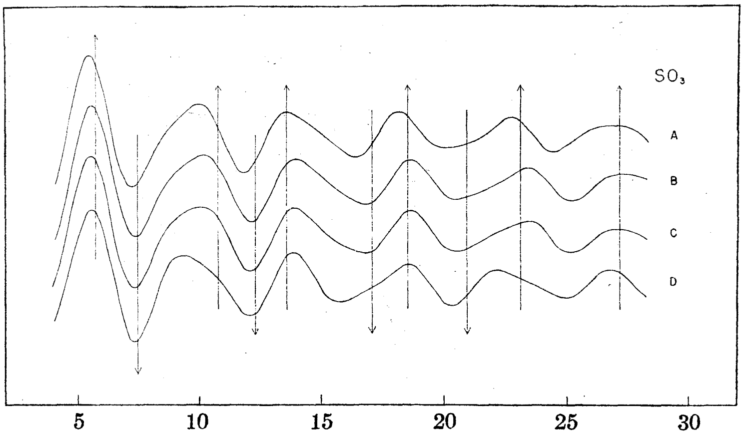

Fig. 5.—Theoretical intensity curves for sulfur trioxide.

TABLE IV

SULFUR TRIOXIDE

Max.	Min.	I	C	s_0	s^a	s/s_0	s^b	s/s_0
1		10	6	5.692	5.38	(0.945)	5.54	(0.973)
	2			7.422	7.13	(.961)	7.35	.990
2		7	10	10.757	9.91	.921	10.20	.948
	3			12.251	11.72	.957	12.10	.988
3		5	8	13.576	13.50	.994	13.90	1.024
	4			17.038	16.30	.994	16.83	0.988
4		4	6	18.461	18.10	.980	18.60	1.007
	5			20.860	20.20	.969	20.50	0.983
5		2	2	23.087	22.63	.981	23.32	1.011
	6			....	...	...	...	...
6		1	1	27.10	26.90	.992	27.20	1.003
					Average	0.974		0.994
					Average deviation	0.019		0.017

(0.974)(1.47) = 1.43 Å.
(0.994)(1.43) = 1.42 Å.
Final values: S–O = 1.43 ± 0.02 Å.
O–S–O ∠ = 120° ⩽ 2°

[a] Calculated for the model with S–O = 1.47 Å., O–S–O angle = 120°. [b] Calculated for the model with S–O = 1.43 Å., O–S–O ∠ = 117°50′.

Sulfuryl Chloride.—The photographs of sulfuryl chloride have eight measurable maxima. The values of s_0, I, and C are given in Table V. The radial distribution curve (curve E of Fig. 1) shows principal peaks at 1.43, 1.99, 2.76, and 3.85

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[8] A. Smits, N. F. Moerman and J. C. Pathuis, *Z. physik. Chem.*, **B35**, 60 (1937).

Å. There is also a small peak at 3.32 Å. The first three values are interpreted as being due to the S–O, S–Cl, and Cl–O distances, respectively. It is geometrically impossible for a model to have these values and at the same time a Cl–Cl distance of 3.85 Å. In agreement with past experience, it is considered that the radial distribution peak at 3.85 Å., which lies rather far out, is unreliable.

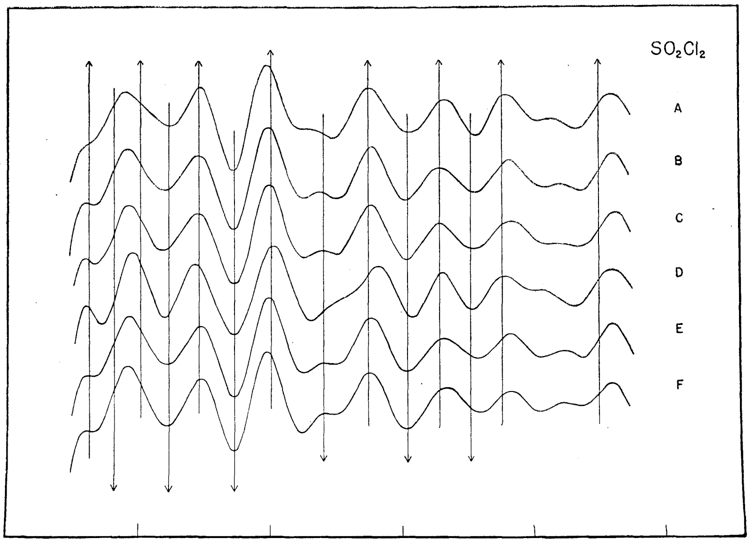

Fig. 6.—Theoretical intensity curves for sulfuryl chloride.

In calculating intensity curves it has been assumed that the S–Cl distance is 1.99 Å., and except in a few curves the Cl–O distance has been taken as 2.76 Å. The S–O distance has been varied from 1.57 to 1.43 Å., and the Cl–Cl distance from 3.55 to 3.06 Å. (except for one planar model in which Cl–Cl = 4.06 Å.). Of the twenty-five curves calculated, only six are reproduced in Fig. 6. Curves A, B, C, and D were calculated for models in which the S–O, S–Cl, and Cl–O distances were assumed equal to 1.43, 1.99, and 2.76 Å., respectively, and the Cl–Cl distance was taken as 3.40, 3.32, 3.28, and 3.15 Å. Curves E and F were calculated for the following models: model E, S–O = 1.45 Å., S–Cl = 1.99 Å., Cl–O = 2.76 Å., and Cl–Cl = 3.32 Å.; model F, S–O = 1.48 Å., S–Cl = 1.99 Å., Cl–O = 2.76 Å., and Cl–Cl = 3.32 Å. All other models for which curves were calculated were eliminated easily as there was obvious disagreement between the intensity curves and the visual appearance of the photographs.

The qualitative appearance of the photographs is approximately the same as for curve C, Fig. 6 (which represents the finally selected model), except for the very small maximum at about $s = 12$ which is not observed on the photographs.

Curve A is not satisfactory because the first maximum is missing. Curves B, C, and D, which represent nearly identical models, are all approximately satisfactory. Curve C is, however, better than curve B because in the latter the first maximum is not sufficiently well defined, and is also superior to curve D because the shelves appearing on the inner edge of the fifth maximum and the outer edge of the seventh maximum of this latter curve cannot be observed on the photographs. Curve E is not satisfactory because the first maximum is not well resolved, and also the structures of the two minima at $s = 12$ and 21 are not compatible with the broad, deep appearance of these minima on the photographs. Curve F is made unsatisfactory by the shelf on the inside of the fifth maximum.

The quantitative comparison for curve C is shown in Table V as the ratio of s to s_0. The final values selected for the parameters are given in Table VI.

TABLE V

SULFURYL CHLORIDE

Max.	Min.	I	C	s_0	s^a	s/s_0
1		6	2	3.140	3.00	(0.956)
	2			4.085	3.29	(.805)
2		8	6	5.082	4.60	(.905)
	3			6.165	5.90	(.957)
3		7	9	7.299	7.24	.992
	4			8.679	8.60	.991
4		10	13	10.036	9.93	.989
	5			12.068	...	...
5		4	8	13.725	13.85	1.009
	6			15.274	15.15	0.999
6		2	4	16.460	16.45	1.000
	7			17.660	17.70	1.002
7		2	3	18.840	19.15	1.016
8		1	1	22.580	23.18	1.026
					Average	1.003
					Average deviation	0.010

[a] Calculated for the model with S–Cl = 1.99, S–O = 1.43 Å., O–S–O angle equal to 119°48′, and Cl–S–Cl angle equal to 111°12′.

Chromyl Chloride.—The photographs of chromyl chloride show seven measurable maxima. The values of s_0, I, and C are listed in Table VII.

TABLE VI

FINAL VALUES OF INTERATOMIC DISTANCES FOR SULFURYL CHLORIDE, CHROMYL CHLORIDE, AND VANADYL OXYTRICHLORIDE

SO_2Cl_2	CrO_2Cl_2	$VOCl_3$
S–O = 1.43 ± 0.02 Å.	Cr–O = 1.57 ± 0.03 Å.	V–O = 1.56 ± 0.04 Å.
S–Cl = 1.99 ± 0.02	Cr–Cl = 2.12 ± 0.02	V–Cl = 2.12 ± 0.03
Cl–O = 2.76 ± 0.03	Cl–O = 3.03 ± 0.03	Cl–O = 3.00 ± 0.04
Cl–Cl = 3.28 ± 0.10	Cl–Cl = 3.54 ± 0.05	Cl–Cl = 3.50 ± 0.03
O–O = 2.48 ± 0.10	O–O = 2.49 ± 0.10	...
O–S–O ∠ = 119°48′ ± 5°	O–Cr–O ∠ = 105°6′ ± 4°	...
Cl–S–Cl ∠ = 111°12′ ± 2°	Cl–Cr–Cl ∠ = 113°16′ ± 3°	Cl–V–Cl ∠ = 111°17′ ± 2°
Cl–S–O ∠ = 106°28′ ± 2°	Cl–Cr–O ∠ = 109°34′ ± 3°	Cl–V–O ∠ = 108°12′ ± 2°

The radial distribution curve (curve F of Fig. 1) shows principal peaks at 1.57, 2.12, 3.03, and 3.54 Å. These are interpreted as the Cr–O, Cr–Cl, Cl–O, and Cl–Cl distances, respectively. The intensity curve calculated for this model agrees very well, both qualitatively and quantitatively, with the photographs. This curve is reproduced as curve C, Fig. 7. Curves A and B were calculated for models in which Cr–O = 1.57, Cr–Cl = 2.12, Cl–O = 3.03, and the O–Cr–O angle was given the values 109°28′ and 107°, respectively. The value of the O–Cr–O angle in model *C* is 105°6′. Both curves A and B are less satisfactory than curve C because of the disappearance of the shelf on the outside of the third maximum and the appearance of a small maximum at approximately *s* = 17. Intensity curves were also calculated for a planar and a tetrahedral model, but the disagreement with the photographs was so marked that the curves have not been reproduced. The quantitative comparison for curve C is given in Table VII, and the finally selected values of the parameters are listed in Table VI.

Vanadium Oxytrichloride.—The photographs of vanadium oxytrichloride have seven measurable maxima. The values of s_0, *I*, and *C* are given in Table VIII. The radial distribution curve (curve G of Fig. 1) shows principal peaks at 1.56, 2.12, 3.01, and 3.50 Å. These values are interpreted as the V–O, V–Cl, Cl–O, and Cl–Cl distances, respectively.

The intensity curve calculated for the model with the above distances is given as curve D, Fig. 7. This curve gives excellent qualitative agreement with the photographs. All other curves which were calculated for models varying slightly from the above were less satisfactory and have not been reproduced. The quantitative agreement is also very good as is evident from the values of the ratio of *s* to s_0 shown in Table VIII. The final values selected for the parameters are given in Table VI.

Discussion

The configurations found for the seven molecules studied in this investigation are all in agreement with expectation. The Cl–S–Cl angle of 101° found in sulfur dichloride lies between the limits 90° for pure *p* bonds and 109°28′ for sp^3 hybridization.

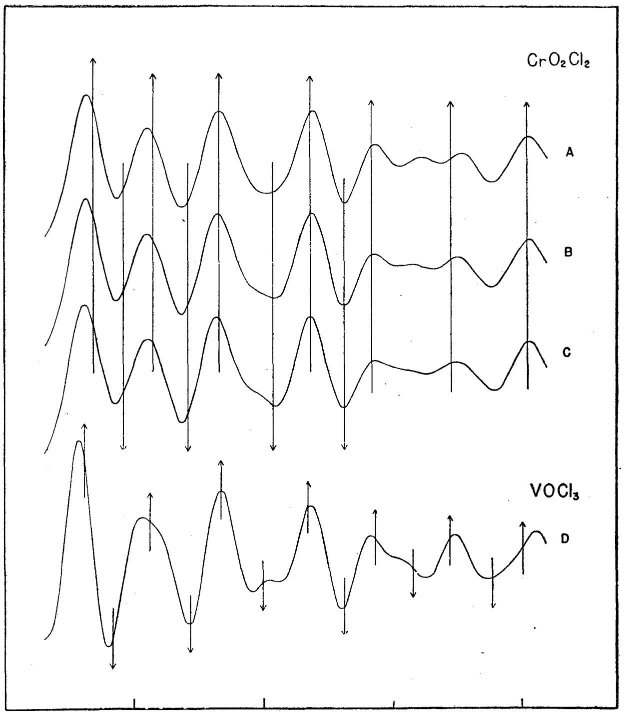

Fig. 7.—Theoretical intensity curves for chromyl chloride and vanadium oxytrichloride.

The generally accepted structure for sulfur monochloride, that in which there is one chlorine atom attached to each sulfur atom, has been confirmed. The Cl–S–S angle of 103° is in agreement with the angle to be expected from a con-

TABLE VII

CHROMYL CHLORIDE

Max.	Min.	*I*	*C*	s_0	s^a	s/s_0
1		10	6	4.438	4.13	(0.933)
	2			5.629	5.33	(.946)
2		7	8	6.783	6.57	.969
	3			8.122	7.90	.973
3		8	15	9.304	9.22	.991
	4			11.310	11.48	1.012
4		8	19	12.788	12.82	1.002
	5			14.076	14.09	1.001
5		3	7	15.157	15.30	1.011
	6			....	...	...
6		1	2	18.210	18.48	1.013
	7			....	...	...
7		2	3	21.216	21.35	1.004
					Average	0.997
					Average deviation	0.013

[a] Calculated for the model with Cr–O = 1.57 Å., Cr–Cl = 2.12 Å., O–Cr–O angle equal to 105°, and Cl–Cr–Cl angle equal to 113°.

TABLE VIII

VANADIUM OXYTRICHLORIDE

Max.	Min.	*I*	*C*	s_0	s^a	s/s_0
1		10	4	4.193	3.95	(0.943)
	2			5.310	5.11	(.964)
2		7	6	6.700	...	...
	3			8.261	8.22	0.995
3		7	10	9.427	9.42	.999
	4			11.150	...	...
4		5	9	12.730	12.88	1.012
	5			14.170	14.07	0.993
5		4	7	15.36	15.20	.990
	6			16.81	...	...
6		2	3	18.23	18.48	1.014
	7			19.91	19.90	0.999
7		1	1	21.10	21.66	1.026
					Average	1.004
					Average deviation	0.011

[a] Calculated for the model with V–O = 1.56 Å., V–Cl = 2.12 Å., O–V–Cl angle equal to 108°, and Cl–V–Cl angle equal to 111°.

sideration of the electronic formula for sulfur monochloride, since, as in sulfur dichloride, the sulfur atom is surrounded by an octet of electrons and both the S–S and S–Cl bonds are single bonds.

Thionyl chloride is pyramidal. The molecule would be planar if the S–O bond were a double bond, and the electronic structure were similar to that of phosgene. The unshared pair of electrons on the sulfur atom, however, causes the molecule to assume a pyramidal configuration.

The sulfur trioxide molecule is isoelectronic with the nitrate and carbonate ions and is expected to be planar for the same reasons that are advanced to explain the structure of these ions. The confirmation of the planarity of sulfur trioxide is also in agreement with the dielectric constant measurements which recently have been carried out.[8]

The electronic formula which usually is written for sulfuryl chloride shows the sulfur atom to be surrounded by eight electrons. This makes each S–O bond a single covalent bond (semipolar double bond), and leads one to anticipate that sulfuryl chloride will have a tetrahedral configuration. The actual configuration is considerably distorted from a regular tetrahedral arrangement, the O–S–O angle being increased from 109°28′ to about 120°. The Cl–S–Cl angle is only slightly larger than that expected, having the value 111°. It is interesting to note that the Cl–O distances in both thionyl and sulfuryl chlorides are nearly equal.

The increase in the O–S–O angle in sulfuryl chloride is probably due to a considerable amount of multiple bond character which is brought about by the swinging in of one or even two pairs of electrons from the oxygen atom. The excited structures no doubt disobey the octet rule which is, however, of little significance in a discussion of second row elements because of the comparative proximity in energy of orbitals such as the 3d or 4s orbitals in sulfur which can be used for bonding purposes.

In chromyl chloride the O–Cr–O angle has decreased to 105° as compared to the large increase in sulfuryl chloride. No explanation of this phenomenon can be given at present. The Cl–Cr–Cl angle shows an increase of a few degrees over the tetrahedral value.

The close analogy in both distances and angles in chromyl chloride and vanadium oxytrichloride is very striking. A similar phenomenon is observed in the case of the sequence of molecules $SiCl_4$, PCl_3, SCl_2, and Cl_2, where the observed interatomic distances are 2.00, 2.00, 1.99, and 1.98 Å., respectively,[9] as compared to the sum of the single bond radii 2.16, 2.09, 2.03, and 1.98 Å., respectively. The constancy of these observed interatomic distances is due to the fact that the double-bond character of each of the above bonds, which is a function of the difference in electronegativity of the bonded atoms, just compensates for the change in value of the sum of the single-bond radii. This same effect accounts for the observed similarities in distance in chromyl chloride and vanadium oxytrichloride.

This phenomenon is not observed for first row

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(9) L. O. Brockway, *Rev. Modern Phys.*, **8**, 231 (1936).

TABLE IX

FINAL VALUES OF INTERATOMIC DISTANCES AND ANGLES

	SCl_2	S_2Cl_2	$SOCl_2$	SO_2Cl_2	SO_3	$VOCl_3$	CrO_2Cl_2
A–Cl, Å.	1.99 ± 0.03	1.99 ± 0.03	2.07 ± 0.03	1.99 ± 0.02	......	2.12 ± 0.03	2.12 ± 0.02
A–O, Å.	......	......	1.45 ± 0.02	1.43 ± 0.02	1.43 ± 0.02	1.56 ± 0.04	1.57 ± 0.03
Cl–O, Å.	......	......	2.84 ± 0.03	2.76 ± 0.03	......	3.00 ± 0.04	3.03 ± 0.03
Cl–Cl, Å.	3.08 ± 0.04	......	3.47 ± 0.03	3.28 ± 0.10	......	3.50 ± 0.03	3.54 ± 0.05
O–O, Å.	......	......	......	2.48 ± 0.10	2.48 ± 0.03	......	2.49 ± 0.10
Cl–A–Cl ∠	101 ± 4°	......	114 ± 2°	111°12′ ± 2°	......	111 ± 2°	113 ± 3°
O–A–O ∠	......	......	......	119°48′ ± 5°	120 ± 2°	......	105 ± 4°
Cl–A–O ∠	......	......	106 ± 1°	106°28′ ± 2°	......	108 ± 2°	109 ± 3°
S–S Å.	......	2.05 ± 0.03	......	......	......	......	......
Cl–S–S ∠	......	103 ± 2°	......	......	......	......	......

chlorides because in these cases double-bond formation can occur only when at least one other bond becomes ionic. This does occur in the case of some fluorides[10] where a very large difference in electronegativity between the bonded atoms exists.

The S–O distances observed in the four molecules sulfur dioxide,[11] sulfur trioxide, thionyl chloride, and sulfuryl chloride are from 0.06 to 0.09 Å. shorter than the sum of the normal double-bond radii which is 1.52 Å. This is particularly surprising when one considers the electronic formulas of these molecules. These formulas indicate that the S–O bond in sulfur dioxide possesses one-half, in sulfur trioxide one-third, and in thionyl and sulfuryl chlorides no double-bond character. Making a correction for the formal charges on the atoms, the values for the S–O distance predicted on the basis of structures of the octet type are 1.52 Å. for sulfur dioxide and sulfur trioxide, and 1.69 Å. for thionyl and sulfuryl chlorides. The fact that the observed distances are all nearly equal and much less than 1.52 Å. indicates that excited electronic structures in which double and triple S–O bonds are present must make a considerable contribution to the normal state of these molecules, being, however, more important for thionyl and sulfuryl chlorides than for sulfur dioxide and sulfur trioxide.

It is difficult to give a quantitative discussion of the observed interatomic distances in chromyl chloride and vanadium oxytrichloride because there is some uncertainty as to the values of the covalent radii of chromium and vanadium. If one assumes reasonable values of about 1.15 for chromium and 1.20 for vanadium, however, it is again evident that the Cr–O and V–O distances are considerably shorter than the sum of the single bond radii, indicating that also in these two molecules structures involving multiple Cr–O and V–O bonds make important contributions to the normal state.

I wish to express my sincere thanks to Mr. Ray Clinton, who prepared the samples of sulfur monochloride, sulfur dichloride, sulfuryl chloride, and chromyl chloride, and especially to Professor Linus Pauling for his many helpful suggestions and for his encouragement during the course of this investigation.

Summary

The molecular structures of sulfur monochloride, sulfur dichloride, thionyl chloride, sulfuryl chloride, sulfur trioxide, vanadium oxytrichloride, and chromyl chloride have been investigated by the electron diffraction method. The final values of the interatomic distances and angles are given in Table IX.

It has been shown that sulfuryl chloride, vanadium oxytrichloride, and chromyl chloride have tetrahedral configurations which are, however, considerably distorted. Thionyl chloride is pyramidal, and sulfur trioxide planar. Sulfur monochloride has been shown to have one chlorine atom attached to each sulfur atom. The positions of the chlorine atoms cannot be determined with certainty.

PASADENA, CALIF. RECEIVED JULY 11, 1938

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(10) L. O. Brockway, *J. Phys. Chem.*, **41**, 185 (1937).

(11) P. C. Cross and L. O. Brockway, *J. Chem. Phys.*, **3**, 821 (1935).

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

Some Trialkyl Trithio-phosphorus, Antimony and Bismuth Compounds

BY ARNOLD LIPPERT AND E. EMMET REID

In 1872 Michaelis[1] reported triethyl trithiophosphite as a heavy oil boiling at 240–280° with sp. gr. 1.24 at 12°. Claesson[2] and Klason[3] described the triethyl trithio-phosphite, arsenite and antimonite and bismuth mercaptide. As the data on these compounds are incomplete it seemed desirable to prepare them again along with several propyl and butyl compounds for comparisons among themselves and with the corresponding oxygen compounds.

It was found that a trithiophosphite can be obtained by refluxing a mercaptan with phosphorus trichloride but that the corresponding reactions with arsenic and antimony stop at the monochloro stage. Following the method for preparing alkyl phosphites[4] pyridine (3 moles) was added to the mixture of mercaptan and phosphorus trichloride. Fair yields were thus obtained but the results were much better (up to 70% yields) with dimethylaniline. This method is satisfactory for the trithioarsenites and trithioantimonites.

The trialkyl trithiophosphites are colorless oils with characteristic and powerful odors, insoluble in water but readily soluble in the usual organic solvents and in concd. sulfuric acid. They are stable in the presence of water, concd. hydrochloric acid or dry hydrogen chloride but are readily hydrolyzed by alkalies. Unlike their oxygen analogs they decompose when heated in air to 90°. They are oxidized by 3% hydrogen peroxide and acetic acid to the trithiophosphates, while stronger oxidizing agents such as 60% hydrogen peroxide, nitric acid and acid permanganate or chromate break them down into phosphoric acid and alkyl sulfonic acids. Chlorine and bromine react with them to give alkyl disulfides and phosphoric acid but one mole of the triethyl ester takes up exactly two atoms of iodine from an alcoholic solution. This addition product was poured into water from which, after several weeks, large transparent hydrated crystals separated. These were soluble in water and sublimed at a high temperature without residue.

The trialkyl trithiophosphites combine with methyl iodide, in several weeks of standing, to give colorless needles; in alcohol or ether solution they react at once with mercuric bromide or iodide or auric chloride to give addition products which have definite melting points. The compounds with mercuric bromide are colorless needles while the others are yellow. More or less unstable addition compounds are formed with mercuric chloride, silver nitrate, lead nitrate and cuprous chloride but none with ammonia, ferric chloride, cupric chloride or pyridine. They reduce alcoholic ferric chloride. Attempts to add sulfur to form the thiophosphates were unsuccessful due to the unstability of the esters when heated above 90°.

Triethyl trithioantimonite was prepared similarly with the aid of dimethylaniline but the yield (30%) was not so good as that with the corresponding phosphorus compounds. A better yield was obtained by using sodium mercaptide. Klason[3] reports making it by the action of antimony trichloride in strong aqueous hydrochloric acid on mercaptan. We were unable to obtain it in this way. The ester is a viscous light yellow oil insoluble in water. On contact with air it decomposes into ethyl disulfide and antimony trioxide. When sealed in glass capsules it slowly turned green with the deposition of metallic antimony. This seemed to be catalyzed by previous exposure to air. In solution in dry ether the ester was stable. It burns with a bright, slightly smoky flame. Addition of iodine to an alcoholic solution gave a pale yellow unstable addition product.

The properties of these esters and their addition compounds are shown in Table I.

The triethyl bismuth mercaptide was formed by the addition of bismuth nitrate crystals to mercaptan. Reaction takes place immediately with the formation of an aqueous layer and a red solution which when poured into ether precipitated the mercaptide as a yellow powder, melting at 200° with decomposition agreeing with the observations of Claesson.

Experimental

To a chloroform solution of 25 g. of ethyl mercaptan in a flask with reflux condenser and mercury-seal stirrer, kept at 0°, 13.7 g. of phosphorus chloride was added slowly with

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(1) Michaelis, *Ber.*, **5**, 7 (1872).

(2) Claesson, *Bull. soc. chim.*, [2] **25**, 183 (1876); *J. prakt. Chem.*, [2] **15**, 209 (1877).

(3) Klason, *Acta Univ. Lund.*, **21**, 3 Abt. Abl. VI, p. 14 (1884–1885).

(4) Milobendzki and Sachnowski, *Chemik Polski*, **15**, 34 (1917); *J. Chem. Soc.*, **114**, i, 477 (1918).

TABLE I

THE TRIALKYL TRITHIOPHOSPHITES AND ANTIMONITE AND THEIR ADDITION COMPOUNDS

Formula	B. p., °C.	Press.	M. p., °C.	n^{25}_D	d^0_4	d^{25}_4	M. p.'s add. comps. with			
							CH_3I	$HgBr_2$	HgI_2	$AuCl_3$
$(EtS)_3P$	140–143	18	− 32–31	1.5689	1.1883[a]	1.1585	191	184	187	225
$(PrS)_3P$	164–169	15	− 65–64	1.5350	1.1277	1.0932	191	176	182	208
$(BuS)_3P$	174–180	15	−101–100	1.5305	1.0773	1.0421	198	148	162	182
$(EtS)_3PO$[b]	165–168	15	− 24–23	....	....	1.1890				
$(EtS)_3Sb$	167–170	4	....	....	1.6224	1.5873				

[a] Claisson gives sp. g. at 12° 1.24. [b] Pischtschimuka gives b. p. 174–175 (20 mm.) d^0_0 1.1969.

stirring which was continued for an hour after all was in. The product was heated to 70° at atmospheric pressure and the residue distilled at 18 mm., yield 7.5 g. or 35%. To a solution of 18.6 g. of mercaptan and 24 g. of dimethylaniline in 100 cc. of ether, 13.7 g. of phosphorus trichloride was added under the same conditions. The dimethylaniline hydrochloride was filtered off and extracted with ether. The ether solution was treated as above, yield 13.3 g. or 62%. Using 10% excess of mercaptan brought the yield to 70%. *Anal.* Calcd.: P, 14.48; S, 44.86. Found: P, 14.58; S, 44.31.

The tripropyl ester was prepared similarly, yield 58%. *Anal.* Calcd.: P, 12.11; S, 37.50. Found: P, 12.25; S, 37.43.

Similarly the tributyl ester was obtained in 58% yield. *Anal.* Calcd.: P, 10.40; S, 32.21. Found: P, 10.41; S, 31.86.

To a solution of 10 g. of the triethyl ester in 200 cc. of acetic acid, 50 cc. of 3% hydrogen peroxide was added and the mixture stirred for twelve hours. The acid was neutralized with ammonia and the oil extracted with ether and distilled, b. p. 165–170° at 15–18 mm., yield 34%.

An ether solution of antimony trichloride was added with rapid stirring and efficient cooling to sodium ethyl mercaptide in a flask with reflux. Reaction took place immediately but the mixture was stirred for six hours, after which the salt was filtered off and the solution distilled. The yield of ester was 80%, analysis Sb found 39.48%, calculated 39.60%.

Summary

Triethyl, tripropyl and tributyl trithiophosphites, triethyl trithioantimonite and bismuth triethyl mercaptide have been prepared and their properties determined. The trithiophosphites form many addition products.

BALTIMORE, MARYLAND RECEIVED JULY 11, 1938

[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY OF YALE UNIVERSITY]

The Conductance of Hydrochloric Acid in Dioxane–Water Mixtures from 15 to 45°

BY BENTON BROOKS OWEN AND GEORGE W. WATERS[1]

The effects of viscosity, temperature and dielectric constant upon the conductivity of solutions of electrolytes have long been popular subjects for investigation. In view of the peculiar conductance mechanism of the hydrogen ion, it is surprising that such a small part of this work has dealt with solutions of acids. Goldschmidt[2] and his co-workers have measured the conductance of several acids at 25° in alcohol–water mixtures rich in alcohol, and a number of investigators[3] have studied acids in pure non-aqueous solvents, for the most part at 25°. In the present research, we have measured the conductance of hydrochloric acid in four dioxane–water mixtures, 20, 45, 70 and 82% dioxane by weight, at 15, 25, 35 and 45°. By subjecting this important electrolyte to considerable variation in both dielectric constant and temperature, we not only extend our knowledge of the effects of these variables upon conductance, but also derive some information regarding its thermodynamic properties. This thermodynamic information is of immediate interest, because it supplements the extensive electrochemical investigation of hydrochloric acid in dioxane–water mixtures by Harned[4] and his students.

Materials, Technique and Fundamental Constants

Conductivity water was distilled from alkaline permanganate in an electrically heated Barnstead still. The dioxane was obtained from the Carbide and Carbon Chemi-

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[1] This communication embodies part of the thesis presented by George W. Waters to the Graduate School of Yale University in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] Goldschmidt, *Z. physik. Chem.*, **89**, 129 (1914); **91**, 46 (1916); **91**, 51 (1916); **70**, 633 (1910).

[3] For bibliography consult the review by Hartley, Gatty, MacFarlane and Murray-Rust, *Ann. Repts. Chem. Soc.* (London), **27**, 326 (1931).

[4] Harned and Morrison, *Am. J. Sci.*, **33**, 161 (1937); THIS JOURNAL, **58**, 1908 (1936); Harned, *ibid.*, **60**, 336 (1938); Harned and Donelson, *ibid.*, **60**, 339 (1938); **60**, 2128 (1938); Harned and Calmon, *ibid.*, **60**, 2130 (1938); Harned, Donelson and Calmon, *ibid.*, **60**, 2133 (1938).

cals Corporation, and purified in the manner described by Harned and Morrison.[4] It was protected carefully from moisture and stopcock grease. The freezing point of the purified product was always within the range 11.76 to 11.78°, in good agreement with the value 11.78° reported by Kraus and Vingee.[5]

Baker "Analyzed" arsenic-free hydrochloric acid was diluted to the constant-boiling mixture, and twice distilled from an all-glass apparatus. Only the middle fractions were retained. The concentrations of stock solutions prepared from this acid were always checked gravimetrically, using recrystallized silver nitrate. The precision of these analyses was 0.05%. The mixed solvents and stock solutions were freshly prepared, by weight, before each run. Carbon dioxide was removed from both the water and pure dioxane by a stream of purified nitrogen. Conversion of concentrations from a weight basis to moles per liter (hereafter designated by c) was performed with the aid of the density data of Harned and Calmon.[6]

The conductivity cells were the Type B described by Saxton and Langer,[7] and the experimental technique was essentially the same. The cell constants were determined at 18 and 25° from the specific conductivity of a 0.1 demal potassium chloride solution proposed by Jones and Bradshaw,[8] and at 15° from the results of Bremner and Thompson.[9] The variation with temperature was linear, and was used to calculate the cell constants at 35 and 45°.

Temperatures were read on Beckmann thermometers calibrated by a platinum resistance thermometer which had been checked by the Bureau of Standards. The regulation of the thermostat temperature was better than 0.01° at 25 and 35°. At 15 and 45° the regulation was not so satisfactory, but was always better than 0.02°.

In order to calculate the theoretical coefficients of the Onsager[10] equation

$$\Lambda = \Lambda_0 - (\alpha\Lambda_0 + \beta)\sqrt{c} \qquad (1)$$

and the Debye–Hückel[11] limiting law

$$\log y = -u\sqrt{c} \qquad (2)$$

we made use of the physical constants given in the "International Critical Tables," the dielectric constant data of Åkerlöf and Short[12] and the viscosity data of Geddes.[13] Since some difficulty was encountered in the necessary interpolation[14] of these data, the interpolated values and the calculated constants, u, α and β are collected in Table I.

TABLE I

CONSTANTS PERTAINING TO EQUATIONS (1) AND (2)

Wt. % dioxane	$t°$	D_0	$100\ \eta_0$	u	α	β
20	15	64.01	1.689	0.7245	0.3258	35.73
20	25	60.79	1.292	.7437	.3345	47.17
20	35	57.73	1.017	.7648	.3439	60.42
20	45	54.83	0.8243	.7877	.3542	75.29
45	15	40.70	2.453	1.429	.6425	30.85
45	25	38.48	1.837	1.477	.6642	41.66
45	35	36.37	1.430	1.530	.6878	54.14
45	45	34.39	1.142	1.586	.7131	68.62
70	15	18.72	2.483	4.581	2.060	44.94
70	25	17.69	1.918	4.738	2.131	58.85
70	35	16.72	1.522	4.907	2.207	75.03
70	45	15.80	1.232	5.092	2.290	93.83
82	15	10.01	2.106	11.72	5.268	72.46
82	25	9.53	1.671	11.98	5.389	92.02
82	35	9.06	1.356	12.30	5.532	114.39
82	45	8.62	1.117	12.64	5.683	140.12

Experimental Results and Discussion

The experimental data are so numerous that they can be given only in abbreviated form. Accordingly we have tabulated Λ and $\sqrt{c}$ as the most convenient and generally useful quantities for further calculations. Table II contains these quantities for the four temperatures and four solvent mixtures. Since we are primarily interested in the initial departures from equation (1), and the estimation of the extent of ionic association from this effect, we have recorded only the two runs at the highest dilutions whenever more than two runs were made.[15] Most runs consisted of ten or less measurements, so for convenience in tabulation we have recorded only the ten lowest concentrations, if more than ten were studied. The specific conductivities of the pure solvents, κ_0, are recorded at the ends of the proper columns. No corrections were applied for solvent conductance. It was assumed that the major part of this factor was due to dissolved substances, the dissociation and conductance of which would be effectively repressed by the strong acid. To simplify future reference, individual experimental data can be identified by temperature and the numbers given in the first column of the table. The prime and double-prime refer to runs one and two, respectively.

The results in 20% dioxane are very similar to those in pure water. The dielectric constant is high enough to permit essentially complete dissociation, so the observed conductivities approach the limiting slope (Equation 1) from above. This

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(5) Kraus and Vingee, THIS JOURNAL, **56**, 511 (1934).

(6) Harned and Calmon, *ibid.*, **60**, 334 (1938).

(7) Saxton and Langer, *ibid.*, **55**, 3638 (1933). The Dike bridge was used throughout with a 1000~ oscillator as source of power.

(8) Jones and Bradshaw, *ibid.*, **55**, 1780 (1933).

(9) Bremner and Thompson, *ibid.*, **59**, 2372 (1937).

(10) Onsager, *Physik. Z.*, **27**, 388 (1926); **28**, 277 (1927).

(11) Debye and Hückel, *ibid.*, **24**, 185 (1923).

(12) Åkerlöf and Short, THIS JOURNAL, **58**, 1241 (1936).

(13) Geddes, *ibid.*, **55**, 4832 (1933).

(14) Dielectric constants interpolated by Harned and Morrison,[4] and by Walker, Thesis, Yale University, 1937. Viscosities interpolated by Waters, Thesis, Yale University, 1938.

(15) For complete tabulations *cf.* Thesis, ref. 1.

is illustrated by the points plotted as open circles in Fig. 1.

In the case of the 45% dioxane mixtures, however, the limiting slope is approached from below, although the negative departures from the slope are very small (see Fig. 2). This is in accord with Bjerrum's[16] definition of ion association under coulomb forces, which predicts that hydrochloric acid should show the first signs of association at dielectric constants corresponding to our 45% dioxane solutions.

The evaluation of Λ_0 in the 20 and 45% mixtures is performed readily by the familiar Shedlovsky[17] extrapolation in which the function

$$\Lambda' = (\Lambda + \beta\sqrt{c})/(1 - \alpha\sqrt{c}) \quad (3)$$

from equation (1), is plotted against c. Values

TABLE II

EXPERIMENTAL DATA

No.	15°		25°		35°		45°	
	$\sqrt{c}$	Λ	$\sqrt{c}$	Λ	$\sqrt{c}$	Λ	$\sqrt{c}$	Λ
	20% Dioxane							
1′	0.01175	249.28	0.03661	297.68	0.02407	349.65	0.01061	405.28
2′	.01638	248.94	.05198	295.56	.03731	347.48	.01553	403.63
3′	.03264	247.04	.06577	293.55	.05280	344.86	.02918	401.02
4′	.04760	245.45	.08017	291.96	.06902	342.36	.06620	393.30
5′	.06544	243.54	.12353	287.01	.08588	339.71	.08490	389.46
6′	.08682	241.48	.13512	285.63	.10467	337.03	.09912	387.08
7′	.10710	239.63	.14518	285.02	.12217	334.75	.11687	384.48
8′	.13062	237.68	.15854	283.68	.14141	332.46	.13701	381.56
9′	.15451	235.84	.17329	282.19	.16717	329.50	.15917	378.13
10′	.17866	234.11	....	....	....	....	....	....
1″	.01142	249.38	.02108	299.81	.02986	349.36	.02543	400.60
2″	.01573	249.00	.03558	297.73	.03949	347.92	.03777	397.95
3″	.02920	247.50	.05650	294.83	.05543	345.16	.05590	394.35
4″	.04738	245.69	.06961	293.04	.07534	342.07	.07222	391.34
5″	.06771	243.59	.12253	286.97	.08869	339.98	.08763	388.52
6″	.08977	241.47	.15637	283.56	....	....	.10478	385.37
7″	.10811	239.80	.18618	280.96	....	....	.12187	382.85
8″	.13052	238.00	.21592	278.53	....	....	.14250	379.58
9″	.15447	236.23	.26133	275.14	....	....	....	....
10″	.17844	234.52	.32311	270.94	....	....	....	....
	$\kappa_0' = 1.29 \times 10^{-6}$		$\kappa_0' = 0.470 \times 10^{-6}$		$\kappa_0' = 0.384 \times 10^{-6}$		$\kappa_0' = 0.779 \times 10^{-6}$	
	$\kappa_0'' = 1.73 \times 10^{-6}$		$\kappa_0'' = 0.504 \times 10^{-6}$		$\kappa_0'' = 0.470 \times 10^{-6}$		$\kappa_0'' = 0.599 \times 10^{-6}$	
	45% Dioxane							
1′	0.01400	144.99	0.01289	178.05	0.02345	211.79	0.01144	249.62
2′	.02749	142.74	.02295	176.40	.03964	208.59	.02406	247.41
3′	.04172	140.86	.03190	174.92	.05505	205.36	.03323	245.14
4′	.05568	139.23	.04259	173.17	.07365	201.83	.05625	239.25
5′	.07298	137.20	.06506	169.65	.09051	198.87	.07146	235.53
6′	.09701	134.68	.07728	167.88	.10734	196.16	.08410	232.82
7′	.11982	132.72	.09685	165.26	.12552	193.63	.10050	229.52
8′	.14143	130.94	.12540	161.84	.14669	190.91	.11804	226.23
9′	.16344	129.39	.14632	159.79	.17403	187.84	.13752	222.94
10′	....	....	.16230	158.29	....	....	....	....
1″	.02318	143.19	.02580	175.86	.01355	213.53	.00816	250.93
2″	.03235	142.17	.04046	173.57	.02650	211.23	.01495	250.08
3″	.04535	140.53	.05255	171.66	.04510	207.27	.02364	248.02
4″	.05985	138.77	.06455	169.80	.06348	203.59	.03368	245.23
5″	.07333	137.23	.08604	166.85	.08231	200.14	.04849	241.60
6″	.08918	135.58	.11620	163.15	.09827	197.49	.06532	237.35
7″	.10494	134.04	.14240	160.35	.11501	194.59	.08089	233.89
8″	.12195	132.56	.18350	156.75	.13605	192.02	.09835	230.35
9″	....	....	.20297	154.78	.15583	189.88	.13399	224.61
10″	....	....	.23196	153.27	....	....	.15547	221.52
	$\kappa_0' = 0.603 \times 10^{-6}$		$\kappa_0' = 0.228 \times 10^{-6}$		$\kappa_0' = 0.179 \times 10^{-6}$		$\kappa_0' = 0.195 \times 10^{-6}$	
	$\kappa_0'' = 0.200 \times 10^{-6}$		$\kappa_0'' = 0.256 \times 10^{-6}$		$\kappa_0'' = 0.192 \times 10^{-6}$		$\kappa_0' = 0.226 \times 10^{-6}$	

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[16] Bjerrum, *Kgl. Danske Vidensk. Selskab.*, **7**, No. 9 (1926).

[17] Shedlovsky, THIS JOURNAL, **54**, 1405 (1932).

TABLE II (*Concluded*)

70% Dioxane

No.	15° $\sqrt{c}$	15° Λ	25° $\sqrt{c}$	25° Λ	35° $\sqrt{c}$	35° Λ	45° $\sqrt{c}$	45° Λ
1′	0.00819	72.54	0.01160	89.14	0.00835	108.88	0.00936	126.93
2′	.01250	71.67	.02037	85.20	.01498	105.22	.02079	119.05
3′	.02602	67.20	.02888	81.45	.02401	99.97	.03046	112.51
4′	.03717	63.81	.03977	77.11	.03475	94.24	.04020	106.54
5′	.05320	59.71	.05079	73.43	.05080	87.16	.05707	98.19
6′	.06935	56.46	.06282	70.05	.06211	83.12	.07401	91.75
7′	.08484	53.94	.08461	65.25	.07881	78.35	.09200	86.51
8′	.10288	51.61	.10421	62.05	.09131	75.44	.11009	82.54
9′	.12057	49.80	.12238	59.74	.10725	72.45	.12985	79.06
10′	.14058	48.17	.13990	57.94	....	....	.15090	76.27
1″	.01075	71.52	.02420	83.26	.02330	100.52	.01721	121.24
2″	.02144	68.42	.03919	77.20	.03213	95.33	.02435	116.14
3″	.03197	65.13	.05823	71.20	.04471	89.45	.03178	111.11
4″	.04609	61.26	.08119	65.88	.05720	84.66	.04050	105.88
5″	.05949	58.19	.10869	61.41	.06918	80.86	.05486	98.64
6″	.07369	55.54	.13644	58.26	.08470	76.79	.06782	93.39
7″	.09058	53.00	.16818	55.72	.09718	74.17	.08423	88.13
8″	.10444	51.30	....	....	.11758	70.68	.10007	84.11
9″	.12383	49.39	....	....	....	....	.11537	81.04
10″	....	....	....	....	....	....	....	....
	$\kappa_0' = 0.226 \times 10^{-6}$		$\kappa_0' = 0.450 \times 10^{-6}$		$\kappa_0' = 0.085 \times 10^{-6}$		$\kappa_0' = 0.150 \times 10^{-6}$	
	$\kappa_0'' = 0.119 \times 10^{-6}$		$\kappa_0'' = 0.107 \times 10^{-6}$		$\kappa_0'' = 0.094 \times 10^{-6}$		$\kappa_0'' = 0.060 \times 10^{-6}$	

82% Dioxane

No.	15° $\sqrt{c}$	15° Λ	25° $\sqrt{c}$	25° Λ	35° $\sqrt{c}$	35° Λ	45° $\sqrt{c}$	45° Λ
1′	0.00819	38.53	0.01212	40.89	0.00563	58.01	0.00751	65.88
2′	.01069	36.38	.01994	33.29	.00956	51.23	.01352	52.25
3′	.02077	28.31	.02842	28.04	.01322	45.63	.02323	39.55
4′	.03293	22.71	.03886	23.83	.01919	38.78	.03342	32.16
5′	.04769	18.86	.05099	20.69	.03239	29.53	.04462	27.25
6′	.06270	16.48	.06343	18.50	.04509	24.65	.06259	22.60
7′	.07662	15.04	.09039	15.75	.06077	21.05	.07695	20.28
8′	.09304	13.87	.10966	14.63	.06916	19.72	.09640	18.36
9′	.10975	13.06	.13067	13.84	.08118	18.28	.11325	17.23
10′	.12698	12.49	.14723	13.42	.11014	16.14	.13223	16.43
1″	.00576	41.73	.01696	36.11	.00903	53.50	.00614	69.15
2″	.00948	37.35	.02840	28.23	.01665	42.00	.00952	60.09
3″	.01880	29.56	.04252	22.86	.02523	34.01	.02038	42.09
4″	.02991	23.80	.05729	19.59	.03989	26.44	.02838	35.03
5″	.04145	20.22	.07372	17.32	.05288	22.67	.04026	28.65
6″	.05635	17.35	.09013	15.85	.06619	20.19	.05307	24.51
7″	.06504	16.18	.11229	14.65	.07745	18.67	.06546	21.87
8″	.07908	14.83	.13450	13.80	.09394	17.17	.07958	19.83
9″	.09370	13.83	.17203	13.10	.12746	15.34	.09254	18.51
10″	.10790	13.13	.20256	12.86	....	....	.10847	17.35
	$\kappa_0' = 0.171 \times 10^{-6}$		$\kappa' = 0.534 \times 10^{-6}$		$\kappa_0' = 0.085 \times 10^{-6}$		$\kappa_0' = 0.102 \times 10^{-6}$	
	$\kappa_0'' = 0.192 \times 10^{-6}$		$\kappa_0'' = 0.064 \times 10^{-6}$		$\kappa_0'' = 0.055 \times 10^{-6}$		$\kappa_0'' = 0.072 \times 10^{-6}$	

of this function are plotted as filled circles in Figs. 1 and 2. Straight lines were used to extrapolate the 20% dioxane data by the method of least squares. A linear extrapolation obviously was unsatisfactory in 45% dioxane, so a stiff spline was used to obtain Λ_0 graphically in this solvent.

The data for the 70 and 82% dioxane solutions are plotted in Figs. 3 and 4. Ionic association is clearly indicated in 70% dioxane by the pronounced negative departures from the Onsager slopes, but the electrolyte is still strong enough to exhibit an inflection in the conductance curve, and approach the limiting law within the experimental concentration range. In the 82% mixtures, the conductance falls off very steeply at the lowest concentrations, and the inflection has been shifted to inaccessible dilutions. At higher concentrations, $c \simeq 0.05$, the curves pass through

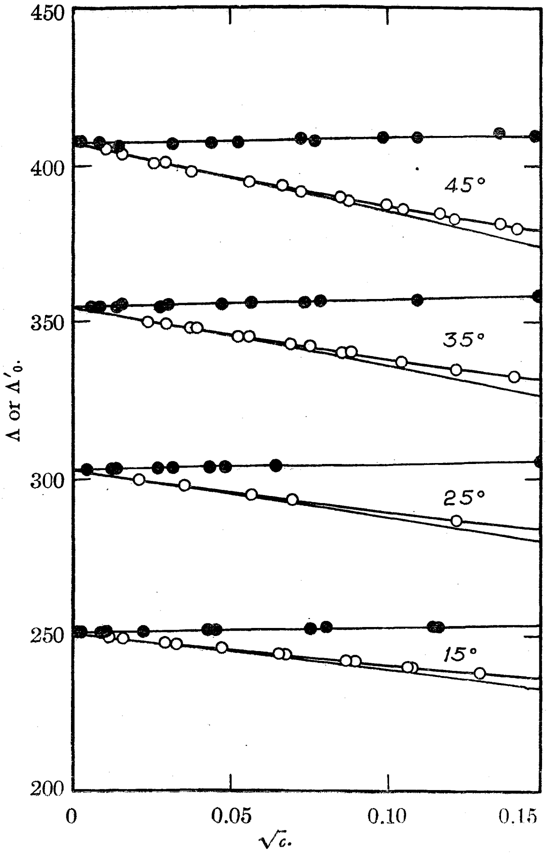

Fig. 1.—Conductance and extrapolation for hydrochloric acid in 20% dioxane.

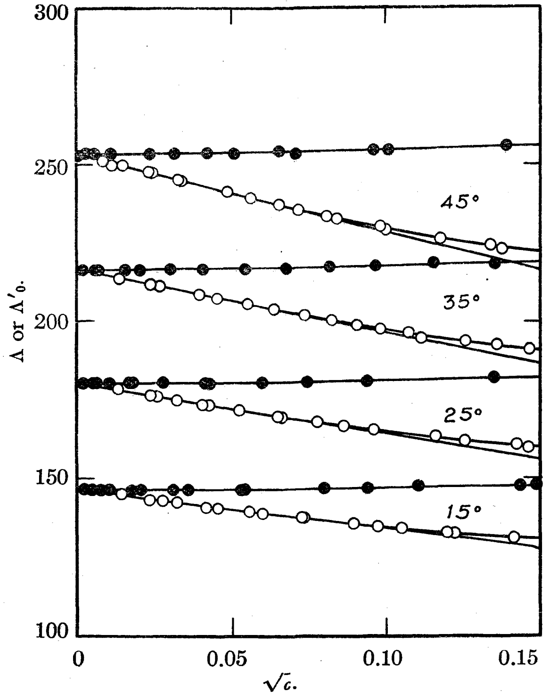

Fig. 2.—Conductance and extrapolation for hydrochloric acid in 45% dioxane.

flat minima not shown on Fig. 4. These minima are attributed to complex ion formation,[18] and have been given approximate quantitative expression by Fuoss and Kraus[19] in terms of triple ion formation. Unfortunately the concentrations at which the minima appear in our data are far beyond the range for which the formulas of Fuoss and Kraus were derived.

The evaluation of Λ_0 for incompletely dissociated electrolytes presents serious difficulties. It is apparent from Figs. 3 and 4 that departures from the Onsager slope are too great to permit satisfactory extrapolation along the limiting slopes. The Shedlovsky extrapolation becomes so strongly curved under these conditions that it is no longer practicable. Accordingly we have employed the method of Fuoss and Kraus,[20] recently simplified and improved by Fuoss.[21] The application of this method depends upon the equation

$$F(z)/\Lambda = 1/\Lambda_0 + (cy^2\Lambda/F(z))/(K\Lambda_0^2) \qquad (4)$$

which is obtained by combining the mass action expression

$$K = c\Theta^2y^2/(1 - \Theta) \qquad (5)$$

with

$$\Lambda = \Theta(\Lambda_0 - (\alpha\Lambda_0 + \beta)\sqrt{c\Theta}) \qquad (6)$$

and

$$\log y = -2u\sqrt{c\Theta} \qquad (7)$$

The last two equations are, of course, equations (1) and (2) modified to account for association of the electrolyte by introduction of its degree of dissociation, Θ. The continued fraction, F(z), permits explicit combination of these equations, and is defined and expressed in tabular form by Fuoss.[21] The extrapolation involves plotting F(z)/Λ against $cy^2\Lambda/F(z)$, and is illustrated in Figs. 5 and 6. These plots should be linear at sufficiently high dilutions for equations (6) and (7) to hold, and the slopes and intercepts are $1/(K\Lambda_0^2)$ and $1/\Lambda_0$, respectively. Although some deviation from linearity is apparent in several individual plots, it is not consistent, and was therefore disregarded in evaluating the line constants. Two points on the 25° isotherm in Fig. 6 are from a third run which could not be included in Table II. The data are as follows: 82% dioxane, $\kappa_0''' = 0.085 \times 10^{-6}$, $\sqrt{c} = 0.01022$, $\Lambda = 42.97$ and $\sqrt{c} = 0.01450$, $\Lambda = 38.56$. Only the data at the highest dilutions were used in the

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(18) Sachanov, *Z. physik. Chem.*, **83**, 129 (1913).

(19) Fuoss and Kraus, THIS JOURNAL, **55**, 2387 (1933).

(20) Fuoss and Kraus, *ibid.*, **55**, 476 (1933).

(21) Fuoss, *ibid.*, **57**, 488 (1935).

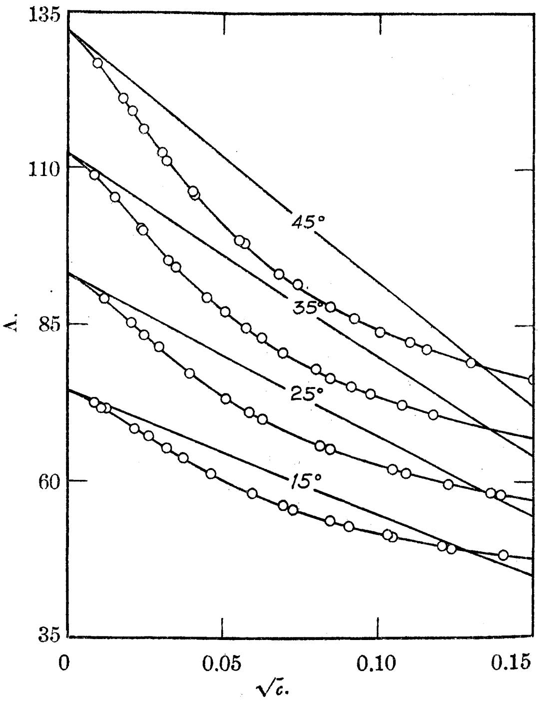

Fig. 3.—Conductance of hydrochloric acid in 70% dioxane.

plots, as it has been pointed out[22] that the concentration

$$c \simeq 12 \times 10^{-15}(DT)^3 \qquad (8)$$

constitutes a theoretical upper limit to the validity of equation (6).

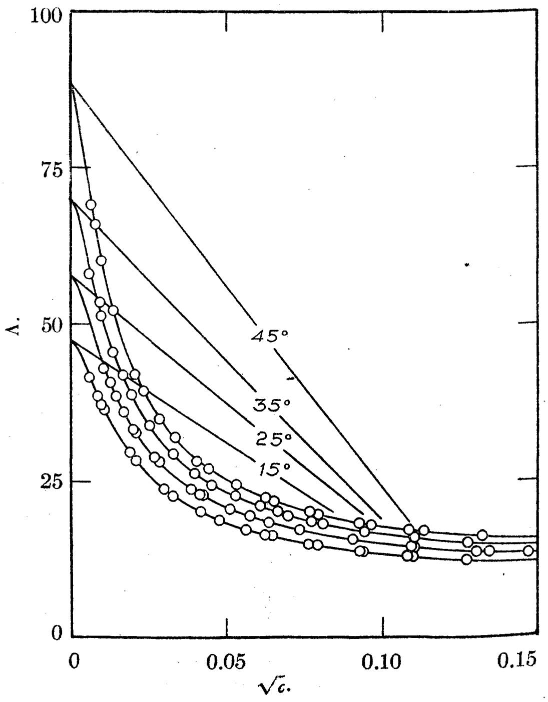

Fig. 4.—Conductance of hydrochloric acid in 82% dioxane.

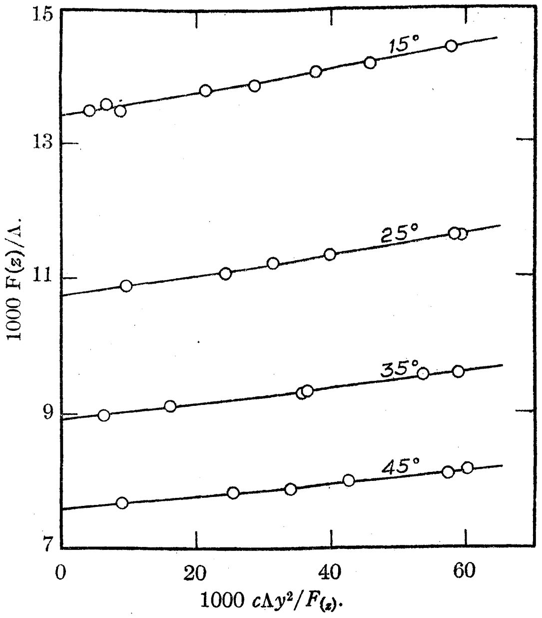

Fig. 5.—Evaluation of Λ_0 and K in 70% dioxane.

The final values of Δ_0 obtained from all of the extrapolations (Figs. 3 to 6) are recorded in Table III. Comparison with Table I brings out several interesting points. At a given temperature Λ_0 decreases very rapidly with increase in dioxane content, being almost halved in passing from one

TABLE III

LIMITING CONDUCTANCE

$t°$	Dioxane percentages 20	 45	 70	 82
15	250.7	146.7	74.5	47.2
25	302.7	180.2	93.1	57.5
35	354.2	216.5	112.4	69.6
45	406.0	253.6	131.9	88.3

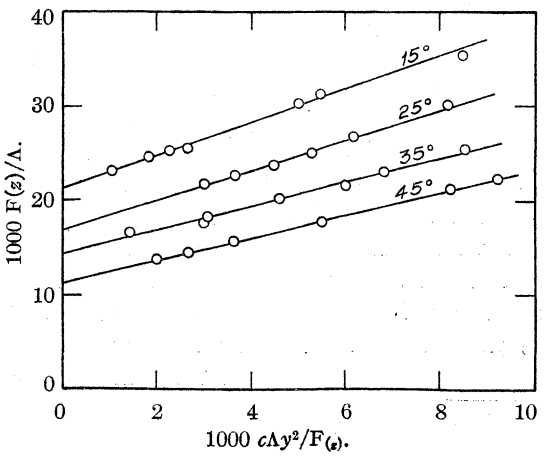

Fig. 6.—Evaluation of Λ_0 and K in 82% dioxane.

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[22] FUOSS, THIS JOURNAL, **57**, 2604 (1935).

mixture to the next. On the other hand, the viscosity passed through a maximum between 45 and 70% dioxane, and hardly experiences a 50% change throughout the whole range of solvents. Figure 7 illustrates this phenomenon by the series of isothermal curves. In the same figure the data fall on a series of straight lines representing mixtures of constant composition in which the variation in viscosity is due to change in temperature only. The slopes, s, of these straight lines are all less than unity, but increase regularly with the dioxane content. The slopes and intercepts of these lines lead to the evaluation of the parameters, s and r, for the equation[23]

$$\Lambda_0 \eta_0^s = r \qquad (9)$$

Values of the parameters are given in Table IV.

TABLE IV

PARAMETERS OF EQUATIONS (9) AND (10)

% Dioxane	s	r	A	B
20	0.650	17.87	173.0	5.19
45	.725	9.95	92.2	3.57
70	.825	3.55	44.7	1.95
82	.90	1.45	30	1.13

Although the difference between s and unity represents a departure from Stokes' law, equation (9) shows that viscosity and conductance are rather simply related in a given solvent at various temperatures.[24]

In terms of the supposition that a large part of the hydrogen ion conductance is due to a succession of proton exchanges,[25] Fig. 7 shows that the presence of dioxane molecules in the solvent decreases the conductance more effectively by lowering the probability of the rapid symmetrical reaction

$$H_3O^+ + H_2O = H_2O + H_3O^+$$

than by increasing the viscosity of the medium.

For a given solvent, the effect of increasing the temperature is not only closely associated with the concomitant decrease in viscosity, but can also be expressed by the relationship

$$\Lambda_0 = A + Bt \qquad (10)$$

The parameters A and B are given in Table IV. With the exception of the value in 82% dioxane at 45°, Λ_0 generally can be reproduced to within about 0.5 conductance unit by equations (9) and (10). Considering the form of equation (9) and the complexity of the accepted hydrogen ion conductance mechanism, it is rather surprising that the temperature dependence of Λ_0 should be as simple as equation (10) for even as much as 30°.

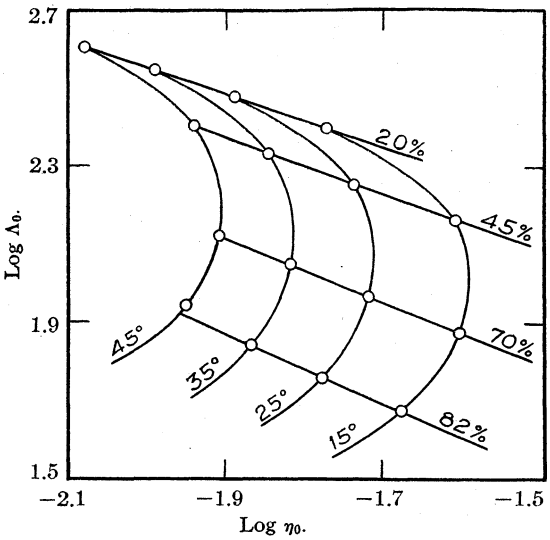

Fig. 7.—Influence of viscosity upon limiting conductance.

The effect of dielectric constant upon conductance is less direct than those of viscosity and temperature, and is given expression mainly through its control of the force of attraction between ions of unlike charges. For this reason we would not expect to find any very close connection between dielectric constant and the conductance at infinite dilution, and must focus our attention upon its influence on ionic association at finite concentrations. The most convenient quantitative measure of ionic association is supplied by the value of the thermodynamic dissociation constant of the electrolyte. The dissociation constant of hydrochloric acid in the various solvents has been calculated from the slopes of the plots in Figs. 5 and 6, and recorded in Table V. No values are given for the 20 and 45% dioxane mixtures because there is at present no satisfactory method of

TABLE V

DISSOCIATION CONSTANTS

t°	70% Dioxane $K \times 10^3$	70% Dioxane $a \times 10^8$	82% Dioxane $K \times 10^4$	82% Dioxane $a \times 10^8$
15	10.7	9.1	2.55	6.6
25	7.7	7.9	2.02	6.3
35	6.7	7.7	1.64	6.2
45	5.7	7.4	1.07	5.8

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(23) This relationship was used by Green [*J. Chem. Soc.*, **93**, 2049 (1908)] to describe the effect of η_0 on Λ_0 of salts at a given temperature, and by Johnston [THIS JOURNAL, **31**, 1010 (1909)] to relate η_0 and Λ_0 in a given medium at various temperatures.

(24) Walden and Ulich, *Z. physik. Chem.*, **107**, 219 (1923); Ulich, *Fortschrit. Chem.*, **18**, No. 10 (1926).

(25) Hückel, *Z. Elektrochem.*, **34**, 546 (1928); Bernal and Fowler, *J. Chem. Phys.*, **1**, 515 (1933); Baker and LaMer, *ibid.*, **3**, 406 (1935); Wannier, *Ann. Physik*, **24**, 545, 569 (1935); Longsworth and MacInnes, THIS JOURNAL, **59**, 1666 (1937).

evaluating, or even giving physical definition to, dissociation constants under the experimental conditions encountered in these solutions. Rough estimates from extrapolations similar to those in Figs. 5 and 6, and calculations based upon the Bjerrum[16] equation, indicate that K is of the order of unity in 45% dioxane solutions, and of a higher but undefined order in 20% dioxane solutions. Even in 70% dioxane the dissociation is quite extensive, corresponding closely to that of the first hydrogen of phosphoric acid in water.[26] In 82% dioxane the strength of hydrochloric acid is comparable to that of formic acid in aqueous solutions.[27]

The maximum uncertainty in K which might be assigned to individual notions of curve fitting was found by trial to be about 10%. This figure may therefore be taken as an estimate of the *relative* accuracy of the tabulated values for either mixture as a function of temperature. The absolute accuracy of any values, or the relative accuracy as a function of composition of solvent, depends upon many factors, both experimental and theoretical. With decreasing K, the ambiguity inherent in the physical definition of ionized, or associated, hydrochloric acid decreases rapidly; unfortunately, the experimental accuracy of the measurements and the concentration range in which equations (6) and (7) may be used with confidence, also decrease under this condition. Furthermore this range is not definitely known for the particular system under investigation.

Shedlovsky[28] has suggested recently a modification of equation (6) which would be expected to increase its concentration range, and hence its usefulness, but its application to the present data does not lead to a significant change in the extrapolated values, or improve the linearity of the plots. Equation (7) might be improved by the introduction of the extended terms of Gronwall, La Mer and Sandved,[29] or the use of activity coefficients recently derived from electromotive force measurements by Harned and his students. Although both of these alternatives lead to values of K of the same order ($\pm 20\%$) as those in Table V, we do not regard such agreement, or disagreement, to be particularly significant. Neither method decreases the uncertainties in curve-fitting, and both introduce characteristic errors of their own. The extended terms should represent a correction in the right direction, but their convergence is not satisfactory under our experimental conditions. The e. m. f. activity coefficients involve the extended terms in their own extrapolation, and therefore do not offer an independent solution of the problem, but rather increase the extrapolative uncertainty if used in conjunction with our data. It therefore does not seem worth while to attempt further refinements in calculation at present. More accurate values of K would then be contingent upon measurements at concentrations far beyond the useful range of our present equipment.

The values of the apparent mean ionic diameter, a, given in Table V, were calculated from the corresponding values of K by the equation of Bjerrum[16] and Fuoss and Kraus.[30] This equation expressed the dissociation constant of an electrolyte in terms of the product DT and the single characteristic parameter, a. For electrolytes yielding large ions, such as tetraisoamylammonium nitrate,[30] the value of a shows little, or no, dependence upon the composition of the solvent. On the other hand, the value of a for acids would be expected to vary with the solvent because of the solvation of the proton. In Table V, however, the variation with solvent is of the opposite sign to that which might be predicted from consideration of the relative sizes of the water and dioxane molecules. For reasons indicated in the last two paragraphs, we are inclined to discount the physical significance of this "observed" variation in the numerical value of a in passing from 70 to 82% dioxane, and attribute it mainly to systematic uncertainties in the absolute values of K in the two solvents. On this basis, the values of a in 70% dioxane would be less reliable than those in 82%. The relative accuracy of K in a given solvent makes it possible that the observed variation of a with temperature is real. It will be noticed that the "observed" values of a decrease regularly (value in 70% at 15° excepted) with increase in temperature, and that the temperature coefficients are the same for both series.

The variation of K with temperature permits evaluation of the heat of ionization and entropy of ionization of hydrochloric acid at unit activity of both ions and associated ion-pairs. At 25°, $\Delta H^0 = -3{,}700$ cal. in 70% dioxane, and $-4{,}900$ cal. in 82% dioxane. The corresponding values of ΔS^0 are -22 and -33 cal., respectively.

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[26] Nims, THIS JOURNAL, **56**, 1110 (1934).

[27] Harned and Embree, *ibid.*, **56**, 1042 (1934).

[28] Shedlovsky, *J. Franklin Inst.*, **225**, 739 (1938).

[29] Gronwall, La Mer and Sandved, *Physik. Z.*, **29**, 358 (1928).

[30] Fuoss and Kraus, THIS JOURNAL, **55**, 1019 (1933).

Summary

The equivalent conductance of hydrochloric acid has been measured in 20, 45, 70 and 82% dioxane solutions at 15, 25, 35 and 45°. The experimental data closely follow the Onsager limiting slope in 20 and 45% dioxane solutions at high dilutions. Ionic association is too pronounced in 70 and 82% dioxane for convergence with the limiting slope within the accessible concentration range.

In a given solvent mixture, it was shown that the temperature dependence of the limiting conductance is linear, and the variation with viscosity can be expressed by $\Lambda_0\eta_0^s = r(s < 1)$.

The effect of the dielectric constant upon conductance and ionic association was illustrated by graphs, and by evaluation of the dissociation constant of hydrochloric acid in 70 and 82% dioxane solutions. At 25° the estimated values of the dissociation constant are 7.7×10^{-3} and $2.0 \times \times 10^{-4}$ in 70 and 82% dioxane solutions, respectively. Rough values of the heat and entropy of ionization were also reported.

NEW HAVEN, CONN. RECEIVED JULY 13, 1938

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, THE UNIVERSITY OF CHICAGO]

The Heat Contents of the Salts of the Alkali Metals in Extremely Dilute Aqueous Solutions

BY T. F. YOUNG AND PAUL SELIGMANN

One of the most significant and interesting tests of the limiting law of Debye and Hückel[1] is the comparison of heats of dilution with the predictions of the theoretical equation. In their review of existing calorimetric data Lange and Robinson[2] concluded that the theory was in fairly satisfactory agreement with experiment. In various other papers, however, they and their respective co-workers have made estimates of the limit, as the concentration approaches zero, of the derivative of the apparent molal heat content with respect to the square root of the concentration ($S = \mathrm{d}\phi H/\mathrm{d}\sqrt{c}$), which differ considerably from the values computed from the modern precise dielectric constant measurements of Wyman.[3] These limiting derivatives for salts of the alkali metals vary from 36% of the theoretical value for potassium nitrate at 12.5° to 89% of the theoretical for lithium sulfate at 25°. They appear to show some significant trends: for example, the limiting derivatives of the five alkali metal sulfates decrease in the order of increasing molecular weights of the salts, whereas the theory demands that the limiting slope be the same for all salts of a given valence type.

In some recent papers of Lange and Robinson and their co-workers,[4] doubt has been expressed of the validity of extrapolations based upon the assumption that S is constant throughout a concentration range such as that between $m = 0$ and 0.01. Young and Groenier[5] have applied to the sodium chloride measurements a method of calculation which avoids the assumption of the constancy of the derivative, S. Their method possesses the further advantage that it deals directly with the measured heats of dilution; the older method[6] of Lange and Robinson was applied to a series of relative values of $-\phi H$ calculated by an addition process which obscured the actual measurements. As applied by Young and Groenier, the method also included a "chord-area" plot of the derivative, S, the property of immediate interest. This representation of the actual dilution data and the derivative on the same graph aids in the selection of a satisfactory type of equation to be used to represent the data, and in an understanding of the significance of the deviations between the derived equation and the experimental values.

In this paper are presented the results of an investigation of the limiting slopes of all salts of the alkali metals for which there are sufficient data for the determination of equations by the method of least squares.[7]

Procedure.—In each dilution experiment, q, the heat absorbed during an isothermal dilution

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(1) Debye and Hückel, *Physik. Z.*, **24**, 185 (1923).

(2) Lange and Robinson, *Chem. Rev.*, **9**, 89 (1931).

(3) Wyman, *Phys. Rev.*, **35**, 623 (1930).

(4) *Cf.* Gulbransen and Robinson, THIS JOURNAL, **56**, 2637 (1934).

(5) Young and Groenier, *ibid.*, **58**, 187 (1936).

(6) For details, see Lange and Robinson, *ibid.*, **52**, 4218 (1930).

(7) We are indebted to Mr. J. C. Hesler, Mr. Fred Karush and Mr. R. P. McCormick who duplicated our calculations.

of n moles of solute is determined. The ratio q/n is the increase in the apparent molal heat content, $\Delta(\phi H)$. From a series of values of $\Delta(\phi H)$, each tabulated with the corresponding initial and final concentrations, an equation of the type

$$\phi H + C = \alpha c^{1/2} + \beta c + \gamma c^{3/2} + \ldots \quad (1)$$

may be derived by conventional least square methods. The precision with which $\Delta(\phi H)$ is determined decreases with the amount of solute in the calorimeter, *i. e.*, with n. The probable error in $\Delta(\phi H)$ would be inversely proportional to n if all q's were determined with the same probable error, and a weighting factor proportional to n^2 would then be applicable to the squares of the residuals in the formation of the "normal equations." The probable errors do not decrease quite this rapidly with increase of n; a factor between unity and n^2 is therefore desirable. The final concentration, c_2, is approximately proportional to n and was used as the factor for the one cubic equation evaluated by this method (equation 26).

A slightly different point of view was adopted by Young and Groenier. For graphical representation of the derivative $S = \mathrm{d}(\phi H)/\mathrm{d}\sqrt{m}$ on a chord–area plot they had computed for each dilution the chord $\overline{P} = \Delta(\phi H)/\delta$, where δ is the increase in $\sqrt{c}$ accompanying the dilution. From the chords, equations of the type

$$S = S^0 + B\sqrt{m} + Cm + \ldots \quad (2)$$

were derived. If, in the formation of the normal equations, the squares of the residuals had been multiplied by the factor $n\delta^2$, the constants obtained from the second method would be precisely equal to the equivalent ones determined by the method described in the preceding paragraph. For convenience the factor $m_2{}^2$ was used instead of $n\delta^2$, since m_2 was nearly proportional to δ^2 in the sodium chloride experiments of Gulbransen and Robinson. In this extension of the calculations to other salts, the same factor $m_2{}^2$ and its approximate equivalent $c_2{}^2$ were adopted for general use. The only data for which this factor is not appropriate are those for potassium nitrate. In the 25° experiments of Lange and Monheim[8] there were two very dissimilar series of dilutions. One series resulted in five chords which are very much shorter than the others. For any value of $X = (\sqrt{c_2} + \sqrt{c_1})/2$ (the abscissa of a chord center), c_2 of a short chord is larger than c_2 of a long chord. The simple factor $c_2{}^2$ would therefore give greater weight to the shorter chords. On the chord–area plot the short chords lie far below the curve drawn through the longer ones. Since all the short ones lie in the region of small concentrations, they affect the tilt of the least square curve and exert a disproportionately large effect upon the extrapolated slope, S^0. The ratio of c_2 of a long chord to c_2 of a short chord having the same X is about 0.62. To give equal weights to the dilutions of both series, the factors $c_2{}^2$ and $(0.62\sqrt{c_2})^4$ were applied to the squares of the residuals of the long and short chords, respectively. The same factors were also applied to Lange and Monheim's potassium nitrate measurements at 12.5°.

The largest value of X in the 10 and 15° sodium chloride data was about 0.4. For the sake of intercomparisons of the four equations, it was desirable that the concentration ranges covered by the data employed in the derivations be the same for all temperatures. Since the quadratic equations appeared to be capable of representing the derivative S throughout the whole range of the existing data, the limit adopted for X was 0.4.

In this extension of the calculations to other salts of the alkali metals, the same limit was adopted for the derivation of a set of preliminary equations. The restriction eliminated data for very few salts, since X for most of them does not exceed 0.2. Each of the preliminary equations was tested by means of a deviation plot. The deviation of the ith chord is the difference between S_i, computed by the substitution of X_i in the empirical equation, and P_i calculated from the chord, $\overline{P}_i$, by the following equation[9]

$$\overline{P}_i - P_i = -C\delta_i{}^2/12 \quad (3)$$

When the deviation plot showed a trend indicative of failure of the quadratic equation for the full concentration range, a new equation was derived. The new equation might be either another quadratic derived for a more limited concentration range, or it might be a cubic equation.

The deviations of only one curve, that for potassium perchlorate at 15°, seemed to show a significant trend. A new quadratic was therefore derived from all of the chords except the last pair. It was adopted as final since a new deviation plot exhibited no significant trend. When the two discarded chords were represented on the new deviation plot it became apparent that they

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[8] Lange and Monheim, *Z. physik. Chem.*, **A150**, 349 (1930).

[9] Ref. 5, equation 6.

were inconsistent with each other, and that only one of them disagreed seriously with the curve derived from the other ten. The deviation of the longer chord, which resulted from a single dilution in the calorimeter, was relatively small; the deviation for the shorter chord produced by an additional dilution was larger. When the S curve is known only approximately in the region of small concentrations, one chord may be calculated from the other. Such a calculation exposed a 4% discrepancy between the two chords. Such a large error is not to be expected in the dilution of relatively concentrated solutions, and is apparently due to an accident. If the accident had occurred in the determination of the longer chord, both would have been affected; if it occurred in the second dilution only the shorter chord would be affected. The longer chord which is in satisfactory agreement with the curve had been confirmed by duplicate measurements, the second dilution was one of the very few dilutions made by Andauer and Lange[10] which was not duplicated. It seems, therefore, that the shorter chord is the faulty one. There is, then, no evidence that the quadratic does not represent the potassium perchlorate curve satisfactorily over the whole concentration range of the data, but merely that it fails to agree satisfactorily with a chord which is almost certainly in error.

Concentration was expressed in most of the work of Lange and Robinson and their co-workers in terms of c (mole/liter). The sodium chloride data are in terms of molality (m). Though the difference is insignificant, these quantities are distinguished by their usual symbols in the equations.

The Equations.—The new equations, together with two of the sodium chloride set, are in Tables I and II. As predicted by theory, the limiting slopes of the alkali sulfates are $3^{3/2}$ times those of salts of the 1–1 valence type. The mean of five values of $S^0/3^{3/2}$ of the salts of the 1–2 type and the eleven values of S^0 for the other alkali metal salts is 47_6 at 25°. This value is about 30% larger than the mean of the limits calculated by the method of Lange, *et al.* The theoretical limit is 47_7. The complete set of curves is shown in Figs. 1 and 2 which illustrate the concordance of the empirical equations with the data and the agreement of theory with experiment. This striking agreement seems to us to be the most impressive quantitative confirmation yet received by the Debye–Hückel limiting law.

TABLE I

25°

$NaCl$[4,5]	$S = 476 - 1{,}452\sqrt{m} + 730m$	(4)
$NaBr$[11]	$S = 470 - 1{,}793\sqrt{c} + 1{,}498c$	(5)
$NaNO_3$[12]	$S = 454 - 2{,}645\sqrt{c} + 1{,}937c$	(6)
$NaClO_3$[12]	$S = 462 - 2{,}497\sqrt{c} + 2{,}103c$	(7)
$NaBrO_3$[12]	$S = 540 - 4{,}428\sqrt{c} + 7{,}299c$	(8)
$NaIO_3$[12]	$S = 501 - 5{,}962\sqrt{c} + 7{,}841c$	(9)
KCl[13]	$S = 444 - 1{,}447\sqrt{c} + 839c$	(10)
KBr[11]	$S = 514 - 3{,}050\sqrt{c} + 5{,}353c$	(11)
KNO_3[8]	$S = 408 - 4{,}128\sqrt{c} + 3{,}636c$	(12)
$KClO_3$[10]	$S = 568 - 5{,}797\sqrt{c} + 8{,}974c$	(13)
$KClO_4$[10]	$S = 440 - 6{,}973\sqrt{c} + 9{,}022c$	(14)

15°

$NaCl$[4,5]	$S = 414 - 1{,}651\sqrt{m} + 924m$	(15)
$KClO_3$[10]	$S = 409 - 4{,}903\sqrt{c} + 5{,}239c$	(16)
$KClO_4$[10]	$S = 417 - 8{,}447\sqrt{c} + 12{,}151c$	(17)

12.5°

KCl[13]	$S = 394 - 1{,}896\sqrt{c} + 1{,}530c$	(18)
KNO_3[8]	$S = 350 - 5{,}314\sqrt{c} + 5{,}862c$	(19)

TABLE II

25°

Li_2SO_4[14]	$S = 2{,}548 - 6{,}948\sqrt{c} + 4{,}958c$	(20)
Na_2SO_4[14]	$S = 2{,}432 - 14{,}896\sqrt{c} + 19{,}532c$	(21)
K_2SO_4[14]	$S = 2{,}399 - 14{,}879\sqrt{c} + 22{,}323c$	(22)
Rb_2SO_4[14]	$S = 2{,}512 - 18{,}333\sqrt{c} + 32{,}635c$	(23)
Cs_2SO_4[14]	$S = 2{,}231 - 18{,}697\sqrt{c} + 34{,}622c$	(24)

The calorimetric measurements of some of the more dilute solutions depended upon precision in temperature measurement of a few ten-millionths of a degree. Some of the curves required extrapolations over wide concentration intervals by means of an arbitrary type of equation, the quadratic power series. The remaining discrepancies between theory and the extrapolated limits, therefore, may be without significance. That they do not, in general, indicate failures of theory becomes more probable when a few of the typical cases are examined further. The two series of chords tabulated for potassium nitrate have been discussed already: one or the other must be wrong. Since the general agreement observed for all the salts suggests that the five short chords are in error, an equation was derived from the long chords only. It is in very close agreement with theory.

$$S = 449 - 4{,}578\sqrt{c} + 4{,}708c \qquad (25)$$

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[10] Andauer and Lange, *Z. physik. Chem.*, **A165**, 89 (1933).

[11] Hammerschmid and Robinson, THIS JOURNAL, **54**, 3120 (1932).

[12] Lange and Robinson, *Z. physik. Chem.*, **A148**, 97 (1930).

[13] Lange and Leighton, *Z. Elektrochem.*, **34**, 566 (1928).

[14] Lange and Streeck, *Z. physik. Chem.*, **A157**, 1 (1931).

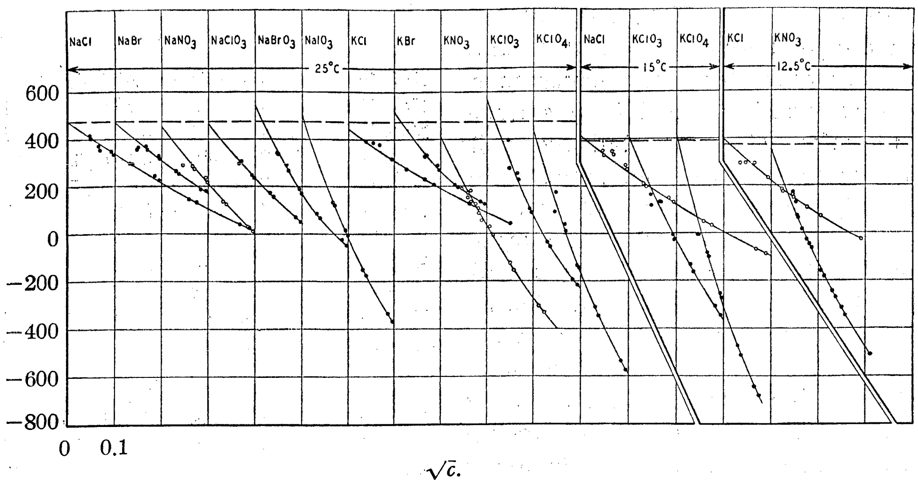

Fig. 1.—The derivative, S, *versus* $\sqrt{c}$. The curves represent the equations of Table I; the symbols ○ and ● are used to distinguish values of P associated with intersecting or adjacent curves. The origin of each successive curve lies one division to the right of the origin of its predecessor. Each horizontal interval represents an increment of 0.1 in $\sqrt{c}$. The respective theoretical limits are shown by the broken horizontal lines.

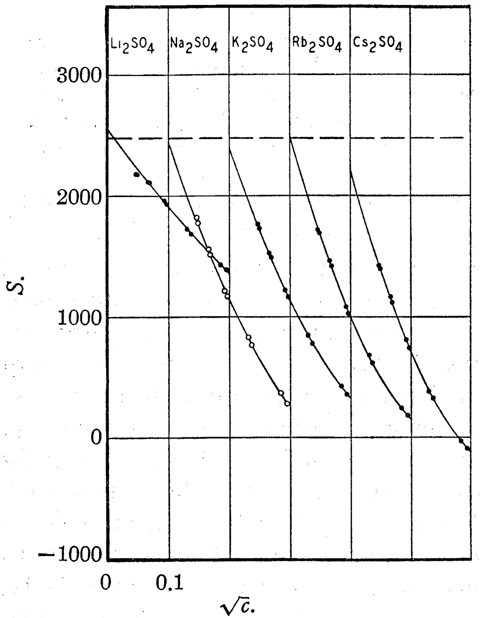

Fig. 2.—The derivative, S, versus $\sqrt{c}$. The curves represent the equations of Table II; the symbols represent values of P.

Though the potassium chloride limit is in satisfactory agreement with theory, the wide range of data available permits a further study of equation types. A cubic was determined from all ten chords

$$S = 460 - 1{,}718\sqrt{c} + 2{,}106c - 1{,}583c^{3/2} \qquad (26)$$

The somewhat better agreement of the extrapolated limit with theory suggests that the quadratic may have been applied to too wide a concentration range. One developed for values of X less than 0.2 actually reverses the algebraic sign of the discrepancy.

$$S = 482 - 1{,}967\sqrt{c} + 2{,}368c \qquad (27)$$

The changes in S^0 produced by these arbitrary variations of method confirm the view that differences of such magnitude are not significant. Moreover, the curves exhibiting the largest discrepancies are, in general, those which are most highly curved, and which are therefore least likely to be well fitted by an equation of arbitrarily chosen type.

The empirical equations, 4 to 24, may be used for calculations of accurate values of the partial molal and apparent molal heat contents. If, however, they are accepted (in addition to other known facts) as evidence that the theory agrees with experiment within the limits of error of the latter, a more precise set of equations may be derived with the aid of theory. Table III contains equations all having the theoretical limit, S^0. The B and C terms were computed by least square methods similar to those described above. Since fewer data are necessary for the determination of two constants the chord centers, X, were restricted to 0.2. Since the five short chords for potassium nitrate at 25° are definitely inconsistent with the theory, as well as with the other measurements, and since theory was being used as a guide for the derivation of this set of equations, the five short chords were not used. To emphasize the somewhat arbitrary character of this pro-

TABLE III

	25°	
NaCl	$S = 477 - 1{,}532\sqrt{m} + 1{,}154m$	(28)
NaBr	$S = 477 - 1{,}888\sqrt{c} + 1{,}770c$	(29)
$NaNO_3$	$S = 477 - 2{,}961\sqrt{c} + 2{,}834c$	(30)
$NaClO_3$	$S = 477 - 2{,}708\sqrt{c} + 2{,}701c$	(31)
$NaBrO_3$	$S = 477 - 3{,}562\sqrt{c} + 4{,}831c$	(32)
$NaIO_3$	$S = 477 - 5{,}635\sqrt{c} + 6{,}913c$	(33)
KCl	$S = 477 - 1{,}893\sqrt{c} + 2{,}144c$	(34)
KBr	$S = 477 - 2{,}541\sqrt{c} + 3{,}902c$	(35)
KNO_3	$(S = 477 - 5{,}006\sqrt{c} + 6{,}079c)$	(36)
$KClO_3$	$S = 477 - 4{,}527\sqrt{c} + 5{,}334c$	(37)
$KClO_4$	$S = 477 - 7{,}492\sqrt{c} + 10{,}510c$	(38)
	15°	
NaCl	$S = 393 - 1{,}411\sqrt{m} + 335m$	(39)
$KClO_3$	$S = 393 - 4{,}681\sqrt{c} + 4{,}602c$	(40)
$KClO_4$	$S = 393 - 8{,}086\sqrt{c} + 11{,}011c$	(41)
	12.5°	
KCl	$S = 374 - 1{,}569\sqrt{c} + 372c$	(42)
KNO_3	$S = 374 - 5{,}753\sqrt{c} + 7{,}522c$	(43)
	25°	
Li_2SO_4	$S = 2{,}481 - 6{,}022\sqrt{c} + 2{,}305c$	(44)
Na_2SO_4	$S = 2{,}481 - 15{,}576\sqrt{c} + 21{,}482c$	(45)
K_2SO_4	$S = 2{,}481 - 16{,}022\sqrt{c} + 25{,}599c$	(46)
Rb_2SO_4	$S = 2{,}481 - 17{,}896\sqrt{c} + 31{,}381c$	(47)
Cs_2SO_4	$S = 2{,}481 - 22{,}169\sqrt{c} + 44{,}570c$	(48)

cedure the 25° equation is enclosed in parentheses. For certain theoretical calculations based upon the assumption that the limiting law is valid, this second set of equations will be preferable to those in Tables I and II. Ion size studies, for example, are often based upon the assumption that the Debye–Hückel theory is quantitatively correct, which implies that S^0 of all salts of a given valence type must be the same.[15]

For most purposes, values of the relative partial molal and apparent molal heat contents computed from the two sets of equations do not differ appreciably, nor do they differ much from the values listed in the original tables of Lange, Robinson, *et al.* About five calories per mole is the largest difference produced by various methods of extrapolation.

A few other salts of the alkali metals have been studied, though sufficient data for them have not been published to justify the derivation of least square equations. A few dilutions of lithium chloride[16] and potassium fluoride,[17] represented on a chord-area plot indicate that these three salts obey the limiting law. Chords for rubidium fluoride[8] are erratic and badly scattered and are useless for our purpose.

For investigation of heat capacities, more dilution measurements are necessary over a temperature range and wide concentration range. Young and Machin[18] already have utilized such data for sodium chloride to demonstrate that existing specific heats do not prove the existence of a conflict between the limiting law and experiment.

At the present time no existing calorimetric data for salts of the alkali metals are in disagreement with the Debye–Hückel limiting law. Indeed, most measurements of their heats of dilution support the law with striking consistency.[19]

Summary

The method applied by Young and Groenier to the heats of dilution of aqueous sodium chloride solutions has been extended to all other salts of the alkali metals for which sufficient data are available for the application of the least square technique. The average value of the limiting derivative, S^0, for eleven salts of the 1–1 valence type at 25° and $S^0/3^{3/2}$ for five salts of the 1–2 valence type is about 30% larger than the average of the older estimates based upon an assumed linear relation between the apparent molal heat content and the square root of the concentration. The new average agrees with the theoretical value calculated from Wyman's dielectric constant measurements and the Debye–Hückel limiting law.

Since the calculated values of S^0 appear to confirm the Debye–Hückel limiting law and Wyman's measurements a second set of derivative equations have been derived in which S^0 was fixed at the theoretical value.

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(15) It already has been pointed out by Young and Vogel, THIS JOURNAL, **54**, 3030 (1932), that reasonable values of the parameter "*a*" may be computed from the *B* terms of the empirical equations. Such a calculation implies that the temperature coefficient of "*a*" is negligible and that certain other factors may be neglected. Lange and Robinson (Ref. 2, p. 111) have pointed out that these assumptions lead to the conclusion that the ion size of the alkali metals increases with atomic weight whereas freezing point measurements and other data indicate the reverse order.

(16) Lange and Messner, *Z. Elektrochem.*, **33**, 431 (1927).

(17) Lange and Eichler, *Z. physik. Chem.*, **129**, 285 (1927).

(18) Young and Machin, THIS JOURNAL, **58**, 2254 (1936).

(19) An incomplete investigation of salts of the alkaline earth metals of the 2–1 valence type indicates similar agreement, at least at 25°. The extrapolations seem to be of poorer precision, and afford less definite support to the Debye–Hückel theory, but no data point to failure of the theory. Existing data for salts of the 2–2 valence type *if treated by the methods described above*, certainly do not lead to limiting values in agreement with theory. *Cf.* Young, *Science*, **85**, 48 (1937).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

The Catalytic Effect of Anions upon the Rate of Dissolution of Hydrous Alumina by Acids

BY JOHN P. CLAY AND ARTHUR W. THOMAS

The effect of certain acids in aqueous solution—hydrobromic, hydrochloric, nitric, sulfuric, oxalic, hydrofluoric, phosphorous and phosphoric—upon the rate of dissolution of certain hydrous alumina specimens has been found by the writers to vary greatly with the nature of the anions of the acids. The first four acids mentioned above are extraordinarily less active in the dissolution of aged hydrous alumina than the latter four, despite the fact that the former have greater activity and diffusion coefficients.

These effects, reported herein, are not in accord with the classical theory[1] that the rate-determining factor in reactions at a solid–liquid interface is the rate of diffusion of the reactants into a film of a saturated solution of the solid at the interface and of the product away from this film.

Neither are the observations reported herein in accord with the hypothesis[2] that anions of high valence will increase the velocity of dissolution of hydrous alumina in acid solutions, owing to adsorption of these anions at the solid–liquid interface and to concomitant lowering of the potential difference at this interface.

The present results indicate that the rate-determining factor is chemical in nature, and the writers submit an explanation involving the formation of a complex at the solid–liquid interface.[3]

Materials

Amalgamated Aluminum.—Aluminum ingots[4] were amalgamated by placing them in contact with redistilled mercury in a 5% aqueous solution of mercuric chloride. When the surface of the aluminum was covered with mercury the ingots were washed free of electrolyte with hot distilled water and were kept under distilled water at room temperature until needed.

Hydrous Alumina.—The specimens of hydrous alumina used in this investigation were prepared in the following manner.

Specimen "A."—Twelve pieces of amalgamated aluminum weighing approximately 200 g. each were placed in two liters of distilled water at 25 ± 2° and allowed to react for twenty-four hours. The suspension was filtered and dried in air at room temperature, pulverized to a fine powder, and allowed to remain in contact with the atmosphere until it showed no change in water content on three successive days. This procedure was continued until 1000 g. of oxide was obtained. The oxide was then thoroughly mixed and screened through a 100-mesh sieve. This specimen showed upon analysis the composition $Al_2O_3 \cdot 2.89 H_2O$.

Specimen "B."—The procedure was the same as for Specimen "A" except that the amalgamated aluminum was placed in boiling water and allowed to react at this temperature for six hours. This specimen showed upon analysis the composition $Al_2O_3 \cdot 2.70 H_2O$.

Acids.—The acids used were reagent grade and the acid solutions were prepared by quantitative dilution of solutions which had been standardized by means of carbonate-free sodium hydroxide solution. The latter was standardized against acid potassium phthalate.

Measurement of the Rate of Solution.—A weighed quantity of the hydrous oxide was transferred through a funnel into a 300-ml. flint glass bottle by means of 200 ml. of the acid solution of the desired concentration. The bottle was placed in a motor-driven rotator which revolved at the rate of seven r. p. m., in a water-bath at 25 ± 0.05°. At the expiration of the desired time of rotation the contents of the bottles were poured into centrifuge tubes. One drop of a saturated solution of ammonium sulfate was added to solutions of Specimen "A" and five drops to solutions of Specimen "B" in order to precipitate colloidally dispersed alumina. The bottles were then centrifuged for ten minutes at 1500 r. p. m. (rotating radius to middle of tube was 42 cm.). After centrifuging, the supernatant liquor was siphoned off and appropriate quantities taken for analysis.

Waxed bottles were used whenever hydrofluoric acid was present.

Methods of Analysis

Three methods of analysis for aluminum were used in this investigation: (I) in the presence of phosphate and phosphite, (II) in the presence of oxalate and (III) in the presence of fluoride, sulfate, chloride, bromide and nitrate.

For (I) aluminum in the presence of phosphate, phosphite and pyrophosphate the method of Hillebrand and Lundell was used.[5a] The pyrophosphate was hydrated[6] to the phosphate by addition of hydrochloric acid to 2 *M* strength and by boiling for three hours.

In the presence of sulfate, chloride, fluoride, bromide, and nitrate (II) the aluminum was precipitated as the hydroxide, according to the method of Blum,[7] and ignited

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[1] (a) Noyes and Whitney, *Z. physik. Chem.*, **23**, 689 (1897); (b) Nernst, *ibid.*, **47**, 52 (1904); (c) Nernst and Brunner, *ibid.*, **47**, 56 (1904).

[2] Tartar, Bryan and Shinn, THIS JOURNAL, **55**, 2266 (1933).

[3] Schwab, Taylor and Spence, "Catalysis," D. Van Nostrand Company, Inc., New York, N. Y., 1937, p. 219.

[4] The aluminum, specified as 99.94% pure, was obtained from The Aluminum Company of America.

[5] (a) Hillebrand and Lundell, "Applied Inorganic Analysis," John Wiley and Sons, Inc., New York, N. Y., 1929, p. 399; (b) *ibid.*, p. 394.

[6] Kiehl and Claussen, THIS JOURNAL, **57**, 2284 (1935).

[7] Blum, *ibid.*, **38**, 1282 (1916).

and weighed as Al_2O_3. Since the maximum concentration of fluoride in any determination was 0.008 molar, its presence did not cause an appreciable incomplete precipitation of aluminum. In all cases, treatment of the aluminum oxide residue with hydrofluoric acid, followed by evaporation and re-ignition,[5b] caused no loss in weight, indicating the absence of an appreciable quantity of silica.

In the presence of oxalic acid (II) the solution was evaporated almost to dryness, cooled and treated with 5 ml. of concentrated sulfuric plus 5 to 10 ml. of concentrated nitric acids. After heating for two hours on a steam-plate to oxidize completely the oxalic acid, the aluminum content was determined as in method III.

Analyses for aluminum in the presence of chloride, bromide, sulfate, nitrate and oxalate were also made by precipitation, as the phosphate. Such analyses showed that when aluminum is precipitated as the phosphate the results are consistently 2–3% higher than when the aluminum is precipitated as the hydroxide. Therefore the results of all analyses for aluminum precipitated as the phosphate were lowered by 3%.

It was also found to be necessary to oxidize the oxalate with nitric acid before precipitating the aluminum phosphate.

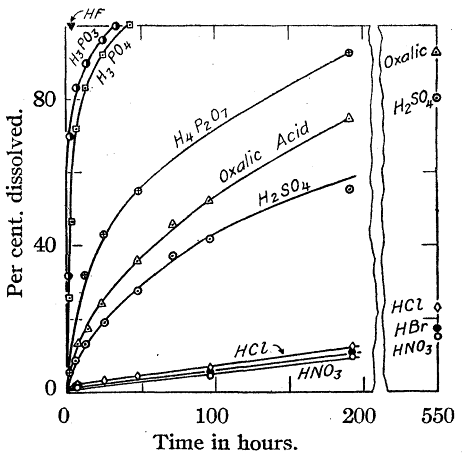

Fig. 1.—The dissolution of $Al_2O_3 \cdot 2.89H_2O$ in diverse acids. This graph contrasts the rates of dissolution of 260 mg. of 100-mesh $Al_2O_3 \cdot 2.89H_2O$ at 25° in 200 ml. of 0.2 *N* solution (H_3PO_3 and H_3PO_4 were 0.1 *M*) of the acids indicated on the curves.

Experimental Results

The curves for the dissolution of Specimen "A" in 0.2 *N* solutions of hydrofluoric, phosphorous, phosphoric, oxalic, sulfuric, hydrochloric, hydrobromic and nitric acids and in a mixture of hydrochloric acid and potassium pyrophosphate, 0.2 *N* to both, are plotted in Fig. 1. In each case there were present 260 mg. of the hydrous alumina (equal to 172 mg. of Al_2O_3) and 200 ml. of the aqueous acid solution. The striking differences in rates of solution are obviously neither a function of hydrogen ion activity nor of diffusibility or valence of the ions. The rate of dissolution in the hydrofluoric acid solution was too great to

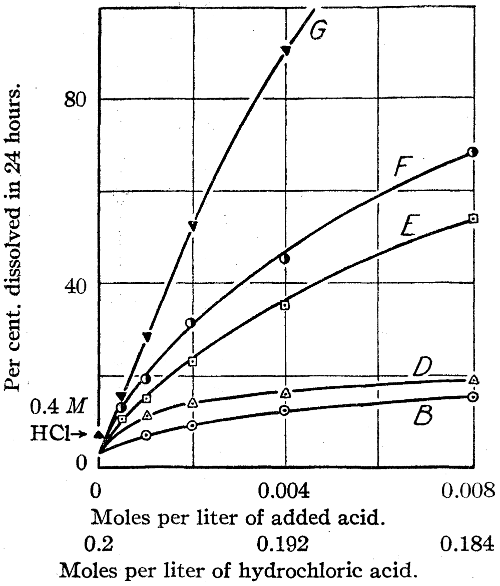

Fig. 2A.—The influence of the concentration of certain acids on the amount of the hydrous oxide (Specimen "A") dissolved in one day, 260 mg. of $Al_2O_3 \cdot 2.89H_2O$ was added to 200 ml. of solutions of HCl containing an added acid (B) H_2SO_4, (D) Oxalic, (E) H_3PO_4, (F) H_3PO_3, (G) H_2F_2. These suspensions were rotated at 25° for 24 hours, centrifuged, and the supernatant solutions analyzed for dissolved aluminum ion. The arrow indicates per cent. dissolved in 0.4 *M* HCl in 24 hours.

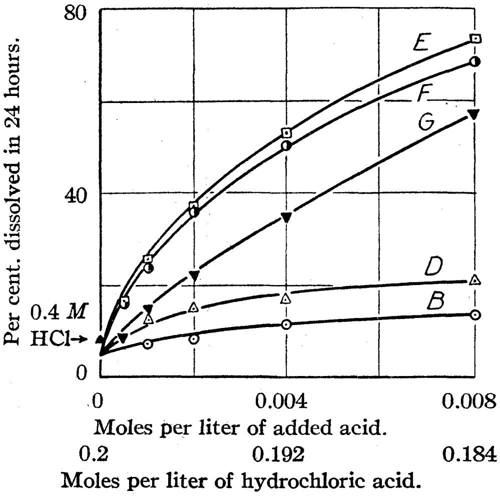

Fig. 2B.—The influence of the concentration of certain acids on the amount of hydrous oxide (Specimen "B") dissolved in one day. 260 mg. of $Al_2O_3 \cdot 2.70H_2O$ was added to 200 ml. of solutions of HCl containing an added acid (B) H_2SO_4, (D) oxalic, (E) H_3PO_4, (F) H_3PO_3, (G) H_2F_2. These suspensions were rotated at 25° for 24 hours, centrifuged, and the supernatant solutions analyzed for dissolved aluminum ion. The arrow indicates per cent. dissolved in 0.4 *M* HCl in 24 hours.

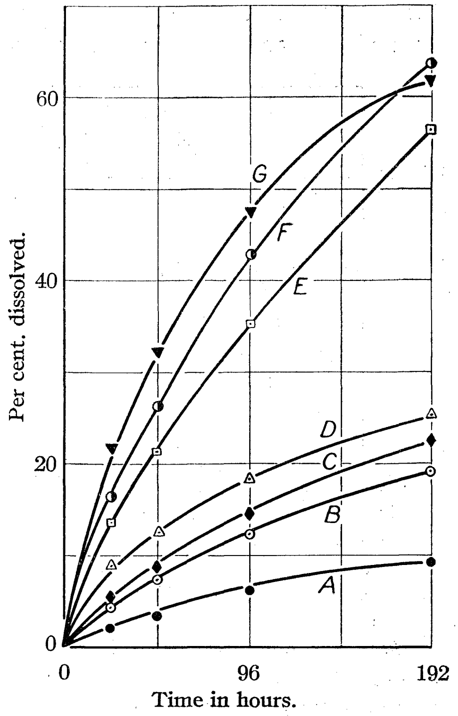

Fig. 3A.—The catalytic effect of anions on the rate of dissolution of the hydrous oxide (Specimen "A") in hydrochloric acid. 520 mg. of $Al_2O_3 \cdot 2.89H_2O$ was added to 200 ml. of 0.198 *M* HCl which was also 0.001 *M* (B) H_2SO_4, (D) Oxalic, (E) H_3PO_4, (F) H_3PO_3, (G) H_2F_2. Curve (A) represents the rate in 0.2 *M* HCl, and (C) the rate in 0.4 *M* HCl.

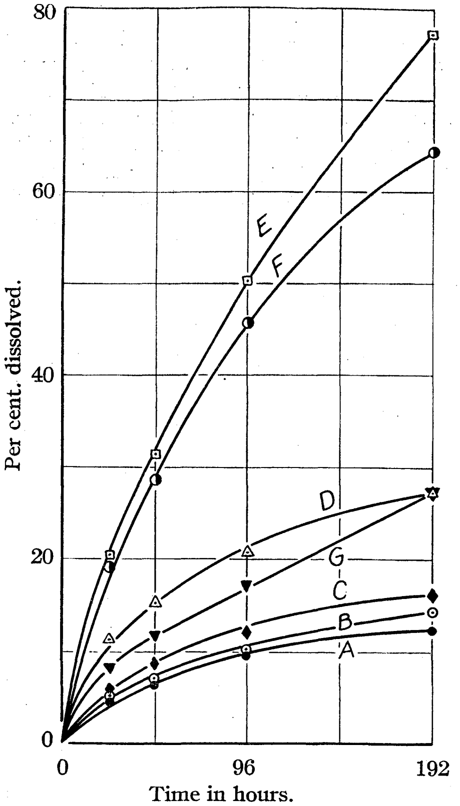

Fig. 3B.—The catalytic effect of anions on the rate of dissolution of hydrous oxide (Specimen "B") in hydrochloric acid. 520 mg. of $Al_2O_3 \cdot 2.70H_2O$ was added to 200 ml. of 0.198 *M* HCl which was also 0.001 *M* (B) H_2SO_4, (D) oxalic, (E) H_3PO_4, (F) H_3PO_3, (G) H_2F_2. Curve (A) represents rate in 0.2 *M* HCl, and (C) the rate in 0.4 *M* HCl.

plot in this figure, the oxide having completely dissolved to a clear crystalloidal solution in about six minutes. In 0.2 *N* hydrofluosilicic acid the solution was complete in about two hours. The measurements were always made in duplicate and sometimes in triplicate, showing a reproducibility to 3%.

In the next series of measurements, the results of which are given in Figs. 2A and 2B, the acid solutions, 200 cc. in each case, consisted of mixtures of hydrochloric acid, 0.2 to 0.184 *M* plus one of the other acids, 0.0 to 0.008 *M*. (For consistency we are using the molecular formula H_2F_2 to represent a mole of hydrofluoric acid.) In the case of Specimen "A," 260 mg. was taken, as in the first instance; the amount of Specimen "B" was also 260 mg. (equal to 176 mg. of Al_2O_3). The time of reaction was twenty-four hours. It is seen that small amounts of the added acids influence greatly the rate of dissolution. In the experiments with both oxide specimens, the effect of 0.4 *M* hydrochloric acid was measured also, the result shown by the arrow on the ordinate axis demonstrating that doubling the concentration of hydrochloric acid was less effective than substituting very small amounts of the diverse acids for part of the 0.2 *M* hydrochloric.

The data in Figs. 2A and 2B show clearly that the amount of oxide dissolved in twenty-four hours in an acid solution is dependent upon the nature and concentration of the anions present and upon the temperatures at which the oxides were prepared.

It is observed that while hydrofluoric, phosphorous, and phosphoric acids greatly accelerate the rate of solution of both oxide specimens, their order of effectiveness differs in the two cases. This change in order will be considered under "Discussion of Results." In passing it might be mentioned that the rates of dissolution of the natural modifications of calcium sulfate—alabaster, fibrous gypsum and selenite—in water have been shown to be different in each of the three cases.[8]

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[8] Wildermann, *Z. physik. Chem.*, **66**, 445 (1909).

A series of measurements upon the time of dissolution of the oxide specimens (520 mg.) in 200-cc. portions of solution mixtures, 0.198 *M* with respect to hydrochloric and 0.001 *M* with respect to other acids, again showed the striking influence of traces of certain anions. These results are plotted in Figs. 3A and 3B. With the exception of the added sulfuric acid, it is noted that the added anions increased the rate in 0.2 *N* solution more than was effected by doubling the concentration of hydrochloric acid.

In order to determine the influence of extent of surface of the oxide, experiments were performed in which 200-ml. portions of acid solutions, 0.198 *M* with respect to hydrochloric and 0.001 *M* with respect to other acids, were allowed to act for twenty-four hours upon various weights of the oxide specimens. Figures 4A and 4B summarize the results. The weight of oxide dissolved in unit time is a function of the weight of solid (surface exposed) present, and of the temperature at which the oxide was prepared. The effect of the anions in accelerating the rate of dissolution tends to reach a maximum. This is the usual type of phenomena encountered in heterogeneous reactions when the catalyst is exerting its maximum influence; a further increase in the surface has relatively no influence on the rate of the reaction. It will be noticed that the small concentration of hydrofluoric acid used is much less effective in catalyzing the dissolution of Specimen "B" than Specimen "A." This is a significant point which will be discussed later in connection with a consideration of the difference in the two types of hydrous oxides.

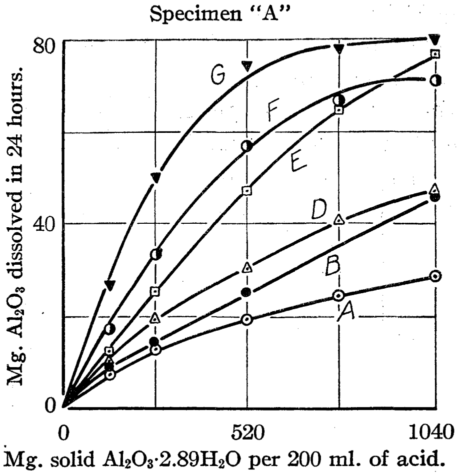

Fig. 4A.—The influence of surface area of hydrous alumina on amount dissolved. Different weights of $Al_2O_3 \cdot 2.89H_2O$ were added to 200 ml. of 0.198 *M* HCl which was also 0.001 *M* (A) H_2SO_4, (D) oxalic, (E) H_3PO_4, (F) H_3PO_3, (G) H_2F_2. Curve (B) represents the amount dissolved in 0.8 *M* HNO_3. The suspension was rotated for 24 hours at 25°, centrifuged, and the supernatant solutions analyzed for aluminum ion.

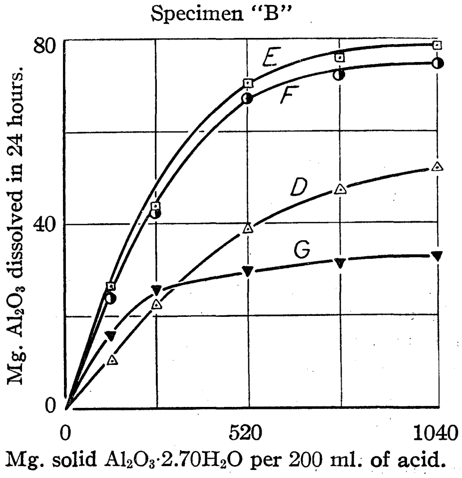

Fig. 4B.—The influence of surface area of hydrous alumina on amount dissolved. Different weights of $Al_2O_3 \cdot 2.70H_2O$ were added to 200 ml. of 0.198 *M* HCl which was also 0.001 *M* (D) oxalic, (E) H_3PO_4, (F) H_3PO_3, (G) H_2F_2. The suspensions were rotated at 25° for 24 hours, centrifuged, and the supernatant solutions analyzed for aluminum ion.

Discussion of Results

The explanation of these facts lies in the structural arrangement of the oxide and the specific nature of the anions, the formula $Al_2O_3 \cdot x(H_2O)$ not adequately representing the structure of the hydrous oxide.

Previous publications from this Laboratory have described the processes of olation and oxolation which take place when hydrous oxide hydrosols are aged at room temperature, which processes are accelerated upon heating.[9] These concepts are based on the Werner–Pfeiffer[10] ideas of hydrolysis and olation, together with Stiasny's[11] concept of oxolation. It is also agreed that oxolation may take place through a reaction of the type suggested originally by Küntzel, Riess and

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[9] (a) Thomas and Whitehead, *J. Phys. Chem.*, **35**, 27 (1931); (b) Thomas and Tai, THIS JOURNAL, **54**, 841 (1932); (c) Thomas and von Wicklen, *ibid.*, **56**, 794 (1934); (d) Thomas and Vartanian, *ibid.*, **57**, 4 (1935); (e) Thomas and Kremer, *ibid.*, **57**, 1821, 2538 (1935); (f) Thomas and Owens, *ibid.*, **57**, 1825, 2131 (1935); (g) Thomas and Miller, *ibid.*, **58**, 2526 (1936).

[10] (a) Pfeiffer, *Ber.*, **40**, 4036 (1907); (b) *Z. anorg. Chem.*, **56**, 275 (1907); (c) Werner, *Ber.*, **40**, 2113 (1907).

[11] (a) Stiasny and Balanyi, *Collegium*, 86 (1927); (b) Stiasny, "Gerbereichemie," Verlag von Theodor Steinkopff, Dresden-Blasewitz, Germany, 1931, p. 351.

Königsfeld.[12] The hydrous alumina specimens are polyolated, polyoxolated structures in which there are also hydroxo and aquo groups sufficient with the ol and oxo bridges to satisfy the coördination number of aluminum.

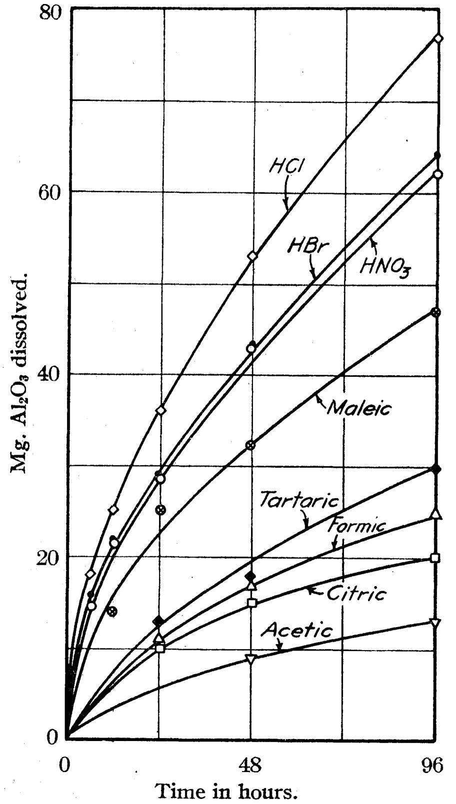

Fig. 5.—The dissolution of the hydrous oxide (Specimen "A") in diverse acids. 2.000 g. of $Al_2O_3 \cdot 2.89H_2O$ was added to 200 ml. of the 0.2 *N* acid solution, rotated at 25° for the desired time, a drop of $(NH_4)_2SO_4$ was added the solutions were then centrifuged and the supernatant solutions analyzed for dissolved aluminum ion.

For an acid to dissolve hydrous alumina and produce crystalloidal solutions of aluminum ions, it is necessary then that (1) the hydroxo groups be converted to aquo groups, (2) the ol bridges be broken and the hydroxo groups thus produced converted to aquo groups and (3) oxo bridges, if present, also be converted to hydroxo groups, etc. The first reaction is accomplished readily by oxonium ion, while (2) ol bridges are well known to be quite stable in the presence of oxonium ion and (3) oxo bridges are extremely resistant to attack by oxonium ion.

Since elevation in temperature favors the conversion of ol bridges to oxo bridges—*i. e.*, favors oxolation—one would expect Specimen "B," the hydrous oxide prepared by the action of boiling water upon aluminum amalgam, to be more oxolated than Specimen "A" which was prepared by the action of water at room temperature. Specimen "A" is perhaps predominantly an ol complex containing some oxo bridges and probably similar in structure to hydrargillite. Megaw[13] has submitted evidence for an olated structure for this mineral. Specimen "B" seems to be predominantly an oxo complex resulting from the partial oxolation of an olated structure possessing, to be sure, hydroxo groups as well as oxo bridges. This latter type, predominating in "B" and present to a minor extent in "A," may be the diaspore or chain-type structure referred to in recent literature.[14]

Considering now the dissolution of these hydrous oxides in aqueous acid solutions, it is apparent, since one of the products of the reaction is water, that the energy of formation of water furnishes the driving force for the reaction. But the potential energy of the ol $(\mathrm{Al\overset{H}{O}Al})$ link in the solid phase, or the oxo $(\mathrm{Al\overset{Al}{O}Al})$ link, is not readily available, as is evident from the slowness of the reaction of the solid hydrous oxide with the strong acids, hydrochloric, hydrobromic and nitric. Before an oxonium ion can react with an ol or oxo link it is necessary to form an intermediate link, the formation of which contributes toward the work required to break an ol or oxo link. Essentially this idea was suggested by London[15] for organic substitution reactions, and has been investigated by Polanyi,[16] Olsen[17] and Hammett.[18]

In other words, an intermediate complex must be formed, the formation of which renders the ol and oxo group reactive toward oxonium ion; and it is obvious that this intermediate complex involves anions, indeed, specific anions.

It is postulated in this paper that the formation of this complex is the rate-determining factor of the dissolution process.

Hydrargillite has been described[19] as an aluminum ion surrounded by six hydroxyl groups at the

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(12) Küntzel, Riess and Königsfeld, *Collegium*, 270 (1935).

(13) Megaw, *Z. Krist.*, **87**, 185 (1934).

(14) (a) Ewing, *J. Chem. Phys.*, **3**, 203 (1935); (b) Jander and Winkel, *Z. anorg. Chem.*, **200**, 257 (1931); (c) Fricke, *Kolloid Z.*, **69**, 312 (1934).

(15) London, *Z. Elektrochem.*, **35**, 552 (1929).

(16) (a) Meer and Polanyi, *Z. physik. Chem.*, **B19**, 164 (1932); (b) Bergman, Polanyi and Szabo, *ibid.*, **B20**, 161 (1933).

(17) (a) Olsen, *J. Chem. Phys.*, **1**, 418 (1933); (b) Olsen and Voge, THIS JOURNAL, **56**, 1690 (1934).

(18) Roberts and Hammett, *ibid.*, **59**, 1063 (1937).

(19) Bernal and Megaw, *Proc. Roy. Soc.* (London), **151A**, 384 (1935).

corners of a distorted octahedron, the oxygen atoms being polarized in such a manner as to have directed bonds at the corners of an irregular tetrahedron. Two of the bonds of a hydroxyl group go to aluminum ions, at a third the hydrogen is found, and the fourth represents a concentration of negative electricity which has directed toward it the hydrogen belonging to another hydroxyl group. In this manner the coördination numbers of six for aluminum, four for oxygen and two for hydrogen are satisfied. It is this kind of hydroxyl group that is postulated to be present in our hydrous oxide, Specimen "A," and which is referred to here as an ol group.

It is easy to understand then why an ol group should not react readily with a proton, the oxygen of the ol group being already attached to three positive ions.

When an anion which forms complexes with an aluminum ion in acid solution, such as fluoride, phosphate, phosphite, oxalate or sulfate, approaches the aluminum ion in an ol $(\mathrm{Al}\overset{\mathrm{H}}{\mathrm{O}}\mathrm{Al})$ link at the surface, the bond between the aluminum approached and the oxygen will be broken. For convenience, we picture this in the following manner: $\mathrm{F}^- \longrightarrow \mathrm{Al}\ldots\overset{\mathrm{H}}{\mathrm{O}}\mathrm{Al}$. The ol group has now been converted into an hydroxo group which readily reacts[20] with a proton from an oxonium ion in the solution.

A similar mechanism would apply to the other anions, such as the $H_2PO_4^-$, $H_2PO_3^-$, $HC_2O_4^-$ and HSO_4^- ions or to their divalent anions.

It has been stated above that Specimen "B" is a more highly oxolated type of oxide than Specimen "A." By oxolation we mean that the proton of an ol group has migrated into a neighboring ol group, the result being an aquo group and an oxo group, with the simultaneous rearrangement of the structure to satisfy the coördination numbers of the atoms concerned. Such oxo groups exist in diaspore, according to Bernal and Megaw[19] and Ewing,[14a] the oxygen atom lying practically in the same plane with three coördinating aluminum ions[21] while the fourth coördination position is that of a weak hydroxyl bond of a neighboring hydroxyl group. Diaspore has the formula AlOHO.

If such oxo groups occur in Specimen "B" one might reasonably expect that an anion such as the $H_2PO_4^-$ ion would be a more effective catalyst than a F^- ion in dissolving Specimen "B." This idea follows from the fact that the $H_2PO_4^-$ ion is a proton donor as well as a coördinative binder, whereas the F^- ion is only a coördinative binder. Perhaps the (FHF^-) ion is the catalyst in breaking up oxo links. Palmer[22] reported that the rate of solution of quartz in hydrofluoric acid was proportional to the concentration of (FHF^-) ion rather than to the concentration of the hydrofluoric acid.

Davies[23] has shown that the (FHF^-) ion is present in aqueous hydrofluoric acid in much smaller amounts than is the F^- ion. If it is assumed that the (FHF^-) ion is the catalyst in breaking up an oxo group, one can account for the difference in the action of hydrofluoric acid on Specimens "A" and "B," this difference being due to the more limited chances of collision between the (FHF^-) ion than the F^- ion with the surface of the oxide.

Both Specimens "A" and "B" dissolve in maleic, tartaric, formic, citric and acetic acids at rates which are less than the rate of dissolution in nitric acid of the same equivalent concentration (Fig. 5). Therefore, since there is no correlation between the strength of the acid and the rate at which the hydrous oxides dissolve, the catalytic effect of certain anions cannot be explained on the basis of general acid–base catalysis. For example, the dissociation constants of phosphoric and maleic acids are very nearly the same, whereas the rates of dissolution of the hydrous oxides in these two acids are markedly different. Furthermore, while tartaric, hydrofluoric and formic acids are all approximately of the same strength, there is a great difference between hydrofluoric on the one hand and tartaric and formic on the other hand in their action upon the oxides.

The dissociation constants of oxalic and phosphorous acids are approximately the same. Figure 1 shows the great difference in the rapidity of dissolution of Specimen "A" in these two acids.

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(20) Hydroxo groups also can be displayed by coördinative binding anions, as shown in this Laboratory by the unpublished results of Mr. P. D. Baker. *E. g.*, the *p*H of 200 cc. of an aqueous suspension containing 260 mg. of hydrous oxide specimens increased from *p*H 7 to 10.5 (Specimen "B") and to *p*H 9.6 (Specimen "A") when sufficient potassium fluoride was added to make the solution 0.1 *M* KF (the *p*H of pure aqueous 0.1 *M* KF was 7.2). The same weight of Specimen "A" also raised the *p*H of 200 cc. of 0.1 *M* solutions of the following salts: (a) $K_2C_2O_4$ from 7.1 to 8.4, (b) K_2SO_4 from 5 to 7.1, (c) KCl from 5.5 to 6.8, (d) KBr from 5.7 to 6.4, (e) KNO_3 from 5.7 to 6.3. Natural specimens of hydrargillite and of diaspore also react with a potassium fluoride solution in a similar manner.

(21) Previously the expression "oxo group" has been used in papers from this Laboratory to designate an oxygen ion coördinated between two metallic ions.[12,14] In this paper the idea of "oxo group" is modified to conform to the recent picture[14a] referred to.

(22) Palmer, *J. Chem. Soc.*, 1656 (1930).

(23) Davies and Huddleston, *ibid.*, **125**, 260 (1924).

While the equivalent conductivities of hydrofluosilicic acid and sulfuric acid are practically the same,[24] only two hours were required to dissolve completely 260 mg. of Specimen "A" in 200 ml. of 0.1 *M* hydrofluosilicic acid, whereas five hundred and fifty hours were required to dissolve 80% of the same weight of Specimen "A" in the same volume and concentration of sulfuric acid.

Neither can the catalytic effect of certain of these anions be ascribed to a "salt effect," since the ionic strength of all the aqueous acid solutions would be less than the ionic strength of sulfuric acid of the same equivalent concentration. Rates of dissolution of both Specimens "A" and "B" were investigated in sulfuric and hydrochloric acid solutions of the same calculated ionic strength, and it was found that the sulfuric acid dissolved the hydrous oxides more rapidly under these conditions than did the hydrochloric acid.

It is concluded that the effect of an anion on the rate of dissolution of hydrous aluminum oxide is a specific property of that anion and is not applicable to any generalization, other than that if the anion is a coördinative binder with the aluminum ion even small amounts of it will catalyze the dissolution of the oxide when added to other acids whose anions are not such strong coördinative binders or complex formers.

The mechanism offered above might be useful in explaining why phosphates and fluorides reduce the passivity of aluminum metal in nitric acid.[25]

Turning back to a further discussion of the relatively slow rate of dissolution of the hydrous oxides in citric and tartaric acids, it should be recalled that the anions of these acids form complexes with the aluminum ion in neutral or alkaline solutions. However, the complexes are supposedly of the chelate type, involving the α-hydroxy group of the anion. The dissociation of the proton of this α-hydroxy group would be exceedingly slight in acid solution. Therefore, one would not expect these acids to catalyze the dissolution of the hydrous oxide in acid solutions, since there could be very little complex formation at the solid–liquid interface.

There is another essential difference in the nature of the two hydrous oxide Specimens "A" and "B" which we have not discussed. This difference is as follows. When a gram of Specimen "B" is shaken for a moment with 200 ml. of 0.2 *M* nitric, hydrochloric or hydrobromic acid, about 90% of the oxide is dispersed to the colloidal state, *i. e.*, (1) it remains in suspension when centrifuged at 3000 r. p. m. for thirty minutes; (2) it passes readily through the pores of filter paper but does not pass through the pores of a nitrocellulose membrane; (3) it shows a pronounced Tyndall effect; and (4) it is readily precipitated by ammonium sulfate. Only about 5% of the same weight of Specimen "A" will be colloidally dispersed by the same acids under the same conditions.

To explain the facts just stated it is assumed that there are more hydroxo groups on the surface[26] of particles of Specimen "B" than of Specimen "A." The hydroxo groups react readily with oxonium ions, rendering the particles positively charged and dispersing these particles as colloidal micelles, which ultimately will be broken to the crystalloidal state.

Summary

Certain anions, *viz.*, fluoride, phosphate, phosphite, oxalate and sulfate, or their acids, greatly accelerate the rate of dissolution of hydrous aluminum oxide in 0.2 molar hydrochloric acid solution even when present at a concentration of 0.001 molar.

This phenomenon cannot be explained on the basis of increased acid strength, increased diffusibility of the acid, valence of the anion or general acid–base catalysis.

An explanation based on the coördination structure of the hydrous oxide and the formation of a complex at the solid–liquid interface has been offered.

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[24] Mellor, "A Comprehensive Treatise on Inorganic and Theoretical Chemistry," Longmans, Green & Co., London, 1925, Vol. VI, p. 942.

[25] (a) Tartar and Cone, THIS JOURNAL, **56**, 48 (1934); (b) Centnerszwer and Wittandt, *Z. Elektrochem.*, **35**, 582 (1929).

[26] The presence of hydroxo groups on the surface of the hydrous oxide (Specimen "B") can be demonstrated readily: Dissolve 1 mg. of dry phenolphthalein in 3 ml. of 1,4-dioxane and divide the solution equally in three separate test-tubes. To (1) add anhydrous sodium carbonate; if the solution contains no water it remains colorless. To (2) add a pellet of dry potassium hydroxide. A pink color appears immediately at the interface between the liquid and the solid. This color will remain indefinitely at the interface and will not diffuse into the solution. This is because of the insolubility of potassium hydroxide in the dioxane. To (3) add 0.1 g. of hydroxy aluminum oxide prepared as Specimen "B" was, and the interface will immediately become pink. This color can be removed by the introduction of carbon dioxide and does not reappear on standing. The addition of water does not restore the color; however, the addition of more solid oxide does cause the color to reappear.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

A Study of the Esterification of Benzoic Acid with Methyl Alcohol Using Isotopic Oxygen

BY IRVING ROBERTS AND HAROLD C. UREY

There has been much discussion as to which linkages are broken in the two reactions: (a) the saponification of an ester, and (b) the esterification of a carboxylic acid. The first of these was studied by Polanyi and Szabo,[1] who demonstrated that the saponification of amyl acetate in heavy oxygen water results in amyl alcohol of ordinary isotopic composition. The solution of the second problem, for which evidence has been inconclusive up to the present, is the subject of this paper.

The formation of water by the acid-catalyzed esterification of benzoic acid with methyl alcohol may be represented by either of the equations

$$C_6H_5CO \,\vdots\, OH + H \,\vdots\, O\,CH_3 \longrightarrow C_6H_5COOCH_3 + H_2O \quad (1)$$

$$C_6H_5CO\,O \,\vdots\, H + HO \,\vdots\, CH_3 \longrightarrow C_6H_5COOCH_3 + H_2O \quad (2)$$

The purpose of this work is to distinguish between (1) and (2) by allowing ordinary benzoic acid to react with methyl alcohol containing an increased concentration of oxygen 18. If mechanism (1) is correct, such an experiment will yield water of ordinary isotopic composition (0.200% oxygen 18), whereas by mechanism (2), heavy oxygen water will be obtained.

Attempts to make the reaction go to completion in a short time resulted in esterification of the large amount of hydrochloric acid catalyst which must be used. Therefore the concentrations of catalyst and reactants were so adjusted as to give a half-time of about two weeks at 25°, and samples were withdrawn at known intervals for determination of the heavy oxygen content of the water. The reaction mixtures had the following composition: methyl alcohol, 68.6% by volume; hydrochloric acid, 0.123 *M*; benzoic acid, 2.70 *M*; water, 2.72 *M* (4.9% by volume). A large concentration of benzoic acid was necessary in order to have appreciable amounts of water formed by the esterification. The initial presence of the water, although it would dilute any heavy oxygen water formed, made it possible in the first stages of the reaction to recover enough water for analysis.

Rate of the Reaction.—In order to calculate the concentration of heavy oxygen in the water at any point, the amount of water formed by the esterification must be known. 20.4 cc. of reaction mixture of the above composition was prepared by dissolving in 14.00 cc. of a freshly prepared methanol–hydrochloric acid solution (0.1803 *M*), 1.00 cc. of water and 6.72 g. of benzoic acid. After putting the solution into the thermostat, 1.00-cc. samples were withdrawn and titrated with standard 0.1121 *N* sodium hydroxide to determine the benzoic acid remaining. The results are given in Table I. A plot of these data was made so that, in the experiments given below, one could readily determine at any time the percentage of reaction and therefore the number of moles of water formed.

TABLE I

RATE OF ESTERIFICATION AT 24.93°

Time, hours	Titer, cc.	% reaction
0.0	25.40	0.00
22.0	23.56	7.58
43.3	21.89	14.46
96.4	19.34	24.97
144.0	17.41	32.92
209.9	15.65	40.17
383.0	12.01	55.17

The amount of the reverse reaction which takes place was determined by allowing a methyl alcohol solution containing 2.50 *M* methyl benzoate, 2.50 *M* water and 0.114 *M* hydrochloric acid to stand in the thermostat. Samples withdrawn for titration of the benzoic acid formed showed that over a period of 196.5 hours, only 1.3% of the possible hydrolysis had taken place. This error is negligible, since in this work the esterification was never continued beyond 55% reaction.

Exchange Experiments.—It is obvious that exchange of oxygen between the water in the system and the methyl alcohol, methyl benzoate or benzoic acid, will give rise to errors whose magnitudes must be determined.

The fact that methyl alcohol does not exchange in the presence of hydrochloric acid already has been reported.[2]

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[1] Polanyi and Szabo, *Trans. Faraday Soc.*, **30**, 508 (1934).

[2] Roberts, *J. Chem. Phys.*, **6**, 294 (1938).

To determine whether methyl benzoate exchanges, a methyl alcohol solution containing 2.49 *M* methyl benzoate, 0.123 *M* hydrochloric acid and 2.96 *M* heavy oxygen water was allowed to stand in the thermostat. Twenty-five-cc. samples were taken and the water was recovered by fractional distillation and analyzed (see experimental part). Table II shows the results obtained. It can be seen that within experimental error no exchange of the methyl benzoate has taken place.

Table II

Exchange Experiment with Methyl Benzoate

Time, hours	H_2O recovered, cc.	% H_2O^{18}
0	....	0.462
172	0.43	.464
314	.67	.460

The amount of exchange of the benzoic acid was determined as follows: 102 cc. of a reaction mixture, having the composition originally given, was set up, using ordinary benzoic acid, ordinary methyl alcohol and water containing 0.509% oxygen 18. If no exchange of the benzoic acid were taking place, the heavy oxygen content of the water would be lowered by dilution with the ordinary water arising from the esterification. The amount of such lowering could be determined by taking the weighted mean of the composition of the water originally present and the water formed. If, on the other hand, the benzoic acid were exchanging, the heavy oxygen content of the water would be decreased even further than that calculated. Table III shows the results obtained.

Table III

Exchange of Benzoic Acid under Conditions of Esterification

Initial composition: 0.2752 mole benzoic acid, 0.2775 mole of H_2O^{18}, 70 cc. of methanol, HCl 0.123 *M*.

Time, hours	% reaction	Mole H_2O formed	% H_2O^{18} calcd.	H_2O recovered, cc.	% H_2O^{18} found
0	0.0	0.0000	0.509	0.08	0.510
94.0	24.5	.0674	.449	.28	.431
206.4	39.9	.1098	.421	.29	.400
378.8	54.7	.1505	.400	.34	.371

A comparison of the fourth and sixth columns will show that some exchange of the benzoic acid is taking place. This observation is in accord with the fact that benzoic acid has been shown to exchange both its oxygens rather readily.[2] That the exchange occurring in these experiments is small can be seen from the following consideration. If immediate complete exchange of the benzoic acid had taken place, the composition of the water would drop to 0.304% oxygen 18. The differences in Table III are of much smaller magnitude than this decrease. Rough calculations of the amount of exchange were made by separating the two simultaneous processes, *i. e.*, by assuming that first the known amount of esterification takes place and then the remaining benzoic acid exchanges with the water. It must be remembered that both oxygens of the benzoic acid are available for the exchange process. The results of these calculations are given in the second column of Table IV.

Esterification with $CH_3O^{18}H$.—The final experiment, performed at the same concentrations, contained ordinary benzoic acid, ordinary water and methyl alcohol containing 0.372% oxygen 18. In calculating the results to be expected by mechanism (2), a correction must be made for the decrease in heavy oxygen content of the water due to exchange with the benzoic acid. This was done by separating the two reactions as outlined above, and using the data on the benzoic acid exchange from the above experiment. These calculations result in the values given in Table IV. It can be seen that the corrections are comparatively small, and that they have very little effect upon the difference of oxygen content to be expected by the two mechanisms.

Table IV

Corrections for Exchange of Benzoic Acid in Data Calculated for Mechanism (2)

% reaction	Equivalents of benzoic acid exchanged	% H_2O^{18} expected for mechanism (2) Original	Corr.
24.5	0.0269	0.234	0.232
39.9	.0407	.249	.244
54.7	.0726	.260	.251

The results of the heavy oxygen methyl alcohol experiment are given in Table V.

Table V

Esterification Using $CH_3O^{18}H$

Time, hours	Percentage H_2O^{18} calculated Mechanism (1)	Mechanism (2)	H_2O recovered, cc.	H_2O^{18} found, %
0	0.200	0.200	....	.....
94.0	.200	.232	0.28	0.204
212.4	.200	.244	.42	.200
334.0	.200	.250	.78	.200

These experiments demonstrate that in the esterification of benzoic acid with methyl alcohol, the oxygen in the water formed originates entirely from the benzoic acid. It is notable that this is in accord with the conclusions drawn from experiments with mercaptans and thioacids.[3]

Experimental

Materials.—Methyl alcohol was purified by the method of Lund and Bjerrum.[4] Benzoic acid of the Mallinckrodt "Analytical Reagent" grade was found by titration to contain a maximum of 0.2% of impurity, and was therefore used directly. Hydrochloric acid was of the C. P. reagent quality. Hydrochloric acid solutions in methanol were prepared by passing the gas into anhydrous methanol; the solutions were used immediately after preparation. Standard 0.1 *N* sodium hydroxide, made up from a saturated carbonate-free solution, was standardized against Bureau of Standards potassium acid phthalate. Methyl benzoate was shaken three times with sodium carbonate solution, three times with water, dried over calcium chloride, and fractionated.

Heavy oxygen water, prepared by fractional distillation,[5] was refluxed with alkaline permanganate for one hour, fractionated and distilled from chromic acid. Heavy oxygen methyl alcohol, also prepared by fractional distillation,[6] was treated with magnesium and iodine in the same manner as the ordinary material[4] and fractionated. The middle fraction was further fractionated after the addition of two drops of phosphoric acid. The middle fraction, which distilled constantly at 65°, contained traces of volatile amines from which the methanol could not be freed completely. These small amounts of impurity caused the slow formation of a light yellow color in the reaction mixture when the methanol was used for the esterification.

Analyses.—The mass spectrograph was of the type described by Bleakney[7]; the procedure for analysis of the water was that of Cohn and Urey.[8] In the present work, the water recovered from the experiments was shaken with 26 cc. of ordinary carbon dioxide gas at atmospheric pressure for five hours. The precision of analyses was generally 1% or better.[9]

The heavy oxygen methyl alcohol was analyzed for its oxygen content by converting it to water and analyzing the water as above. This was done by passing a mixture of the methanol vapor and hydrogen through a quartz tube which contained a nickel spiral at about 650° and a thoriated nickel catalyst[10] at about 400°. The water was caught in a trap enclosed in solid carbon dioxide–acetone mixture; the yields were practically quantitative. Heavy oxygen water, passed through the apparatus under the same conditions, was recovered with no decrease in heavy oxygen content, demonstrating that exchange with the quartz tube or with any oxide in the catalyst had not taken place. Analysis of ordinary methyl alcohol by this method gave 0.204% oxygen 18.

Esterification Experiments.—All operations were carried out in glass apparatus fitted with interchangeable ground joints. Esterification experiments were carried out in the thermostat kept at 24.93 ± 0.02°. Twenty-five cc. samples of reaction mixture were pipetted for recovery of the water, and from these the methanol, water and a small amount of the methyl benzoate were distilled *in vacuo* at room temperature. This initial process took thirty minutes at a maximum, thus causing a negligible error in the reaction time recorded. The distillate was then fractionated at atmospheric pressure, the water and methyl benzoate remaining behind. In the final step, the water was distilled off *in vacuo* from the methyl benzoate. The water samples obtained by this method were always contaminated by small amounts of methanol and methyl benzoate; these impurities can have no effect on the results obtained by the method of analysis given above.

Summary

Ordinary benzoic acid has been esterified with heavy oxygen methyl alcohol in the presence of a small amount of hydrochloric acid catalyst. The water resulting from the reaction is of ordinary isotopic composition, demonstrating that the oxygen in the water formed originates entirely from the benzoic acid. Slow exchange of the benzoic acid proceeds simultaneously with the esterification, necessitating a small correction in the calculated results.

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[3] Reid, *Am. Chem. J.*, **43**, 489 (1910).

[4] Lund and Bjerrum, *Ber.*, **64**, 210 (1931).

[5] Huffman and Urey, *Ind. Eng. Chem.*, **29**, 531 (1937).

[6] Unpublished work of Huffman and Keston in this Laboratory.

[7] Bleakney, *Phys. Rev.*, **40**, 496 (1932).

[8] Cohn and Urey, THIS JOURNAL, **60**, 679 (1938).

[9] Mass spectrograph analyses done by Dr. John E. Gorham.

[10] Russell and Fulton, *Ind. Eng. Chem., Anal. Ed.*, **5**, 384 (1933).

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE GENERAL ELECTRIC CO.]

Conductance of Mixtures of Lead Abietate and Tributylammonium Chloride in Toluene

BY VICTOR DEITZ WITH RAYMOND M. FUOSS

I. Introduction.—While the properties of a number of 1–1 salts in solvents of low dielectric constant have been determined,[1-4] the properties of higher salt types in such solvents have not been investigated. One difficulty in the way of a study of the problem is the low solubility of most 2–1 salts in the hydrocarbon solvents. Two classes of salts are, however, soluble: the higher quaternary salts of dicarboxylic acids and the salts of heavy metals with the higher carboxylic acids. In this paper will be presented the results of an investigation of the properties of lead abietate in benzene and toluene solution.

II. Materials, Apparatus and Method.—**Benzene** was purified by washing with concentrated sulfuric acid, water, dilute caustic and water. It was then dried with calcium chloride and refluxed with potassium. Samples for use in the conductance experiments or analyses were distilled from potassium just before using. **Toluene** was treated in the same way, except that the potassium was replaced by sodium.

Tributylammonium picrate was prepared by adding a nearly saturated hot alcoholic solution of picric acid to a slight excess of tributylamine in alcohol. The crude product, which separates on cooling, was recrystallized once from alcohol, m. p. 106.9° (corr.).

Tributylammonium chloride was precipitated by *dry* hydrogen chloride from a solution of tributylamine in *dry* petroleum ether. It is advisable to precipitate less than half of the available amine, in order to prevent the coprecipitation of impurities which are difficult to separate. The precipitate was washed with dry petroleum ether, and then pumped dry over phosphorus pentoxide in a desiccator. Samples for use were dried to constant weight at 70–75° in weighing bottles in a miniature vacuum oven.

Several samples were analyzed by titration in 50% acetone solution with sodium hydroxide, using phenolphthalein as indicator. A small blank correction for acid in the acetone was made. Equivalents of $(C_4H_9)_3HNCl$ calculated from weight of salt taken: 0.001384, 0.001725, 0.001896; equivalents sodium hydroxide found by titration: 0.001390, 0.001749, 0.001896.

Lead Abietate.—Considerable difficulty was encountered in preparing pure lead abietate. Precipitation from lead nitrate or lead acetate solutions gives basic or double salts, whose composition depends on concentration, sequence and relative amounts of reagents.[5] It also proved useless to try to purify lead abietate made from impure abietic acid; it is essential that the abietic acid be in the highest state of purity initially. We obtained nearly colorless abietic acid, completely free from tacky impurities, by recrystallizing a good commercial grade (from Hercules Powder Co.) from methyl alcohol and washing the crystals with cold methyl alcohol. The crystallization yield was poor, but the quality of the product was compensation for the loss of raw material. The abietic acid was then dissolved in an equivalent amount of sodium hydroxide in water and this (very slightly yellow) solution was slowly added in turn to a hot dilute aqueous solution of an equivalent amount of lead chloride. The lead abietate formed as a pure white crystalline precipitate. This was recrystallized from ethyl acetate (2 g./100 cc.) which had been purified by shaking with aluminum oxide and distilling just before use. The final product consisted of small twinned needles. It was necessary to store the lead abietate in an evacuated phosphorus pentoxide desiccator, because exposure to air converted it into a product (presumably one of oxidation) insoluble in ethyl acetate and aromatic hydrocarbons. Heating to 100° in air causes the crystals to darken.

Of several new methods of analysis for lead in lead abietate, we found the most reliable to be the precipitation of the lead as lead chloride from a toluene solution of the abietate by means of dry hydrogen chloride. Moisture was excluded by working in a dry box; this precaution is necessary, because any water which condenses into the solution containing hydrogen chloride separates and preferentially wets the lead chloride precipitate, causing it to adhere so firmly to the walls of the vessel that quantitative transfer is very tedious.

The dry box was fed with air passed over activated aluminum oxide. At the start of an analysis, several weighed samples of lead abietate in capped weighing bottles, several weighed Gooch crucibles with fine asbestos mats, toluene wash bottle, toluene supply bottle, suction flask, hydrogen chloride generator and hot plate were placed in the dry box, which was swept out overnight with dry air. The next day, the abietate was dissolved in toluene (*ca.* 1 mg./cc.) in an Erlenmeyer flask which had a tea-kettle spout attached to the bottom. Hydrogen chloride from sulfuric acid and potassium chloride was passed slowly in through the spout, after which the precipitate was digested for about thirty minutes. Then the lead chloride was transferred to the Gooch crucible by sluicing it through the spout. (This procedure entirely eliminated the necessity of policing the precipitate.) After washing, the precipitate was sucked dry. After all the precipitations were complete, the dry box was opened and the crucibles were transferred to an oven at 110° where they were dried to constant weight. In some of the preliminary work, the crucibles were next washed with hot water and again dried to constant weight. The water insoluble resi-

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(1) C. A. Kraus and R. M. Fuoss, THIS JOURNAL, **55**, 21 (1933).

(2) R. M. Fuoss and C. A. Kraus, *ibid.*, **55**, 3614 (1933).

(3) G. S. Bien, C. A. Kraus and R. M. Fuoss, *ibid.*, **56**, 1860 (1934).

(4) W. F. Luder, P. B. Kraus, C. A. Kraus and R. M. Fuoss, *ibid.*, **58**, 255 (1936).

(5) Wolff and Rabinowicz, *Fettchem. Umschau*, **41**, 66 (1934).

due (of the order of 0.1 mg.) was probably abietic acid adsorbed on the lead chloride. The results of several typical analyses by this method are given below: wt. lead abietate, 0.2165, 0.2471, 0.1420; wt. $PbCl_2$ found, 0.0751, 0.0854, 0.0485; % Pb, 25.84, 25.75, 25.46; calcd. for $Pb(C_{20}H_{30}O_2)_2$, 25.61%.

As a control on the method, a sample of recrystallized silver perchlorate, which is toluene soluble, was analyzed by the same method: wt. $AgClO_4$, 0.1644, 0.3211; wt. AgCl found, 0.1138, 0.2218; wt. AgCl calcd. 0.1137, 0.2221.

Conductance Cells.—For the preliminary conductimetric titrations, several types of cells were used. The simplest and most convenient consisted of a beaker containing two concentric cylindrical platinum gauze electrodes, at the center of which was a motor driven glass stirrer.

For the final work, a three terminal cell was used. Figure 1 is a simplified sketch of the cell. The inner (test) electrode was a platinum cylinder 6.5 cm. long and 2.0 cm. in outside diameter. To each end of this cylinder and on the same axis, by means of platinum wires and lead glass beads, were attached two cylinders of the same diameter, 5 mm. long, and separated from the test electrode by about 1 mm. These end cylinders were the guard electrodes. The guard-test combination was then mounted by more platinum wire supports with lead glass insulators inside a platinum cylinder 7.7 cm. long and 2.3-cm. diameter, which served as the high potential electrode. The seams on the cylinders were soldered with gold. The electrode assembly was then sealed into an electrode capsule of Corning 332 glass by means of platinum tube supports coated with Corning 707 glass.[6] The capsule (40-cc. volume) was in turn sealed to a Pyrex mixing chamber (300-cc. volume), the inlet tube of which was equipped with a ground glass cap carrying a stopcock. The stopcock permitted rapid drying of the cell, by exhausting the cell after washing and heating. The three lead wires (high potential, test and guard) were brought up beside the neck of the cell in small glass tubes. (For simplicity, only one of these is shown in Fig. 1.) These, as well as the electrode capsule, were coated with gold by firing on at 500° a layer of Dupont "Liquid Bright Gold ZW." The gold screening was connected to the guard line. The bridge cable, which consisted of the test lead, sheathed with an insulated copper screen attached to the guard circuit, was plugged into the end of the test lead from the cell, so that the test electrode and its lead to the bridge were unbrokenly shielded.

The cell constant was determined by measuring the capacity of the empty cell on a Schering bridge[7] at 60 cycles; since the cell contains guard electrodes, the cell constant k can be obtained from the capacity by the relationship

$$C = 0.08842 \times 10^{-12}/k$$

(For an ideal cell consisting of parallel plates of area A separated by a distance d, $k = d/A$, if fringing is eliminated.) For the cell of Fig. 1, $k = 0.004423$.

The conductance determinations were made either at 60 cycles on the Schering or resistance bridge[8] which have been used for other work in this Laboratory, or on a d. c. bridge which has also been described previously.[8]

Method.—In the preliminary titrations, a solution of tributylammonium chloride in benzene or toluene was delivered in successive portions from a buret into the gauze electrode cell, which contained the lead abietate solution. The resistance was determined on the d. c. bridge after each portion. It was observed that both moisture and oxygen affected the results; titrations in the dry box gave steadier conductances.

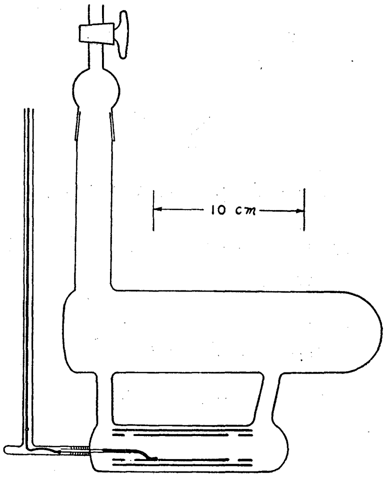

Fig. 1.—Conductance cell.

In the final work, toluene was distilled in a nitrogen stream from sodium directly into the carefully dried three terminal conductance cell. Access of moisture was prevented by a drying tube. After determining the solvent conductance,[9] a sample of lead abietate was weighed into the cell, and the solution was allowed to come to equilibrium in an oil thermostat held at 35.00 ± 0.03°. The conductance was determined and then a small portion of a solution of tributylammonium chloride in toluene was added from a weight buret. A conductance run consisted in adding several stoichiometrical equivalents of chloride to the lead salt in successive portions, and determining the conductance at 60 cycles at each point. The field strength was kept below one kilovolt per centimeter, in order to minimize both heating effects and a possible Wien effect.[10,11]

Polarization.—A very marked dependence of apparent resistance on voltage was noted when solutions were measured on the d. c. bridge. An analysis of the results indicates that a fairly high polarization e. m. f. is responsible. The bridge is shown schematically in Fig. 2, where R_1 is the cell resistance, R_2 and R_3 are Shallcross high resistance coils and R_4 is a variable decade box. Suppose the voltage applied to the bridge is V and

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[6] N. L. Cox, C. A. Kraus and R. M. Fuoss, *Trans. Faraday Soc.*, **31**, 749 (1935).

[7] Fuoss, THIS JOURNAL, **59**, 1703 (1937).

[8] Fuoss, *ibid.*, **60**, 451 (1938).

[9] The solvent conductance was of the order of 10^{-14} and represented a negligible correction.

[10] M. Wien, *Physik. Z.*, **29**, 751 (1928); L. Onsager, *J. Chem. Phys.*, **2**, 599 (1934).

[11] An appreciable dissociation effect in accordance with Onsager's theory appears in solvents of low dielectric constant at fairly low field strengths. (Unpublished observations of D. J. Mead and R. M. Fuoss, made in this Laboratory.)

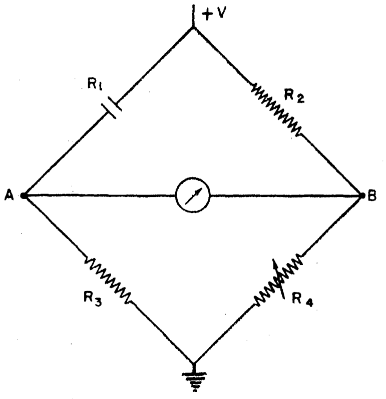

Fig. 2.—Diagram of d. c. bridge.

the back e. m. f. of the cell is E. Then at balance, $V_a = V_b$ and we have

$$V = I_a(R_1 + R_3) - E = I_b(R_2 + R_4) \qquad (1)$$

$$(I_aR_1 - E)/I_aR_3 = R_2/R_4 \qquad (2)$$

Combining (1) and (2), and noting that $R_1 >> R_3$, we find

$$\frac{R_1R_4}{R_2R_3} = 1 + \frac{E}{V} \qquad (3)$$

A typical result for a 5.85×10^{-3} molar solution of lead abietate in benzene at 25° in a cell with chromium plated brass electrodes is shown in Fig. 3. According to (3), if we plot R_4V against V, we should obtain a straight line whose slope determines R_1, and whose intercept determines E. Having determined R_1, a plot of R_1R_4/R_2R_3 against $(1/V)$ should give a straight line with slope E and intercept unity at infinite voltage $(1/V) = 0$. The data satisfy these requirements, and give, for this example, $E = 10$ v. Lack of time unfortunately forced us to postpone a detailed study of this phenomenon. A study of the rates of decay of these polarization voltages should give useful information concerning the diffusion coefficients and mobilities of the ions involved.

Subsequent d. c. titrations were made at a fixed cell voltage (100 v.) and the final titrations were made with alternating current. Since the latter was low frequency (60 cycles), some polarization error undoubtedly is present, but experiments made at several frequencies between 60 and 500 cycles showed that the effects were considerably less than with d. c. and our a. c. results at 60 cycles are no more than several per cent. in error in absolute value due to polarization. Since we were primarily interested in relative values, the study of polarization effects was dropped.

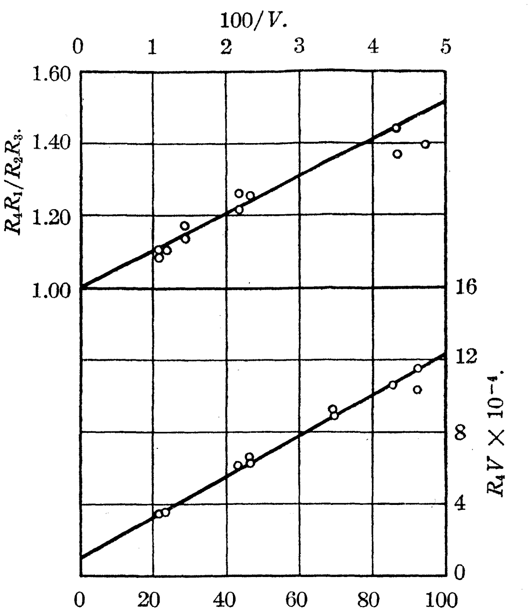

Fig. 3.—Polarization curves.

III. Experimental Results and Discussion.

In order to test the reliability of the conductance methods, the conductance of tributylammonium picrate in toluene at 35° was determined. Three dilution runs were made. The results are given in Table I.

TABLE I

CONDUCTANCE AND DIELECTRIC CONSTANT OF TRIBUTYLAMMONIUM PICRATE IN TOLUENE AT 35°

Series	$C \times 10^3$	$\Lambda \times 10^6$	ϵ'
1	13.04	2.650	...
	8.12	1.500	...
	5.03	0.957	...
	2.82	.603	...
	1.62	.442	...
2	2.65	.597	2.391
	1.21	.370	2.368
3	4.88	.926	2.428
	3.05	.548	2.400
	0.0	..	2.347

For comparison with earlier work, the only available data are those of Kraus and Fuoss[1] on tri-*i*-amylammonium picrate in benzene at 25°. These data, multiplied by the ratio of the viscosity of benzene at 25° to that of toluene at 35° are shown as the dotted curve in Fig. 4, where the present data are given as the circles on curve IV. It will be noted that the behavior of the two systems is, as expected, very similar.

The conductance of tributylammonium chloride as a function of concentration was determined by adding successive portions of an approxi-

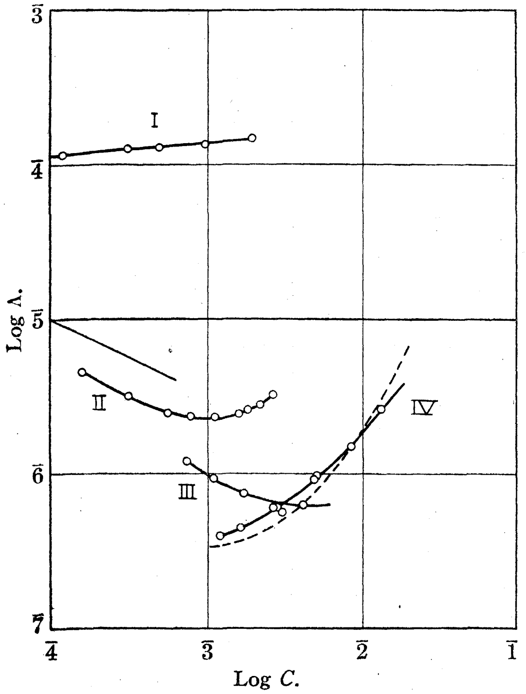

Fig. 4.—Conductance curves: I, PbAbCl in C_6H_6; II, Bu_3HNCl in $C_6H_5CH_3$; III, $PbAb_2$ in $C_6H_5CH_3$; IV, Bu_3HNPi in $C_6H_5CH_3$.

mately 0.01 normal solution of the salt in toluene to 66 g. of pure solvent in the conductance cell. The results are given in Table II, and are shown as curve II in Fig. 4, where the logarithm of the equivalent conductance Λ is plotted against the logarithm of the concentration. The appearance of a characteristic minimum in the equivalent conductance[12] near thousandth normal will be noted.

TABLE II

CONDUCTANCE AND DIELECTRIC CONSTANT OF TRIBUTYLAMMONIUM CHLORIDE IN TOLUENE AT 35°

$C \times 10^3$	$\Lambda \times 10^6$	ϵ'
0.000	..	2.347
.159	4.49	2.348
.290	3.13	2.348
.568	2.45	2.352
.790	2.32	2.352
1.116	2.30	2.356
1.575	2.38	2.359
1.819	2.58	2.362
2.203	2.76	2.365
2.692	3.22	2.368

The conductance and dielectric constants of a series of lead abietate solutions in toluene at 35° are given in Table III. Each solution was made up by weighing a definite amount of salt and solvent.

TABLE III

CONDUCTANCE AND DIELECTRIC CONSTANTS OF LEAD ABIETATE IN TOLUENE AT 35°

$C \times 10^3$	$\Lambda \times 10^6$	ϵ'	ϵ_0'
4.083	0.626	2.349_5	2.348_2
1.686	0.762	2.348_8	2.348_2
1.073	0.936	2.349_0	2.347_8
0.740	1.213	2.348_6	2.348_2

No dilution runs were made for this salt; the solutions of Table III were the initial solutions for the conductimetric titrations to be described later. In the last column, the dielectric constant ϵ_0' of the solvent, as measured before addition of the salt, is given for each solution.

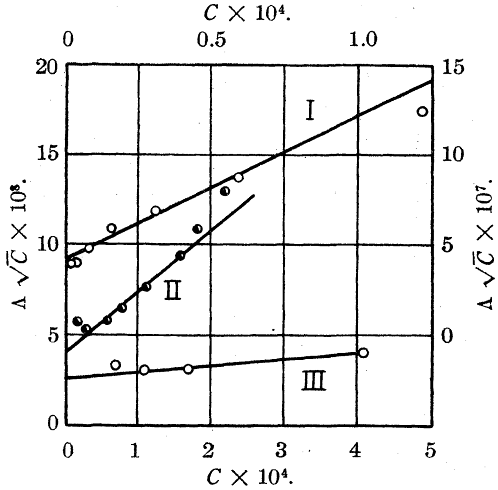

Fig. 5.—Triple ion test plots: I, PbAbCl in C_6H_6 (coördinates, top and right); II, Bu_3HNCl in $C_6H_5CH_3$ (coördinates, bottom and left); III $PbAb_2$ in $C_6H_5CH_3$ (coördinates, bottom and left).

If $\Lambda\sqrt{c}$ is plotted (Fig. 5, curve II) against concentration for the tributylammonium chloride,[11] a straight line is obtained, whose intercept at $c = 0$ gives $K\Lambda_0^2 = 3.8 \times 10^{-8}$ for this salt. If we set Λ_0, the limiting conductance, equal to 100 in order of magnitude (a reasonable value, assuming Walden's rule to apply), we find for the dissociation constant $K \approx 1.5 \times 10^{-19}$. This is of the order expected.[2] For lead abietate, a value about one half as large is obtained. The dissociation constant of lead abietate refers, of course, to the initial dissociation

$$PbAb_2 \rightleftarrows PbAb^+ + Ab^-$$

because it seems impossible that the second abietate ion should be free in any appreciable amount in solvents of low dielectric constant. Confirmation of this opinion is furnished by the numerical

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(12) R. M. Fuoss and C. A. Kraus, THIS JOURNAL, **55**, 2387 (1933).

value of the dissociation constant of silver perchlorate in benzene,[4] 8×10^{-20}, which is a 1-1 salt with a metallic cation.

The dependence of the dielectric constants of the solutions on concentration is shown in Fig. 6.

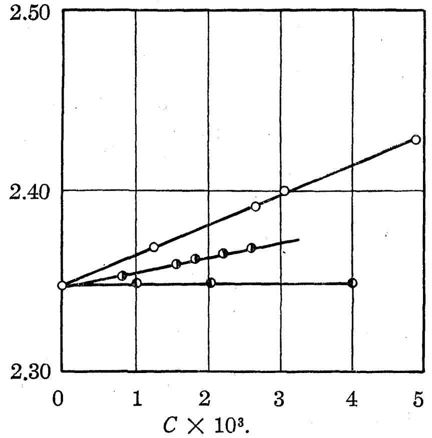

Fig. 6.—Dielectric constant–concentration curves for salts in toluene at 35°: ○, Bu_3HNPi; ◑, Bu_3HNCl; ◐, $PbAb_2$.

It is seen at once that the tributylammonium picrate has a higher dipole moment than the chloride and that the lead abietate has zero moment. Calculation of the moments from the data gives $\mu\,(Bu_3HNP_i) = 11.7 \times 10^{-18}$ and $\mu\,(Bu_3HN{\cdot}Cl) = 7.3 \times 10^{-18}$. These are of the expected order of magnitude and agree very well with Geddes' values,[13] $\mu\,(Bu_3HNP_i) = 13.1 \times 10^{-18}$, $\mu\,(Bu_3HN\text{-}Cl) = 7.2 \times 10^{-18}$. It should be pointed out that our values were determined by bridge measurements at 60 cycles, while Geddes' values were determined by Wyman's resonance method[14] at several megacycles. The value of zero for the moment of lead abietate is entirely in agreement with the theory of ion association[15] because one naturally assumes the abietate ions symmetrically located with respect to the lead ion.

We shall next consider a few of the preliminary conductimetric titrations. The examples chosen are shown in Fig. 7; in order to save space, no tabulation of data will be presented. The vertical scale is specific conductance; as abscissas are chosen the ratio r of equivalents of chloride to the equivalents of lead present in the cell. At $r = 0.5$, the empirical composition is $(Bu_3HNCl + PbAb_2)$; at $r = 1$, it is $(2Bu_3HNCl + PbAb_2)$.

Curve I represents the conductance curve obtained on the d. c. bridge when successive portions of 0.01 normal tributylammonium chloride solution in benzene were added to a 6.84×10^{-4} N solution of lead abietate in benzene. It will be seen that the conductance rises to a very high peak near the point where one mole of chloride has been added to one mole of lead, after which the conductance rapidly drops. Beyond the equivalence point, the conductance slowly rises again. The appearance of the maximum was entirely unexpected and its presence suggested that some hitherto unsuspected reaction was taking place. If the titration is carried out using hydrogen chloride in benzene, curve II, where the initial lead concentration was 7.64×10^{-4}, is obtained. It is similar to curve I in that a maximum appears, but the maximum is not nearly so high. Finally, curve III represents the reverse titration in which lead abietate was added to a solution of the amine hydrochloride. (The initial point of the titration here corresponds to $r = \infty$, of course.) As more and more lead is added (moving from right to left in Fig. 7), the conductance goes through a shallow minimum and then rises, going through

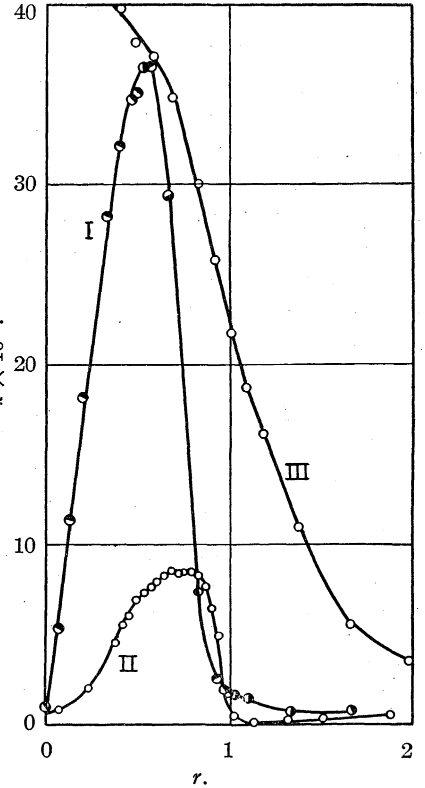

Fig. 7.—D. c. titrations in benzene.

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[13] J. A. Geddes and C. A. Kraus, *Trans. Faraday Soc.*, **32**, 585 (1936).

[14] J. Wyman, *Phys. Rev.*, **33**, 623 (1930).

[15] Fuoss, *Chem. Rev.*, **17**, 27 (1935).

an inflection point at the equivalence point corresponding to lead chloride. The initial solutions were clear; then an opalescence appeared, and finally a precipitate formed as the amount of lead was increased.

The increase of conductance on adding tributylammonium chloride to lead abietate was certainly not due solely to the formation of tributylammonium abietate by metathesis: a 5×10^{-4} normal solution of abietic acid in benzene had a specific conductance of 0.07×10^{-12} and the addition of an equivalent amount of tributylamine raised this to only 0.15×10^{-12}, showing that the amine abietate is, as expected, an exceedingly weak electrolyte. An estimate from the above conductance gives it a dissociation constant of the order of 10^{-21} in benzene. Incidentally, it would be interesting to study the properties of acids and of their salts with weak bases in non-protonic solvents: this field is practically unexplored. In this particular case, the conductance of the tributylammonium abietate is completely negligible compared to the maximum specific conductance observed near $r = 0.5$ in the titration curves.

In Tables IV and V are given the results of the titrations in the closed cell, where moisture and oxygen were excluded and, as has been mentioned, where the determinations were made at 60 cycles on the Schering bridge.

TABLE IV

CONDUCTIMETRIC TITRATION OF LEAD ABIETATE WITH TRIBUTYLAMMONIUM CHLORIDE IN TOLUENE AT 35°. CONCENTRATION DATA

Series	$10^3 C_{Pb}$	$10^3 C_{Cl}$	w_0	w_{Cl}
1	4.083	13.29	74.85	27.86
2	1.686	9.51	79.27	16.62
3	1.073	9.51	69.50	12.99
4	0.740	9.51	73.89	14.43

In the second column of Table IV is given the initial concentration of lead abietate in equivalents per liter; in the third, the concentration of the tributylammonium chloride; in the fourth, the initial weight of toluene in the cell and in the last, the total weight of chloride solution added by the end of the titration. We used the density of the solvent (0.8538 g./cc. at 35°) as an approximation for the density of the solutions in calculating normalities from weight concentrations.

In Table V are given the conductances for the various solutions, corresponding to successive values of the ratio r of equivalents of chloride added to equivalents of lead initially present. For the most concentrated solution (Series 1), dielectric constants are also given.

Examples of the titration curves are shown in Fig. 8, where the logarithm of the specific conductance is plotted against r. It will be noted that the conductance rises by approximately two decades for the first half equivalent of chloride added. During the addition of the second half equivalent, the conductance drops to a very low value, and then rises again, corresponding to the conductance of the excess tributylammonium chloride now present in the solution.

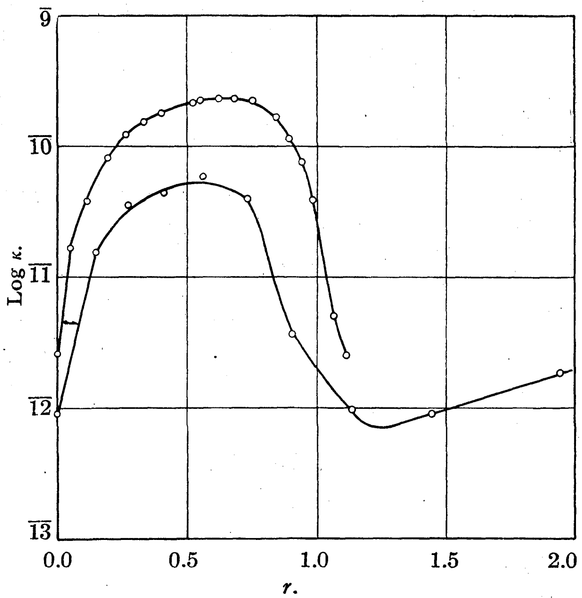

Fig. 8.—A. c. titrations in toluene.

The interesting part of the curve is, of course, the maximum. The following explanation is proposed. We know from the conductance curves of the tributylammonium chloride and lead abietate (Fig. 4, curves II and III) that these salts exist almost completely as ion pairs at the concentrations in question; only a minute fraction is present as free ions (singles or triples). The degree of dissociation involved is of the order of *one millionth* per cent. We also know that tributylammonium abietate is almost completely associated ($K \approx 10^{-21}$). In the first part of the titration, we therefore assume that the few free tributylammonium ions, present in the titrating solution added, combine with the abietate ions from the lead abietate solution in the cell, giving completely associated ion pairs of tributylammonium abietate.[16] This leaves $(PbAb)^+$ and

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[16] We shall use the abbreviation "Ab" for $(C_{20}H_{29}O_2)^-$, the abietate ion.

TABLE V

CONDUCTIMETRIC TITRATION OF LEAD ABIETATE WITH TRIBUTYLAMMONIUM CHLORIDE IN TOLUENE AT 35°. ELECTRICAL DATA

Series 1			Series 2		Series 3		Series 4	
r	$10^{12}\kappa$	ϵ'	r	$10^{12}\kappa$	r	$10^{12}\kappa$	r	$10^{12}\kappa$
0.000	2.544	2.350	0.000	1.285	0.000	1.004	0.000	0.90
.050	16.44	2.349	.037	4.24	.050	5.20	.150	15.5
.113	38.0	2.351	.063	10.12	.101	9.40	.273	34.5
.191	80.4	2.364	.201	33.7	.247	38.2	.411	44.8
.338	153.3	2.370	.294	54.9	.352	50.7	.562	59.0
.404	176.6	2.371	.332	65.3	.464	65.5	.909	3.60
.557	225	2.380	.432	88.6	.599	77.0	1.136	0.96
.622	228	2.374	.534	106.6	.702	76.0	1.445	0.89
.684	227	2.375	.655	122.4	.859	18.7	1.945	1.88
.756	222	2.358	.766	136.2	.996	2.80	2.510	3.64
.848	168	2.360	1.048	18.0	1.186	0.72	...	...
.895	145	2.348	1.182	3.5	1.420	1.08	...	...
.941	75	2.353	...	....	1.656	1.74	...	...
.987	39	2.358	...	....	...	...	...	...
1.067	5	2.355	...	....	...	...	...	...
1.212	2.5	2.359	...	....	...	...	...	...

Cl^- ions in solution. But the ion pair $(PbAb)^+(Cl^-)$ has a smaller coulomb binding energy than the $(PbAb^+)(Ab^-)$ pair, because the negative oxygens of the carboxyl group in the abietate ion can approach the lead ion closer than the chloride ion, a fact which makes for higher conductance. The practically irreversible reaction

$$Bu_3HN^+ + Ab^- \longrightarrow Bu_3N{\cdot}HAb$$

eventually removes all the free abietate ions from solution, leaving the ion pair equilibrium

$$PbAb^+ + Cl^- \rightleftarrows (PbAb^+)(Cl^-)$$

Then as more chloride is added, we get the reactions

$$(PbAb^+)(Cl^-) + (Cl^-) \rightleftarrows (Cl^-)(PbAb^+)(Cl^-)$$
$$(Cl^-)(PbAb^+)(Cl^-) \rightleftarrows Ab^- + PbCl_2\downarrow$$

In other words, the triple ion[12] formed from the abietate–chloride ion pair and a chloride ion rearranges to give lead chloride, which is insoluble and precipitates out, leaving (Bu_3HN^+) and (Ab^-) ions in solution. But since this ion pair is much more highly associated than the $(Cl^-)(PbAb^+)$ pair, the conductance again drops. The final rise is simply due to increasing $Bu_3HN{\cdot}Cl$ concentration, after the available lead has been precipitated as lead chloride.

The assumption that a soluble mixed salt, lead chloride–abietate (PbAb·Cl), is formed is in accordance with the observation that the initial additions of chloride to the lead solution produce no precipitate, and that the lead chloride only begins to precipitate in quantity as the $r = 0.5$ point is approached. The opalescence before this point corresponds to the formation of some lead chloride, and accounts for the displacement of the maximum to the right of the point where $r = 0.5$.

We also observed that lead chloride could be dissolved in a solution of tributylammonium chloride (evidence: increased conductance; black precipitate with hydrogen sulfide) which indicates that complexes can be formed in which lead is in the negative ion. This is in accord with the fact that the conductance minimum corresponds to a value of r somewhat greater than unity. We are inclined to ascribe the maximum in the preliminary $HCl–PbAb_2$ titration (Fig. 7) to the presence of moisture in the benzene; this experiment was made without exclusion of atmospheric moisture. Here the much weaker $H_3O^+{\cdot}Cl^-$ was probably the actual titrating solution.

The behavior of the solutions on the addition of chloride during titration was particularly interesting. In the first part of the titration, the conductance increased with time, approaching an asymptotic value (the values given in Table V) exponentially. On the down-side of the titration, the conductance decreased exponentially to an asymptotic value. Approach to within a per cent. or so of the limiting value was reached in serveral hours. If reactions of the type postulated above occur, we would expect finite times to be required for their completion, because the dissociation constants of the two reagents are of the order of 10^{-19}. The marked contrast to electrolytic reactions in water, which take place almost instantaneously, is easily understood when we recall that association of ions in aqueous solutions is negligible for salts of low valence type. These observations suggest a study of the rates of electrolytic dissociation in solvents of low dielectric constant through their conductance–time curves. With dissociation constants of the order of 10^{-20}, there should exist a measurable rate of establishment of equilibrium when an electrolytic solution in benzene, for example, is diluted. We hope that further work on this phase of the problem will be done.

The dielectric constant–concentration curve (Fig. 9) for series 1 of Table V gives further evidence for the existence of a stable mixed salt $(PbAb^+)(Cl^-)$. The dielectric constant goes through a maximum at the same point as the conductance curve, and, after a following minimum, rises at a rate corresponding to the presence of free $Bu_3HN{\cdot}Cl$ ion pairs. From the dielectric constant at the maximum point for Series 1, we have the data $\epsilon' = 2.378$ at $C = 3.52 \times 10^{-3}$. From these, we calculate $\mu(PbAb{\cdot}Cl) = 8.6 \times 10^{-18}$. This value is of the same order as that of the ion pair $Bu_3HN{\cdot}Cl$, and since it is due to the vectorially opposed (Pb^+Ab^-) and (Pb^+Cl^-) moments, we conclude that either the $(Cl^-)(PbAb^+)$ ion pair is not linear, or that the Pb–Cl bond is much more polar than the lead–carboxyl bond. The latter view is more probable, if we compare the dissociation constants of the two ion-pairs $(PbAb^+)(Ab^-)$ and $(PbAb^+)(Cl^-)$.

Finally, we consider the conductance curve of the mixed salt $(PbAb^+)(Cl^-)$. To a solution of 1.314×10^{-4} equivalent (0.1063 g.) of lead abietate in benzene was added an equivalent amount of tributylammonium chloride in benzene, giving a solution 1.943×10^{-3} normal in PbAbCl. No precipitate appeared, although the solution became opalescent. A regular dilution run was made on this solution, giving the conductance curve I of Fig. 4, where the equivalent conductance was calculated as that of PbAbCl. A typical conductance curve for a 1–1 salt appears. In Fig. 4 is given a $\Lambda\sqrt{c} - c$ plot for these data. From the intercept at $c = 0$, we obtain for the reaction

$$PbAb^+ + Cl^- \rightleftarrows PbAbCl$$

$K = 1.5 \times 10^{-17}$, assuming $\Lambda_0 = 100$. This result confirms the assumption made above that a chloride ion is less firmly bound to a lead ion than an abietate ion. The value 1.5×10^{-17} is of the order as that of the strongest electrolytes previously studied in benzene: for example, K for tetra-*i*-amylammonium picrate in benzene at 25° is 1.0×10^{-17}.

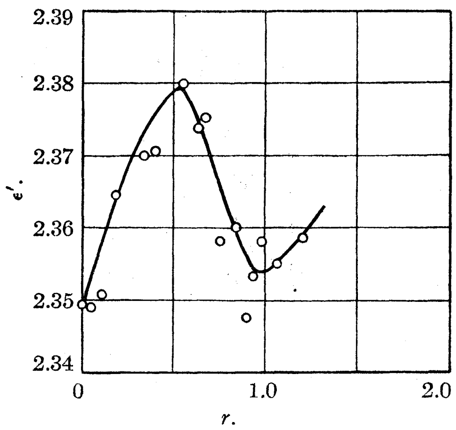


Fig. 9.—Change of dielectric constant during titration.

Summary

1. The conductances of lead abietate and of tributylammonium picrate and chloride in toluene at 35° have been determined at 60 cycles by means of the Schering bridge.

2. The polar moment of lead abietate in toluene is zero. Values for the other two salts check values in the literature.

3. The reaction between lead abietate and tributylammonium chloride in aromatic hydrocarbons has been studied. It is suggested that an intermediate soluble mixed salt, PbAbCl, is formed. The moment of the corresponding ion pair is 8.6×10^{-18} and its dissociation constant is approximately 1.5×10^{-17}.

4. An analytical method for the determination of lead in compounds soluble in aromatic hydrocarbons is described. The method depends on the fact that dry hydrogen chloride precipitates lead chloride quantitatively from benzene or toluene solutions of lead salts.

5. The preparation of pure lead abietate is described.

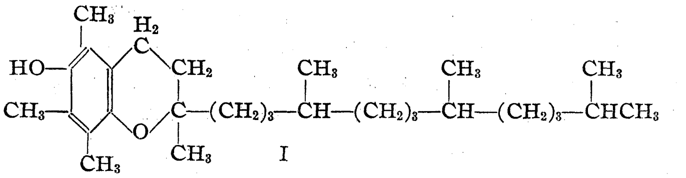
SCHENECTADY, N. Y. RECEIVED JUNE 24, 1938

[CONTRIBUTION FROM RESEARCH LABORATORIES, MERCK & CO., INC.]

Studies on Vitamin E. Ethers of Durohydroquinone

BY E. FERNHOLZ[1] AND JACOB FINKELSTEIN

Ethers of durohydroquinone have attained significance to those conducting research on vitamin E since the discovery[2] that α-tocopherol gives this phenol in a high yield on thermal decomposition. In a recent publication[3] the reasons which led to the abandonment of the original idea that α-tocopherol might be a monoether of durohydroquinone were summarized. Experimental evidence was cited to prove that α-tocopherol is a derivative of 6-hydroxychromane of the probable structure I.



I

Our interest in the preparation of monoethers of durohydroquinone did not cease, at the end of last year, after we had convincing evidence that α-tocopherol was a chromane derivative of durene. This was due to the discovery by H. M. Evans and G. A. Emerson of the University of California that certain of these ethers showed definite vitamin E-like activity.[4]

The absorption spectra and reducing properties of the primary and secondary ethers, the preparations of which are described below, previously have been reported briefly.[3] With the exception of the monocetyl ether, all mono- and diethers were formed simultaneously by adding an equivalent amount of alcoholic potassium hydroxide to a gently refluxing alcoholic solution of durohydroquinone and the halide. The two ethers were separated by distillation or by taking advantage of their difference in solubility in alcohol. To prepare the monocetyl ether, the diether was refluxed with one mole of aluminum chloride in benzene. When two moles of aluminum chloride were used with the diether the cleavage was complete. The properties of our mono- and dicetyl ethers are in good agreement with the properties of those prepared by John,[5] who used a method similar to that first mentioned. These ethers were also prepared by Bergel, *et. al.*,[6] by a slightly different method, but the melting points and analyses indicated that they were not quite pure.

In order to synthesize 2-methyl-*n*-octadecyl alcohol, an intermediate for one of the ethers, we first prepared ethylmethylcetyl malonate. Partial hydrolysis and decarboxylation of this gave ethyl α-methylstearate. This ester was reduced to the corresponding alcohol by hydrogen under high pressure in the presence of copper chromite catalyst.[7]

Although the preparation of the primary and secondary ethers did not prove to be difficult, the preparation of tertiary ethers of durohydroquinone failed completely as might have been expected.

Experimental

Mono-*s*-butyl Ether of Durohydroquinone.—To a gently boiling alcoholic solution of 8.6 g. of durohydroquinone and 20.2 g. of *s*-butyl iodide in an atmosphere of hydrogen, 111 cc. of 0.9 normal alcoholic potassium hydroxide was added in small drops over a period of fifteen minutes. After several hours of refluxing, the solution was cooled, diluted with an equal volume of water and extracted with ether. After it had been dried and concentrated, the oil was distilled.

After a forerun, consisting mainly of duroquinone, the monoether distilled at air-bath temperature of 145 to 150° at 0.05 mm. It was recrystallized from petroleum ether and obtained in the form of small needles; m. p. 85–86°; yield 0.5 g. This compound reduced silver nitrate slowly.

Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.57; H, 10.20.

The acetyl derivative was prepared by refluxing with excess acetic anhydride for twenty-four hours. The compound was obtained as long needles from alcohol; m. p. 62–63°.

Anal. Calcd. for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found C, 72.88; H, 9.13.

Ethers of Durohydroquinone and Dodecyl Iodide.—As described above, 20 g. of dodecyl iodide, 8.3 g. of durohydroquinone in 50 cc. of alcoholic potassium hydroxide were interacted and worked up.

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(1) Present address: E. R. Squibb & Sons, New Brunswick, N. J.

(2) E. Fernholz, THIS JOURNAL, **59**, 1154 (1937).

(3) E. Fernholz, *ibid.*, **60**, 700 (1938).

(4) H. M. Evans, G. A. Emerson and O. H. Emerson, *Science*, **88**, 38 (1938).

(5) W. John, E. Dietzel and Ph. Günther, *Z. physiol. Chem.*, **252**, 208 (1938).

(6) F. Bergel, A. R. Todd and T. S. Work, *J. Chem. Soc.*, 257 (1938).

(7) Adkins and Folkers, THIS JOURNAL, **53**, 1095 (1931); **54**, 1145 (1932).

The monoether distilled at an air-bath temperature of 160° at 0.05 mm., and recrystallized from alcohol; m. p. 96–97°; yield 5 g.

Anal. Calcd. for $C_{22}H_{38}O_2$: C, 78.99; H, 11.45. Found: C, 79.30; H, 11.25.

The residue from the above distillation, which contained the diether, was dissolved in chloroform and filtered through charcoal. Upon evaporation of the solvent a white crystalline substance was obtained which was further purified by recrystallization from alcohol; m. p. 79–80°; yield 3.5 g.

Anal. Calcd. for $C_{34}H_{62}O_2$: C, 81.21; H, 12.43. Found: C, 81.13; H, 12.39.

Ethers of Durohydroquinone and Cetyl Iodide.[5,6]—As described above, 6.6 g. of durohydroquinone, 14 g. of cetyl iodide in 100 cc. of amyl alcohol and 200 cc. of 2 normal solution of potassium hydroxide in amyl alcohol were interacted. After refluxing several hours and as a crystalline substance formed, the mixture was diluted with water and ether and filtered. The undissolved crystals were purified by first crystallizing from chloroform-alcohol mixture and then from butanol and obtained as white leaflets. The crystals do not reduce silver nitrate, as the product is the diether; m. p. 88–89°.

Anal. Calcd. for $C_{42}H_{78}O_2$: C, 82.02; H, 12.78. Found: C, 82.06; H, 12.76.

The mono-ether was obtained from the diether, as follows.

To 3.6 g. of dicetyl ether of durohydroquinone in 50 cc. of benzene, 0.9 g. of aluminum chloride (1.1 mol) was added and the mixture refluxed for eight hours. It was washed successively with dilute hydrochloric acid, dilute sodium hydroxide, water and then concentrated until crystals appeared. It was now diluted with alcohol and filtered. After dissolving the precipitate in ether, the solution was washed with Claisen solution (equal parts of 50% potassium hydroxide solution in water and methanol), dried and distilled. After a forerun of duroquinone and some halide, the monoether distilled at air-bath temperature at about 190° at 0.05 mm. After recrystallizing from alcohol, it melted at 99–100.5° and reduced silver nitrate; yield 0.4 g.

Anal. Calcd. for $C_{26}H_{46}O_2$: C, 79.94; H, 11.87. Found: C, 79.98; H, 11.74.

When the above procedure was repeated using 2.7 g. of dicetyl ether and 1.35 g. of aluminum chloride in 50 cc. of benzene, the cleavage was so complete that no monoether was isolated.

Ethers of Durohydroquinone and Octadecyl Iodide.—In the usual way, 8.3 g. of durohydroquinone, 24 g. of octadecyl iodide in 50 cc. of alcohol and 50 cc. of normal alcoholic potassium hydroxide were interacted. After three hours, the mixture was cooled and the crystals which separated were filtered. The product was recrystallized from a hot mixture of alcohol and benzene to give the pure diether; m. p. 95–97°.

Anal. Calcd. for $C_{46}H_{86}O_2$: C, 82.32; H, 12.91. Found: C, 82.49, 82.25; H, 12.92, 12.84.

The mother liquor was concentrated to dryness and the residue dissolved in ether. This solution was washed with Claisen solution, dried and concentrated. The monoether distilled at 0.05 mm. with air-bath temperature at 170–190°. It was then recrystallized from alcohol and obtained as white leaflets. It reduces silver nitrate; m. p. 105.5°.

Anal. Calcd. for $C_{28}H_{50}O_2$: C, 80.32; H, 12.04. Found: C, 80.43, 80.16; H, 11.92, 12.18.

Methyl *n*-Heptadecyl Ketone.—This compound was prepared from barium stearate and barium acetate by the method of Morgan and Holmes.[8]

Methyl-*n*-heptadecylcarbinol.—A solution of 29 g. of the above ketone in 500 cc. of glacial acetic acid was hydrogenated at room temperature and atmospheric pressure using Adams platinum catalyst. The required amount of hydrogen was absorbed in twenty-five minutes and the solution was filtered. Upon the addition of water to the filtrate, a precipitate was obtained which was dissolved in ether and washed with dilute caustic and water. After drying, the ether was distilled and the remaining liquid was treated with excess alcoholic potash to saponify any ester that might have formed. The product was extracted with ether, dried and the oil obtained on concentration was treated with 21 g. of *p*-nitrobenzoyl chloride in pyridine. After recrystallization from petroleum ether, the derivative melted at 95.5°; yield 40 g.

Anal. Calcd. for $C_{26}H_{43}O_4N$: C, 72.02; H, 10.00. Found: C, 72.22, 72.14; H, 9.87, 9.64.

A solution of 38 g. of the above *p*-nitrobenzoate in 90 cc. of alcohol containing 4.5 g. of potassium hydroxide was refluxed for one hour. After diluting with water, extracting with ether and concentrating, a crystalline compound was obtained. After recrystallizing it from petroleum ether the m. p. was 48–49°; yield 17 g.

Anal. Calcd. for $C_{19}H_{41}O$: C, 79.93; H, 14.47. Found: C, 80.11; H, 14.30.

***n*-Nonadecyl Bromide-2.**—A stream of hydrogen bromide was passed into 15 g. of the above alcohol, heated in an oil-bath at 110–120° until the reaction was completed. The product was cooled, dissolved in chloroform, washed with concentrated sulfuric acid, water and then dried over calcium chloride. The chloroform was evaporated under reduced pressure and the oil which remained distilled at an air-bath temperature of 170° at 0.05 mm. The distillate was slightly yellow and turned darker on standing; yield 13 g.

Anal. Calcd. for $C_{19}H_{39}Br$: Br, 23.00. Found: Br, 23.65.

Ethers of Durohydroquinone and *n*-Nonadecyl Bromide-2.—In the usual way, 5.7 g. of durohydroquinone, 11 g. of *n*-nonadecyl bromide-2 in 50 cc. of alcohol and 37 cc. of 0.9 normal alcoholic potassium hydroxide were interacted. When the reaction mixture was neutral, it was diluted with water and extracted with a large volume of ether. After drying and concentrating, a crystalline product was obtained. Upon distillation at 0.05 mm. and air-bath temperature of 180–200°, the monoether was obtained. It was recrystallized from alcohol; m. p. 94–95°; yield 5 g. This compound reduced silver nitrate solution.

Anal. Calcd. for $C_{29}H_{42}O_2$: C, 80.49; H, 12.12. Found: C, 80.21; H, 11.93.

To obtain the diether, the residue in the flask was dissolved in chloroform and treated with charcoal. The

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(8) Morgan and Holmes, *J. Soc. Chem. Ind.*, 108 T (1925).

solvent was evaporated and the product recrystallized from alcohol–benzene mixture; yield 3.5 g., m. p. 75–76°.

Anal. Calcd. for $C_{48}H_{90}O_2$: C, 82.45; H, 12.97. Found: C, 82.20; H, 13.00.

Ethyl Methyl Cetyl Malonate.—To a solution of 5.2 g. of sodium in 100 cc. of absolute alcohol, 40 g. of ethyl methylmalonate was added. Then, 77 g. of cetyl iodide was added and the mixture refluxed until neutral. The alcohol was distilled *in vacuo* and the residue extracted with ether. The oil obtained after concentration was fractionated at reduced pressure: at 1 mm., b. p. 185–190°; yield 63 g.

Anal. Calcd. for $C_{24}H_{48}O_4$: C, 71.95; H, 12.07. Found: C, 72.47; H, 11.82.

Ethyl α-Methylstearate.—A mixture of 30 g. of the above malonate and 4.6 g. of potassium hydroxide in 52 cc. of alcohol was refluxed for sixteen hours. The solution was diluted with water and alcoholic potassium hydroxide and extracted with ether. The aqueous solution was acidified to congo with concentrated hydrochloric acid and the oil separated. After drying, the oil was heated at 180° until no more carbon dioxide was evolved. After cooling, it was taken up with ether and washed with dilute sodium carbonate and water and distilled, after drying: at 1 mm., b. p. 161–163°; yield 20 g.

Anal. Calcd. for $C_{21}H_{42}O_2$: C, 77.24; H, 12.96. Found: C, 77.56; H, 12.70.

2-Methyl-*n*-octadecyl Alcohol.—An alcoholic solution of 14 g. of the above ester, in the presence of 1 g. of copper chromite, was heated at 250° under 2000 lb. (133 atm.) pressure of hydrogen for eight hours. After cooling and filtering, the product was distilled. At air-bath temperature of 125–130° and 0.05 mm., the alcohol was obtained and upon cooling it solidified; m. p. 32–33°; yield 12 g.

Anal. Calcd. for $C_{19}H_{40}O$: C, 80.21; H, 14.17. Found: C, 80.25; H, 14.00.

2-Methyl-*n*-Octadecyl Iodide.—A mixture of 12 g. of the above alcohol, 6 g. of iodine and 1 g. of red phosphorus was heated at 170–180° for one hour. The product was dissolved in ether and washed with water, thiosulfate, water and then dried. On distilling at 0.05 mm. and air-bath temperature of 185°, a colorless liquid is obtained which soon turns pink; yield 14 g.

Anal. Calcd. for $C_{19}H_{39}I$: C, 57.86; H, 9.96. Found: C, 57.74; H, 10.04.

Ethers of Durohydroquinone and 2-Methyl-*n*-octadecyl Iodide.—In the usual way, 5.5 g. of durohydroquinone, 13 g. of the above iodide in alcohol and 28 cc. of 1.15 *n* alcoholic potassium hydroxide interacted. After several hours of refluxing, water was added and the precipitate dissolved in ether. The extract was washed with Claisen solution, water and then dried. On distillation at 0.05 mm., a fore-run of a hydrocarbon and duroquinone was obtained and then at an air-bath temperature of 210–220°, the mono-ether distilled. After recrystallization from alcohol, it was obtained pure, m. p. 94–95°; yield 2 g. The reducing power of this ether was rather strong but not like that of α-tocopherol.

Anal. Calcd. for $C_{29}H_{52}O_2$: C, 80.49; H, 12.12. Found: C, 80.44; H, 11.91.

The residue was dissolved in chloroform and filtered through charcoal several times. The solvent was evaporated and the diether recrystallized from alcohol, m. p. 76–78°; yield 1 g.

Anal. Calcd. for $C_{48}H_{90}O_2$: C, 82.45; H, 12.97. Found: C, 82.34; H, 12.99.

We gratefully acknowledge our indebtedness to Messrs. D. F. Hayman and W. Reiss for the microanalyses.

Summary

Several mono- and diethers of durohydroquinone have been prepared.

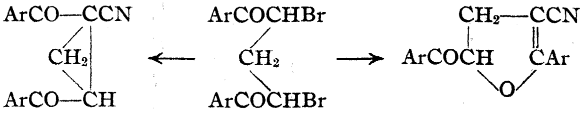
RAHWAY, NEW JERSEY RECEIVED JULY 22, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

The Action of Sodium Cyanide on 1,3-Dibromo-1,3-dibenzoylpropane

BY REYNOLD C. FUSON, J. R. LITTLE AND GAIL MILLER

The successful closure of the cyclobutane ring by treatment of α,α′-dibromoadipic esters with sodium cyanide[1] could not be extended to 1,4-dibromo-1,4-diaroylbutanes. The latter underwent closure to cyanodihydro-1,4-pyrans, *i. e.*, to six-membered rings.[2] The present work grew out of an attempt to extend the method to the closure of a 1,3-dibromo-1,3-diaroylpropane (I). It was thought that this compound might yield a cyclopropane derivative (II) or a cyanodihydrofuran derivative (III) depending on whether the reaction resembled the cyclobutane or the dihydro-1,4-pyran closure.



II I III

In an effort to determine which of these two courses the reaction would follow, we have treated 1,3-dibromo-1,3-dibenzoylpropane (IV) with sodium cyanide. A rapid reaction took

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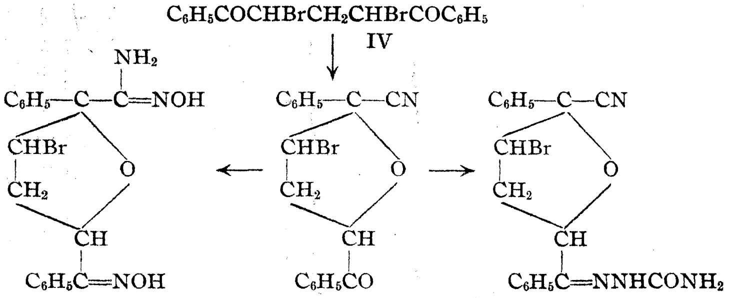
[1] Fuson and Kao, THIS JOURNAL, **51**, 1536 (1929); Fuson, Kreimeier and Nimmo, *ibid.*, **52**, 4074 (1930); Rydon, *J. Chem. Soc.*, 593 (1936).

[2] Fuson, Kuykendall and Wilhelm, THIS JOURNAL, **53**, 4187 (1931).

place, but there were no cyclopropane or dihydrofuran derivatives among the products. A mixture of four isomeric compounds was obtained. The molecular formula was $C_{18}H_{14}O_2NBr$. The net change in the molecule, therefore, consisted in the loss of one bromine atom and the gain of one carbon atom and one nitrogen atom.

The observation that there are four isomers and that they do not give a precipitate with alcoholic silver nitrate greatly restricts the number of possible structures. Of these only that of 2-cyano-2-phenyl-3-bromo-5-benzoyltetrahydrofurans (V) satisfies all of the requirements. In particular, the fact that it is a β-bromo ether would account for the inertness of the bromine atom toward silver nitrate.[3]

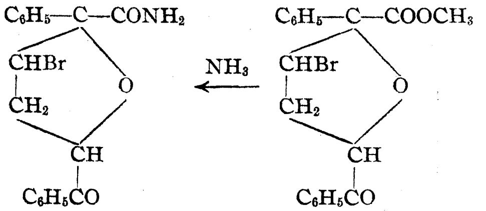
The products correspond to the four pairs of optical isomers theoretically possible on the basis of formula V, and for convenience have been called A, B, C and D. A few reactions have been run on all four compounds to show their similarity, but many of the reactions have been carried out only with A, the most plentiful isomer.



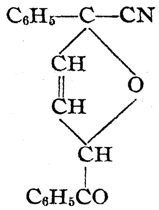
VI V VII

Treatment with hydroxylamine converted the four compounds into similar derivatives having the formula $C_{18}H_{18}O_3N_3Br$. These have been assigned formula VI—that of 2-phenyl-3-bromo-5-oximinobenzoyltetrahydrofuramidoxime. The change in composition indicates that the ketone group has been converted to an oximino group and the cyano group to an amidoxime group as reported by Tiemann.[4]

Isomers A, B and D yielded different monosemicarbazones (VII) which confirm the presence of one carbonyl group. Treatment of A and B with acids gave amides (VIII) which resisted attempts to bring about hydrolysis to the corresponding acids. Isomer A was transformed into a mixture of the amide (VIII) and the methyl ester (IX) by treatment with a solution of hydrogen chloride in methanol. Ammonia converted the ester to the amide.



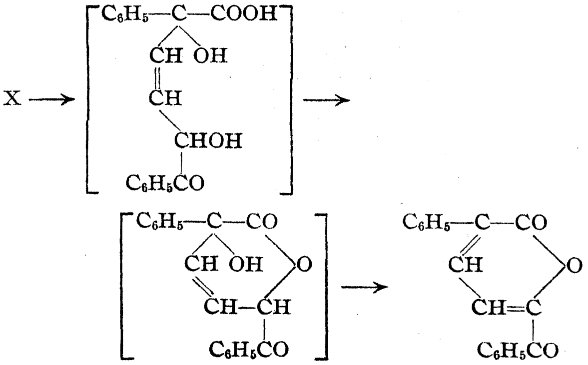
VIII IX



X

The most interesting reaction of A, B, C and D occurred when they were treated with aqueous alkali. All lost a molecule of hydrogen bromide and gave the same product. This result may be explained by reference to formula X which has two asymmetric carbon atoms one of which—that attached to the benzoyl group—might be expected to undergo inversion due to enolization. The latter process would be favored by the alkalinity of the reaction medium. In this connection it is interesting to note that isomer C was found to change spontaneously into isomer B—a result which can be explained in a similar manner.

Further evidence for the structure of the dihydrofuran (X) was obtained by treating it with strong acid. By this process a nitrogen-free product was obtained which had the formula $C_{18}H_{12}O_3$, and was shown to be 3-phenyl-6-benzoyl-1,2-pyrone (XI). The following sequence of reactions appears probable



XI

In an attempt to benzoylate the 1,2-pyrone (XI) it was dissolved in hot alkali and treated with benzoyl chloride. From the alkaline solution it was possible to isolate an acid whose com-

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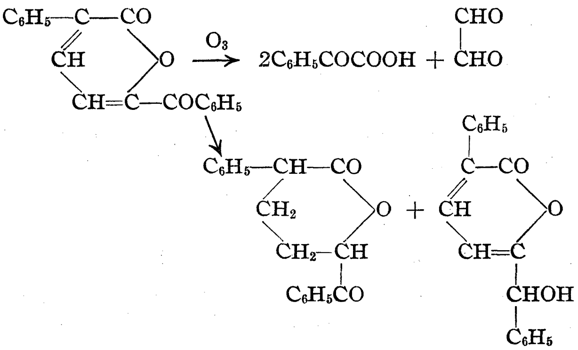
(3) See Kirner, THIS JOURNAL, **48**, 2745 (1926).

(4) Tiemann, *Ber.*, **17**, 126 (1884).

position corresponded to that of the monohydrate of the diketo acid, $C_6H_5COCOCH_2CH{=}C(C_6H_5)COOH$. The presence of a ketone group in the 1,2-pyrone (XI) was established by oximation; two forms of the oxime were isolated. Degradation of the 1,2-pyrone into known compounds was accomplished by ozonization followed by catalytic reduction of the ozonide. Phenylglyoxylic acid and glyoxal were isolated in the form of their phenylhydrazine derivatives

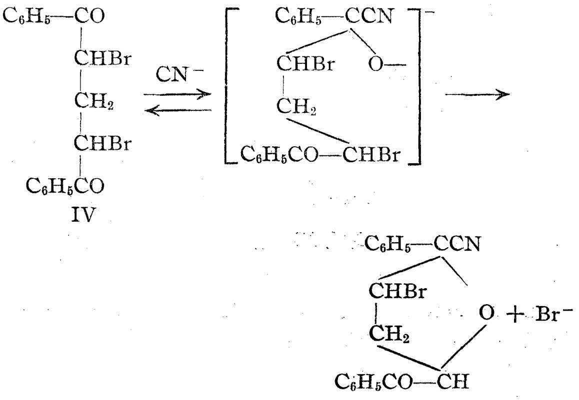


XII XIII

When the pyrone was reduced catalytically α-phenyl-δ-benzoyl-δ-valerolactone (XII) was isolated. It was accompanied by a dihydro derivative of the pyrone which formed an acetate, and may be the carbinol (XIII) resulting from reduction of the carbonyl group.

Discussion of Results

The transformation of 1,3-dibromo-1,3-dibenzoylpropane (IV) into the 2-cyano-2-phenyl-3-bromo-5-benzoyltetrahydrofurans (V) is complete in a minute or two and no appreciable amount of heat is liberated. It does not take place at all unless water is present. Apparently the first step in the reaction is the addition of cyanide ion to one of the carbonyl groups.[5] Ring closure is then effected by the elimination of a bromide ion.

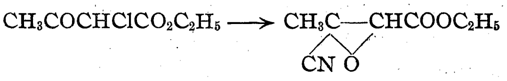


IV

V

This suggests that the addition of the cyanide ion is a rapid reversible reaction which goes to completion because the ring closure is irreversible.

The process is similar to that involved in the formation of α-epoxy nitriles from α-halo ketones. Favrel and Provost,[6] for example, showed that potassium cyanide converted ethyl α-chloroacetoacetate into the corresponding epoxy nitrile



$$CH_3COCHClCO_2C_2H_5 \longrightarrow \underset{CN\ O}{CH_3C}{-}CHCOOC_2H_5$$

Similar results were obtained by Kohler and Brown[7] and by Richard[8] with desyl chloride. Richard[9] also converted α-chloro-α-phenylacetone into α-epoxy-α-methyl-β-phenylpropionitrile by this method.

These examples might lead one to think that this type of reaction would be general for ketones which have a halogen atom in the α-, γ- or perhaps δ-position. Yet Wohlgemuth[10] reported that it could not be carried out with γ-chloropropyl ethyl ketone. Allen and Boyer[11] found that γ-chlorobutyrophenone when treated with potassium cyanide in absolute alcohol gave cyclopropyl phenyl ketone and none of the cyanotetrahydrofuran which might have been expected. Since the closure under consideration occurs only in the presence of water, we repeated the experiment of Allen and Boyer using, however, aqueous alcohol as the solvent; there was no reaction after two hours at room temperature.

Another and perhaps more striking example of this sort is afforded by the work on 1,4-dibromo-1,4-diaroylbutanes which, as has been indicated earlier, react in a manner entirely different from that observed with the next lower homolog.

In conclusion it may, therefore, be said that the action of sodium cyanide on 1,3-dibromo-1,3-dibenzoylbutane to give 2-cyano-2-phenyl-3-bromo-5-benzoyltetrahydrofurans is an extension of a new type of reaction hitherto limited to the formation of epoxy nitriles. The conditions which have obtained in all of the examples cited are the following:

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(5) See Jones, *J. Chem. Soc.*, **105**, 1561 (1914); Lapworth, *ibid.*, **83**, 995 (1903).

(6) Favrel and Provost, *Bull. soc. chim.*, [4] **49**, 243 (1931).

(7) Kohler and Brown, THIS JOURNAL, **55**, 4299 (1933).

(8) Richard, *Compt. rend.*, **198**, 943 (1934).

(9) Richard, *ibid.*, **199**, 71 (1934).

(10) Wohlgemuth, *Ann. chim.*, **3**, 141 (1915).

(11) Allen and Boyer, *Can. J. Research*, **9**, 159 (1933).

1. Water is present in the solvent. 2. The halogen atom directly involved is in the α-position relative to an activating group such as a carbonyl or phenyl group. 3. The carbonyl group which enters into the reaction has a halogen atom in the α-position with respect to it. 4. The reactive groups involved are conveniently spaced for ring formation.

That the foregoing conditions are necessary remains to be shown. That they are not always sufficient is indicated by the results with 1,4-dibromo-1,4-dibenzoylbutane. This and other types of halo ketones are being examined in an effort to determine more precisely the generality of the reaction.

Experimental Part

The Preparation of the Isomeric 1,3-Dibromo-1,3-dibenzoylpropanes.—1,3-Dibenzoylpropane made by the method of Auger[12] was brominated according to the procedure of Conant and Lutz.[13] The latter authors reported two isomeric dibromides melting at 115–115.5 and 89°. In the present work the crude bromination product was fractionally crystallized from carbon tetrachloride. From 74 g. of crude product there was obtained 40 g. of a dibromide melting at 117–118° and 21 g. of a mixture which melted at 90–94°.

In an effort to separate the mixture absolute alcohol was used as a solvent. A chance seeding gave crystals which melted at 112–113°. A mixture of these with those melting at 117–118° melted at 92–95°. It appears probable that the low-melting isomer reported by Conant and Lutz is really a mixture of the two forms.

Anal. Calcd. for $C_{17}H_{14}O_2Br_2$: C, 49.8; H, 3.4. Found for the compound melting at 117–118°: C, 49.8; H, 3.7. Found for the compound melting at 112–113°: C, 50.2; H, 4.2.

Conversion of 1,3-Dibromo-1,3-dibenzoylpropane into the Isomeric 2-Cyano-2-phenyl-3-bromo-5-benzoyltetrahydrofurans.—Sixty grams of 1,3-dibromo-1,3-dibenzoylpropane was suspended in 800 cc. of 95% ethyl alcohol in a flask equipped with a mechanical stirrer. A solution of 10 g. of sodium cyanide in 40 cc. of water was added gradually, with stirring, over a period of about three minutes. A slight coloration occurred and the dibromide went partially—sometimes wholly—into solution. A few minutes after the addition of the cyanide was complete a heavy precipitate formed suddenly. The stirring was discontinued after about fifteen minutes, the solid collected on a filter, dried and crystallized from carbon tetrachloride. In this way isomer A was obtained in white cotton-like needles melting at 166–167°.

The alcoholic mother liquors from the reaction were poured into water and the semi-solid material which separated was extracted with benzene. Acidification of the water–alcohol solution with hydrochloric acid seemed to hasten the extraction. The benzene layer was dried over sodium sulfate and concentrated under diminished pressure. Absolute alcohol was added to the viscous concentrate; cooling and triturating induced the formation of a finely divided crystalline precipitate. Alternate concentration of alcohol solutions and trituration with absolute alcohol gave several more crops of a mixture which proved to consist of A and its isomers.

No successful method was found for separating the isomers by fractional crystallization. This was finally accomplished by dissolving the mixture in hot methyl alcohol (about 200 cc. for each 10 g. of crystals), allowing the solution to cool so that the crystals formed slowly. The crystallization was carried out by pouring the hot methyl alcohol solution into a large crystallizing dish such that the depth of the solution was from 1 to 2 cm. The dish was then covered with a watch glass and allowed to stand for several days without disturbance.

When the crystals had grown to a sufficient size for handling, the mother liquor was carefully decanted and the different types of crystals were separated by picking them out mechanically. Compound A was found in clusters of very fine needles. Long oblong crystals occurring singly or in rosets melted at 101–102° and were designated Compound B. Compact clusters of opaque needles usually having a slight color melted at 120–123° and were called Compound D. Thick square plates softening at 101–102° and melting at 120° were found to contain both B and a third isomer, D. These square crystals formed only occasionally with methyl alcohol as the solvent, more frequently with a mixture of benzene and petroleum ether as solvent. The crystals of isomer D were tough and hard to grind whereas those of the other isomers were brittle. Isomer D was also found to exist in long slender needles melting at 108–109°. By rapid cooling and stirring the lower-melting form usually could be isolated; slower crystallization gave the higher-melting form.

Diamond-shaped crystals melting at 86–88°—obtained in only two of the several runs—were called isomer C. On being allowed to stand for long periods of time this isomer underwent isomerization to Compound B. The fact that C was not found in all preparations was probably due to its tendency to rearrange to B during the process of recrystallization.

The yields of the isomers were: A, 52–68%; B, 12–16%; C, 0–2%; D, about 6%. Approximately the same ratio of isomers was obtained from either the high-melting or the low-melting dibromide. Similarly, sodium cyanide and potassium cyanide gave about the same results.

Anal. Calcd. for $C_{18}H_{14}O_2NBr$: C, 60.7; H, 4.0; Br, 22.5; mol. wt., 356. Found for A (m. p. 166–167°): C, 60.4, 60.3; H, 4.0, 4.1; Br, 22.3; mol. wt., 346. Found for B (m. p. 101–102°): C, 60.3, 60.3; H, 4.1, 4.1. Found for C (m. p. 86–88°): C, 60.4, 60.4; H, 4.0, 4.1. Found for D (m. p. 120–123°): C, 60.5; H, 4.2.

Each of the four isomers was shown to contain bromine and nitrogen. None, however, gave even a turbidity when treated with boiling alcoholic solutions of silver nitrate.

Treatment of 1,3-Dibromo-1,3-dibenzoylpropane with Potassium Cyanide in Absolute Alcohol.—To a suspension of 1 g. of the dibromide (m. p. 116–118°) in 300 cc. of carefully prepared absolute ethyl alcohol was added 0.4 g. of

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[12] Auger, *Ann. chim.*, [6] **22**, 358 (1891).

[13] Conant and Lutz, THIS JOURNAL, **49**, 1083 (1927).

potassium cyanide. After three days the mixture was found to contain none of isomers A, B, C and D but a new compound melting at 127–128.5°. It contained halogen, but was not further investigated.

The Isomeric 2-Phenyl-3-bromo-5-oximinobenzoyltetrahydrofuramidoximes.—The usual procedure for oxime formation was employed. The following table shows solvents used for recrystallization, the melting points and the analytical data. Mixed melting point determinations showed the four derivatives to be different.

Furamidoxime from	M. p., °C.	Recrystallization solvent	Analyses, % C	H	N	Br
A	171–173	Methyl alcohol	53.4	4.2	10.5	19.6
			53.5	4.5		
			53.7	4.5		
B	179–181	Methyl alcohol	53.6	4.7		
C	182–183	Ethyl alcohol			10.5	
D	180–182	Chloroform	53.4	4.5		
Calcd. for $C_{18}H_{18}O_3N_3Br$			53.5	4.5	10.4	19.8

The Semicarbazones of Isomers A, B and D.—These derivatives were prepared in the customary manner. Their melting points and analytical data are listed in the table.

Semicarbazone from	M. p., °C.	Analyses, % C	H	N	Br
A	202	55.2	4.3	13.4	19.4[a]
B	178–179	55.4	4.0	13.9	
D	202	55.5	4.1	13.2	
Calcd. for $C_{19}H_{17}O_2N_4Br$		55.2	4.1	13.5	19.4

[a] This compound was prepared and analyzed by Sister M. Faith Hand.

2-Phenyl-3-bromo-5-benzoyltetrahydrofuramide.—Three grams of isomer A was dissolved in a solution of 50 cc. of concentrated hydrochloric acid and 50 cc. of glacial acetic acid and the mixture was heated on a steam-bath for three hours. The resulting dark green solution was poured into water and the mixture neutralized with sodium bicarbonate and extracted with benzene. In addition to some unchanged A there was obtained colorless crystals of the amide which after recrystallization twice from ethyl alcohol and then once from methyl alcohol melted at 200–201°. The compound was insoluble in alkali. It contained nitrogen and halogen but gave no precipitate with hot alcoholic silver nitrate.

Anal. Calcd. for $C_{18}H_{16}O_3NBr$: C, 57.8; H, 4.3; N, 3.8. Found: C, 57.5; H, 4.4; N, 3.8.

Methyl 2-Phenyl-3-bromo-5-benzoyltetrahydrofuroate.—An ice-cold suspension of 6 g. of isomer A in 400 cc. of absolute methyl alcohol was saturated with dry hydrogen chloride gas. After the mixture had stood at room temperature for fifteen hours it was poured into 2 liters of water. The ester was extracted with benzene, the benzene evaporated and the residue crystallized from methyl alcohol. The compound formed compact crystals melting at 101–102°. It contained nitrogen and halogen but was not soluble in alkali and gave no precipitate with hot alcoholic silver nitrate.

Anal. Calcd. for $C_{18}H_{17}O_3Br$: C, 58.6; H, 4.4. Found: C, 58.4, 58.6; H, 4.6, 4.4.

A small amount of the corresponding amide (m. p. 200–201°) was also obtained.

A similar treatment of isomer B (later found to contain some of isomer D) gave no ester but an amide probably derived from isomer B but possibly from isomer D. It melted (from alcohol) at 207°, with decomposition.

Anal. Calcd. for $C_{18}H_{16}O_3NBr$: C, 57.8; H, 4.3; N, 3.8. Found: C, 58.0; H, 3.4; N, 3.9.

2-Cyano-2-phenyl-5-benzoyl-2,5-dihydrofuran (X).—To a solution of 50 g. of isomer A in 400 cc. of hot methyl alcohol was added a solution of 9 g. of sodium hydroxide in 250 cc. of water. After being refluxed for one hour on the steam-bath the hot solution was poured into 2 liters of water. Acidification with dilute hydrochloric acid changed the dark red color of the solution to a bright yellow. By extraction of this acidified solution with benzene the dihydrofuran was obtained which crystallized from benzene in bright yellow, cotton-like needles, melting at 136–137°, with darkening at 130°. These crystals turn brown in the light. The yield was 28 g.

Anal. Calcd. for $C_{18}H_{13}O_2N$: C, 78.6; H, 4.7; N, 5.1. Found: C, 78.5; H, 4.5; N, 5.2.

The same product was obtained from isomers B, C and D by similar treatment with sodium hydroxide. Potassium cyanide or sodium acetate could be used in place of sodium hydroxide but with those reagents conversion was incomplete.

3-Phenyl-6-benzoyl-1,2-pyrone (XI).—A mixture of 20.5 g. of dihydrofuran, 400 cc. of glacial acetic acid and 180 cc. of concentrated hydrochloric acid was heated on a steam-bath for fifteen hours and poured into 2500 cc. of water. The brown crystals which formed were treated with decolorizing charcoal and recrystallized from alcohol. In this way 16.5 g. of the pyrone was obtained as slightly colored crystals melting at 126–127°. The compound was insoluble in alkali, contained neither halogen nor nitrogen and readily decolorized an acetone solution of potassium permanganate.

Anal. Calcd. for $C_{18}H_{12}O_3$: C, 78.3; H, 4.4. Found: C, 78.2; H, 4.4.

The oxime crystallized from alcohol in large needles melting at 193–194°.

Anal. Calcd. for $C_{18}H_{13}O_3N$: N, 4.8. Found: N, 4.8.

From the mother liquors was obtained **an isomeric oxime** which crystallized from alcohol in large squares melting at 159–161°.

Anal. Calcd. for $C_{18}H_{13}O_3N$: N, 4.8. Found: N, 4.9.

The Ozonolysis of the 1,2-Pyrone.—In a large test-tube were placed 1.0 g. of the pyrone and 30 cc. of glacial acetic acid. The mixture was cooled in an ice-bath and ozonized oxygen was bubbled through it for five hours at 0° and then continued overnight, during which time the bath came to room temperature. About 0.1 g. of palladium catalyst on charcoal was added to the mixture and the test-tube was placed in the shaker of a catalytic reduction machine equipped with an open mercury manometer. The apparatus was evacuated until bubbles formed in the solution, and then hydrogen was admitted up to 800 mm. pressure. After the mixture had been shaken for four hours the pressure was 680 mm. The catalyst was removed by filtration and 5 cc. of water and 2 cc. of phenylhydrazine were added to the filtrate. The precipitate which formed almost immediately was collected on a filter and recrystallized several times from alcohol and from benzene. The **phenylosazone of glyoxal** was obtained in almost colorless crystals melting at 162–166°. The melting point of a mixture of this sample with an authentic one (m. p. 166–169°) was 163–167°.

The filtrate was poured into water and the solution extracted with benzene. The benzene was extracted with sodium carbonate solution. The resulting solution when acidified gave **the phenylhydrazone of phenylglyoxylic acid** which crystallized from benzene in bright yellow crystals melting at 159–160°. A mixture of this compound with an authentic specimen (m. p. 159–160°) melted at 159–160°.

α-Phenyl-δ-benzoyl-δ-valerolactone.—The 1,2-pyrone in methyl cellosolve was reduced catalytically in the presence of a platinum oxide catalyst. In addition to a small amount of unchanged 1,2-pyrone there were formed two hydrogenation products. These were separated by crystallization from carbon tetrachloride. The less soluble was purified by crystallization from benzene or aqueous alcohol. It melted at 137–138°. It was very soluble in alcohol, did not decolorize bromine in chloroform solution and was not attacked by chromic acid in acetic acid solution.

Anal. Calcd. for $C_{18}H_{14}O_3$: C, 77.7; H, 5.1. Found: C, 77.8; H, 5.1.

The acetate was formed by treatment with acetic anhydride and sodium acetate. It melted at 102–103°.

Anal. Calcd. for $C_{20}H_{16}O_4$: C, 75.1; H, 5.0. Found: C, 75.7; H, 5.0.

The oily residue left after the carbon tetrachloride mother liquor had evaporated was solidified when triturated with ethyl alcohol. Recrystallization from ethyl alcohol gave the valerolactone in diamond-shaped crystals mixed with crystals of the original 1,2-pyrone. The two types of crystals were separated mechanically. The new compound when pure melted at 142–143°. It was very soluble in carbon tetrachloride and did not decolorize a solution of bromine in carbon tetrachloride.

Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.1; H, 5.8. Found: C, 77.3; H, 5.8.

In a second run in which fresh catalyst was introduced twice during the course of the hydrogenation the lactone was the only product which could be isolated.

Summary

1,3-Dibromo-1,3-dibenzoylpropane (IV) reacts with sodium cyanide to give a mixture of the four theoretically possible 2-cyano-2-phenyl-3-bromo-5-benzoyltetrahydrofurans (V).

Treatment with alkali converts the four isomeric tetrahydrofurans into 2-cyano-2-phenyl-5-benzoyl-2,5-dihydrofuran (X).

The dihydrofuran is transformed into 3-phenyl-6-benzoyl-1,2-pyrone (XI).

Ozonolysis of the 1,2-pyrone gave glyoxal and phenylglyoxylic acid. Reduction converted the 1,2-pyrone into α-phenyl-δ-benzoyl-δ-valerolactone (XII).

Urbana, Illinois Received June 18, 1938

[Contribution from the Cobb Chemical Laboratory, University of Virginia]

Studies in the Phenanthrene Series. XVIII. Synthesis of Acyl Compounds Derived from 1- and 4-Phenanthrol

By Harry M. Duvall[1] and Erich Mosettig

In the search for substances with oestrogenic activity, the plan has been developed to synthesize more or less simple phenanthrene derivatives containing a phenolic hydroxyl group and a carbonyl group, the latter being located either in a side chain attached to, or in a five- or six-membered hydroaromatic ring condensed with, the phenanthrene nucleus.

This communication describes the preparation by means of the Fries rearrangement and the Friedel–Crafts reaction of methyl and ethyl ketones derived from 1- and 4-phenanthrol. It was found that in the "1-series" the Fries rearrangement was much superior to the Friedel–Crafts reaction. 1-Hydroxy-2-acetylphenanthrene (I) and 1-hydroxy-2-propionylphenanthrene (II) were obtained in yields of 60 and 72%, respectively, in the Fries rearrangement, and in yields of only 30 and 26% by the Friedel–Crafts reaction.

In the "4-series," 4-hydroxy-*y*-acetylphenanthrene was formed in a poor yield only (30%) in the rearrangement of 4-acetoxyphenanthrene together with a small amount (6%) of another compound that is probably 4-hydroxydiacetylphenanthrene. In the Friedel–Crafts reaction, employing acetyl and propionyl chloride, diketones could be isolated in satisfactory yield (60–70%), but no monoketones were found.

While 4-methoxyphenanthrene reacted smoothly with acetyl and propionyl chlorides in the pres-

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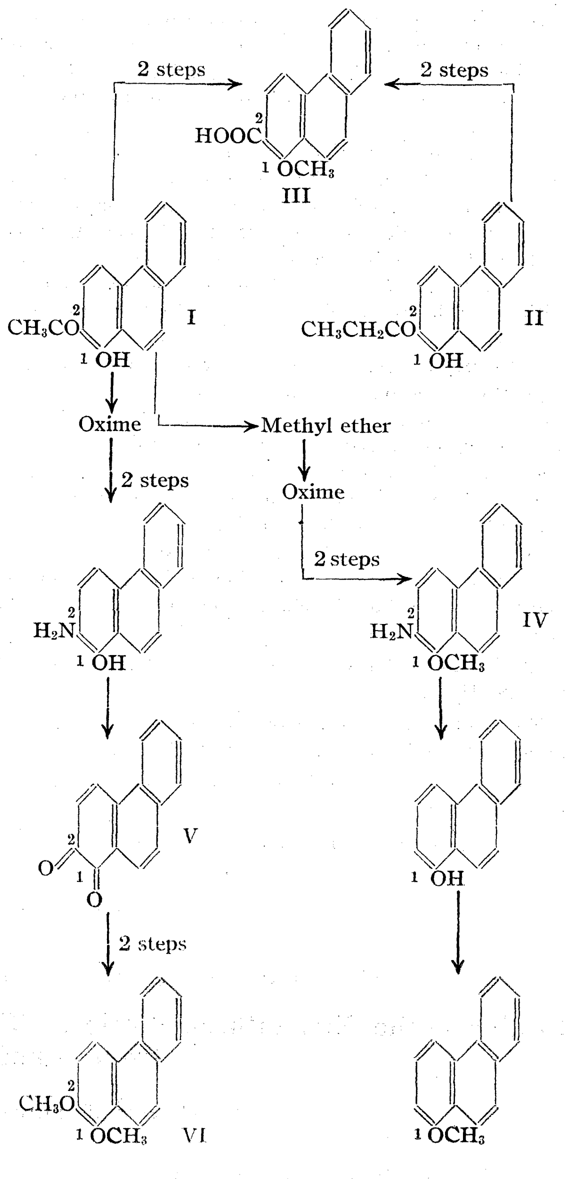
(1) E. R. Squibb and Sons Research Fellow.

ence of aluminum chloride to give 4-methoxy-*x*-acetylphenanthrene and 4-methoxy-*x*-propionylphenanthrene in yields of 70%, the analogous reactions with 1-methoxyphenanthrene, employing the solvents nitrobenzene, *sym*-tetrachloroethane, or a mixture of both, were entirely unsuccessful, resulting only in tarry products from which no individual compounds could be isolated.

That the acyl groups in both 1-hydroxy-2-acetylphenanthrene (I) and 1-hydroxy-2-propionylphenanthrene (II) occupy the same relative position was shown by the identity of the acids resulting from the oxidation of the methylated ketones with sodium hypochlorite.

The first attempt to determine the position of the acetyl group in the ketone I, though not successful, appears to be worthy of mention. The hydroxy ketone was methylated and its oxime subjected to the Beckmann rearrangement. The resulting methoxyacetylamino derivative was hydrolyzed and the methoxyaminophenanthrene (IV) was diazotized, with the expectation of arriving at a methoxyhydroxyphenanthrene that might be converted to a known dimethoxyphenanthrene. In the diazotization, however, elimination of the amino group, with simultaneous demethylation of the methoxyl group, took place and 1-phenanthrol was formed (identified through its methyl ether). The yield was about 10% and speculation concerning the mechanism of the formation of 1-phenanthrol seems to be, therefore, unimportant.

The structure of 1-hydroxy-2-acetylphenanthrene was established by transforming the oxime of ketone I to a hydroxyamino compound, which was oxidized with chromic acid to a quinone (V), the properties of which corresponded closely to those of 1,2-phenanthrenequinone described by Fieser.[2] We converted the quinone (V), via the hydroquinone, to a dimethoxy compound (VI), according to the directions of Fieser.[2] The latter compound (VI) was identified with an authentic sample of 1,2-dimethoxyphenanthrene, which was prepared in this Laboratory from 2-phenanthrol, according to Fieser.[2]



The acyl groups in 4-methoxy-*x*-acetylphenanthrene and 4-methoxy-*x*-propionylphenanthrene were shown to occupy the same relative position, by oxidation of the methoxy ketones with sodium hypochlorite to identical methoxycarboxylic acids. 4-Methoxy-*x*-acetylphenanthrene proved to be different from the methyl ether of 4-hydroxy-*y*-acetylphenanthrene (obtained by Fries rearrangement). Thereby the difference of the location of the acetyl group in both compounds became evident.

Attempts to locate the positions *x* and *y* by various methods have been without success so far. In a series of efforts to demethylate 4-methoxy-*x*-acetylphenanthrene (30% hydrogen bromide in glacial acetic acid, concentrated hydrochloric acid in a sealed tube, aluminum chloride in benzene, phosphoric acid), the methoxy ketone either was not attacked at all, or was destroyed. With a mixture of 48% aqueous hydrobromic acid and glacial acetic acid, demethylation

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[2] Fieser, This Journal, 51, 1896 (1929).

PHENANTHRENE DERIVATIVES

Substituent	Appearance, needles	Solvent	Yield, %	M. p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1-Hydroxy-2-acetyl[a]	Yellow	EtOH	60	154–155	$C_{16}H_{12}O_2$	81.34	81.31	5.12	5.14
1-Hydroxy-2-propionyl[b]	Yellow	EtOH	72	149–150	$C_{17}H_{14}O_2$	81.58	81.82	5.64	5.99
4-Hydroxy-*y*-acetyl[c]	Yellow	EtOH	30	112–113	$C_{16}H_{12}O_2$	81.34	81.39	5.12	5.35
4-Methoxy-*y*-acetyl[d]	Colorless	MeOH	Quant.	80–81.5	$C_{17}H_{14}O_2$		OCH_3	12.40	11.64
4-Methoxy-*x*-acetyl[e]	Colorless	EtOH	73	122.5–123.5	$C_{17}H_{14}O_2$	81.58	81.67	5.64	5.75
4-Methoxy-*x*-propionyl[f]	Colorless	EtOH	72	116	$C_{18}H_{16}O_2$	81.80	81.78	6.10	6.23
4-Hydroxydiacetyl[g]	Yellow	EtOH	61	193	$C_{18}H_{14}O_3$	77.69	77.81	5.07	5.27
Dioxime[h]	Yellow	EtOH	Quant.	228–229 dec.	$C_{18}H_{16}O_3N_2$	70.13	70.48	5.23	5.35
							N	9.09	9.00
4-Hydroxydipropionyl[i]	Yellow	EtOH	70	165.0–165.5	$C_{20}H_{18}O_3$	78.42	78.52	5.93	5.90

[a] A solution of 9.00 g. of 1-acetoxyphenanthrene in 110 ml. of nitrobenzene and a solution of 11.3 g. of aluminum chloride in 45 ml. of nitrobenzene were mixed and allowed to stand for forty-eight hours. [b] A solution of 3.30 g. of 1-propionoxyphenanthrene (prepared from 1-phenanthrol by the action of propionyl chloride in pyridine; m. p. 94–96°) in 15 ml. of nitrobenzene and a solution of 3.87 g. of aluminum chloride in 15 ml. of nitrobenzene were mixed and allowed to stand for seventy-two hours. [c] A solution of 8.00 g. of 4-acetoxyphenanthrene in 60 ml. of nitrobenzene and a solution of 10.0 g. of aluminum chloride in 40 ml. of nitrobenzene were mixed and allowed to stand for forty-eight hours. A small amount of a by-product, m. p. 193–194°, was obtained. This compound was probably 4-hydroxydiacetylphenanthrene. [d] Prepared from 4-hydroxy-*y*-acetylphenanthrene by methylation in the usual manner. [e] A solution of 7.10 g. of 4-methoxyphenanthrene and 2.70 g. of acetyl chloride in 36 ml. of nitrobenzene and a solution of 10.0 g. of aluminum chloride in 35 ml. of nitrobenzene were mixed and allowed to stand for forty-eight hours. [f] A solution of 4.00 g. of 4-methoxyphenanthrene and 1.84 ml. of propionyl chloride in 20 ml. of nitrobenzene and a solution of 5.64 g. of aluminum chloride in 20 ml. of nitrobenzene were mixed and allowed to stand for forty-eight hours. [g] A solution of 9.00 g. of 4-acetoxyphenanthrene and 3.96 ml. of acetic anhydride in 45 ml. of nitrobenzene and a solution of 11.3 g. of aluminum chloride in 45 ml. of nitrobenzene were mixed and allowed to stand for forty-eight hours. [h] Prepared from 4-hydroxydiacetylphenanthrene in the usual manner. [i] A solution of 6.40 g. of 4-phenanthrol and 6.31 ml. of propionyl chloride in 32 ml. of nitrobenzene and a solution of 9.70 g. of aluminum chloride in 32 ml. of nitrobenzene were mixed and allowed to stand for seventy-two hours.

was effected, but only with simultaneous elimination of the acetyl group.[3]

Furthermore, 4-methoxy-*y*-acetylphenanthrene was converted, through the oxime, and the rearrangement of the latter, to 4-methoxy-*x*-aminophenanthrene. It was planned to demethylate this compound and oxidize the expected hydroxy amine to a quinone. Unfortunately, we were unable to effect demethylation under varied experimental conditions.

It is not unlikely that one of the two positions, *x* and *y*, is position 1, and the other is position 3. Further, we believe it probable that in the diacetyl compound, at least one of the acetyl groups is located in position *x* or *y*.

Attempts to elucidate the structures of the compounds in the 4-series are being continued.

Experimental

1- and 4-acetoxyphenanthrene were prepared by boiling under reflux for five hours a solution of five parts of the respective phenanthrol and one part of anhydrous sodium acetate in fifty parts of acetic anhydride. The reaction mixture, after cooling to room temperature, was poured into water, whereupon the acetoxyphenanthrene separated in a practically pure state; m. p. 131–134, and 58–60°, respectively; yields, nearly quantitative.

1- and 4-methoxyphenanthrene were prepared, according to the method of Stevens and Tucker,[4] by adding dimethyl sulfate dropwise, with vigorous stirring, to a suspension of the acetoxyphenanthrene in a mixture of 66% potassium hydroxide solution and acetone (by weight, 1 part of acetoxyphenanthrene and 2.80 parts of potassium hydroxide; by volume, 1.45 parts of water, 10 parts of acetone and 1.60 parts of dimethyl sulfate). The reaction mixture was then poured into a large excess of water. The methyl ethers were obtained in a practically pure state (m. p. 101–103, and 65–67°, respectively), and were crystallized once from ethyl and methyl alcohol, respectively. The yields were nearly quantitative.

All other methylations cited in this communication were carried out by the procedure described above.

Friedel–Crafts Reaction.—Hydroxy-, acetoxy- or methoxyphenanthrene was dissolved in nitrobenzene and to the solution was added one or two moles, plus 10% excess, of acid chloride or acid anhydride. A solution of two moles, plus 10% excess, of aluminum chloride in nitrobenzene was poured slowly into the first solution, both solutions having been cooled previously in an ice-bath. The reaction mixture was kept at 0–5° for forty-eight or seventy-two hours and then decomposed by pouring onto ice and concentrated hydrochloric acid. The nitrobenzene was removed by steam distillation.

The reaction product from methoxyphenanthrene was

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(3) An analogous elimination has been observed recently by Robinson and Walker, *J. Chem. Soc.*, 185 (1938). 1-Acetyl-2-hydroxynaphthalene, by boiling with hydriodic acid, readily gave 2-hydroxynaphthalene. See also Hill, Short and Stromberg, *ibid.*, 1619 (1937).

(4) Stevens and Tucker, *J. Chem. Soc.*, **123**, 2140 (1923).

purified by crystallization from alcohol, with use of Norite.

The reaction product from hydroxy- and acetoxyphenanthrenes was dissolved in an excess of 5% potassium hydroxide solution and alcohol, heated to boiling, to ensure complete saponification of any ester present. The hot solution was filtered and, after cooling to room temperature, acidified with concentrated hydrochloric acid. The hydroxyacylphenanthrene thus precipitated was collected and purified by crystallization from alcohol, with the use of Norite.

Fries Rearrangement.—The experimental procedure for the Fries rearrangement differed from that described for the Friedel–Crafts reaction only in that no acid chloride or acid anhydride was used.

Proof of Structure

1-Methoxyphenanthrene-2-carboxylic Acid (III).—A suspension of 0.20 g. of the methyl ether of ketone I (m. p. 80–81°) in 38 ml. of a 1% aqueous hypochlorite solution was boiled under reflux until a practically clear solution resulted. (The hypochlorite solution was prepared from calcium hypochlorite "HTH" and sodium carbonate.) The hot reaction mixture was filtered and cooled, and two grams of sodium thiosulfate was added. The acid (III), along with some sulfur, was liberated by acidification with concentrated hydrochloric acid. The sulfur was removed by digesting the precipitate with saturated sodium bicarbonate solution and filtering the solution while hot. The acid was regenerated by acidifying the filtrate at room temperature. Crystallized from alcohol, the acid was obtained as colorless needles; m. p. 224–225° (dec.).

Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.18; H, 4.79. Found: C, 76.17; H, 5.12.

The same acid was obtained by hypochlorite oxidation of the methyl ether of ketone II (m. p. 74–76°). The identity of these two acids was established by their melting points (224.5 and 223–224°, respectively) and a mixture melting point determination (224–225°) and by the melting points (109–110 and 109°) and mixture melting point (109–110°) of their respective methyl esters.

1-Methoxy-2-acetylphenanthrene.—The methyl ether of ketone I was prepared in quantitative yield by the methylation procedure described above. Crystallized from methyl alcohol, it was obtained as colorless plates; m. p. 81–82°.

Anal. Calcd. for $C_{17}H_{14}O_2$: OCH_3, 12.40. Found: OCH_3, 12.12.

Oxime.—A solution of one molecular equivalent of the above ketone, two moles of hydroxylamine hydrochloride and two and one-half moles of anhydrous sodium acetate in alcohol was boiled under reflux for four hours. The solution was then concentrated, cooled to room temperature and diluted with water until the oxime had separated completely. The yield was quantitative. Crystallized from methyl alcohol, the oxime was obtained as colorless needles; m. p. 166–167° (dec.).

Anal. Calcd. for $C_{17}H_{15}O_2$: N, 5.28. Found: N, 5.47.

1-Methoxy-2-acetylaminophenanthrene.—A solution of 1.00 g. of the above oxime in a mixture of 5 ml. of glacial acetic acid and 5 ml. of acetic anhydride was saturated with dry hydrogen chloride. The reaction mixture, now a solid paste, was allowed to stand for twenty hours, and was then poured onto ice and water. The acetylamino compound was collected, washed with water and dried; m. p. 220–222° (dec.). The yield was quantitative. After crystallization from methyl alcohol, 1-methoxy-2-acetylaminophenanthrene was obtained as colorless plates; m. p. 222–223° (dec.).

Anal. Calcd. for $C_{17}H_{15}O_2$: N, 5.28. Found: N, 5.12.

1-Methoxy-2-aminophenanthrene (IV).—A solution of 0.90 g. of the above N-acetylamine in a mixture of 10 ml. of 6 *N* hydrochloric acid and 10 ml. of glacial acetic acid was boiled under reflux for one hour. The amine hydrochloride, which separated on cooling the reaction mixture, was filtered off and converted to the free base by treatment with ammonium hydroxide. The amine (IV), obtained in a yield of 87%, was crystallized from alcohol: colorless needles, m. p. 139.5–141°.

Anal. Calcd. for $C_{15}H_{13}ON$: C, 80.70; H, 5.87; N, 6.27; OCH_3, 13.90. Found: C, 80.63; H, 5.93; N, 6.41; OCH_3, 13.34.

The amine was diazotized according to the method of De Milt and van Zandt.[5] A solution of 0.50 g. of the amine in 2.3 ml. of pyridine was added slowly (one hour) to a solution of nitrosyl sulfuric acid cooled to 0° with ice and salt. (The nitrosyl sulfuric acid solution was prepared by first adding 0.34 g. of sodium nitrite to a cold mixture of 3.4 ml. of concentrated sulfuric acid and 1.7 ml. of water, and then carefully warming the mixture to 40° until a clear solution resulted.) The mixture was stirred for an hour at 0° and then was diluted with ice and water to a volume of about 100 ml. An aqueous solution of 0.22 g. of urea was added and stirring was continued for another hour at 0°. The solution of the diazonium sulfate was filtered and added, in small portions, to 300 ml. of boiling water. Boiling was continued for about fifteen minutes. After standing overnight, the precipitate which had separated was filtered off and dissolved in 5% potassium hydroxide solution. The filtered alkaline solution was acidified with concentrated hydrochloric acid and the phenolic product (0.06 g.) thus obtained was methylated in the usual manner. The methylated product was purified by sublimation and crystallization and melted at 102–103°. It was shown to be 1-methoxyphenanthrene; a mixture melting point determination with an authentic sample (m. p. 103–104°) showed no depression (m. p. 103°).

Oxime of I.—The oxime of ketone I was prepared in the usual manner, yield quantitative. When first isolated, the oxime was nearly colorless, but it turned yellow on short standing. It crystallized from alcohol in yellow needles, m. p. 224–225° (dec.).

Anal. Calcd. for $C_{16}H_{13}O_2N$: C, 76.48; H, 5.21; N, 5.58. Found: C, 76.57; H, 5.42; N, 5.40.

1,2-Dimethoxyphenanthrene (VI).—A solution of 3.84 g. of the above oxime and 4 g. of phosphorus pentachloride in 500 ml. of dry benzene was boiled under reflux for thirty minutes, according to the method of Bachmann and Boatner.[6] The solution, after cooling to room temperature, was extracted with water, sodium bicarbonate solu-

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[5] De Milt and van Zandt, This Journal, **58**, 2044 (1936); see also Bachmann and Boatner, *ibid.*, **58**, 2194 (1936).

[6] Bachmann and Boatner, *ibid.*, **58**, 2097 (1936).

tion and water again to remove phosphorus compounds. The dried benzene solution yielded 3.12 g. of crude 1-hydroxy-2-acetylaminophenanthrene.

The crude hydroxyacetylaminophenanthrene was hydrolyzed to the corresponding amine hydrochloride by boiling under reflux for one hour with 28 ml. of 6 *N* hydrochloric acid and 28 ml. of glacial acetic acid. The reaction mixture, after cooling in an ice-bath, was diluted with several volumes of water, and the amine hydrochloride which had separated was collected; yield 2.31 g.

The amine hydrochloride was converted, through the quinone (V) and the hydroquinone, to 1,2-dimethoxyphenanthrene (VI), according to the directions of Fieser,[2] as given for the analogous conversion of 1-amino-2-hydroxyphenanthrene hydrochloride to 1,2-dimethoxyphenanthrene. The dimethoxyphenanthrene thus obtained, after purification by sublimation and crystallization, melted at 103–104° (corr.). A mixture melting point determination with an authentic sample (m. p. 103–104°) showed no depression (m. p. 103–104°).

Anal. Calcd. for $C_{16}H_{14}O_2$: OCH_3, 26.05. Found: OCH_3, 25.91.

Samples of 1,2-phenanthrenequinone (V) from the above hydroxyamine hydrochloride and from 1-amino-2-hydroxyphenanthrene hydrochloride were purified by sublimation and crystallization. Both samples were brilliant red in color and gave in concentrated sulfuric acid the characteristic color change from blue to green. We found the melting point of both samples of the quinone to be indefinite and unsatisfactory for the purpose of identification (the quinone did not soften, but decomposed over a variable range of about ten to twenty degrees, starting at 190–195°).

4-Methoxyphenanthrene-*x*-carboxylic Acid.—4-Methoxy-*x*-acetylphenanthrene was oxidized to the corresponding carboxylic acid by the hypochlorite method described above. The acid, crystallized from toluene as colorless needles, melted at 238–239°.

Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.18; H, 4.79. Found: C, 76.92; H, 5.32.

The same acid was obtained by hypochlorite oxidation of 4-methoxy-*x*-propionylphenanthrene. The identity of these two acids was established by their melting points (238–239°) and a mixture melting point (238–239°).

Methyl Ester.—Both acids described above, from 4-methoxy-*x*-acetylphenanthrene and from 4-methoxy-*x*-propionylphenanthrene, were methylated in the usual manner. Both esters, crystallized from methyl alcohol and obtained as colorless needles, melted at 93–94°. A mixture melting point determination showed no depression (m. p. 93–94°).

Anal. Calcd. for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30. Found: C, 76.63; H, 5.36.

Oxime of 4-Methoxy-*x*-acetylphenanthrene.—This oxime was prepared in the usual manner from 4-methoxy-*x*-acetylphenanthrene, yield quantitative. It crystallized from ethyl alcohol as colorless needles of m. p. 190–191° (dec.).

Anal. Calcd. for $C_{17}H_{15}O_2N$: N, 5.28. Found: N, 5.11.

4-Methoxy-*x*-acetylaminophenanthrene.—The above oxime rearranged to 4-methoxy-*x*-acetylaminophenanthrene in quantitative yield by the glacial acetic acid–acetic anhydride–hydrogen chloride method already described. Crystallized from methyl alcohol, the N-acetylamino compound appeared as colorless needles of m. p. 201°.

Anal. Calcd. for $C_{17}H_{15}O_2N$: N, 5.28. Found: N, 5.44.

Summary

1. A series of acyl compounds derived from 1- and 4-phenanthrol has been synthesized by means of the Fries rearrangement and the Friedel–Crafts reaction.

2. 1-Hydroxy-2-acetylphenanthrene and 1-hydroxy-2-propionylphenanthrene have been described and their structures have been established.

3. 4-Hydroxy-*y*-acetylphenanthrene, 4-hydroxydiacetylphenanthrene, 4-hydroxydipropionylphenanthrene, 4-methoxy-*x*-acetylphenanthrene and 4-methoxy-*x*-propionylphenanthrene have been described.

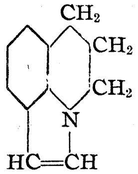
UNIVERSITY, VIRGINIA RECEIVED JULY 20, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF MEDICAL CHEMISTRY OF THE UNIVERSITY OF EDINBURGH]

Synthesis of Polycyclic Indoles

BY GEORGE BARGER AND ELIZABETH DYER[1]

This research originated in an attempt to synthesize an indole, which had been obtained[2] by the degradation of the alkaloid calycanthine, and for which the following possible structure had been proposed



The synthesis of this indole was accomplished by condensing N-aminotetrahydroquinoline[3] with pyruvic acid, and converting the hydrazone thus obtained into 2-carboxy-1,8-trimethyleneindole by an application of the Fischer method.[4] Decarboxylation yielded the above 1,8-trimethyleneindole.

The structure of this indole was established by its conversion on reduction to 2,3-dihydro-1,8-trimethyleneindole or lilolidine, previously obtained by von Braun and co-workers through an independent synthesis.[5] The synthetic 1,8-trimethyleneindole was found to be not identical with the indole previously obtained from calycanthine. The properties of the calycanthine fragment differ also from those of the 3,4-trimethyleneindole described by Jacobs and Gould.[6]

The chemistry of polycyclic indoles of the type of 1,8-trimethyleneindole, a type which comprises both the tetrahydroquinoline and indole systems, was extended by the study of other members of the series. The 2-phenyl derivative of 1,8-trimethyleneindole was obtained from the hydrazone of acetophenone and N-aminotetrahydroquinoline. All attempts to prepare the corresponding 2-methyl derivative from the acetone hydrazone of N-aminotetrahydroquinoline were unsuccessful. A similar difficulty in preparing an indole from acetone-2-quinolyl hydrazone was experienced by Perkin and Robinson.[7]

With a view to applying the same type of reaction in the tetrahydrobenzoquinoline series, N-amino-1,2,3,4-tetrahydro-5,6-benzoquinoline was prepared. Although this readily formed a hydrazone with pyruvic acid, the corresponding indole could not be obtained. A similar resistance to indole formation was observed with the pyruvic acid hydrazone of N-amino-carbazole.

Grateful acknowledgment is made to the American Association of University Women for the Sarah Berliner Research Fellowship held by one of us (E. D.); and to the Moray Fund of Edinburgh University for a grant in support of the research.

Experimental Part

N-Amino-1,2,3,4-tetrahydroquinoline.—This substance was prepared from N-nitrosotetrahydroquinoline[8] by the method of Hoffmann and Königs.[3] To obtain 50% yields, care must be taken to keep the temperature of the reduction mixture between 60 and 75°. The product, purified by recrystallizing the sulfate, yielded a picrate (not previously described) which crystallized from alcohol as long, brownish-yellow needles, m. p. 140–141° with decomposition.

Anal. Calcd. for $C_{15}H_{12}O_7N_5$: N, 18.58. Found: N, 18.50.

Hydrazones.—The following table summarizes the successful methods of preparing the new hydrazones needed for indole syntheses. The hydrazones I and II were convertible to indoles, but all attempts to cyclize III, IV and V failed. The methods investigated included: heating with (a) zinc chloride at 100–130, 180–190° at 760 mm. or 110–120° at 12 mm.; (b) 10% aqueous hydrochloric acid at 50–60 or 80–100°; (c) dry hydrogen chloride gas in ethanol or *n*-butanol solution.

2-Carboxy-1,8-trimethyleneindole.—When a mixture of 2 g. of the pyruvic acid hydrazone of N-aminotetrahydroquinoline and 25 cc. of 10% hydrochloric acid was heated at 55° for one hour, the hydrazone gradually dissolved with the precipitation of the indole together with a dark impurity. The precipitate was filtered, dried, dissolved in ether and filtered from the small quantity of amorphous impurity. The ether solution was extracted with sodium carbonate, and 0.95 g. of the acid obtained on acidification of the basic extract (50% yield). For analysis the substance was recrystallized from benzene, from which it separated as needles, melting with decomposition at 210–212° when pure.

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[1] Sarah Berliner Research Fellow of the American Association of University Women. Present address: Women's College, University of Delaware, Newark, Del.

[2] Unpublished work of Barger and Streuli, at the Department of Medical Chemistry of the University of Edinburgh.

[3] Hoffmann and Königs, *Ber.*, **16**, 730 (1883).

[4] Fischer and Hess, *ibid.*, **17**, 561 (1884).

[5] Von Braun, Heider and Wyczatkowska, *ibid.*, **51**, 1219 (1918).

[6] Jacobs and Gould, *J. Biol. Chem.*, **120**, 144 (1937).

[7] Perkin and Robinson, *J. Chem. Soc.*, **103**, 1974 (1913).

[8] Ziegler, *Ber.*, **21**, 862 (1888).

TABLE I

PREPARATION OF HYDRAZONES

	Hydrazine[a]	>CO Cpd.	Conditions	Cryst. form and recryst. solvent	% Yield	M. p., °C.	Analyses, %	
							Calcd.	Found
I	4.4 g. A	3.2 g. pyruvic acid	Cold, dil. acetic acid	Hexagonal plates, 1:2 benzene-petroleum ether	92	98–99 dec.	N 12.85	12.56
II	3.0 g. A	2.4 g. acetophenone	Reflux 1 hr. in alc. with 5 drops conc. H_2SO_4	Needles, alc.-water	87	84.5–85.5	N 11.20	11.11
III	1.0 g. A	2 cc. acetone	Reflux 2 hr., distil		90	b. p. 153 at 12 mm.	C 76.50 H 8.57 N 14.89	76.37 8.50 14.68
	Picrate of III		Ethereal picric acid	Needles, alc.		138–140	N 16.78	16.71
IV	0.7 g. B	0.5 cc. pyruvic acid	Alc., reflux 5 min.	Plates, alc.	58	122–123	N 10.45	10.22
V	.5 g. C	.4 cc. pyruvic acid	Same as IV	Plates, alc.	85	148–150, dec.	N 11.12	11.37

[a] A = N-amino-1,2,3,4-tetrahydroquinoline; B = N-amino-1,2,3,4-tetrahydro-5,6-benzoquinoline; C = N-aminocarbazole.

Anal. Calcd. for $C_{12}H_{11}O_2N$: C, 71.61; H, 5.51; N, 6.97. Found: C, 71.49; H, 5.54; N, 7.02.

The substance was easily soluble in cold methanol and ethanol, and in acetone, moderately soluble in ether and practically insoluble in water. It gave a violet Ehrlich reaction on boiling.

1,8-Trimethyleneindole.—This indole was obtained in 68% yield from the corresponding acid by an adaptation of Reichstein's procedure for decarboxylation.[9] A mixture of 1.5 g. of 2-carboxy-1,8-trimethyleneindole, 0.4 g. of copper chromite[10] and 4 cc. of quinoline was heated at 180–190° in a stream of hydrogen. After one hour the absence of a further precipitate in a barium hydroxide trap indicated completion of the reaction. The mixture was diluted with ether, filtered from the copper chromite and extracted with 2 *N* hydrochloric acid until no more quinoline was removed. A further extraction with dilute sodium carbonate removed traces of the carboxy acid. The ether solution was dried, the solvent evaporated and the residue distilled with steam. The indole, obtained from the distillate by filtration, was recrystallized from a small volume of petroleum ether (b. p. 40–60°). The product separated as large, colorless plates, m. p. 86.5–88° when pure.

Anal. Calcd. for $C_{11}H_{11}N$: C, 84.01; H, 7.06; N, 8.92. Found: C, 84.11; H, 7.02; N, 9.31.

The indole is very soluble in alcohol, acetone, benzene, moderately soluble in petroleum ether and insoluble in water. It is a neutral substance, insoluble in acids and bases. It gives a purple coloration with the Ehrlich reagent in the cold.

An unstable picrate of the indole was obtained by treating a concentrated benzene solution of the substance with a benzene solution containing slightly less than one equivalent of picric acid. The resulting red solution, when diluted with cold petroleum ether to faint turbidity, deposited red needles, melting at 138–139°.

Anal. Calcd. for $C_{17}H_{14}O_7N_4$: N, 14.51. Found: N, 14.67.

The picrate is decomposed by boiling water, by hot alcohol and even by hot benzene and petroleum ether.

2,3-Dihydro-1,8-trimethyleneindole.—When 0.2 g. of 1,8-trimethyleneindole in alcohol solution was reduced with zinc dust and hydrochloric acid, according to the procedure of Schlieper[11] for α-naphthindole, an oil was obtained which boiled at about 140° at 12 mm., and which yielded a yellow picrate that precipitated from ether solution. When recrystallized from alcohol, it separated in two forms, plates and needles, which, however, were identical in mixed melting point. The twice recrystallized picrate sintered at 165°, and liquefied at 168–170° to a red oil, which soon effervesced. The same substance was obtained by reduction of the indole with tin and hydrochloric acid.

Anal. Calcd. for $C_{17}H_{16}O_7N_4$: C, 52.56; H, 4.16; N, 14.43. Found: C, 52.80; H, 4.14; N, 14.47.

This picrate was identical in analysis and properties with the picrate of lilolidine, which was prepared according to von Braun[5] by condensation of trimethylene chlorobromide with dihydroindole.[12] The product was carefully fractionated to separate any unchanged dihydroindole from the lilolidine. The picrate of the highest fraction, after two recrystallizations from alcohol, did not lower the melting point of the picrate from dihydro-1,8-trimethyleneindole. It is to be noted, however, that although the melting point of the picrate was unchanged by this recrystallization, it is higher than that reported by von Braun.[5] The substance gave no evidence of melting at 138°, although held at that temperature for fifteen minutes, but sintered at 165°, and melted to a red oil at 168–170°. A duplicate preparation of lilolidine gave the same results. We have communicated with Professor von Braun, who admits the identity of our reduction product with lilolidine, and states that his original preparation was done under very adverse circumstances.

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[9] Reichstein, Zschokke and Grüssner, *Helv. Chim. Acta*, **15**, 1069 (1932).

[10] Adkins and Connor, THIS JOURNAL, **53**, 1092 (1931).

[11] Schlieper, *Ann.*, **239**, 229 (1887).

[12] Willstätter and Jaquet, *Ber.*, **51**, 777 (1918).

2-Phenyl-1,8-trimethyleneindole.—One gram of the hydrazone of N-aminotetrahydroquinoline and acetophenone was ground in a mortar with 5 g. of powdered anhydrous zinc chloride and the mixture was heated at 120° for one hour. The mass was then warmed with several small quantities of dilute hydrochloric acid to dissolve the zinc chloride. The residual gummy brown precipitate was filtered, dried, powdered and extracted with ether to separate the indole from brown ether-insoluble by-products. The residue obtained on evaporation of the extracts, when recrystallized from 10 cc. of alcohol, yielded 0.2 g. of the indole, m. p. 130–132° (22% yield). After two recrystallizations from alcohol, from which the substance separated as glittering, colorless leaves, it melted at 133–134°.

Anal. Calcd. for $C_{17}H_{15}N$: C, 87.50; H, 6.49; N, 6.01. Found: C, 87.32; H, 6.41; N, 5.91.

The substance gave with Ehrlich's reagent in the cold a violet color which turned blue on standing.

N - Amino-1,2,3,4-tetrahydro-5,6-benzoquinoline.—The necessary N-nitrosotetrahydrobenzoquinoline was prepared by the procedure of Bamberger and Müller.[13] Yields of 60–70% were obtainable if an adequate quantity of water was used to keep dissolved at 0° the rather insoluble salt of the tetrahydrobenzoquinoline.

The N-aminotetrahydrobenzoquinoline was prepared in yields of 35–40% by mild reduction of the nitroso compound with zinc dust and acetic acid in aqueous alcoholic solution, according to the procedure for N-aminotetrahydroquinoline. The product was isolated as the sulfate, which, after recrystallization from 0.6 N sulfuric acid, separated as glistening brown needles and leaves, m. p. 182° with decomposition.

Anal. Calcd. for $C_{26}H_{30}O_4N_4S \cdot 4H_2O$: N, 9.90. Found: N, 10.15.

Anal. of salt after drying at 120°. Calcd. for $C_{26}H_{30}O_4N_4S$: N, 11.34. Found: N, 11.30, 11.35.

The free base, formed by decomposition of the sulfate in hot aqueous–alcoholic solution with dilute alkali, consisted of tan crystals which melted at 107–108° after two recrystallizations from ligroin.

Anal. Calcd. for $C_{13}H_{14}N_2$: N, 14.18. Found: N, 13.94.

This hydrazine was moderately soluble in alcohol, nearly insoluble in water. It reduced Tollens' solution rapidly in the cold, and Fehling's solution slowly on boiling.

Summary

1. The chemistry of a new tricyclic indole, 1,8-trimethyleneindole, has been studied. The 2-carboxy and 2-phenyl derivatives are also reported, but the 2-methyl derivative could not be obtained. The preparation of the intermediate hydrazones, the pyruvic acid, acetophenone and acetone hydrazones of N-amino-1,2,3,4-tetrahydroquinoline is reported.

2. N-Amino-1,2,3,4-tetrahydro-5,6-benzoquinoline and its pyruvic acid hydrazone have been prepared. The latter is inactive toward indolizing agents.

3. The pyruvic acid hydrazone of N-aminocarbazole is likewise not convertible to an indole.

EDINBURGH, SCOTLAND RECEIVED JULY 19, 1938

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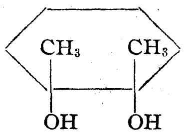
[13] Bamberger and Müller, *Ber.*, **24**, 2644 (1891).

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

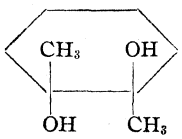
Inversion in the Pinacol Rearrangement of 1,2-Dimethylcyclopentanediol-1,2*

BY PAUL D. BARTLETT AND ABRAHAM BAVLEY

It has been pointed out[1] that in the pinacol rearrangement of the geometrical isomers of 1,2-dimethylcyclohexanediol-1,2 (I and II)



I



II

the methyl group migrates in preference to the ring carbon atom only in the *cis*-pinacol, in which the methyl group is, on a time average, remote from the hydroxyl which it displaces. Because the cyclohexane ring is non-planar and allows many different orientations of adjacent substituents with respect to each other, this example leaves something to be desired in exactness of interpretation. For this reason we have investigated the case of *cis*- and *trans*-1,2-dimethylcyclopentanediol-1,2, in which the planar nature of the five-membered ring makes the relative positions of the groups in space much more certain.

The assignment of configurations to the *cis*- and *trans*-isomers is made on the same basis as in the case of the analogous pinacols with six-membered rings. The *cis* isomer, a liquid boiling at 142–146° (20 mm.), is prepared by the action of potassium permanganate in cold aqueous acetone solution on 1,2-dimethylcyclopentene-1. The *trans* isomer, m. p. 99.5–101° (corr.), results

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(*) Presented at the Milwaukee meeting of the American Chemical Society, September 6, 1938.

(1) Bartlett and Pöckel, THIS JOURNAL, **59**, 820 (1937).

from the hydrolysis of the oxide of the same hydrocarbon. The assignment of configurations is confirmed by the fact that lead tetraacetate reacts more than a thousand times as fast with the "*cis*" as with the "*trans*" isomer, in accordance with the findings of Criegee, Kraft and Rank[2] for cases where the configuration is in no doubt.

When the *cis* isomer is refluxed with 30% aqueous sulfuric acid, a ketone can be isolated in 87% yield (as semicarbazone) whose physical constants and whose oxime and semicarbazone show it to be identical with the 2,2-dimethylcyclopentanone-1 prepared in different ways by Blanc[3] and by Haller and Cornubert.[4] Thus the methyl group has migrated in that pinacol in which it is in a position to displace the adjacent hydroxyl group by attacking the opposite side of the carbon atom holding it, as in the Walden inversion.

Identical treatment of the *trans* pinacol gives only involatile brown tars, which on standing become progressively more viscous. All our efforts to isolate an unpolymerized product from this reaction have been without avail. Experiments with gentler acid conditions have led to the same type of product, when there was any reaction at all. It seems probable that the pinacol is being dehydrated without rearrangement to yield a dimethylcyclopentadiene which is polymerized irreversibly by any acid strong enough to bring about dehydration. We tried to prove this by carrying out the dehydration in the presence of maleic anhydride and of benzoquinone, but, as might have been anticipated, the diene addition to these reagents was unable to compete with the polymerization reaction under these acid conditions, and again only tar was obtained. An attempt to catch the diene by bromination also failed.

For the interpretation of these reactions it becomes important to know whether this resinification process occurs because the structure and configuration of this pinacol are especially favorable to it, or especially unfavorable to rearrangement, which must be regarded as the normal reaction. To answer this question we carried out some semiquantitative experiments on the reaction rates of the two pinacols when treated under identical conditions with sulfuric acid in aqueous solution at 52°. Under these conditions, with 0.2 *N* acid, the *cis* pinacol was 53.9% converted in two and one-half hours, while only 24% of the *trans* isomer had disappeared in the same length of time. The actual difference in rate between the two isomers is somewhat greater than appears from these figures; for the *cis* pinacol reacts fast enough with lead tetraacetate to be titrated by this reagent, whereas actual isolation of the *trans* pinacol, with attendant manipulative losses, was the only way we found to follow its reaction. The results are consistent with the view that the constitution of the *trans* pinacol is so unfavorable to rearrangement that here alone the slow simple dehydration takes precedence over the pinacol rearrangement.

The results with the five- and six-membered rings support the generalization that a group cannot migrate in the pinacol rearrangement unless by a simple movement it can reach the adjacent carbon atom on the face opposite to the hydroxyl group which it is replacing. Thus in these pinacols the methyl group can migrate only in the *cis* modifications. In the *trans* form of the six-ring pinacol, ring contraction occurs with much greater ease than in its five-ring analog which by this same reaction would have to yield the strained four-membered ring. Here, therefore, rearrangement is no longer a faster process than dehydration to the allylic alcohol and diene. It seems that under comparable conditions these three modes of reaction of the cyclic pinacols do not differ enormously in the ease with which they occur.

Experimental

Ethyl cyclopentanone-2-carboxylate was prepared by the method of Haller and Cornubert.[5] Yields from 65 to 70% were obtained, using 200-g. quantities. The product boiled at 114–116° at 20 mm.

Ethyl 2-methylcyclopentanone-2-carboxylate was made according to the directions of the same authors. The yield was 80%, of material boiling at 108.5–112° at 16 mm. pressure, and having $n^{20}D$ 1.4461.

2-Methylcyclopentanone was prepared by Van Rysselberge's method[6] which consists of refluxing the keto ester with 4 *N* hydrochloric acid. Yields of 82–86% were obtained. The product boiled at 139–142°, and yielded a semicarbazone melting at 174–174.8°.

1,2-Dimethylcyclopentanol-1 was prepared in 70–73% yield by the action of the methyl Grignard reagent upon 2-methylcyclopentanone. The product boils from 56 to 62.5° under 16 mm. pressure, showing an inhomogeneity which is attributed by Van Rysselberge to the presence of

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[2] (a) Criegee, *Ann.*, **481**, 263 (1930); (b) Criegee, Kraft and Rank, *ibid.*, **507**, 159 (1933).

[3] Blanc, *Bull. soc. chim.*, [4] **3**, 780 (1908).

[4] Haller and Cornubert, *Compt. rend.*, **179**, 315 (1924).

[5] Haller and Cornubert, *Bull. soc. chim.*, [4] **39**, 1726 (1926).

[6] Van Rysselberge, *Bull. soc. chim. Belg.*, **35**, 311 (1926).

geometrical isomers. No attempt was made to separate these.

1,2-Dimethylcyclopentene-1 was obtained in 83–87% yield by refluxing 1,2-dimethylcyclopentanol-1 with iodine for ten hours with a water trap in the return, and distilling. The fraction boiling at 102.5–105.8° was collected, $d^{20}{}_4$ 0.7950.

1,2-Dimethyl-1,2-epoxycyclopentane.—A solution of 38.5 g. of perbenzoic acid in 700 cc. of chloroform was stirred vigorously and cooled to 0°; 23.5 g. of 1,2-dimethylcyclopentene-1 was added over a period of two and one-half hours, the temperature being held at 0°. Stirring was continued for ten hours, the temperature being held at $-5°$. After standing at $+5°$ for two days, the solution was extracted with 10% sodium hydroxide to remove benzoic acid, washed, dried with sodium sulfate, and distilled; 23 g. of a liquid boiling at 120–122.5° at 20 mm. was obtained, yield 85%.

Anal. Calcd. for $C_7H_{12}O$: C, 75.0; H, 10.7. Found: C, 74.7, 74.9; H, 10.5, 10.7.

trans **Pinacol by Hydrolysis of the Epoxide.**—Twenty-one grams of the oxide was allowed to drop slowly into 20 cc. of water acidified with 6–8 drops of concentrated sulfuric acid, to which ice was added. On gentle shaking the oxide went into solution. By saturation with potassium carbonate the glycol was salted out of solution as a powdery precipitate. It was taken up in ether, from which it crystallized in long needles melting at 99.5–101° (corr.). The yield was 74% of the theoretical.

Anal. Calcd. for $C_7H_{14}O_2$: C, 65.1; H, 11.6. Found: C, 64.7, 64.9; H, 11.3, 11.6.

cis-**1,2-Dimethylcyclopentanediol-1,2** was prepared following a general procedure of Harries.[7] To a solution of 25 g. of 1,2-dimethylcyclopentene-1 in 50 cc. of acetone, cooled to $-5°$, a solution of 47 g. of potassium permanganate in 100 cc. of water and 1 liter of acetone was added slowly. After standing for one hour, the manganese dioxide slime was filtered off. Carbon dioxide was passed into the solution until potassium bicarbonate precipitated. From the filtrate, the acetone was removed on the water-bath and by distillation the fraction boiling at 142–146° at 20 mm. was collected. This amounted to 14 g. (45.2% of the theoretical yield) of a colorless liquid.

Anal. Calcd. for $C_7H_{14}O_2$: C, 65.1; H, 11.6. Found: C, 64.8, 64.7; H, 11.5, 11.5.

We were not successful in preparing any esters of this pinacol, but it could be condensed with benzaldehyde in the presence of ammonium sulfate to a solid crystallizing in plates, m. p. 120–122.5° (corr.).

Anal. Calcd. for the acetal, $C_{14}H_{18}O_2$: C, 77.5; H, 8.2. Found: C, 77.0, 77.1; H, 7.9, 8.1.

Rearrangement of the ***cis*** **Pinacol.**—Five grams of the liquid "*cis*" pinacol was dissolved in 20 cc. of water containing 5 cc. of concentrated sulfuric acid. The solution turned green immediately. After refluxing for three hours a brown oil had appeared, while the aqueous solution was practically colorless. To the steam distillate, semicarbazide hydrochloride and sodium acetate were added, yielding 5.2 g. (87.1%) of crude semicarbazone. In another run the ketone was isolated directly, distilled through a Widmer column, and the fraction boiling at 142–143.8° was collected. Its semicarbazone, recrystallized from methyl alcohol, melted at 191.5–191.8° (corr.). The oxime melted at 68.7° (corr.). Blanc[3] reports 142° as the boiling point of 2,2-dimethylcyclopentanone-1, and 69° as the melting point of the oxime. Haller and Cornubert[4] report the melting point of the semicarbazone as 191°.

Dehydration of the ***trans*** **Pinacol.**—On treatment identical with that applied to the *cis* pinacol, the *trans* isomer yielded no volatile product but, after showing similar color changes, gave a brown tar which rapidly became more viscous on standing and set to an almost black glass. No product which could be characterized was had from attempts to use less dilute acid, to carry out the experiment in acetic anhydride, glacial acetic acid, acetyl chloride, or in the presence of bromine, maleic anhydride, or benzoquinone.

Rates of Reaction with Lead Tetraacetate.—This reagent was prepared by the method of Dimroth[8] and the titrations with it were carried out according to the directions of Criegee and his co-workers.[2b] In a thermostat at 25°, the following results were obtained: 0.0595 g. of the *cis* pinacol was put into solution in 9.92 cc. of acetic acid (f. p. 16.2°) which had been refluxed with lead tetraacetate for ten hours and distilled. To this was added 9.92 cc. of a standard solution containing 0.02266 g. of lead tetraacetate per cc. of acetic acid. By iodometric titration the reaction was found to be 98.6% complete after five hours. Thus this reaction can be made the basis of a satisfactory titration method for the *cis* pinacol.

0.0573 g. of the *trans* pinacol was dissolved in 9.92 cc. of acetic acid and added to the same volume of standard lead tetraacetate solution. After seven hours and seven minutes, only 69.7% of the pinacol had reacted. A rough calculation based upon several such runs shows a 1600-fold difference between the rates of reaction of the isomeric pinacols with lead tetraacetate. Evidently the reaction in the case of the *trans* pinacol is too slow to serve as the basis of a titration method for the pinacol.

Rate of Rearrangement of the ***cis*** **Pinacol.**—0.209 g. of *cis* pinacol was dissolved in 10 cc. of water, and 10 cc. of 0.2 *N* sulfuric acid was added. The whole was kept at 52° in the thermostat. After two and one-half hours excess sodium acetate was added and 20.1 cc. of standard lead tetraacetate. This was allowed to stand at 35° for eight hours and the lead tetraacetate was then titrated iodometrically. The rearrangement was 53.9% complete.

Rate of Dehydration of ***trans*** **Pinacol.**—In order to gain an idea of the rate of reaction of the *trans* pinacol with sulfuric acid, it was necessary to resort to isolation of the unchanged *trans* pinacol, since a suitable titration method was not found. 0.210 g. of *trans* pinacol was dissolved in 10 cc. of water and 10 cc. of 0.2 *N* sulfuric acid was added. The reaction was allowed to proceed at 52° for two and a half hours, at the end of which time barium oxide was added, the barium sulfate precipitate digested on the steam-bath overnight, and filtered off. The pinacol was recovered by ether extraction of the filtrate, after concentrating *in vacuo*, and recrystallization from ether of the crude product. 1.6 g. of the pinacol was recovered (76%

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[7] Harries, *Ber.*, **34**, 2979 (1901).

[8] Dimroth, *ibid.*, **63**, 483 (1930).

of the starting material) melting at 100.5–100.7° alone and when mixed with the original material.

Summary

1. *cis*-1,2-Dimethylcyclopentanediol-1,2 undergoes the pinacol rearrangement with migration of a methyl group and production of 2,2-dimethylcyclopentanone.

2. *trans* - 1,2 - Dimethylcyclopentanediol - 1,2 when boiled with dilute aqueous acid undergoes resinification. It has not been possible to characterize any product from this reaction. It is suggested that dehydration without rearrangement is here occurring, yielding a product which is rapidly polymerized by the acid.

3. These observations confirm the conclusion previously reached that in the pinacol rearrangement elimination of a hydroxyl group and the arrival of a migrating radical occur on opposite sides of the same carbon atom.

CAMBRIDGE, MASS. RECEIVED AUGUST 5, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Pyrolysis of Esters

BY CHARLES D. HURD AND FORD H. BLUNCK

Although much is known about the pyrolysis of esters, most of the evidence is fragmentary. To supply additional information of a critical nature seven esters were selected for detailed study. These were ethyl, phenyl, *i*-propyl, *i*-butyl, and *t*-butyl acetates and methyl and ethyl phenylacetates.

The known facts concerning simple esters may be summarized briefly. If a β-H is present in the alkyl portion of the ester, $RCOOCR_2CHR_2$, the decomposition into acid (RCOOH) and olefin ($R_2C{=}CR_2$) is general. This was established by Oppenheim and Precht[1] for ethyl acetate and was confirmed recently by Bilger and Hibbert.[2] The latter investigators also extended the reaction (470–500°, 1.2 sec. contact time) to several other esters which included not only the propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl and β-chloroethyl acetates but also the ethyl esters of benzoic, formic, butyric and chloroacetic acids. In their work an unsuccessful search was made for aldehydes among the reaction products, the reagent being a solution of *p*-nitrophenylhydrazine in acetic acid. Bilger and Hibbert noted that methyl and benzyl esters (of acetic and benzoic acids) did not decompose under conditions which caused breakdown of the other esters.

The decomposition products of methyl phenylacetate (sealed tube at 360°) have been reported[3] to be toluene, methane, methanol and oxides of carbon. Methyl acetate,[4] at 1100°, has been found to change into acetic acid, formaldehyde and acetaldehyde (or their decomposition products) and ethylene.

Five of the esters studied in the present investigation possessed a β-H on the alkyl group. Greatest instability was noticed when this alkyl was tertiary as in *t*-butyl acetate. It decomposed even at 360°. Secondary alkyl (*i*-propyl acetate) exhibited intermediate stability. Greatest stability was noticed when the alkyl was primary (ethyl or *i*-butyl acetates, ethyl phenylacetate).

Nearly equivalent amounts of acetic acid and isobutylene were observed from *t*-butyl acetate at 360–430° and no other products were found. Also, no products other than ethylene and phenylacetic acid (formed in equivalent amounts) were obtained from ethyl phenylacetate at 435–545°. At 625°, however, the latter gave rise to small amounts of toluene and carbon dioxide which were formed obviously from phenylacetic acid by secondary decomposition. The percentage yields of products based on the ester decomposed were found to be as follows: phenylacetic acid 58, toluene 22, carbon dioxide 21, ethylene 78.

The acetic acid and propylene from *i*-propyl acetate were formed in nearly equimolar amounts, but small amounts of acetaldehyde (4%), acetone (3%) and carbon monoxide (12%) were also observed in an experiment at 460°.

Ethyl acetate yielded acetic acid and ethylene in approximately equivalent amounts as expected, but the presence of other products was established

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[1] Oppenheim and Precht, *Ber.*, **9**, 325 (1876); Burns, Jones and Ritchie, *J. Chem. Soc.*, 400 (1935).

[2] Bilger and Hibbert, THIS JOURNAL, **58**, 823 (1936).

[3] Engler and Löw, *Ber.*, **26**, 1440 (1893).

[4] Peytral, *Bull. soc. chim.*, **31**, 118 (1922).

definitely. These substances were identified in an experiment at 550° (% yields): acetic acid 82, ethylene 83, acetaldehyde 9, formaldehyde 6, acetic anhydride 0.5, methane 8, hydrogen 4, carbon monoxide 1, and a trace of ketene. Similarly, isobutyraldehyde (but not acetaldehyde or formaldehyde), carbon monoxide and methane were found in the products from *i*-butyl acetate, but of course the chief products were acetic acid and isobutylene.

It was established that the olefin from both *t*- and *i*-butyl acetates was isobutylene, unadmixed with isomers. This was determined carefully because *i*-butyl acetate, $Me_2CH—CH_2—OAc$, bears a structural resemblance to 1,1-diphenyl-2-chloroethane, $Ph_2CH—CH_2—Cl$, which is known to pyrolyze[5] into hydrogen chloride and stilbene, PhCH=CHPh. Were isobutyl acetate to behave analogously, one would anticipate 2-butene as the olefin of the reaction, but only 2-methylpropene (isobutylene) was found.

Phenyl acetate and methyl phenylacetate were much more stable than the other esters. At either 435 or 535° practically no change occurred, but at 625° there was decomposition. Evidently, therefore, an interval of about 200° separates the decomposition temperatures of the two groups. Phenyl acetate pyrolyzed smoothly into ketene and phenol. The yield of ketene at 625° was 84%.

$$CH_3COOC_6H_5 \longrightarrow CH_2{=}C{=}O + C_6H_5OH$$

The decomposition of methyl phenylacetate was much more complex. The products formed in greatest amounts were carbon monoxide, benzaldehyde and toluene, but other products included hydrogen, ethylene, methane, formaldehyde, carbon dioxide, water and an organic acid. Formaldehyde, which is known to decompose rapidly above 500°, may have been the precursor of much of the carbon monoxide and hydrogen, and probably much of the hydrogen was consumed at the high temperature. The striking product of the reaction was benzaldehyde. The carbonyl group in it is attached to the aromatic nucleus, whereas the carbonyl group in the ester is separated from the nucleus by a methylene group. Evidently, therefore, something more complex than a simple splitting must have occurred to have caused the formation of benzaldehyde.

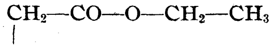
These average percentage yields of products were formed, based on the ester which was decomposed. The experiments were performed at 625° and about five seconds contact time: benzaldehyde 71, toluene 49, carbon monoxide 92, formaldehyde 25, ethylene 29, hydrogen 27, methane 15, carbon dioxide 12 and an organic acid 4. The benzaldehyde and toluene were isolated directly and, therefore, represent minimum values.

Mechanisms.—No single mechanism accounts for the facts adequately, and three processes seem to be involved. One of them is the chain mechanism, with univalent radicals as intermediates, but it cannot apply, except in small measure, to the esters which possess a β-hydrogen. A few considerations will make this evident.

If the chain mechanism is applied to *t*-butyl acetate, the predicted products include not only isobutylene and acetic acid but also ketene (or acetic anhydride, from ketene and acetic acid), acetone and methane. Since this mechanism calls for five products instead of two, it is obviously inadequate.

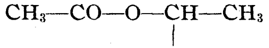
Similar reasoning shows that the chain mechanism cannot serve in the pyrolysis of ethyl phenylacetate since, besides ethylene and phenylacetic acid, it would require the production of formaldehyde, methane, phenylketene, toluene, carbon monoxide and acetaldehyde. None of the last six compounds was formed in experiments at 435–545°.

The steps with ethyl acetate will be taken up in detail. With the chain mechanism, interaction of a radical R with $CH_3COOCH_2CH_3$ would yield RH and residues I, II or III.



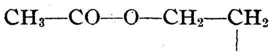
$\underset{|}{C}H_2—CO—O—CH_2—CH_3$

I



$CH_3—CO—O—\underset{|}{C}H—CH_3$

II



$CH_3—CO—O—CH_2—\underset{|}{C}H_2$

III

Breakdown of I should lead to formaldehyde, ketene (or acetic anhydride), and methane: I $\longrightarrow$ $CH_2{=}C{=}O$ + $—O—CH_2—CH_3 \longrightarrow O{=}CH_2$ + $CH_3—$. In previous work with ethyl acetate, the presence of formaldehyde and methane among the pyrolytic products has escaped detection, but the "odor of ketene" has been noticed.[6] Breakdown of II should yield acetaldehyde, carbon monoxide and methane: II $\longrightarrow CH_3— + CO + O{=}CH—CH_3$. III should give rise to ethylene and acetic acid: III $\longrightarrow CH_3—CO—O— + CH_2{=}CH_2$.

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[5] Hepp, *Ber.*, **6**, 1439 (1873).

[6] Stewart and Wilsmore, *Nature*, **75**, 510 (1907); Wilsmore, *J. Chem. Soc.*, **91**, 1939 (1907).

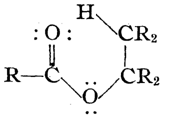
Possibly the aldehydes which were produced did come via I and II but, if so, it seems obvious that no more than a small fraction of the observed acetic acid should come via III because the yields of I, II and III should be comparable. The bulk of the acetic acid, therefore, requires another mechanism to account for it.

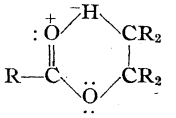
As was mentioned earlier, ethyl acetate is more stable than *t*-butyl acetate. The temperature required for pyrolysis of the latter was so low that scission into radicals appeared to be completely inhibited. With the higher temperature required for the decomposition of ethyl acetate the breakdown into radicals was starting to be a factor, although not yet one of importance.

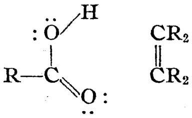
A similar situation exists with *i*-propyl and *i*-butyl acetates. Compounds predicted by the chain mechanism are observed but they comprise only a small portion of the products.

Cyclic Hydrogen Bridge.—The concept of hydrogen bonds or hydrogen bridges[7] has been developed in recent years to explain such facts as the association of water or hydrogen fluoride, the weakness of carboxylic acids, the weakness of ammonium hydroxide and many other facts, all of which, however, have been low temperature phenomena. The concept seems applicable also to some high temperature processes and it is proposed that the esters which require only moderately high temperatures for their pyrolysis break down by a mechanism involving hydrogen bridges.

Esters which possess a β-H in the alkyl group (IV) may undergo a chelate type of 6-atom ring closure by way of a hydrogen bridge (V). Readjustment of the electrons would give rise to acid and olefin (VI).


IV


V


VI

Methyl esters cannot change into 6-atom rings comparable to V, which may account for their greater stability.

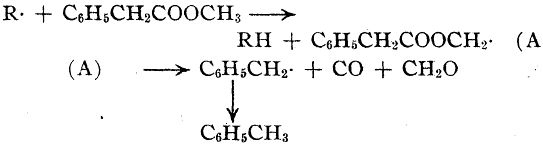
When hydrogen bridges occur in stable structures, negative atoms are involved on both sides of the bridge (such as O–H–O, or O–H–N or F–H–F). The O–H–C bridge has not been observed at ordinary temperatures, but it is reasonable to assume for it a transient existence at elevated temperatures. Also, because oxygen is more negative than carbon, hydrogen should remain with the oxygen when this bridge is broken.

This mechanism calls for only moderately high temperatures. Ethyl phenylacetate, which yielded only ethylene and phenylacetic acid at 435°, was studied at 545 and 625° to see if the mechanism was changed at higher temperatures. No such change was found for no aldehydes were produced. The temperature of 625° is sufficient in some cases to initiate C–C scission with the formation of radicals, but apparently the only effect of the increased temperature in this reaction was to increase the velocity of the original process.

Radicals as Intermediates.—The chain reaction mechanism may account for the pyrolysis of phenylacetate, since the products obtained, namely, ketene and phenol, are those predicted by the theory.

$$R\cdot + CH_3—CO—OC_6H_5 \longrightarrow RH + \cdot CH_2—CO—OC_6H_5$$
$$\cdot CH_2—CO—OC_6H_5 \longrightarrow CH_2{=}C{=}O + \cdot OC_6H_5$$

When a similar mechanism is applied in its simplest form to methyl phenylacetate the products predicted include toluene, carbon monoxide, formaldehyde and hydrogen, all of which were found. Phenylketene was indicated also but was not found. This is not surprising in view of its instability. The steps are as follows



$$R\cdot + C_6H_5CH_2COOCH_3 \longrightarrow RH + C_6H_5CH_2COOCH_2\cdot \quad (A)$$
$$(A) \longrightarrow \underset{\displaystyle \downarrow \atop \displaystyle C_6H_5CH_3}{C_6H_5CH_2\cdot} + CO + CH_2O$$

$$R\cdot + C_6H_5CH_2COOCH_3 \longrightarrow RH + C_6H_5\dot{C}H—CO—OCH_3 \quad (B)$$
$$(B) \longrightarrow C_6H_5CH{=}C{=}O + \cdot OCH_3$$

The $\cdot OCH_3$ radical may change to methanol (RH, in the equation), or to hydrogen and formaldehyde. With methanol, phenylketene would regenerate methyl phenylacetate.

Methylene Radicals as Intermediates.—The above mechanism for methyl phenylacetate is not self-sufficient because it fails to account for the most important product of the reaction, namely, benzaldehyde. Its production may be explained satisfactorily by assuming that phenylmethylene is an intermediate radical. In the pyrolysis of methane, which calls for severe thermal conditions, the methylene radical is

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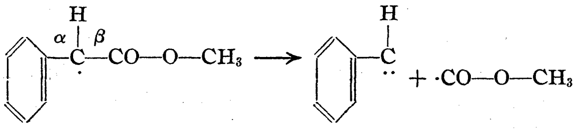
(7) For a review of the material, see Huggins, *J. Org. Chem.*, **1**, 407 (1937).

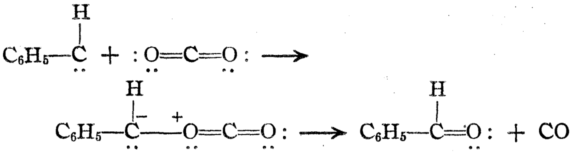
thought by Kassel[8] to be a fundamental intermediate. Storch and Kassel[9] also favor it as an intermediate in the pyrolysis of ethane, but they point out that a chain reaction which involves univalent radicals proceeds concurrently.

With methyl phenylacetate, it is proposed that radical B, because of high temperature and structural weakness, breaks as follows



The C–C bond which undergoes scission is beta to the unsaturation of the phenyl nucleus and, therefore, possesses an instability[10] not found in the acetic esters. The resulting carbomethoxyl radical may break into CO + $\cdot OCH_3$ or into $CO_2 + \cdot CH_3$.

The phenylmethylene radical, possessing as it does only six electrons on the carbon atom, must attach itself to neighboring unshared electrons to create the necessary octet. Most probably, these unshared electrons would come from some oxygen-containing substance, as the original ester, or carbon dioxide, etc. The oxygen atom which is attracted to the carbon atom in this way is the one which appears as benzaldehyde. This may be illustrated most simply with carbon dioxide as the source of the oxygen, but a similar plan would follow for other compounds.



$$C_6H_5-\overset{H}{\underset{\cdot\cdot}{C}} + :\underset{\cdot\cdot}{O}=C=\underset{\cdot\cdot}{O}: \longrightarrow$$

$$C_6H_5-\overset{H}{\underset{\cdot\cdot}{C}}{}^{-}-{}^{+}\underset{\cdot\cdot}{O}=C=\underset{\cdot\cdot}{O}: \longrightarrow C_6H_5-\overset{H}{C}=\underset{\cdot\cdot}{O}: + CO$$

The fact that a much higher decomposition temperature was required for the breakdown of methyl phenylacetate than for ethyl phenylacetate explains why benzaldehyde was not formed in the latter case. Obviously, a formidable energy barrier must be hurdled to bring about this effect.

The fact that several mechanisms are involved in the pyrolysis of esters suggests that several mechanisms may be involved also in the pyrolysis of compounds in other series, particularly if sizeable temperature differences are involved in initiating the breakdown. Most of the earlier thought on this subject has presumed that one type of mechanism alone was adequate for a particular series if not for all series.

Experimental Part

Substances Used.—The following esters were washed, dried and closely refractionated before use: ethyl acetate, b. p. 77.0–77.1°; phenyl acetate, b. p. 96.5–96.6° at 30 mm.; methyl phenylacetate, b. p. 214° (735 mm.), sapon. equiv., 150. Hydrolysis of the last of these yielded phenylacetic acid, m. p. 74–75°, free from benzoic acid.

For some of the runs, methyl phenylacetate and ethyl phenylacetate were synthesized from pure phenylacetic acid, m. p. 75.5–76.0°. The latter was dissolved in anhydrous methanol or ethanol which contained dry hydrogen chloride and the mixture was refluxed for eight hours. The esters were separated and purified in the usual way. After two distillations at 65 mm. the methyl ester was collected at 137.0–137.1° (yield 90%), and the ethyl ester at 141–142°.

Synthetic *i*-propyl acetate was used in all the runs. The *i*-propyl alcohol was thrice distilled through an efficient column. The fraction obtained, b. p. 82.5–82.6°, was shown by oxidation with dichromate to contain less than 0.1% of *n*-propyl alcohol. About 1% of concd. sulfuric acid was added to 9 moles of the alcohol and an equimolar quantity of pure acetic anhydride was added at such a rate as to maintain refluxing. Then the reaction mixture was cooled, the ester salted out and neutralized with sodium bicarbonate, washed with water and dried over calcium chloride. An 80% yield of *i*-propyl acetate, b. p. 89.4–89.5°, was obtained.

The *i*-butyl acetate was made from carefully fractionated *i*-butyl alcohol, b. p. 107.1–107.2°. Esterification of this alcohol with acetic anhydride, or with refluxing glacial acetic acid in the presence of a little hydrogen chloride or *p*-toluenesulfonic acid, yielded *i*-butyl acetate which boiled at 118.1–118.2°.

t-Butyl acetate was prepared from *t*-butyl alcohol (distilled from sodium), acetic anhydride and a little zinc chloride according to the method of Norris and Rigby.[11] The yields were only 48–50%, but the purity was excellent (b. p. 97.4–97.6°).

Apparatus.—The esters were introduced into the top of a vertical Pyrex reaction tube by displacement with mercury. In most runs, a 15-cm. electric furnace was used but in some runs it was replaced by a 30-cm. furnace. The temperature was controlled and recorded by a chromel–alumel thermocouple attached to a Leeds and Northrup recorder-controller. The glass-encased thermocouple was placed in the middle of the reaction tube.

An iced receiver was attached to the bottom of the reaction tube and it in turn was connected to a low-pitched spiral reflux column which was cooled by ice-salt. This served to condense all of the higher boiling products as well as the undecomposed ester. The uncondensed vapors from ethyl acetate were then passed through a second receiver at −80° to collect formaldehyde, acetaldehyde or ketene. The same was used with *i*-propyl, *i*-butyl and *t*-butyl acetates but in these runs no appreciable quantity of liquid was condensed. The remaining gas was passed to a gas-collecting bottle over salt water. With methyl

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[8] Kassel, THIS JOURNAL, **57**, 833 (1935).

[9] Storch and Kassel, *ibid.*, **59**, 1245 (1937).

[10] Hurd and Bollman, *ibid.*, **55**, 699 (1933); **56**, 447 (1934).

[11] Norris and Rigby, *ibid.*, **54**, 2088 (1932).

phenylacetate, the second trap contained water at 3° to collect formaldehyde. In runs with the acetic esters an aniline trap or a trap containing standard alkali was inserted between the second receiver and the bottle, to absorb ketene.

Analytical Methods

Qualitative.—Qualitative tests for formaldehyde, acetaldehyde and ketene were performed to precede the quantitative experiments. Formaldehyde was identified as methylenedi-β-naphthol. For this purpose, one-third of the products (diluted with water) from the second receiver from the ethyl acetate experiments was mixed with 10 cc. of alcohol, 2 cc. of dilute hydrochloric acid and 1 g. of β-naphthol. After heating for fifteen minutes and cooling, 0.5 g. of the derivative, m. p. 204°, was obtained. Formaldehyde was identified similarly in the products of the second receiver from methyl phenylacetate.

To identify acetaldehyde from ethyl acetate, a portion of the solution in the second receiver was neutralized with dilute sodium hydroxide and distilled. The distillate, diluted with water, responded positively to the fuchsin test. It was oxidized with chromic acid and the volatile acid removed by distillation. The latter was neutralized by sodium hydroxide and evaporated to dryness. The sodium acetate in the residue was converted to *p*-bromophenacyl acetate, m. p. 85°, on treatment with *p*-bromophenacyl bromide. Acetaldehyde was detected qualitatively in like manner from the low-boiling products of the first receiver with *i*-propyl acetate.

Direct evidence for ketene was obtained in the run at 525° with ethyl acetate by inserting a trap containing 20 cc. of aniline between the second receiver and the gas-collecting bottle. In working up the products, any acetic acid was extracted by sodium bicarbonate solution.[12] The water solution was ether-extracted and the extract was placed with the aniline. The ether and aniline were distilled off and the residue was extracted with boiling water. About 0.1 g. of acetanilide, m. p. 113°, separated on cooling. A trace of ketene was revealed similarly in runs with *i*-propyl and *i*-butyl acetates. With phenyl acetate it was the chief product.

That the liquid products from the pyrolysis of phenyl acetate contained phenol was established readily by distillation. The fraction which was collected at 179–182° reacted strongly with ferric chloride and gave an α-naphthylurethan, melting at 132°.

The gas from the first receiver and its attached spiral condenser was treated in three different ways. For a time in the first run it was passed into a trap containing 45 cc. of water. Then it was passed into a trap containing 20 cc. of aniline. In the second run, it was passed into an empty trap at −78° which was connected to an aniline trap.

The water in the first trap was free from aldehydes (Schiff reagent). From the aniline traps, acetanilide was isolated in quantity (m. p. 113.5°). No gaseous product was obtained in either run. At the end of the second run, about 1 cc. of ketene had collected in the trap at −78°. When this was vaporized and passed into the aniline, there was no residual acetylketene. The yield of ketene was calculated from the weight of acetanilide isolated.

The liquid products consisted only of phenyl acetate and phenol. The former was determined by acetyl analysis,[13] and the latter by bromate–bromide titration.[14] To analyze for phenol in the presence of phenyl acetate, it was found that phenyl acetate underwent quantitative hydrolysis into phenol on refluxing for thirty minutes with sodium ethoxide solution. Therefore, the mixture of phenyl acetate and phenol was subjected to this hydrolysis prior to the bromate–bromide titration. Since the ester content was known, that portion of the phenol which came from the ester was computed readily.

The qualitative presence of acetone in the liquid products (first receiver) from *i*-propyl acetate was established by neutralizing a portion of it and treating that part which boiled below 80° with semicarbazide hydrochloride and sodium acetate. After standing, 0.5 g. of acetone semicarbazone, m. p. 189–190°, was obtained. No acetone was detected from *t*-butyl acetate.

Acetic acid was identified by boiling point and by its derivative, *p*-bromophenacyl acetate, m. p. 85°. No more than traces of acetic anhydride were present by quantitative determination (below).

No allyl acetate was found by distillation of the products from *i*-butyl acetate. The fraction boiling from 85–116° revealed no ester for no alkali was consumed by saponification test, but it contained much isobutyraldehyde for it gave a strong fuchsin test and yielded a 2,4-dinitrophenylhydrazone, m. p. 182°.

A slight fuchsin test was obtained in the products from the 625°-run of ethyl phenylacetate, but otherwise all tests for aldehydes were negative. Phenylacetic acid and toluene (only from the run at 625°) were identified by direct isolation. The toluene was confirmed as 2,4-dinitrotoluene, m. p. 70°. Water, toluene and benzaldehyde (b. p. 177–183°, semicarbazone m. p. and mixed m. p. 222°) from methyl phenylacetate were isolated directly. No evidence was secured for phenylacetaldehyde, and the trace of acid observed could not be isolated for characterization.

Data summarizing both the qualitative and quantitative data of some representative runs are collected in Table I.

Quantitative.—Quantitative determinations on the various products were carried out volumetrically. The acid content was determined by direct titration on an aliquot portion of the products with standard sodium hydroxide. The ester content was determined on another portion by saponification, using a known amount of standard alkali and back titration with dilute standard sulfuric acid. The acetic anhydride was determined on an aliquot portion by means of the reaction with anhydrous pyridine and oxalic acid,[15] the volume of carbon monoxide and carbon dioxide evolved being indicative of the anhydride content.

The total aldehyde content of both receivers was determined on aliquot portions by oxidation with 0.1 *N* potassium dichromate solution and sulfuric acid. It was necessary to correct this value in the ethyl acetate experi-

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[12] Hurd and Martin, THIS JOURNAL, **51**, 3615 (1929).

[13] Freudenberg, *Ann.*, **433**, 230 (1923).

[14] Francis and Hill, THIS JOURNAL, **46**, 2498 (1924).

[15] Whitford, *ibid.*, **47**, 2939 (1925).

TABLE I

PYROLYSIS OF SEVEN ESTERS

Ester	Ethyl acetate		*i*-Propyl acetate			*t*-Butyl acetate	*i*-Butyl acetate		Phenyl acetate		Ethyl phenylacetate				Methyl phenylacetate			
Run no.	1	2	1	2	3	1	1	2	1	2	1	2	3	4	1	2	3	4
Vol. of tube, cc.	98	136	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150
Temp., °C.	525	550	430	430	460	360	420	650	625	645	435	485	545	625	535	625	625	625
Duration, min.	489	440	35	130	95	12	68	120	26	53	25	28	28	33	41	38	35	51
Contact time, sec.	14.8	53.5	3.9	20.3	17.9	2.6	7.6	27.4	7.0	14.3	7.7	8.7	8.8	7.7	6.8	4.8	5.2	6.6
Ester taken, moles	3.00	1.00	1.00	1.00	0.90	0.77	1.52	0.56	0.485	0.485	0.539	0.445	0.439	0.503	0.69	1.00	0.69	1.00
Ester taken, cc.	289.5	96.5	117	117	105	100	203	56	61	61	86	71	70	80	100	145	100	145
Gas formed (STP), liters	47.95	19.50	2.10	6.10	10.35	0.38	3.9	9.0	...	...	0.90	1.30	4.70	9.60	1.1	6.18	4.41	7.02
Extent of decn., %	63.7	90.1	18.9	37.7	55.0	2.70	13.6	98.1	12.7	24.8	8.3	17.3	56.0	85.2	0.87	15.0	16.9	18.5
Vol. of liquid products, cc.	215.5	55.0	110	100	78.0	97	194	30	59.5	57.3	85	70	60	36.5	99.5	140	94	135.5
Gas analysis, % by vol.																		
CO_2	1.31	1.53	...	...	...	...	...	...	...	...	...	...	...	21.42	...	5.66	5.32	6.95
C_2H_4	85.80	85.53	...	...	...	...	...	...	...	...	100.0	100.0	100.0	78.58	...	15.62	14.97	19.71
H_2	4.74	3.95	...	...	...	...	...	...	...	...	...	...	...	...	...	18.96	15.30	12.50
CO	1.31	0.66	5.00	4.15	1.83	...	2.68	10.20	...	...	...	...	...	...	...	53.10	56.55	49.45
CH_4	6.84	8.33	13.86	10.65	12.84	...	10.76	6.40	...	...	...	...	...	...	...	6.66	7.82	11.39
C_3H_6	...	...	81.14	85.20	85.32	...	...	...	...	...	...	...	...	...	...	...	...	...
C_4H_8 (iso)	...	...	...	...	...	100.0	85.56	83.40	...	...	...	...	...	...	...	...	...	...
Yield of products, mole per mole decomposed																		
Acetic acid	0.80	0.82	0.507	0.664	0.806	0.86	0.885	0.684	...	...	...	...	...	...	...	...	...	...
Acetaldehyde	.032	.097	.169	.122	.042	...	...	...	...	...	...	...	...	...	...	...	...	...
Formaldehyde	.081	.064	...	...	...	...	...	...	...	...	...	...	...	...	...	0.21	0.33	0.20
Acetic anhydride	.010	.004	tr.	tr.	tr.	...	tr.	tr.	...	...	...	...	...	...	...	...	...	...
Ketene	tr.	tr.	tr.	tr.	tr.	...	tr.	tr.	0.84	0.63	...	...	...	...	...	...	...	...
Acetone	...	...	.275	.066	.028	...	...	...	...	...	...	...	...	...	...	...	...	...
Isobutyraldehyde	...	...	...	...	...	...	[a]	.156	...	...	...	...	...	...	...	...	...	...
Phenol	...	...	...	...	...	...	...	...	.89	.98	...	...	...	...	...	...	...	...
Phenylacetic acid	...	...	...	...	...	...	...	...	...	...	0.98	0.77	0.82	0.58	...	...	...	...
Toluene	...	...	...	...	...	...	...	...	...	...	...	...	...	.22	...	.33	.53	.60
Benzaldehyde	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	.94	.68	.51
Organic acid	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	.044	.047	.032
Carbon dioxide	0.015	0.014	...	...	...	...	...	...	...	...	...	...	...	.21	...	.10	.13	.12
Ethylene	.96	.83	...	...	...	...	...	...	...	...	.89	.75	.85	.78	...	.29	.25	.33
Hydrogen	.053	.038	...	...	...	...	...	...	...	...	...	...	...	...	...	.35	.26	.21
Carbon monoxide	.015	.007	.027	.029	.016	...	.023	.075	...	...	...	...	...	...	...	.97	.96	.84
Methane	.076	.080	.069	.077	.119	...	.092	.047	...	...	...	...	...	...	...	.12	.13	.19
Propylene	...	...	.402	.616	.796	...	...	...	...	...	...	...	...	...	...	...	...	...
Isobutylene	...	...	...	...	...	.81	.730	.600	...	...	...	...	...	...	...	...	...	...

[a] Isobutyraldehyde was established qualitatively by its 2,4-dinitrophenylhydrazone.

ments for the dichromate which was consumed in oxidizing the ester concurrently ($CH_3COOC_2H_5 \longrightarrow 2CH_3COOH$). The difference between the total equivalents of dichromate and the equivalents consumed by the ester gave the value for total aldehydes. The procedure was tested on a known mixture of ethyl acetate and acetaldehyde, as follows.

A definite volume of acetaldehyde (capillary pipet) was heated for three hours on the steam-bath with 150.00 cc. of 0.1024 *N* potassium dichromate and sulfuric acid, after which potassium iodide was added. Then, 34.30 cc. of 0.1410 *N* sodium thiosulfate was required. From this 102.77 cc. of 0.1024 *N* dichromate was consumed. Then a mixture of this same quantity of acetaldehyde and 0.050 cc. of ethyl acetate (0.0005 mole) was treated similarly. This time, 122.46 cc. of 0.1024 *N* dichromate was consumed. The difference of 19.69 cc. ($\approx$ 2.01 cc. of 1 *N*) represents 0.002 equivalent, which agrees with the ethyl acetate taken ($0.0005 \times 4 = 0.002$) since four oxidation equivalents are involved in the oxidation of ethyl alcohol to acetic acid.

In a similar manner it was established that the oxidation equivalent for *i*-propyl acetate (*i. e.*, the correction factor) was twice the molecular weight. Thus, there was hydrolysis and oxidation quantitatively to acetone on heating with 0.0789 *N* potassium dichromate and sulfuric acid: $CH_3COOCH(CH_3)_2 \longrightarrow CH_3COOH + (CH_3)_2CO$.

No such corrections were necessary to analyze for isobutyraldehyde from *i*-butyl acetate for it was separated from the ester before oxidation. The benzaldehyde and toluene from methyl phenylacetate were determined by direct distillation analysis.

The acetone content of the products from *i*-propyl acetate was estimated in a manner patterned after the suggestion of Marseo.[16] The aldehyde and ketone both react with a 2% solution of hydroxylamine hydrochloride in water. The aldehyde releases 94.40% of the theoretical amount of hydrochloric acid while 1.00 cc. of 0.1000 *N* sodium hydroxide is required for the hydrochloric acid set free by each 0.0001 mole of acetone. The sample (an aliquot of the liquid products) was neutralized with standard alkali to the methyl orange end-point. Six hundrd cc. of 2% hydroxylamine hydrochloride solution was then added. The solution was titrated to near neutrality and allowed to stand for twenty seconds. This process was repeated several times and the mixture was neutralized after one minute of stirring. By a previous knowledge of the acetaldehyde content the acetone content was determined.

The gaseous products were identified and analyzed by absorption methods in a modified Orsat apparatus.[17] The olefin in the gas from *i*-butyl and *t*-butyl acetates was exclusively isobutylene. In both cases the gas dissolved completely in 63% sulfuric acid. This conclusion was confirmed by distillation analysis in a Podbielniak column. No propylene was found. The C_4-fraction from the distillation was liquefied and distilled analytically from a Frey–Hepp column[18] with ethylene oxide as a "pusher." There was a long distillation plateau for isobutylene at −6° but no plateau at a higher temperature for 2-butene. Methane was the exclusive paraffin in the gas from methyl phenylacetate since n in C_nH_{2n+2} was found to be 1.0.

The acetic acid was determined quantitatively by direct titration. Analysis of the unused ester with some of the esters called for the use of a solution of sodium ethoxide in ethanol, since aqueous solutions of sodium hydroxide were ineffectual. For example, after an eight-hour period of refluxing of 10 cc. of *t*-butyl acetate and 25 cc. of 28% sodium hydroxide an insoluble layer of ester remained. Distillation of this layer yielded 9 cc., b. p. 90–96°. Correct saponification values for the pure ester (1 cc.) were obtained by refluxing for half an hour with 50 cc. of *N* sodium ethoxide solution and back-titrating with *N* sulfuric acid.

Summary

t-Butyl acetate underwent pyrolysis at 360° to yield acetic acid and isobutylene as exclusive products. Ethyl phenylacetate also underwent this simple type of scission into phenylacetic acid and ethylene at 435–545°.

In the case of ethyl acetate, pyrolysis into acetic acid and ethylene also occurred at temperatures of 525–550°, but smaller quantities of aldehydes and other gases were identified. Likewise, *i*-propyl acetate at 430–460° gave rise not only to acetic acid and propylene but also to significant amounts of acetone, acetaldehyde, carbon monoxide and methane. Also, at either 420 or 650°, small amounts of isobutyraldehyde, carbon monoxide and methane were found mixed with the acetic acid and isobutylene produced from isobutyl acetate.

It was demonstrated that no 2-butene was formed during pyrolysis of either *t*- or *i*-butyl acetates.

Phenyl acetate and methyl phenylacetate were much more thermostable than the other five esters. The extent of decomposition was negligible at 530°. At 625–645°, phenyl acetate pyrolyzed smoothly into phenol and ketene. Methyl phenylacetate, at 625°, yielded benzaldehyde, toluene and carbon monoxide in quantity, but formaldehyde, methane, hydrogen, ethylene and carbon dioxide were also formed.

A mechanism involving a cyclic hydrogen bridge is proposed to explain the low-temperature pyrolysis of esters into acid and olefin. The chain reaction mechanism, involving free radicals, cannot account for this process but it becomes important with the thermostable esters. To account for benzaldehyde from methyl phenylacetate, it is suggested that the phenylmethylene radical is an essential intermediate.

EVANSTON, ILLINOIS RECEIVED JULY 5, 1938

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(16) Marseo, *Ind. Eng. Chem.*, **18**, 701 (1926).

(17) Hurd and Spence, THIS JOURNAL, **51**, 3356 (1929).

(18) Frey and Hepp, *Ind. Eng. Chem.*, **25**, 444 (1933); Hurd and Goldsby, THIS JOURNAL, **56**, 1812 (1934).

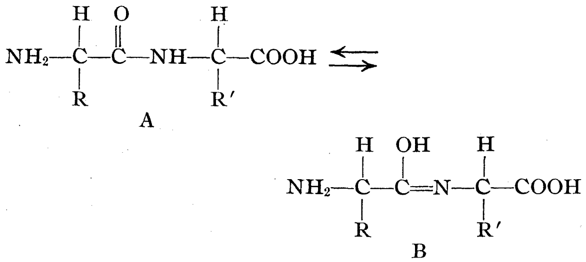
[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL CHEMISTRY, COLUMBIA UNIVERSITY]

Racemization of Tripeptides and Hydantoins[1]

BY M. BOVARNICK AND H. T. CLARKE

In 1910 Dakin[2] first described the racemization of optically active hydantoins under the influence of mild alkali. At the same time he demonstrated that the presence of a hydrogen atom on the asymmetric carbon atom was a necessary condition for the occurrence of the racemization and further observed that neither the optically active amino acids themselves, their uramino acid derivatives, nor optically active dipeptides, were racemized under the conditions.[2a] He therefore concluded that the mechanism of racemization involved a keto–enol tautomerism and that it was essential that both the α-amino group and the carboxyl group attached to the asymmetric carbon atom be bound up in order for the amino acid to undergo racemization by this method.[3] Extending this work, Dakin and others[4] later identified the terminal amino acids of protein peptide chains by making use of the assumption that, having free amino and carboxyl groups, they would not racemize on alkaline hydrolysis. Levene,[5] working with smaller peptide chains, substantiated the findings of Dakin and reached the conclusion that in a peptide composed of three optically active amino acids only the middle amino acid was racemized by alkali.

On comparing the formulas of dipeptides and tripeptides, a theoretical reason presents itself for the observed difference in racemizability of the two. In both there are two types of structures capable of undergoing tautomerization. One is the familiar keto–enol system, and the other is the amide–imide system. In the dipeptide only the non-racemizing tautomeric equilibrium need be considered; the keto–enol tautomerization obviously does not take place to any appreciable extent as the dipeptides do not racemize.



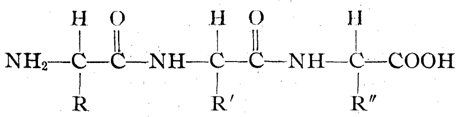
$$\mathrm{NH_2{-}\underset{R}{\overset{H}{C}}{-}\overset{O}{\overset{\|}{C}}{-}NH{-}\underset{R'}{\overset{H}{C}}{-}COOH} \rightleftarrows$$

A

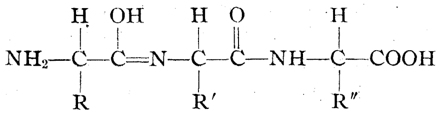
$$\mathrm{NH_2{-}\underset{R}{\overset{H}{C}}{-}\overset{OH}{C}{=}N{-}\underset{R'}{\overset{H}{C}}{-}COOH}$$

B

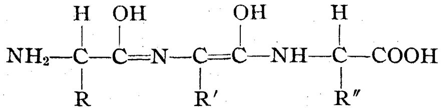
In a tripeptide a wide variety of tautomeric forms is possible, of which only those represented below need be considered here. It is a well-recognized fact that the presence of a double bond in a molecule tends to favor the production (when this is at all possible) of other double bonds in conjugation with it. It was therefore thought that an explanation of the racemizability of the tripeptides might reside in the possibility that in these peptide chains a previous or simultaneous occurrence of an enolized peptide linkage (D), analogous to that outlined above (B) for a dipeptide, might be necessary to induce the formation of a second enolic double bond (E) whereby the asymmetry of the central constituent amino acid is destroyed.



$$\mathrm{NH_2{-}\underset{R}{\overset{H}{C}}{-}\overset{O}{\overset{\|}{C}}{-}NH{-}\underset{R'}{\overset{H}{C}}{-}\overset{O}{\overset{\|}{C}}{-}NH{-}\underset{R''}{\overset{H}{C}}{-}COOH} \quad C$$

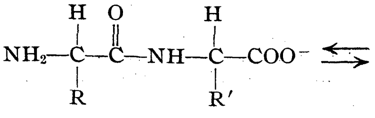


$$\mathrm{NH_2{-}\underset{R}{\overset{H}{C}}{-}\overset{OH}{C}{=}N{-}\underset{R'}{\overset{H}{C}}{-}\overset{O}{\overset{\|}{C}}{-}NH{-}\underset{R''}{\overset{H}{C}}{-}COOH} \quad D$$



$$\mathrm{NH_2{-}\underset{R}{\overset{H}{C}}{-}\overset{OH}{C}{=}N{-}\underset{R'}{C}{=}\overset{OH}{C}{-}NH{-}\underset{R''}{\overset{H}{C}}{-}COOH} \quad E$$

In order for this mechanism to be effective in the case of a dipeptide the following reaction would have to take place



$$\mathrm{NH_2{-}\underset{R}{\overset{H}{C}}{-}\overset{O}{\overset{\|}{C}}{-}NH{-}\underset{R'}{\overset{H}{C}}{-}COO^-} \rightleftarrows$$

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[1] This report is from a dissertation submitted by Max Bovarnick in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the Faculty of Pure Science, Columbia University.

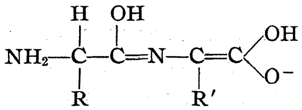
[2] Dakin, *Am. Chem. J.*, **44**, 48 (1910).

[2a] The optical stability of dipeptides may be further illustrated by the case of alanylglycine, which on treatment with normal sodium hydroxide at room temperature for two days showed no appreciable loss in activity [Levene and Pfaltz, *J. Biol. Chem.*, **70**, 219 (1926)], whereas in half-normal sodium hydroxide under the same conditions it was hydrolyzed to an extent of over 15% [Levene, Bass and Steiger, *J. Biol. Chem.*, **82**, 167 (1929)]. Racemization of the resulting amino acids can be effected by alkali only under very vigorous conditions, such as heating with 15% barium hydroxide at 155–160° for forty-eight hours [E. Fischer, *Z. physiol. Chem.*, **33**, 151, 173 (1901)].

[3] Dakin, *J. Biol. Chem.*, **13**, 357 (1913).

[4] Dakin and Dudley, *ibid.*, **15**, 263 (1913); Dakin and Dale, *Biochem. J.*, **13**, 248 (1919).

[5] Levene, Steiger and Marker, *J. Biol. Chem.*, **93**, 605 (1931).

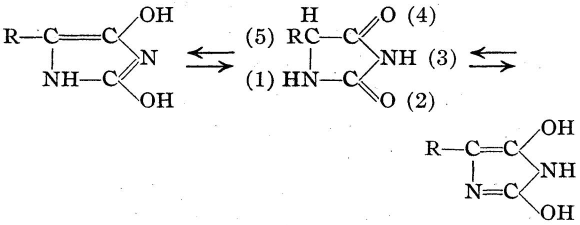


$$\mathrm{NH_2—\underset{R}{\overset{H}{C}}—\overset{OH}{C}{=}N—\underset{R'}{C}{=}C\begin{smallmatrix}OH\\ O^-\end{smallmatrix}}$$

Enolization involving carboxylate ions is not in harmony with the concept of resonance in these ions,[6] and the known non-racemizability of dipeptides conforms with its improbability.

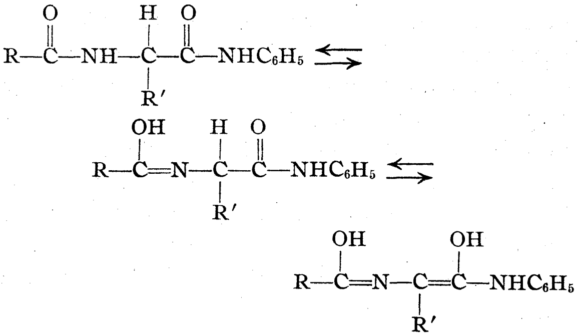
If the above hypothesis, as applied to tripeptides, is to be tenable, then replacement of the hydrogen in the system —CONH— by a methyl group should, by blocking the formation of the modification —C(OH)=N— and thereby preventing conjugation involving the asymmetric carbon atom, prevent racemization in the tripeptide.

In the case of hydantoins there are two possibilities for the occurrence of conjugation involving the asymmetric carbon atom



and if this be a factor controlling racemization, replacement of one of the H atoms in positions 1 or 3 of the ring by an alkyl or aryl group might retard racemization, and replacement of both should prevent it.

Accordingly a series of optically active substituted hydantoins, and a series of α-acylaminoacyl anilides were prepared. For each series the rates of racemization in suitable concentrations of alkali were measured. The latter derivatives contain an amino acid in which both the amino group and carboxyl group are modified. They differ from tripeptides in that they lack the terminal amino and carboxyl groups, but these are not essential for testing the theory as the requisite enolization can take place with equal probability



$$\mathrm{R—\overset{O}{\overset{\|}{C}}—NH—\underset{R'}{\overset{H}{C}}—\overset{O}{\overset{\|}{C}}—NHC_6H_5 \rightleftarrows}$$

$$\mathrm{R—\overset{OH}{C}{=}N—\underset{R'}{\overset{H}{C}}—\overset{O}{\overset{\|}{C}}—NHC_6H_5 \rightleftarrows}$$

$$\mathrm{R—\overset{OH}{C}{=}N—\underset{R'}{C}{=}\overset{OH}{C}—NHC_6H_5}$$

The derivatives studied were chosen because it was thought they might be more accessible than the tripeptides.

The results, given in Table I, have little quantitative significance since practical considerations precluded the use of standard concentrations of the optically active compounds and the precise evaluation of hydroxyl ion activity. Contrary to expectation, the loss of activity did not always follow a monomolecular course, as should have been the case if a single reaction had been involved.[9]

TABLE I

HALF RACEMIZATION TIME OF HYDANTOINS AND ACYL AMINO ANILIDES IN ALKALI

	Compound	Molarity	Medium	Half-time, hours
I	N-Acetyl-tyrosyl anilide	0.0255	0.37 *N* NaOH in 67% EtOH	74
II	N-Acetyl-N-methyltyrosyl anilide	.025	.37 *N* NaOH in 67% EtOH	9
III	N-Acetyl-*p*-methoxyphenylalanyl anilide	.0227	.37 *N* NaOH in 67% EtOH	40
IV	N-Benzoyl-*p*-methoxyphenylalanyl anilide	.0013	.33 *N* NaOH in 2:1 BuOH–EtOH	0.25
V	N-Carbobenzoxy-*p*-methoxyphenylalanyl anilide	.025	.37 *N* NaOH in 67% EtOH	∞
VI	N-Toluenesulfonyl-*p*-methoxyphenylalanyl methylanilide	.025	.37 *N* NaOH in 67% EtOH	∞
VII	5-*p*-Hydroxybenzylhydantoin[1]	.0046	.002 *N* NaOH in 95% EtOH	15
VIII	3-Phenyl-5-*p*-hydroxybenzylhydantoin[7]	.0222	.002 *N* NaOH in 95% EtOH	2.5
IX	1-Methyl-5-*p*-hydroxybenzylhydantoin	.030	.002 *N* NaOH in 95% EtOH	11.5
X	1-Methyl-3-phenyl-*p*-hydroxybenzylhydantoin	.0287	.002 *N* NaOH in 95% EtOH	0.5
XI	5-*p*-Methoxybenzylhydantoin	.0267	.002 *N* NaOH in 95% EtOH	45
XIa	5-*p*-Methoxybenzylhydantoin	.0046	.002 *N* NaOH in 95% EtOH	9
XII	3-Phenyl-5-*p*-methoxybenzylhydantoin[8]	.026	.002 *N* NaOH in 95% EtOH	<0.1

On comparing some of the rates of racemization, I with II, VII with IX and X, X with VIII,

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[6] Pauling, *Proc. Nat. Acad. Sci.*, **18**, 293 (1932).

[7] Paal and Zitelmann, *Ber.*, **36**, 3344 (1903).

[8] Behr and Clarke, THIS JOURNAL, **54**, 1630 (1932).

[9] With the acylaminoacyl anilides, the values of *K* drifted upward for compounds I and IV, downward for II and III; with the hydantoins, relatively constant values were observed for VII, VIII, and XI, and those for the 1-methyl hydantoins IX and X showed an upward drift.

and XI with XII, it can be seen that the substitution of H by R groups not only fails to prevent racemization but in some cases even hastens it. These findings completely invalidate the hypothesis that the ease of racemization depends upon the possibility of conjugation.

An alternative explanation is that the racemization, whether or not it is identical with enolization, is similar to enolization in its dependence on the ionization of the hydrogen on the asymmetric carbon atom. That this ionization is the essential step in such processes of racemization or enolization has been demonstrated for various systems including the racemization of *l*-phenyl, *β*-*α*-butyl ketone;[10] mutarotation of an acetoacetic ester derivative;[11] bromination of ketones;[12,13] racemization of alkyl nitromethanes.[14] Even where racemization takes place[15] and enolization is improbable[16] or impossible,[17] there occurs an activation of the hydrogen which is most probably ionization.

This ionization is in turn dependent on two factors: (a) the alkalinity of the medium, and (b) the activating effects of the groups attached to the asymmetric carbon atom. It is obvious that the more alkaline the medium, the greater is the tendency of any hydrogen atom to ionize. The nature of the activating effect is more obscure. If its mechanism involves internal electron displacements,[18–20] then the adjacent activating groups must act by lowering the electron density around the asymmetric carbon atom to the requisite point where those electrons shared as a covalent pair by the hydrogen and carbon are so displaced toward the carbon as to enable the hydrogen to ionize under the influence of the hydroxyl ions. Activation would then depend on electron-attraction, and the problem of racemization of these compounds would resolve itself into a question of the relative electron-attracting effects of the various groups attached to the asymmetric carbon atom. On this basis we can, from our data and the known behavior of di- and tripeptides, uramino acids and hydantoins with respect to racemization of this type, draw certain conclusions about the relative activating effects of different radicals.

Whereas the effect of the carboxyl is not sufficient to induce racemization in either free or N-acylated amino acids under the conditions, the —CO—NHC$_6$H$_5$ group can induce racemization in the N-acetyl and N-benzoyl aminoacyl anilides (I, II, III, IV). Ring closure in the hydantoic acids is essentially substitution of the free carboxyl of a uramino acid by a CONR group, with the result that the non-racemizing uramino acids become racemizable. The greater ease of racemization of the hydantoins as compared with the open-chain compounds indicates that ring closure in itself has a large effect, but this cannot be interpreted from the data here presented.

Amino and methylamino groups are unable to induce racemization when free, as is shown by the failure of dipeptides and aminoacyl anilides to racemize under the conditions. However, acylation of the amino groups in these anilides does not necessarily lead to racemizability, for whereas the —NHCOCH$_3$ and —NHCOC$_6$H$_5$ groups are activating (I, IV), the —NHCOOCH$_2$C$_6$H$_5$ and —NHSO$_2$C$_7$H$_7$ groups have no such effect (V, VI).

In the hydantoins, replacement of the imide hydrogen atoms in position 3 by a phenyl group increases the rate of racemization (compare VII with VIII, IX with X, and XI with XII). This may be due either to an activating effect of the phenyl group or to the possibility that in the simple hydantoins the imide hydrogen atom dissociates sufficiently to decrease the (already low) hydroxyl ion concentration. Suppression of hydroxyl ion activity by ionization of the phenolic hydrogen atoms may be partially responsible for the slower rates of racemization of the tyrosine derivatives as compared with their methyl ethers (compare VII with XI, VIII with XII).

Experimental

The observed optical rotatory powers of the various preparations recorded below do not necessarily represent the maximum possible values. In the racemization experiments carried out at 20–25° the half-times are based on the initial values observed for the alkaline solutions employed.

Carbobenzoxymethoxyphenylalanine.—To 20 g. of *p*-methoxyphenylalanine dissolved in 1 equivalent of 4 *N* sodium hydroxide were added alternately during the course of one-half hour with shaking and cooling 1 equivalent of

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(10) Sheng, Ingold and Wilson, *J. Chem. Soc.*, 78 (1938).
(11) Kimball, This Journal, **58**, 1967 (1936).
(12) Watson, *Chem. Rev.*, **7**, 173 (1930).
(13) Leuchs, *Ber.*, **46**, 2435 (1913).
(14) Kuhn, *ibid.*, **60**, 1297 (1927).
(15) Ashley and Shriner, This Journal, **54**, 4410 (1932); Kipping, *J. Chem. Soc.*, 18 (1935).
(16) Kohler and Potter, This Journal, **58**, 2166 (1936).
(17) Shriner, Struck and Jorison, *ibid.*, **52**, 2060 (1930).
(18) Ingold, *Chem. Rev.*, **15**, 225 (1934).
(19) Pauling, This Journal, **57**, 2086 (1935).
(20) Hammett, *ibid.*, **59**, 96 (1937).

carbobenzoxy chloride and 1 equivalent of 4 *N* sodium hydroxide. Shaking was continued until the mixture was homogeneous. On dilution and acidification to congo red an amorphous white solid precipitated out. The crude product weighing 32 g., was recrystallized from ether–petroleum ether, yielding long, flattened needles, m. p. 106–107°; soluble in alkali, ether, acetone, alcohol, benzene; insoluble in water; rotation, $[\alpha]^{25}_D$ +12° in 95% alcohol.

Anal. Calcd. for $C_{18}H_{19}O_5N$: C, 65.7; H, 5.8; N, 4.3. Found: C, 65.6; H, 5.8; N, 4.1.

N-Carbobenzoxy-*p*-methoxyphenylalanyl Anilide (V).—To 4.5 g. of carbobenzoxy-*p*-methoxyphenylalanine suspended in 150 cc. of dry ether was added 3.6 g. of finely powdered phosphorus pentachloride, and the mixture was allowed to stand at room temperature with occasional shaking until homogeneous (four hours). The ether was removed *in vacuo* and the oily residue quickly washed twice with dry petroleum ether. The amorphous residue was redissolved in 150 cc. of dry ether and 15 cc. of freshly distilled aniline in 50 cc. of dry ether was added. After twenty hours at room temperature the mixture was poured into cold dilute hydrochloric acid. The ether-soluble product was recrystallized twice from hot dilute acetone; yield 4.3 g., m. p. 171–173°; soluble in acetone, ether, alcohol; insoluble in water and carbon tetrachloride; rotation, $[\alpha]^{25}_D$ +22.3° in acetone.

Anal. Calcd. for $C_{24}H_{24}O_4N_2$: C, 71.3; H, 5.9; N, 6.9. Found: C, 71.2; H, 6.1; N, 7.0.

***p*-Methoxyphenylalanyl Anilide.**—Hydrogen gas was bubbled through a suspension of 1 g. of carbobenzoxy-*p*-methoxyphenylalanine-anilide in 50 cc. of 70% alcohol in the presence of palladium catalyst until no more carbon dioxide was evolved. The mixture was filtered and the filtrate concentrated at room temperature to 10 cc. A crop of white glistening squares crystallized out. Another crop was obtained from the mother liquor on standing in the ice box overnight; yield 584 mg., m. p. 121–123°; soluble in alcohol, acetone; slightly soluble in water and ether; rotation, $[\alpha]^{25}_D$ +34.3° in 95% alcohol.

Anal. Calcd. for $C_{16}H_{18}O_2N_2$: C, 71.1; H, 6.7; N, 10.4. Found: C, 71.1; H, 6.8; N, 10.4.

N-Acetyl-*p*-methoxyphenylalanyl Anilide (III).—To 0.100 g. of *p*-methoxyphenylalanine anilide in 3 cc. of 50% acetone was added 0.3 cc. of freshly distilled acetic anhydride. After twenty hours another 0.3 cc. of anhydride was added, and the solution was allowed to stand at room temperature for twenty-four hours. On dilution with water and cooling in the ice box overnight clusters of needles separated out; yield 95 mg., m. p. 168–170°; soluble in alcohol and acetone; insoluble in water; rotation, $[\alpha]^{25}_D$ +56.4° in 95% alcohol.

Anal. Calcd. for $C_{18}H_{20}O_3N_2$: C, 69.2; H, 6.4; N, 9.0. Found: C, 69.1; H, 6.7; N, 9.1.

Tyrosyl Anilide.—A mixture of 282 mg. of *p*-methoxyphenylalanine anilide, 10 cc. of concentrated hydriodic acid (sp. gr. 1.7), and a few crystals of phosphonium iodide was allowed to stand in a sealed tube at room temperature for forty-eight hours. The contents were then diluted with water and taken to dryness at room temperature over phosphorus pentoxide. The glassy residue was dissolved in a small amount of water and the solution made alkaline to litmus with ammonia. On cooling overnight in the ice box needles separated out which were recrystallized from hot dilute alcohol; yield 160 mg., m. p. 145–147°; soluble in acetone, alcohol and acid; insoluble in water; rotation, $[\alpha]^{25}_D$ +28.4° in 95% alcohol.

Anal. Calcd. for $C_{15}H_{16}O_2N_2$: C, 70.3; H, 6.3. Found: C, 70.2; H, 6.2.

N-Acetyltyrosyl Anilide (I).—A solution of 0.100 g. of tyrosine anilide in 3 cc. of 50% acetone was treated with acetic anhydride as previously described. On diluting with water and cooling in the ice box 98 mg. of crystalline material was obtained. This was recrystallized from dilute acetone in short rods, m. p. 236–237°; soluble in alcohol and acetone; insoluble in water; rotation, $[\alpha]^{25}_D$ +61.0° in 95% alcohol.

Anal. Calcd. for $C_{17}H_{18}O_3N_2$: C, 68.5; H, 6.0. Found: C, 68.7; H, 6.1.

N-*p*-Toluenesulfonyl-*p*-methoxyphenylalanine.—A mixture of 6 g. of *p*-methoxyphenylalanine dissolved in 1 equivalent of 1 *N* sodium hydroxide and 2 equivalents of toluenesulfonyl chloride in 50 cc. of ether was shaken for one hour. One equivalent of 1 *N* sodium hydroxide was then added and the mixture shaken for another hour. This process was repeated two more times. The aqueous layer was strongly acidified with 5 *N* hydrochloric acid and an oil separated out which solidified on standing overnight. The solid was recrystallized from hot water in long white needles, m. p. 138–140°; soluble in hot water, alcohol, ether, acetone and benzene; yield 8 g.

Anal. Calcd. for $C_{17}H_{19}O_5NS$: N, 4.0. Found: N, 4.0.

N-*p*-Toluenesulfonyl-*p*-methoxyphenylalanyl Methylanilide (VI).—To a solution of 5.5 g. of N-*p*-toluenesulfonyl-*p*-methoxyphenylalanine in 200 cc. of dry ether was added 3.6 g. of finely powdered phosphorus pentachloride and the mixture allowed to stand at room temperature with occasional shaking for four hours. The ether was removed *in vacuo* and the oily residue quickly washed twice with dry petroleum ether. It solidified in clusters of needles. These were redissolved in 150 cc. of dry ether and a solution of 17 cc. of freshly distilled methylaniline in 50 cc. of dry ether was added. The mixture was allowed to stand at room temperature for two days and then poured into cold dilute hydrochloric acid. The ether layer was washed with dilute hydrochloric acid, bicarbonate, water, and dried over sodium sulfate. On concentrating, glistening platelets together with a small amount of needles came out. On recrystallization from ether–petroleum ether 5 g. of platelets was secured; soluble in alcohol, ether, acetone; insoluble in water; m. p. 120°; rotation, $[\alpha]^{25}_D$ +18.8° in 95% alcohol.

Anal. Calcd. for $C_{24}H_{26}O_4N_2S$: C, 65.8; H, 5.9; N, 6.4. Found: C, 65.8; H, 5.9; N, 6.2.

The needles were not investigated.

N-Methyl-N-*p*-toluenesulfonyl-*p*-methoxyphenylalanyl Anilide.—A solution of 5 g. of N-*p*-toluenesulfonyl-O-N-dimethyltyrosine (prepared according to Fischer[21]) in 150 cc. of dry ether was treated with phosphorus pentachloride and aniline and worked up in the manner described above. After finally removing the ether, the glassy

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(21) Fischer and Lipschitz, *Ber.*, **48**, 360 (1915).

residue was recrystallized twice from hot dilute alcohol. Clusters of long white prisms were obtained; yield 5.2 g.; m. p. 96–98°; soluble in ether, acetone, alcohol, benzene; insoluble in petroleum ether and water; rotation, $[\alpha]^{25}\text{D}$ +15.3° in 95% alcohol.

Anal. Calcd. for $C_{24}H_{26}O_4N_2S$: C, 65.8; H, 5.9; N, 6.4. Found: C, 65.8; H, 5.9; N, 6.3.

N-Methyltyrosyl Anilide.—A mixture of 4 g. of the above compound, 2.5 g. of phosphonium iodide, and 50 g. of concentrated hydriodic acid (sp. gr. 1.7) was shaken in a sealed tube at room temperature for six hours. The mixture was mixed with ice and allowed to stand for one hour. The thiocresol was filtered off; the filtrate was concentrated *in vacuo*, made alkaline with ammonia and allowed to stand in the ice box overnight. A semi-solid mass came out which was crystallized twice from hot dilute alcohol; yield 1.4 g., m. p. 139–140°; soluble in alcohol, acetone, and acid; slightly soluble in water; rotation, $[\alpha]^{25}\text{D}$ +46.8° in 95% alcohol.

Anal. Calcd. for $C_{16}H_{18}O_2N_2$: C, 71.1; H, 6.7. Found: C, 71.0; H, 6.3.

N-Acetyl-N-methyltyrosyl Anilide (II).—A solution of 200 mg. of N-methyltyrosyl anilide in 6 cc. of 50% acetone was treated with 0.6 cc. of freshly distilled acetic anhydride, allowed to stand overnight at room temperature, and again treated with 0.6 cc. of acetic anhydride and allowed to stand another twenty-four hours at room temperature. On diluting with water and cooling in the ice box for a few days, clusters of rods separated out; yield 190 mg., m. p. 185–186°; soluble in acetone and alcohol; insoluble in water; rotation, $[\alpha]^{25}\text{D}$ −32.1° in 95% alcohol.

Anal. Calcd. for $C_{18}H_{20}O_3N_2$: C, 69.2; H, 6.4; N, 9.0. Found: C, 69.1; H, 6.3; N, 8.9.

N-Benzoyl-*p*-methoxyphenylalanyl Anilide (IV).—To a solution of 74 mg. of *p*-methoxyphenylalanyl anilide in 5 cc. of benzene was added 44 mg. of freshly distilled benzoyl chloride. After standing at room temperature overnight, 0.15 cc. of 1.1 *N* sodium hydroxide was added and the mixture allowed to stand at room temperature for ten hours with occasional shaking. The solid which separated out was centrifuged down, washed with benzene and water, and then recrystallized from dilute acetone; yield 95 mg., m. p. 224–225°; long, white needles; soluble in acetone; very slightly soluble in alcohol and butyl alcohol; insoluble in water and benzene; rotation, $[\alpha]^{25}\text{D}$ +14.7° in acetone.

Anal. Calcd. for $C_{23}H_{22}O_3N_2$: C, 73.8; H, 5.9; N, 7.5. Found: C, 74.0; H, 6.1; N, 7.8.

1-Methyl-5-*p*-hydroxybenzylhydantoin (IX).—To a suspension of 1 g. of N-methyltyrosine[21] in 40 cc. of boiling water was added solid potassium cyanate until everything went into solution. The cooled solution was treated with 20% sulfuric acid until approximately one normal, and then refluxed for three hours. On cooling a white solid separated out. This was recrystallized twice from hot water, yielding 1.1 g. of flat platelets, m. p. 123–124°; soluble in hot water and alcohol; insoluble in cold water; rotation, $[\alpha]^{25}\text{D}$ −12.0° in 95% alcohol.

Anal. Calcd. for $C_{11}H_{12}O_3N_2$: C, 60.0; H, 5.5. Found: C, 59.7; H, 5.3.

1-Methyl-3-phenyl-5-*p*-hydroxybenzylhydantoin (X).—To a solution of 1 g. of N-methyltyrosine in 2 equivalents of half-normal sodium hydroxide was added 1 equivalent of phenyl isocyanate. The mixture was shaken for two hours, filtered, and the filtrate made acid to congo red. A white amorphous mass separated out which was recrystallized from hot dilute alcohol; yield 1.5 g., m. p. 153–155°; short thick rods; soluble in acetone, alcohol, and alkali; insoluble in water; rotation, $[\alpha]^{25}\text{D}$ −15.5° in 95% alcohol.

Anal. Calcd. for $C_{17}H_{16}O_3N_2$: C, 68.9; H, 5.4. Found: C, 68.8; H, 5.5.

5-*p*-Methoxybenzylhydantoin (XI).—To a solution of 0.5 g. of *p*-methoxyphenylalanine in 25 cc. of boiling water was added 2 equivalents of solid potassium cyanate. The solution was cooled and made approximately normal with 20% sulfuric acid, and then refluxed for three hours. On cooling, white leaflets came out which were recrystallized from hot water; yield 0.47 g., m. p. 171–173°; soluble in hot water, acetone and alcohol; slightly soluble in cold water; rotation, $[\alpha]^{25}\text{D}$ −89.0° in 95% alcohol.

Anal. Calcd. for $C_{11}H_{12}O_3N_2$: C, 60.0; H, 5.5. Found: C, 59.8; H, 5.4.

The authors are deeply indebted to Dr. Louis P. Hammett for advice and criticism of the theoretical portions of this paper. They also express their thanks to Mr. W. Saschek, who performed the analyses here reported.

Summary

Racemization of acylaminoacyl anilides and of hydantoins by alkali is not prevented by the introduction of groups which would restrain the formation of conjugated enolic double bonds. It is suggested that such racemization is a reflection of the electronic condition of the various groups attached to the asymmetric carbon atom.

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY AND PHARMACOLOGY, SCHOOL OF MEDICINE AND DENTISTRY, THE UNIVERSITY OF ROCHESTER]

Spinastanol and its Identity with Fucostanol and Stigmastanol

BY C. DONALD LARSEN

α-Spinasterol, first isolated from the unsaponifiable fraction of spinach fat by Clenshaw and Smedley-MacLean,[1] by Heyl, Wise and Speer,[2] and later by Simpson,[3] on the basis of the latest experimental evidence, is an isomer of stigmasterol and fucosterol. α-Spinasterol, like stigmasterol[4] and fucosterol,[5] was formerly shown,[6] by quantitative hydrogenation and perbenzoic acid titration experiments, to be doubly unsaturated. Whereas stigmasterol has been proved to be unsaturated in the 22,23-position[7] and, like fucosterol,[8] unsaturated in the 5,6-position,[9] α-spinasterol, although its points of unsaturation are unknown, apparently exhibits saturation in the more common sites of sterol unsaturation, the 5,6- and 22,23-positions. Exclusion of the 22,23-position as a site of one of the ethylenic linkages in α-spinasterol was demonstrated by the negative results of attempted ozonization.[6] Simpson[3] has drawn attention to the anomalous reactions of α-spinasterol, as compared to sterols with known 5,6-unsaturation, from which he has concluded that "this sterol differs from other sterols in that it does not contain the 5:6-double bond characteristic of the latter."

α-Spinasterol further differs from stigmasterol and fucosterol in that the former possesses a double bond that is unresponsive to hydrogenation[6] or has been caused to migrate, as has been postulated for the 7,8 double bond of ergosterol,[10] to a non-reducible position. In contrast to the nuclear double bond conjugation in ergosterol, Simpson has excluded, by the absence of a maleic anhydride reaction, the existence of conjugated unsaturations in the α-spinasterol nucleus.

Recent investigation of a series of derivatives of the completely saturated spinastanol and comparison of them with the constants of those similarly prepared from fucostanol by Heilbron and co-workers[8] and from stigmastanol[11–13] has established the identity of these three saturated sterols, and corroborates the isomerity of the unsaturated sterols from which they were derived.

Originally[2,14,15] $C_{27}H_{46}O$ was thought to be the correct formula for α-spinasterol. Later,[6,16] quantitative hydrolysis of numerous esters of α- and γ-spinasterol, and of the α- and β-spinastenols, gave molecular weight values for a C_{28} or C_{29} sterol, but preponderantly in favor of the former. Hydrolysis of the acetyl and benzoyl esters of entirely pure spinastanol and titrational determination of the equivalent weight of spinastanedicarboxylic acid now indicate for spinastanol the formula $C_{29}H_{52}O$, identical with the accepted formula for stigmastanol and fucostanol.

Critical examination of the data in Table II on the derivatives of spinastanol and comparison of their physical constants with those of the more carefully investigated C_{29} saturated sterols in Table I establishes the identity of spinastanol, fucostanol and stigmastanol. On the other hand, the melting points and specific rotations of spinastanol, spinastanyl acetate and hydrocarbon, spinastane, are significantly lower than the corresponding values of Bengtsson's sitostanol and sitostane and Bergmann's sitostanyl (ostreastanyl) acetate (Table I). Therefore, it is concluded that spinastanol, fucostanol and stigmastanol are one and the same compound, and that they are different from sitostanol and ostreastanol, in accordance with the views previously set forth by Coffey, Heilbron and Spring[8] and Bergmann.[17] Comparative and mixed melting points of fucostanyl acetate and fucostanyl 3,5-dinitrobenzoate, for samples of which the writer is indebted to Dr. Heilbron, with the respective spinastanyl esters bear out the above conclusion of identity. Likewise, samples of ostreastanol and its phenylurethan, kindly furnished by Dr. Bergmann,

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(1) Clenshaw and Smedley-MacLean, *Biochem. J.*, **23**, 107 (1929).

(2) Heyl, Wise and Speer, *J. Biol. Chem.*, **82**, 111 (1929).

(3) Simpson, *J. Chem. Soc.*, 730 (1937).

(4) Windaus and Hauth, *Ber.*, **39**, 4378 (1906).

(5) Heilbron, Phipers and Wright, *J. Chem. Soc.*, 1572 (1934).

(6) Larsen and Heyl, THIS JOURNAL, **56**, 2663 (1934).

(7) Guiteras, Nakamiya and Imhoffen, *Ann.*, **494**, 116 (1932).

(8) Coffey, Heilbron and Spring, *J. Chem. Soc.*, 738 (1936).

(9) Fernholz, *Ann.*, **508**, 215 (1934).

(10) Windaus and Langer, *ibid.*, **508**, 105 (1934).

(11) Bengtsson, *Z. physiol. Chem.*, **237**, 46 (1935).

(12) Windaus and Brunken, *ibid.*, **140**, 47 (1924).

(13) Dalmer, v. Werder, Honigmann and Heyns, *Ber.*, **68**, 1814 (1935).

(14) Collison and Smedley-MacLean, *Biochem. J.*, **25**, 606 (1931).

(15) Hart and Heyl, *J. Biol. Chem.*, **95**, 311 (1932).

(16) Heyl and Larsen, THIS JOURNAL, **56**, 942 (1934).

(17) Bergmann, *J. Biol. Chem.*, **104**, 317, 553 (1934).

TABLE I

COMPARISON OF SATURATED PHYTOSTEROLS

	Fucostanol Heilbron		Stigmastanol Windaus	Stigmastanol Dalmer		Stigmastanol Bengtsson		Sitostanol Bengtsson		Ostreastanol Bergmann	
Derivative	M. p.	$[\alpha]^{20}_{\mathrm{D}}$	M. p.	M. p.	$[\alpha]^{20}_{\mathrm{D}}$	M. p.	$[\alpha]^{20}_{\mathrm{D}}$	M. p.	$[\alpha]^{20}_{\mathrm{D}}$	M. p.	$[\alpha]^{20}_{\mathrm{D}}$
-stanol	136	+24.7	135			137	+24.8	140	+25.6	141	+23.7
Acetate	130	+15.1	128			131	+15.3			137	+14.6
3,5-Dinitrobenzoate	215	+13.8[a]				215	+13.1[a]	215	+14.0		
Benzoate	136					137		139			
Phenylurethan										175	
-stanone	157	+40.2	156	157	+42.0	157	+40.6	158	+40.8	157	+41.9
-stanone oxime	218	+30.1	216	219	+30.0						
-stanedicarboxylic acid	229		230								
Dimethyl ester	90										
-stane			84.5								

[a] Rotations in benzene; all others in chloroform.

TABLE II

PREPARED DERIVATIVES OF SPINASTANOL

Compound	Formula	M. p., °C.	$[\alpha]^{20}_{\mathrm{D}}$	Mol. wt. Calcd.	Mol. wt. Found	Analyses, % C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
Spinastanol	$C_{29}H_{52}O$	136	+24.4	416.4		83.6	81.7[a] 82.2[a]	12.6	12.6 12.4		
Acetate	$C_{31}H_{54}O_2$	132	+14.9	458.4	457.4	81.2	81.1	11.9	11.8		
3,5-Dinitrobenzoate	$C_{36}H_{54}O_6N_2$	215	+13.1[b]	610.4		70.8	70.7	8.9	9.0	4.6	4.7
Benzoate	$C_{36}H_{56}O_2$	136	+19.6	520.4	516.6	83.0	83.1	10.8	11.0		
Phenylurethan	$C_{36}H_{57}O_2N$	172.5		535.5		80.7	80.6	10.7	10.8	2.7	2.7
Spinastanone	$C_{29}H_{50}O$	157	+40.5	414.4		83.9	83.7	12.1	12.0		
Oxime	$C_{29}H_{51}ON$	217	+29.2	429.4		81.0	81.0	12.0	11.8	3.3	3.1
Dicarboxylic acid	$C_{29}H_{50}O_4$	230	+33.1	462.4	458.6	75.3	75.2	10.9	11.0		
Dimethyl ester	$C_{31}H_{54}O_4$	90	+23.4	490.4		75.8	75.8	11.1	11.0		
Spinastane	$C_{29}H_{52}$	84.5	+25.5	400.4		86.9	86.7	13.1	12.9		

[a] Deviation from theory due to unremovable solvent of crystallization. [b] Rotation in benzene; all others in chloroform.

when compared with spinastanol and its phenylurethan, corroborate the non-identity of these saturated sterols.

It will be noted that spinastanedicarboxylic acid melts at 236–237° (corr.), 7–8° higher than the reported values for the acid from fucostanol and stigmastanol. Thanks to Dr. Heilbron, a sample of fucostanedicarboxylic acid has been available for comparison, for which the reported m. p. of 227–229° (corr.) was verified; when mixed with the acid from spinastanol a m. p. of 234–235° (corr.) was obtained. Due to the very close agreement in m. p. of the several derivatives of spinastanol with available data for derivatives of fucostanol and stigmastanol, such variation in m. p. of the respective acids must be not without reason. The sample of fucostanyl acetate furnished by Dr. Heilbron melted, as reported in the literature,[8] at 129–130°, and when mixed with spinastanyl acetate did not cause any m. p. depression. Nevertheless, subjection of fucostanyl acetate to the Liebermann–Burchard reaction was met with a comparatively faint but distinct development of green color. This fact seems to indicate that fucostanyl acetate contains a small amount of unsaturated, difficultly removable sterol. Analogously, it has been found that spinastanyl acetate is obtained pure only with difficulty; unless one recrystallizes the hydrogenation product of β-spinastenyl acetate from one of the better sterol solvents, such as ether or ethyl acetate, a pure, non-chromogenic spinastanyl acetate is not obtained. The pure, saturated ester is best obtained by treatment of the recrystallized hydrogenation product in chloroform with acetic anhydride and sulfuric acid according to the technique of Anderson and Nabenhauer.[18] Therefore, it seems possible that fucostanol, from which fucostanedicarboxylic acid was obtained by oxidation with chromic acid, might very well have contained a small amount of unsaturated sterol, oxidation of which may have led to a fucostanedicarboxylic acid contaminated with very small amounts of other, difficultly removable, acidic products. Similarly, the melting

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(18) Anderson and Nabenhauer, THIS JOURNAL, **46**, 1957 (1924).

point[12] of stigmastanedicarboxylic acid, reported as 229–230°, may be due to a small amount of contaminating oxidation product. It should be noted that the only recorded stigmastanedicarboxylic acid was prepared by Windaus and Brunken from a stigmastanol which melted at 134°; this alcohol, when pure, has since been found to melt at 136–7°.[11] It is possible that the low-melting stigmastanol of Windaus and Brunken contained a small quantity of contaminant which, through oxidation, led to a slightly contaminated dicarboxylic acid product of stigmastanol. A study of the dicarboxylic acids from fucostanol and stigmastanol of unquestioned homogeneity appears to be warranted.

Experimental

Spinastanyl Acetate.—The preparation of spinastanyl acetate was accomplished by hydrogenation of β-spinastenyl acetate in the manner previously described.[6] The product was recrystallized repeatedly from ethyl acetate and from ethyl ether. Ten grams of the acetate, m. p. 130–131°, was dissolved in 50 cc. of chloroform, to which was added slowly 10 cc. of acetic anhydride and 1 cc. of sulfuric acid. The mixture was shaken and allowed to stand for a half hour, the small amount of colored material removed by washing with water, and the solution dried and evaporated to dryness. The residue, after crystallization from ethyl acetate or acetone, melted at 131.5–132°; $[\alpha]^{20}\text{D}$ +14.9°.

Spinastanol.—The above acetyl ester was hydrolyzed by boiling for one hour in 3% alcoholic potassium hydroxide. The recovered sterol, after crystallization from alcohol and from acetone, melted at 136.5–137.0°; $[\alpha]^{20}\text{D}$ +24.4°.

Spinastanyl 3,5-Dinitrobenzoate.—This ester was prepared in the usual manner from the sterol and the acid chloride in pyridine. The ester was crystallized from acetone and from ether; m. p. 214–215°; $[\alpha]^{20}\text{D}$ +13.1° (benzene).

Spinastanyl Benzoate.—The preparation of this ester was analogous to that of the 3,5-dinitrobenzoate. It was crystallized from acetone and ethyl acetate; m. p. 135–136°; $[\alpha]^{20}\text{D}$ +19.6°.

Spinastanone.—One gram of spinastanol was dissolved in 360 cc. of 96% acetic acid, to which was added 250 mg. of chromic anhydride in 60 cc. of acetic acid and 2 cc. of water with constant stirring during one-half hour. After standing for twenty hours the acetic acid was removed under reduced pressure, the residue digested with 100 cc. of 6 *N* sulfuric acid, and the oxidation products dissolved in ether. The acidic fraction was removed by extraction with 7% aqueous potassium hydroxide, the ether was evaporated from the neutral fraction, and the residue recrystallized from methyl and ethyl alcohol; m. p. 156.5–157°; $[\alpha]^{20}\text{D}$ +40.5°; yield, 50%.

Spinastanone Oxime.—The oxime of spinastanone was prepared in the usual manner with hydroxylamine hydrochloride and sodium acetate in alcoholic solution. The recovered oxime was crystallized from methyl alcohol and from acetone; m. p. 218–219°; $[\alpha]^{20}\text{D}$ +29.2°.

Spinastanedicarboxylic Acid.—Two grams of spinastanol was dissolved in 100 cc. of warm 96% acetic acid, to which was added 2.6 g. of chromic anhydride dissolved in a few drops of water. The mixture was heated on the steam-bath for two hours with occasional stirring. The solution was cooled, after which the oxidation products were precipitated with excess water and extracted with ether. Separation of the acidic fraction was made with 7% aqueous potassium hydroxide; about 0.2 g. of spinastanone was isolated from the neutral fraction. The acidic fraction was precipitated from the alkaline extract by acidification, extracted with ether, the ether evaporated and the residue recrystallized from methyl alcohol and from acetone. The nearly pure dicarboxylic acid, m. p. 234–235°, was dissolved in ether, again extracted as the potassium salt, precipitated with dilute hydrochloric acid and extracted with fresh ether. The residue from the evaporated ether solution was recrystallized from an alcohol–chloroform mixture (3:1); m. p. 236–237; $[\alpha]^{20}\text{D}$ +33.1°; yield 30%.

Dimethyl Ester.—The methylation of spinastanedicarboxylic acid was carried out in the cold with diazomethane. The recovered dimethyl ester was crystallized from methyl and ethyl alcohol; m. p. 89.5–90°; $[\alpha]^{20}\text{D}$ +23.4°.

Spinastane.—The reduction of 0.5 g. of spinastanone to the hydrocarbon was accomplished according to the directions of Windaus and Brunken.[12] The recovered hydrocarbon was crystallized from alcohol and acetone; m. p. 84.0–84.5°; $[\alpha]^{20}\text{D}$ +25.5°.

Spinastanyl Phenylurethan.—Preparation of the phenylurethan of spinastanol was carried out in benzene with phenyl isocyanate, in the usual manner. The derivative was crystallized from methyl and ethyl alcohol; m. p. 172.0–172.5°; $[\alpha]^{20}\text{D}$ +14.3.

Molecular Weight Determinations.—Samples of spinastanyl acetate were boiled for one hour in 0.1 *N* alcoholic potassium hydroxide, and the excess alkali titrated with accurately standardized 0.1 *N* hydrochloric acid. Blank samples of alkali were boiled and titrated simultaneously. Hydrolysis of 0.3141, 0.2770, 0.2919, 0.1980, 0.1657, 0.3222 and 0.2054 g. of spinastanyl acetate consumed 6.91, 6.02, 6.43, 4.32, 3.56, 7.31 and 4.47 cc. of 0.1000 *N* alkali, respectively, corresponding to molecular weights of 455.7, 460.1, 452.7, 458.3, 464.8, 454.4 and 459.4; average molecular weight found, 457.9; calculated on the basis of $C_{31}H_{54}O_2$, 458.4.

Samples of spinastanyl benzoate were hydrolyzed in a manner analogous to that for the acetyl ester. Hydrolysis of 0.2810 and 0.1413 g. of spinastanyl benzoate consumed 5.45 and 2.73 cc. of 0.1000 *N* alkali, respectively, corresponding to molecular weights of 515.6 and 517.6; average, 516.6; calculated on the basis of $C_{36}H_{56}O_2$, 520.4.

Samples of spinastanedicarboxylic acid were titrated with dilute potassium hydroxide for equivalent weight determination. Samples of 0.1020 and 0.0761 g. of the acid were dissolved in neutral alcohol, to which was added 7.49 and 6.50 cc. 0.1000 *N* hydrochloric acid, respectively. Total 0.1000 *N* alkali required for neutralization was 11.95 and 9.81 cc., respectively; net, 4.46 and 3.31 cc. Equivalent weights found, 228.7 and 229.9; average, 229.3; calculated on the basis of $C_{29}H_{50}O_4$, 231.2.

Summary

1. A series of derivatives of spinastanol have been prepared, the physical constants of which warrant the conclusion that this saturated sterol is identical with fucostanol and stigmastanol.

2. The identity of spinastanol, fucostanol and stigmastanol points out the isomerity of the naturally occurring sterols from which these saturated derivatives are obtained.

3. Spinastanol appears to differ from ostreastanol and sitostanol, probably in the arrangement of the side chain rather than in the carbon skeleton of the nucleus.

4. Hydrolysis of the acetyl and benzoyl esters of spinastanol, and titration of the equivalent weight of spinastanedicarboxylic acid, establish for the spinach sterols a skeleton of twenty-nine carbon atoms, in common with other well investigated phytosterols.

ROCHESTER, N. Y. RECEIVED JULY 25, 1938

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, No. 174]

Studies in Organic Peroxides. V. *t*-Butyl Hydroperoxide[1]

BY NICHOLAS A. MILAS AND S. ARTHUR HARRIS[2]

The extraordinary stability of *t*-butyl hydrogen peroxide solution[3] and its therapeutic efficacy in the treatment of various fungus diseases[4] have stimulated our interest in the investigation of its chemical nature. In view of the lability of the hydroxyl group in tertiary alcohols, it was early suspected that pure hydrogen peroxide in non-aqueous solution would react with *t*-butyl alcohol reversibly to form *t*-butyl hydroperoxide. Although such a reaction between alcohols and hydrogen peroxide is unknown, an analogous reaction between organic acids and hydrogen peroxide in non-aqueous solvents has been known for some time.[5]

$$(CH_3)_3COH + HOOH \rightleftarrows (CH_3)_3COOH + H_2O$$

All of the alkyl hydroperoxides known, methyl,[6] ethyl,[6] isopropyl,[7] are much less stable than *t*-butyl hydroperoxide, which, besides being stable at room temperature, decomposes very slowly in alkalies or in the presence of pure liver catalase or horse-radish peroxidase. A distinct advantage, however, lies in the simplicity of its preparation. While the other hydroperoxides have been made by the alkylation of hydrogen peroxide with the corresponding dialkyl sulfates, *t*-butyl hydroperoxide can be prepared very easily from the anhydrous *t*-butyl alcoholic solution of hydrogen peroxide[3] by subjecting the latter to fractionation under reduced pressure in the presence of dehydrating agents such as anhydrous magnesium sulfate or preferably glacial metaphosphoric acid.

Experimental Part

Preparation of *t*-Butyl Hydroperoxide.—To 600 cc. of 30% aqueous hydrogen peroxide "Albone C" was added with frequent shaking 2340 cc. of *t*-butyl alcohol (b. p. 81.7–81.8°) and the solution allowed to stand for fifteen minutes, when 225 g. of anhydrous sodium sulfate was added slowly with vigorous shaking. The mixture separated into two layers and the non-aqueous layer containing most of the peroxide was removed and shaken first with 225 g. more of anhydrous sodium sulfate, then with two 225-g. portions of anhydrous magnesium sulfate. The final mixture which was essentially free from water was filtered and the filtrate allowed to stand several days over 400 g. of glacial metaphosphoric acid. This treatment produced a peroxide solution having an active oxygen content equivalent to about 17% *t*-butyl hydroperoxide.

To obtain the pure hydroperoxide, samples of the above were fractionated several times under diminished pressure over glacial metaphosphoric acid or anhydrous magnesium sulfate using an all-glass apparatus and the fraction boiling at 38–38.5° (18 mm.) collected and analyzed. Both the metaphosphoric acid and the magnesium sulfate, when used as dehydrating agents, brought about the production of the same peroxide. That this peroxide is not a constant boiling mixture between hydrogen peroxide and *t*-butyl alcohol, is shown by its physical and chemical properties.

Anal. Calcd. for $C_4H_{10}O_2$: C, 53.33; H, 11.11; active (O), 17.78. Found: C, 53.68, 53.63; H, 11.10, 11.17; active (O), 17.84, 18.10, 18.21.

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[1] For other papers in this series see THIS JOURNAL, **55**, 349, 352 (1933); **56**, 1219, 1221 (1934).

[2] Fellow of the Massachusetts Pharmaceutical Corporation.

[3] Milas and Sussman, THIS JOURNAL, **58**, 1302 (1936).

[4] Combes, *N. Y. State J. Med.*, **37**, No. 22 (1937).

[5] D'Ans and Frey, *Ber.*, **45**, 1845 (1912); Hatcher and Sturrock, *Can. J. Research*, **4**, 35 (1931).

[6] Baeyer and Villiger, *Ber.*, **33**, 3387 (1900); **34**, 738 (1901); Rieche and Hitz, *ibid.*, **61**, 951 (1928); **62**, 218, 2458 (1929); Rieche, "Alkylperoxide und Ozonide," Theodor Steinkopff, Dresden, 1931, and "Die Bedeutung der organische Peroxyde für die chemische Wissenschaft und Technik," Ahrens Sammlung, **34**, 1 (1936), Ferdinand Enke, Stuttgart.

[7] Medwedew and Alexejewa, *Ber.*, **65**, 133 (1932).

The peroxide is a colorless ethereal liquid with a sharp irritating odor having a density at 25° of 0.91063 and a freezing point of −13.5°. It is soluble in most of the ordinary organic solvents and unlike hydrogen peroxide is completely soluble in saturated hydrocarbons such as petroleum ether; in water it goes into solution slowly. It explodes violently when heated in the open flame although it has been refluxed for several hours in *t*-butyl alcohol without any appreciable decomposition. It liberates iodine slowly from an acidified solution of potassium iodide; it decomposes rapidly when heated with dilute alkalies, but retains its peroxide strength for several months when mixed at room temperature with a 10% solution of sodium hydroxide.

t-Butyl hydroperoxide is not easily converted into *t*-butyl chloride unless a reducing agent is used together with concentrated hydrochloric acid. Thus, when an ice-cold solution of concentrated hydrochloric acid containing 20 g. of ferrous chloride was mixed with about 4 g. of pure *t*-butyl hydroperoxide, an immediate reaction occurred with the separation of *t*-butyl chloride, which was separated, shaken with sodium bicarbonate solution, dried over calcium chloride and distilled; a yield of 2.5 g. of *t*-butyl chloride, b. p. 51°, was obtained.

The Effect of Catalase on the Decomposition of *t*-Butyl Hydroperoxide.—It has been known for some time that catalase has a specific action on the decomposition of hydrogen peroxide but has no effect on alkyl hydroperoxides.[8] Contrary to these early observations Stern[9] recently has reported that ethyl hydroperoxide is slowly attacked by catalase although Keilin and Hartree[10] are not in agreement with this observation and attributed the decomposition of this peroxide to a secondary reaction.

Catalase has very little or no effect on the decomposition of *t*-butyl hydroperoxide as can be seen readily by the results given in Table I. The catalase used in these experiments was a crystalline preparation[11] suspended in ammonium sulfate solution and kindly supplied to us by Professor Sumner of Cornell University. The *p*H of the catalase was adjusted just before use with disodium phosphate to 8.2[12] and 1 cc. of this solution was added to each of several glass-stoppered tubes. By means of a calibrated 0.1-cc. special pipet, 0.1 cc. of *t*-butyl hydroperoxide was added to each tube except one which was reserved for a blank with 0.1 cc. of 30% aqueous hydrogen peroxide solution. All tubes were shaken during the experiments at about 26.5°. At the end of a definite time the entire contents of each tube was treated with an acidified solution of sodium iodide and the iodine liberated titrated against standard thiosulfate solution. The hydrogen peroxide in the blank was destroyed completely by the catalase preparation in less than two minutes. With *t*-butyl hydroperoxide, on the other hand, the catalase turned red from a straw color and back again to its original color after fifteen hours of shaking with no evolution of gas. This color change may indicate the formation of an intermediate complex between the peroxide and catalase. An analogous observation was made by Stern[9b] with ethyl hydroperoxide. The results of seven experiments are shown in Table I.

TABLE I

EFFECT OF CATALASE ON THE DECOMPOSITION OF *t*-BUTYL HYDROPEROXIDE

Time, min.	0	3	9	12	30	60	930
0.01982 *N* thio, cc.	71.0	68.6	66.0	67.5	70.0	68.2	68.0

Effect of Peroxidase on the Decomposition of *t*-Butyl Hydroperoxide.—Peroxidase, unlike catalase, has been found to activate the decomposition of alkyl hydroperoxides in the presence of acceptors such as pyrogallol which is simultaneously oxidized to purpurogallin.[13] Although the decomposition of *t*-butyl hydroperoxide is activated slowly by peroxidase, we failed to observe any precipitate of purpurogallin. The peroxidase preparation used in our experiments was an extract of horse-radish kindly supplied to us by Professor Gould of our Biology Department. The *p*H of the preparation was adjusted to 6.21 and all of the experiments were carried out at 28°.

The experimental procedure was as follows: 2 g. of pure pyrogallol was dissolved in 800 cc. of distilled water and to each of several 250-cc. glass-stoppered Erlenmeyer flasks was added 80 cc. of this solution, 5 cc. of the peroxidase preparation and 0.1 cc. of *t*-butyl hydroperoxide; one sample was retained as a blank to which was added 0.1 cc. of 30% hydrogen peroxide instead of *t*-butyl hydroperoxide. At the end of a definite time each sample was titrated as before for the presence of peroxide. Hydrogen peroxide was destroyed completely in about four minutes with considerable evolution of heat and abundant precipitation of purpurogallin. In the experiments with *t*-butyl hydroperoxide, the solution turned orange in color but no precipitate appeared even after one hour of standing. The peroxide was used up very slowly, as the results indicate in Table II.

TABLE II

EFFECT OF PEROXIDASE ON THE DECOMPOSITION OF *t*-BUTYL HYDROPEROXIDE

Time, min.	0	5	10	60
0.01982 *N* thio, cc.	71.5	61.2	63.0	60.6

Effect of Palladium Black on the Decomposition of *t*-Butyl Hydroperoxide.—The palladium black used in these experiments was prepared in accordance with the method of Wieland.[14] Ten mg. of this catalyst was mixed in each of several experiments with 1 cc. of disodium phosphate solution (*p*H 8.2) containing 0.1 cc. of *t*-butyl hydroperoxide and the mixture shaken at room temperature in glass-stoppered tubes similar to those used with the catalase experiments. The results of four experiments are shown in Table III. Hydrogen peroxide under the same conditions was destroyed completely by our palladium catalyst in less than one minute.

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[8] Bach and Chodat, *Ber.*, **36**, 1756 (1903).

[9] Stern, (a) *J. Biol. Chem.*, **114**, 473 (1936); (b) *Enzymologia*, **4**, 145 (1937).

[10] Keilin and Hartree, *Proc. Roy. Soc.* (London), **B121**, 172 (1937).

[11] Sumner and Dounce, *Science*, **85**, 366 (1937); *J. Biol. Chem.*, **121**, 417 (1937).

[12] Michaelis [*Biochem. Z.*, **53**, 320 (1912)] found that the catalytic activity of catalase was best at *p*H range 7–9.

[13] Bach and Chodat, *Ber.*, **36**, 604 (1903); Wieland and Sutter, *ibid.*, **63**, 73 (1930).

[14] Wieland, *ibid.*, **45**, 489 (1912).

TABLE III

EFFECT OF PALLADIUM ON THE DECOMPOSITION OF *t*-BUTYL HYDROPEROXIDE

Time, min.	0	10	23	52
0.01982 *N* thio, cc.	66.0	38.0	22.0	21.7

The results in Table III seem to indicate that palladium black slowly accelerates the decomposition of *t*-butyl hydroperoxide in a dilute solution of disodium phosphate. However, pure *t*-butyl hydroperoxide is only slowly attacked by palladium black and a pure sample of it stirred over this catalyst for several months was still strongly peroxidic.

Summary

1. *t*-Butyl hydroperoxide has been prepared by the fractionation of an anhydrous solution of hydrogen peroxide in *t*-butyl alcohol in the presence of dehydrating agents.

2. This peroxide has been found to be very stable under ordinary conditions.

3. Pure liver catalase and horse-radish peroxidase have very little or no effect on the decomposition of *t*-butyl hydroperoxide.

4. Palladium black catalyzes slowly the decomposition of *t*-butyl hydroperoxide in dilute solution of disodium phosphate, although the decomposition of the peroxide is only slightly affected by this catalyst.

CAMBRIDGE, MASS. RECEIVED JULY 2, 1938

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF JOHNS HOPKINS UNIVERSITY]

Lengthening Carbon Chains by Three Units: Assay of Primary Bromides from the Addition of Hydrogen Bromide

BY A. P. KOZACIK AND E. EMMET REID

It is well known that an alkyl bromide may be converted into a primary alcohol with either one or two additional carbon atoms in the chain. The object of this investigation was to provide a method of lengthening a carbon chain by three —CH_2— units: $RBr \longrightarrow RMgBr \longrightarrow RCH_2CH{=}CH_2 \longrightarrow RCH_2CH_2CH_2Br$. This combines an old reaction with one[1] that has been studied only recently. In addition to lengthening the chain this gives odd-numbered bromides from the readily obtainable even. It was particularly interesting to extend these reactions to the higher alkyls and to aromatics. Another object was to identify the primary bromides by crystalline derivatives and to get a rough estimate of their purity. The abnormal addition of hydrogen bromide is of great theoretical interest; the availability of the primary bromides so produced for syntheses is a practical question of importance. The alkenes are given in Table I.

The addition of the hydrogen bromide was carried out by Professor Kharasch.[2] Our results show conclusively that the primary bromides are obtained. The melting points of these are in Table II. It was too much to expect that the technique which he has developed for the lower alkenes would apply to the higher without some modification. Unfortunately the whole amounts of the alkenes that were available were run through with the standard technique before any of the products were tested. The results were good with nonene-1 but very poor for heptadecene-1 and nonadecene-1. The identity of the synthetic bromides was shown and their approximate purity estimated by their reaction with para substituted phenols. For compari-

TABLE I

PROPERTIES OF THE ALKENES

Alkenes	B. p., °C.	Press., mm.	M. p., °C.	d^0_4	d^{25}_4	$n^{25}D$	Bromine no. Calcd.	Bromine no. Found		Yield, %
n-$C_{11}H_{23}CH{=}CH_2$	102–103	10	−13	0.7856	0.7670	1.4328	62.8	63.6	63.7	77
n-$C_{13}H_{27}CH{=}CH_2$	127.5–128.5	10	− 2.8	.7921	.7751	1.4353	55.7	54.5	54.6	67
n-$C_{15}H_{31}CH{=}CH_2$	155.4–156.4	10	11.2	$.7892^{20}_4$	.7859	1.4417	49.7	47.7	48.5	43
n-$C_{17}H_{35}CH{=}CH_2$	177	10	21.7	$.7889^{30}_4$	$.7858^{35}_4$		46.9	45.7		56
$C_6H_5(CH_2)_2CH{=}CH_2$	181–182	757								77
$C_6H_5(CH_2)_4CH{=}CH_2$	94.5-95	10								87

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[1] Kharasch and co-workers, THIS JOURNAL, **55**, 2469, 2521 and 2531 (1933).

[2] M. S. Kharasch and Wm. M. Potts, *J. Org. Chem.*, **2**, 195 (1937).

son the authentic bromides previously prepared[3] were treated with the same phenols, under the same conditions and usually at the same time. The products were crystallized two or more times. The phenyl derivatives were treated with β-naphthol. Only in the case of 3-phenylpropyl bromide was an authentic sample available for comparison.

TABLE II

MELTING POINTS OF AUTHENTIC (A) AND SYNTHETIC (S) BROMIDES AS RECEIVED

Carbons	A	S	Diff.	Minimum estimated purity
9				82
11	−13.15	−25	12	65
13	5.94	−15	21	41
15	18.63	7.4–8.4	10	60
17	28.40	1–2	26	12
19	38	13–15	23	3

From the results in Table III it will be seen that the products from the synthetic bromides are somewhat less in amount and melt lower than those from the authentic. The losses on the first crystallization are even more significant. Taking the data for the nonyl bromides, we find this loss to average 11% for the authentic and 28 for the synthetic. In the second crystallization the losses were nearly the same. For practical purposes the primary bromide present may be estimated by comparing the final yields of the twice crystallized derivatives with those from the authentic bromides. These estimates may be regarded as minimum values. Thus we can say that there was at least 82% of the primary bromide, and probably somewhat more, present in the synthetic nonyl bromide. The other syn-

TABLE III

DERIVATIVES FROM AUTHENTIC AND SYNTHETIC BROMIDES AND *p*-SUBSTITUTED PHENOLS, *p*-XC_6H_4OH, YIELDS AND MELTING POINTS OF CRUDE AND CRYSTALLIZED

X		Yields, %		Loss on recrystallization, %		Melting points, °C.	
		A	S	A	S	A	S
		From *n*-nonyl bromides					
$C_8H_{17}O$	Crude	87	81			58–59	
	1st cr.	78	60	10	26	58–59.5	54–55
	2nd cr.	73	56	6	7	60.0	60.0
$C_{10}H_{21}O$	Crude	85	84			62–63	57–59
	1st cr.	78	62	8	26	62.5–63	62–62.5
	2nd cr.	72	58	8	7	63.8	63.4
$C_{12}H_{25}O$	Crude	86	88			62–63.5	55–59
	1st cr.	76	61	12	31	64–64.5	63–64.5
	2nd cr.	..	57		7	65.2	64.8
$C_{14}H_{29}O$	Crude	86	86			64–66	60–63
	1st cr.	76	64	12	26	65–66	65–66
	2nd cr.	73	60	4	6	67.4	65–66
		From *n*-undecyl bromides					
$C_8H_{17}O$	Crude	99	67			59–60	52–56
	1st cr.	81	45	18	33	59–60	58–59
	2nd cr.	75	41	7	9	60.4	60.6
$C_{10}H_{21}O$	Crude	93	83			66–68	57–62
	1st cr.	76	51	18	38	68–69.5	67–68
	2nd cr.	71	46	7	10	69.8	69.8
$C_{12}H_{25}O$	Crude	76	73			66–69	58–63
	1st cr.	60	43	21	41	71–71.5	70–70.5
	2nd cr.	59	36	2	16	71.8	71.8
		From *n*-tridecyl bromides					
C_4H_9O	Crude	92	69			57–60	55–59
	1st cr.	82	29	11	58	61–62	60–61.5
	2nd cr.	70	27	15	7	62.8	62.8
$C_8H_{17}O$	Crude	95	67			62–63	55–60
	1st cr.	78	32	18	52	64–64.5	64–65
	2nd cr.	73	30	6	6	64.8	65.2
$C_{10}H_{21}O$	Crude	90	75			67–68	58–63
	1st cr.	79	25	12	67	67.5–68	67–67.5
	2nd cr.	72	23	8	8	67.6	67.5
		From *n*-pentadecyl bromides					
$C_{12}H_{25}O$	Crude	92	83			73–74	62
	1st cr.	73	54	21	35	74–75	72–74
	2nd cr.	67	40	8	26	75.6	74.2
Cl	Crude	95	71			44–47	39–44
	1st cr.	76	34	20	52	46–47	44–45.5
	2nd cr.	67	19	12	44	48.0	47.2
I	Crude	89	77			53–55	45–50
	1st cr.	65	37	27	52	56–57	55–56.5
	2nd cr.	57	33	12	11	57.2	57.0
		From *n*-heptadecyl bromides					
$PhCH_2O$	Crude	89	67			88	80–84
	1st cr.	..	..			91.2	84–88
	2nd cr.	70	..			91.8	89.8
	3rd cr.	...	8				91.6
Cl	Crude	97	27			50–52	45
	1st cr.	86	3	11	89	53–54	52–53
	2nd cr.	81	..	6		54.2	53.8
I	Crude	96	44			60–61	57–59
	1st cr.	82	10	15	77	62–62.5	61–62
	2nd cr.	78	6	5	40	64.0	63.4
		From *n*-nonadecyl bromides					
H	Crude	98	8			51–55	47–51
	1st cr.	73	4	25	50	55–56	47–51
	2nd cr.	69	2	5	50	56.0	56.0

TABLE IV

DERIVATIVES FROM AUTHENTIC AND SYNTHETIC PHENYLALKYL BROMIDES AND β-NAPHTHOL

	Yields, %		Loss on recrystallization		Melting points, °C.	
	A	S	A	S	A	S
	From phenyl-propyl bromides					
Crude	63	59			66–67	62–64
1st cr.	47	44	25	25	69–69.5	68.5–69
2nd cr.	43	38	9	14	69.5–70	69.0–69.5
	From phenyl-butyl bromide					
Crude	..	48				47–53
1st cr.	..	32		38		54–55
2nd cr.	..	26		19		54.5–55.5
	From phenyl-hexyl bromide					
Crude	..	31				63–77
1st cr.	..	18		42		78–78.5
2nd cr.	..	15		17		78.5–79

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[3] Meyer and Reid, THIS JOURNAL, **55**, 1577 (1933).

thetic bromides do not show up so well: the undecyl may be estimated to contain at least 65% of the primary, the tridecyl, 41, the pentadecyl 60, the heptadecyl 12 and the nonadecyl only 3. The melting points of the bromides put them in the same order as to purity.

Experimental

The procedure of Gilman[4] for the preparation of the Grignard reagents was followed. These reagents were used according to the method of Wilkinson,[5] for making the alkenes, which were separated from the disproportionation by-products of the Grignard reaction, heated with sodium and distilled. The properties of the new alkenes are to be found in Table I. The bromine numbers were determined by the method of Francis[6] as modified by Cortese.[7]

Preparation of Derivatives.—To prepare a derivative, 0.3 to 0.5 cc. of the alkyl halide was measured into a test-tube with 3 cc. of alcohol and about 10% excess of the phenol. As $C_{19}H_{39}Br$ is a solid, it was weighed. This mixture was heated to effect solution and a slight excess of 1 *N* alcoholic potash added. The test-tube was stoppered loosely and placed with others in a beaker of water kept at about 70° for about twelve hours. At the end of the heating any alcohol that had evaporated was replaced and 2 cc. of hot water added. The mixture was boiled for a moment and then cooled quickly with violent shaking. This caused the derivative to separate as a granular solid which was collected on a filter and washed twice with water. The product was crystallized twice or thrice from alcohol. For better comparison the derivatives of the authentic and synthetic bromides were prepared at the same time with the same reagents and the crystallizations were carried on side by side. The final melting points were kindly taken by Mrs. Carrie Gutman Moses with a standardized thermometer.

For preparing derivatives para substituted phenols were used. Experience in another investigation had shown that these give derivatives that are readily purified and melt at convenient temperatures. The monoalkyl hydroquinone ethers will be described later along with other derivatives made from them.

Summary

1. A method has been devised for transforming an alkyl bromide into another alkyl bromide having a carbon chain longer by three units.

2. A method has been worked out for assaying the mixture of bromides obtained by the addition of hydrobromic acid to unsaturates.

3. By the preparation of known crystalline derivatives the formation of primary bromides by the addition of hydrobromic acid to alpha alkenes in the presence of peroxides has been confirmed.

BALTIMORE, MD. RECEIVED JULY 1, 1938

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(4) Gilman, Zoellner and Dickey, THIS JOURNAL, **51**, 1579 (1929).

(5) Wilkinson, *J. Chem. Soc.*, **120**, 3057 (1931).

(6) Francis, *Ind. Eng. Chem.*, **18**, 821 (1926).

(7) Cortese, *Rec. trav. chim.*, **48**, 564 (1929).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. XLIV. Pregnanone-3 and Related Compounds[*]

BY RUSSELL E. MARKER AND ELMER J. LAWSON

Although all the pregnanediols, pregnanolones, and pregnanediones isomeric about C_3, C_5 and C_{20} have been described,[1] none of the corresponding pregnanols and pregnanones are known. Since we now have indications of the occurrence in urines of pregnane derivatives having only one oxygen atom,[2] we have begun the synthesis of compounds of this type for purposes of comparison and physiological testing. The present paper describes the preparation of pregnanone-3 and the isomeric 3-pregnanols.

Pregnanol-3(α)-one-20 was reduced by the Clemmensen method with amalgamated zinc and a mixture of acetic and concentrated hydrochloric acids. The reaction mixture, carried through the acid succinate separation, yielded only 19 mg. of pregnanol-3(α), but about 250 mg. (m. p. 102°) of what proved to be pregnanol-3 acetate could be crystallized from the non-hydroxylated fraction, and a further crop of pregnanol-3(α) was obtained from the mother liquor after alkaline hydrolysis and acid succinate separation. The non-hydroxylated fraction, amounting to about 20% of the reaction mixture, did not yield any crystalline products.

Since it was thought at first that the crystalline product might be a pregnene, which could be identified by ozonolysis to give $3\|4$ pregnane-3,4-diacid,[3] or an isomer, this acid was prepared by the Clemmensen reduction of 20-keto-$3\|4$-pregnane-3,4-diacid.[4] The latter forms a 2,4

(*) Paper XLIII, THIS JOURNAL, **60**, 1904 (1938).

(1) Marker, Kamm, Wittle, Oakwood, Lawson and Laucius, THIS JOURNAL, **59**, 2291 (1937).

(2) Unpublished results from This Laboratory.

(3) This nomenclature is suggested by Sobotka, "Chemistry of the Sterids," Williams and Wilkins, Baltimore, Md., 1938, p. 163.

(4) Butenandt, *Ber.*, **63**, 659 (1930); **64**, 2529 (1931).

dinitrophenylhydrazone, but, after the reaction with zinc and hydrochloric acid, the product no longer forms such a derivative. The same 3||4-pregnane-3,4-diacid was formed in small amounts when pregnanol-3(α) was oxidized with chromic acid. The major reaction product, pregnanone-3, was hydrogenated in acid solution to give pregnanol-3(β).

Since most of the pregnanol-3(α) formed in the Clemmensen reduction of pregnanol-3(α)-one-20 was converted by the acetic acid present into its acetate, model experiments were tried with *epi*- and β-cholestanol. When these were refluxed with amalgamated zinc and acetic acid–hydrochloric acid the chief reaction products were unreacted *epi*-cholestanol, and β-cholestyl acetate, respectively. Evidently, when a Clemmensen reaction is run on a hydroxy ketone, the reaction mixture should be subjected to alkaline hydrolysis to isolate the product. In this connection it also should be noted that the Clemmensen reduction of hydroxylated steroids frequently removes the hydroxyl groups. For example, the diacetate of 4-hydroxystigmasterol is reduced to stigmastane[5] and the hydroxyketocholanic acids give some cholanic acid.

Experimental Part

The pregnanol-3(α)-one-2 used in these experiments was isolated from human pregnancy urine[6] and melted at 134°. Apparently it can exist in two polymorphic forms, for sometimes crystals, m. p. 148°, are obtained. It forms a 2,4-dinitrophenylhydrazone which melts at 229° after recrystallization from alcohol.

Anal. Calcd. for $C_{27}H_{38}O_5N_4$: C, 64.9; H, 7.7. Found: C, 64.8; H, 8.0.

Pregnanol-3(α).—A mixture of 40 g. of amalgamated zinc, 100 cc. of concentrated hydrochloric acid, and 1 g. of pregnanol-3(α)-one-20 in 100 cc. of acetic acid was refluxed gently. The initial pink color of the solution was discharged in ten minutes, and after another ten minutes an oil had separated. After two hours of heating the solution was cooled, diluted with water, and extracted with ether. The ethereal extract was washed with sodium carbonate solution and water, and the ether removed. The sirupy residue was treated with Girard's reagent to remove traces of ketonic material, and then separated into hydroxylated and non-hydroxylated fractions in the usual manner.

The non-hydroxylated sirup, consisting almost all of the product, crystallized on standing a week; so it was triturated with 5 cc. of alcohol, collected on a funnel, and washed with small amounts of alcohol to give 370 mg. of crystals, m. p. 87–93°. One recrystallization from methanol gave 190 mg. of plates, m. p. 101–102°. This was recrystallized to a constant m. p., 106°. It was saturated to bromine and catalytic hydrogenation and did not give a Beilstein test for halogens. Analysis showed it to be the acetate of pregnanol-3(α).

Anal. Calcd. for $C_{23}H_{38}O_2$: C, 79.7; H, 11.1. Found: C, 79.3; H, 11.1.

One hundred and ninety milligrams of the acetate was hydrolyzed by heating with 0.2 g. of sodium hydroxide in 5 cc. of alcohol for one-half hour. The product, isolated by extraction of the diluted solution with ether, was recrystallized from slightly diluted alcohol and methanol to give pure pregnanol-3(α), m. p. 148°, as needle-rosets.

Anal. Calcd. for $C_{21}H_{36}O$: C, 83.2; H, 11.4. Found: C, 83.4; H, 11.4.

The total mother liquor from the crystallization of the acetate was hydrolyzed and carried through the acid-succinate separation, to give an additional quantity of pregnanol-3(α). The yield of pregnanol-3(α) from pregnanol-3(α)-one-20 was about 50%, of which only 19 mg. was obtained from the original hydroxylated fraction.

Pregnanone-3.—To a solution of 200 mg. of pregnanol-3(α) in 10 cc. of acetic acid was added 80 mg. of chromic anhydride in 5 cc. of 90% acetic acid. After standing for one and one-half hours at room temperature, a little methanol was added to destroy any excess chromic acid, and the solution was concentrated *in vacuo*. The residue was diluted and extracted with ether, and the ether extract washed free of chromium salts with dilute hydrochloric acid and water. The ether solution was extracted with 5% sodium carbonate and washed with water.

Acidification of the alkaline extract gave a flocculent acid which coagulated on standing. It was collected and washed with water and small amounts of hot alcohol to give 7 mg. of 3||4-pregnane-3,4-diacid, m. p. 297°, as proved by mixed melting point determination with an authentic sample (*vide infra*).

The neutral ethereal extract was evaporated and the residue crystallized several times from diluted alcohol to give 140 mg. of pregnanone-3, as needles, m. p. 115°. It gave a red coloration with alcoholic *m*-dinitrobenzene and aqueous potassium hydroxide, showing the presence of a 3-carbonyl group.

Anal. Calcd. for $C_{21}H_{34}O$: C, 83.4; H, 11.3. Found: C, 83.6; H, 11.3.

Fifteen milligrams of pregnanone-3 was treated in the usual manner with alcoholic semicarbazide acetate solution. The resulting semicarbazone, m. p. 133°, proved to be difficult to purify because of its great solubility in all ordinary solvents except ether. The 2,4-dinitrophenylhydrazone, however, proved to be a satisfactory derivative. After crystallization from alcohol, it melted at 163°.

Anal. Calcd. for $C_{27}H_{38}O_4N_4$: C, 67.0; H, 8.0. Found: C, 66.7; H, 8.2.

Pregnanol-3(β).—A solution of 100 mg. of pregnanone-3 in 20 cc. of acetic acid and five drops of 48% aqueous hydrobromic acid was added to 50 mg. of previously reduced platinum oxide in 20 cc. of acetic acid, and the mixture was shaken in a hydrogen atmosphere at 35 lb. (2.3 atm.) pressure for two hours. The catalyst was removed by filtration, and the acetic acid removed *in vacuo*. The residue was heated for twenty minutes with 0.3 g. of sodium

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(5) Marker and Rohrmann, THIS JOURNAL, **60**, 1073 (1938).

(6) Marker and Kamm, *ibid.*, **59**, 1373 (1937).

hydroxide in 8 cc. of alcohol, diluted and extracted with ether. The washed ethereal extract was evaporated, and the crystalline residue dissolved in 10 cc. of hot alcohol. To this solution was added a hot solution of 0.4 g. of digitonin in 20 cc. of alcohol. The next day the digitonide was filtered, dried and decomposed in the usual manner to give the carbinol. After recrystallization from slightly diluted alcohol, the pregnanol-3(β) was obtained as needles, m. p. 144°, which depressed with pregnanol-3(α) to 115–120°.

Anal. Calcd. for $C_{21}H_{36}O$: C, 82.8; H, 11.8. Found: C, 82.9; H, 11.8.

Twenty milligrams of pregnanol-3(β) was converted into its acetate by refluxing for a half hour with 2 cc. of acetic anhydride. After recrystallization from dilute alcohol, it melted at 87°.

Anal. Calcd. for $C_{23}H_{38}O_2$: C, 80.1; H, 11.3. Found: C, 80.4; H, 11.5.

3||4-Pregnane-3,4-diacid.—The 20-keto-3||4-pregnane-3,4-diacid used in these experiments was obtained by D. M. Jones of this Laboratory as a by-product in the preparation of pregnanedione, and it had a melting point of 270°. It formed a 2,4-dinitrophenylhydrazone which was crystallized from alcohol to a constant m. p. 210°.

Anal. Calcd. for $C_{27}H_{36}O_8N_4$: C, 59.6; H, 6.7. Found: C, 59.5; H, 7.0.

A mixture of 40 g. of amalgamated zinc, 1 g. of 20-keto-3||4-pregnane-3,4-diacid, 100 cc. of concentrated hydrochloric acid, and 100 cc. of acetic acid was refluxed for five hours, small portions of acetic acid and hydrochloric acid being added from time to time. The suspended acid was collected and washed with ether to give 0.53 g., m. p. 260–270°. This product was purified by leaching with boiling alcohol, in which, in contrast to 20-keto-3||4-pregnane-3,4-diacid, it is very insoluble. Extraction of the acetic acid–hydrochloric acid filtrate with ether, and concentration of the latter gave an additional quantity of the product, 3||4-pregnane-3,4-diacid, m. p. 297°. This acid is extremely insoluble in all ordinary solvents.

Anal. Calcd. for $C_{21}H_{34}O_4$: C, 71.4; H, 9.7. Found: C, 71.3; H, 9.5.

A solution of 30 mg. of 3||4-pregnane-3,4-diacid in 20 cc. of methanol and 10 drops of concentrated sulfuric acid was concentrated to one-third volume by heating for two hours on a steam-bath. The solution was diluted with water, extracted with ether, and the ethereal extract washed with sodium carbonate solution and water. After evaporation of the ether, the residue was crystallized from methanol to give the dimethyl ester of 3||4-pregnane-3,4-diacid, m. p. 147°.

Anal. Calcd. for $C_{23}H_{38}O_4$: C, 72.5; H, 10.1. Found: C, 72.2; H, 9.9.

We wish to thank Dr. Oliver Kamm and Parke, Davis and Company for their generous support of this work. We also wish to thank Dr. A. H. Popkin for the microanalyses reported in this paper.

Summary

The preparations of pregnanone-3 and the isomeric 3-pregnanols are described. The Clemmensen reduction, in the presence of acetic acid, of hydroxylated compounds may give rise to acetylated products.

STATE COLLEGE, PENNA. RECEIVED AUGUST 8, 1938

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. XLV. The Neutral Reduction Products of Equilenin*

BY RUSSELL E. MARKER, EWALD ROHRMANN, EUGENE L. WITTLE AND FRANK H. TENDICK

While the phenolic reduction products of equilenin have been studied rather extensively[1–3] no such study has been reported on the neutral reduction products which often accompany the phenolic reduction products. Marker *et al.*[2] carried out the catalytic hydrogenation of equilenin in acidic solution and found that the main product of the reaction was $\Delta^{5,7,9}$-oestratrienol-17. All searches for completely saturated compounds in the reaction were unsuccessful, indicating the extreme stability of the $\Delta^{5,7,9}$-oestratrienol-17 to further reduction.

Marker[3] made an extensive study of the phenolic reduction products of equilenin, α-dihydroequilenin, and β-dihydroequilenin, using sodium and amyl alcohol. In every case it was found that the reaction gave approximately 20% of phenolic reduction products, the remainder consisting largely of neutral reduction products. The phenolic reduction products were shown to be the α- and β-oestradiols. We have now extended these studies to the neutral reduction products of these reactions. The neutral fraction from the reduction of equilenin gave a diol (I) $C_{18}H_{24}O_2$, melting at 172°. This same compound was produced by the analogous reduction of α-dihydroequilenin, thus establishing the configuration of the hydroxyl group at C_{17}. The

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(*) Paper XLIV, THIS JOURNAL, **60**, 2438 (1938).

[1] Wintersteiner, Schwenk, Hirschmann and Whitman, THIS JOURNAL, **58**, 2652 (1936).

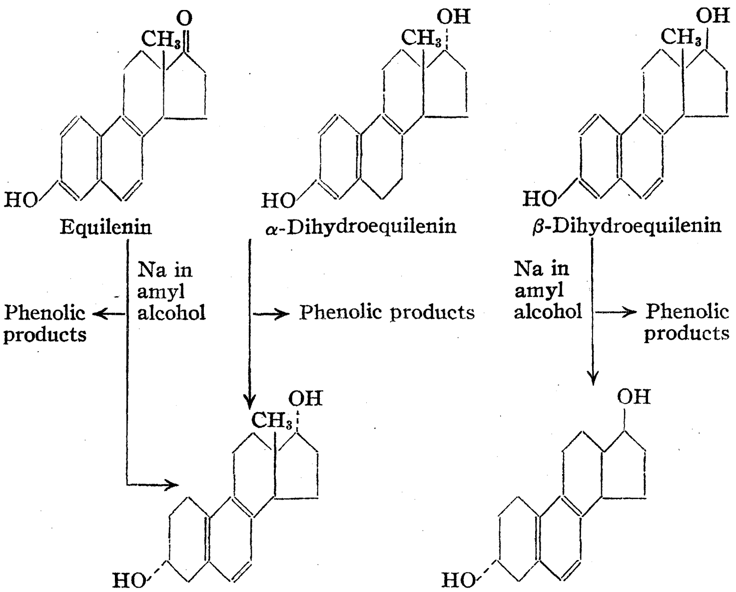
[2] Marker, Kamm, Oakwood and Tendick, *ibid.*, **59**, 768 (1937).

[3] Marker, *ibid.*, **60**, 1897 (1938).

reduction of β-dihydroequilenin gave a diol (II) melting at 179° and possessing the β-configuration at C_{17}. Attempts to oxidize these diols to diketones resulted in the formation of uncrystallizable oils. The fact that the only diol isolated from the equilenin reduction possessed the α-configuration at C_{17} indicates that the sodium and amyl alcohol reduction gives largely the α-form at C_{17} as in the case of oestrone reduction.

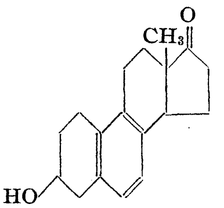
It is not possible to assign a definite configuration to the hydroxyl group at C_3, although it is most probable that the same configuration at C_3 is obtained in both of the diols.

A compound apparently related to the two reduction products which we have prepared is that obtained by Remesov[4] by the degradative oxidation of the side chain of neoergosterol. This compound, being derived from neoergosterol, must possess the β-configuration at C_3. Aside from the differences at C_{17}, this compound may differ from the present diols in the configuration of the hydroxyl group at C_3. Inasmuch as Remesov's compound possessed oestrogenic activity comparable to that of oestrone, one might expect the corresponding dihydro compounds to be high in oestrogenic activity. The fact that Windaus and Deppe[5] obtained *epi*-neoergosterol by the reduction of dehydroneoergosterol with sodium and amyl alcohol suggests that our reduction products of equilenin probably possess the α-configuration at C_3 in contrast to the β-configuration which Remesov's compound possesses.



I, 5,7,9-Oestratrienediol-3(α), 17(α)

II, 5,7,9-Oestratrienediol-3(α), 17(β)



III, 5,7,9-Oestratrieneol-3(β)-one-17 (Remesov)

We wish to thank Dr. Oliver Kamm and Parke, Davis and Company for their generous help and assistance in various phases of this work.

Experimental Part

5,7,9-Oestratrienediol-3(α),17(α) from Equilenin.—The neutral fraction obtained by the reduction of equilenin with sodium and amyl alcohol was used.[3] The crude fraction was sublimed in high vacuum at 160–200°. The sublimed material was crystallized from acetone to give white crystals melting at 172°.

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.3; H, 8.9. Found: C, 79.2; H, 8.9.

A monobenzoate was prepared by allowing a solution of the diol in pyridine and a slight excess of benzoyl chloride to stand for two days at room temperature. The solution was diluted with water and after standing for several hours the product was extracted with ether. The ether solution was washed well with a saturated sodium carbonate solution and then with water, and evaporated to dryness. The benzoate thus obtained, after crystallization from ethyl acetate, melted at 195°.

Anal. Calcd. for $C_{25}H_{28}O_3$: C, 79.7; H, 7.5. Found: C, 79.7; H, 7.7.

5,7,9-Oestratrienediol-3(α),17(α).—The neutral fraction obtained by the reduction of α-dihydroequilenin with sodium and amyl alcohol was used.[3] The material was distilled in high vacuum, most of it distilling at 160–200°. The sublimed material was crystallized from acetone to give white crystals melting at 172°, uncorr. This gave no depression in melting point when mixed with a sample obtained by the reduction of equilenin with sodium and amyl alcohol.

5,7,9-Oestratrienediol-3(α),17(β) from β-Dihydroequilenin.—The neutral fraction from the reduction of β-dihydroequilenin with sodium and amyl alcohol[3] was purified by leaching with cold ether, followed by crystallization from dilute acetone. It gave a product crystallizing in thick needles, m. p. 179°. It gave a large depression in melting point when mixed with the 17(α)-diol.

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[4] Remesov, *Rec. trav. chim.*, **56**, 1093 (1937).

[5] Windaus and Deppe, *Ber.*, **70**, 76 (1937).

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.3; H, 8.9. Found: C, 79.4; H, 8.9.

Summary

5,7,9 - Oestratrienediol - 3(α),17(α) and 5,7,9-oestratrienediol-3(α),17(β) were obtained in the non-phenolic fraction from the reduction of α- and β-dihydroequilenin with sodium in amyl alcohol.

STATE COLLEGE, PENNA. RECEIVED AUGUST 8, 1938

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. XLVI. The Steroid Content of Cows' Pregnancy Urine*

BY RUSSELL E. MARKER

Although numerous investigations of the steroid content of human and mare urines have been described,[1] relatively little work has been done with other urines. In order to supply this deficiency we have undertaken to investigate the steroids present in the urines of other *mammalia*. A preliminary study[2] has revealed the presence in stallions' urine of β-equistanol, an *allo*-triol, $C_{21}H_{36}O_3$, an *allo*-tetrol, $C_{21}H_{36}O_4$, and a uranetriol-3,11,20. A similar preliminary study of cows' pregnancy urine is presented in this paper.

The butanol extract of 200 gallons (760 liters) of cows' pregnancy urine was extracted with alkali to remove phenols, and then hydrolyzed by steam distillation in the presence of an excess of strong alkali. From a concentrated ethereal solution of the resulting non-volatile tar, a crude pregnanediol mixture was obtained. Fractional crystallization of the acetate mixture from this crude crop yielded the diacetate of pregnanediol-3(α),20(α), m. p. 179°, and from this the diol was obtained. The soluble acetate mother liquor after hydrolysis yielded *allo*-pregnanediol-3(α),20(α). The mother liquor from the crude pregnanediol mixture was freed of traces of ketones by the use of Girard's reagent, and treated with digitonin. The insoluble digitonide was decomposed, and after treatment with bromine this 3(β)-OH sterol mixture was again treated with digitonin. The insoluble digitonide gave, after decomposition, *allo*-pregnanediol-3(β),20(α), and the mother liquor from this digitonide gave cholesterol. The mother liquor from the original digitonin treatment yielded the soluble digitonide of β-equistanol, from which the latter was obtained on decomposition, and an ethereal solution free of 3(β)-OH sterols. After the latter was separated into hydroxylated and non-hydroxylated fractions by means of the acid succinates, the non-hydroxylated fraction was distilled in a high vacuum, and yielded a hydrocarbon, $C_{28}H_{58}$, m. p. 63°. The carbinol fraction was epimerized with sodium in boiling xylene, and then treated with digitonin. The insoluble digitonide yielded *allo*-pregnanediol-3(β),20(α), which had been formed from some *allo*-pregnanediol-3(α),20(α) not removed in the original separation of the crude pregnanediol mixture. The soluble digitonide yielded β-equistanol, which must have been produced by the epimerization of α-equistanol originally present. The mother liquor from the digitonides, containing no 3(β)-OH sterols, was distilled in a high vacuum, and sirupy fractions collected at 115–150° and 150–200°. Since these fractions could not be crystallized readily, they were oxidized with chromic acid. The higher boiling fraction gave no definite products, while the lower boiling fraction gave an aliphatic acid, $C_{18}H_{36}O_2$, m. p. 55°, suggesting the presence of an aliphatic primary alcohol in the original urine extract.

The isolation from cows' pregnancy urine of the three pregnanediols, in about half the amounts present in human pregnancy urine, lends further support to the theory of the interrelationships of the sex hormones advanced in a paper of this series.[1] The occurrence of both the β- and α-equistanols in cows' pregnancy as well as in stallions, urine[2] and in mares' pregnancy urine[3] but not in human pregnancy urine seems to indicate, as suggested earlier,[2] that their presence may be traced to the herbivorous diet of these animals. The hydrocarbon $C_{28}H_{58}$, m. p. 63°, has been found to occur in human pregnancy urine,[4] in stallions' urine,[4] and in mares' pregnancy urine[4] as well as

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(*) Paper XLV, THIS JOURNAL, **60**, 2440 (1938).

(1) These investigations are reviewed by Marker, THIS JOURNAL, **60**, 1725 (1938).

(2) Marker, Lawson, Rohrmann and Wittle, *ibid.*, **60**, 1555 (1938).

(3) Marker, Rohrmann and Wittle, *ibid.*, **60**, 1561 (1938).

(4) Unpublished results from this Laboratory.

in cows' pregnancy urine. Apparently other hydrocarbons are also present in some of these sources, for Hart and Northrup[5] found heptacosane, $C_{27}H_{56}$, m. p. 59°, and a hydrocarbon, $C_{25}H_{52}$, m. p. 52–54°, in large amounts in human pregnancy urine. Likewise, we find that the hydrocarbons in human and mares' pregnancy urine are rather complex mixtures. The acid, $C_{18}H_{36}O_2$, m. p. 55°, has been obtained by the oxidation of carbinol fractions from human[4] and mares' pregnancy urine[4] as well as from cows' urine. Besides the compounds discussed above, evidence has also been obtained for the presence in cows' pregnancy urine of polyhydroxysteroids, but in quantities too minute for investigation. A more exhaustive study on a much larger quantity of urine is in progress, and the results of this investigation will be reported later.

We wish to thank Dr. Oliver Kamm and Parke, Davis and Company for their generous support of this work.

Experimental Part

The butanol extract of 200 gallons (760 liters) of cows' pregnancy urine after removal of the phenolic fraction was hydrolyzed by steam distilling for three hours with an excess of aqueous 20% sodium hydroxide solution. The tarry product was filtered and washed with water. The residue was dissolved in a minimal amount of hot methanol and one liter of ether was added. The methanol was removed by several washings with water, and the ether was evaporated to 50 cc. The solution was cooled in ice–salt and the crystals collected and washed with a small amount of cold acetone. The resulting product, wt. 6.2 g., was treated in methanol with Norite and then crystallized from methanol and acetone to give a product melting unsharply at 215–228°.

Pregnanediol-3(α),20(α) and *allo*-Pregnanediol-3(α), 20(α).—The crystalline product above was refluxed for thirty minutes with 35 cc. of acetic anhydride. The solution was cooled to 0°, and filtered. The product thus obtained was crystallized from methanol and melted at 179°. A mixture with pregnanediol diacetate gave no depression in melting point. Upon hydrolysis with alcoholic potassium hydroxide it gave pregnanediol-3(α),20-(α), m. p. and mixed m. p. 242°.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.8; H, 11.3. Found: C, 78.8; H, 11.4.

The mother liquors from the crystallization of pregnanediol-3(α),20(α) diacetate were evaporated to dryness, and the residue hydrolyzed with alcoholic potassium hydroxide. The product was then crystallized from methanol, ethyl alcohol and acetone. It melted at 240° and gave no depression in melting point when mixed with *allo*-pregnanediol-3(α),20(α), but depressed the melting point of pregnanediol-3(α),20(α) to 215–220°.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.8; H, 11.3. Found: C, 78.6; H, 11.3.

The filtrate from the original pregnanediol(α),(α) mixture was treated in ethanol with Norite and filtered. The ketones were removed by the use of Girard's reagent. The non-ketonic fraction in alcohol was mixed with a solution of 20 g. of digitonin in 500 cc. of 95% alcohol, and the solution diluted to one liter. After standing overnight, the digitonide was filtered. When dry, it weighed 10 g. This digitonide was dissolved in 75 cc. of pyridine by heating on a steam-bath for fifteen minutes, and the solution poured into 500 cc. of ether and filtered. The pyridine was removed from the filtrate by shaking with dilute hydrochloric acid, the ether evaporated, and the residue, 2.2 g., sublimed in a high vacuum, taking the fraction distilling at 110–200°. This sublimate was dissolved in ethanol and enough bromine added at 0° to give a faint yellow color. Then an excess of 1% digitonin solution was added. The solution was filtered the next day. From the filtrate was obtained, after debromination in the usual manner, 320 mg. of cholesterol, m. p. 146°, which gave no depression in melting point when mixed with an authentic sample.

The digitonide was dried and then decomposed by heating for thirty minutes on a steam-bath with 30 cc. of dry pyridine. Ether was added and the digitonin filtered. The pyridine was removed from the ether solution, and the solvent was evaporated. The residue, after crystallization from dilute acetone, melted at 215°. Mixed with pregnanediol-3(α),20(α) and *allo*-pregnanediol-3(α),20(α) it gave a depression in melting point. When mixed with *allo*-pregnanediol-3(β),20(α) it gave no depression in melting point.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.8; H, 11.3. Found: C, 78.7; H, 11.3.

β-Equistanol.—The mother liquor from the original digitonin precipitation of the β-sterols was concentrated to 50 cc. and one liter of ether added. The digitonin–digitonide mixture was filtered and the dried product treated in the usual way with pyridine. The product thus obtained was sublimed in a high vacuum at 120–150°. After crystallization from a mixture of acetone and methanol, the sublimate gave a product melting at 132–134°. When mixed with equistanol obtained from mares' pregnancy urine or from stallions' urine it gave no depression in melting point; yield 1.2 g. of crude product.

The α-Sterol Fraction.—The filtrate from the digitonide from which the equistanol was obtained was evaporated to dryness and then dried by distilling benzene from it. The residual sirup was heated for thirty minutes with 10 g. of succinic anhydride and 15 cc. of pyridine. Ether was added and the pyridine was removed by shaking with hydrochloric acid. The acid-succinates were removed by shaking with sodium carbonate solution. The ether layer was reserved for investigation of the non-hydroxylated material. The alkaline solution was acidified and the succinate then hydrolyzed with alcoholic potassium hydroxide. The carbinol mixture was extracted with ether and the ether removed to give sirupy carbinols. Five and three-tenths grams of this sirup was refluxed with 10 g. of sodium and 150 cc. of xylene for eight hours, the excess product extracted with ether and washed well with water. The solvent was removed and the residue dissolved in 95%

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[5] Hart and Northrup, THIS JOURNAL, **57**, 2726 (1935).

alcohol and 5 g. of digitonin dissolved in 200 cc. of hot ethanol was added. After standing overnight, the digitonide was filtered, dried, and decomposed by warming with pyridine in the usual manner. The product thus obtained was distilled in a high vacuum, collecting the portion distilling below 200°. This fraction was crystallized from methanol to give *allo*-pregnanediol-3(β),20(α); m. p. and mixed m. p., 214°.

The digitonin mother liquors were evaporated to about 30 cc. and 500 cc. of ether added. The digitonide was filtered, dried and then decomposed with pyridine. The crude product was distilled and crystallized from methanol. It proved to be β-equistanol, m. p. 133°. This was formed by the epimerization of α-equistanol, as the β-form had been removed previously.

The filtrate from the equistanol digitonide was evaporated to dryness and sublimed *in vacuo*. Two fractions were taken, one at 115–150° and the other at 150–200°. The lower boiling fraction after separation of some crystalline pregnanediol-3(α),20(α) was oxidized in acetic acid with an equal weight of chromic acid for thirty minutes. The oxidation mixture yielded mostly acidic material, and only a very small neutral fraction. The acidic fraction was extracted with ether and removed from the ethereal solution with sodium carbonate solution. Acidification of the alkaline solution yielded a crystalline acid which was recrystallized from ethanol to a constant m. p., 55°. Calcd. for $C_{18}H_{36}O_2$: neut. equiv., 284; found, 277.

Anal. Calcd. for $C_{18}H_{36}O_2$: C, 75.9; H, 12.7. Found: C, 76.2; H, 12.9.

Although polyhydroxy sterols probably belonging to the cortical series were present, the quantities were too minute for separation from the small amount of urine processed.

Hydrocarbon Fraction.—The ether soluble material from the preparation of the succinates of the sterols was distilled *in vacuo*. The portion distilling at 80–110° was dissolved in acetone and methanol was added. It was allowed to stand for two days at room temperature in an unstoppered flask. The crystalline material was recrystallized from acetone to give a product of m. p. 63°. Molecular weight calcd. for $C_{28}H_{58}$, 394; found (Rast), 393. It gave no depression in melting point with a hydrocarbon isolated from human pregnancy urine.

Anal. Calcd. for $C_{28}H_{58}$: C, 85.3; H, 14.8. Found: C, 85.2; H, 14.6.

Summary

An investigation of the sterols present in cows' pregnancy urine gave pregnanediol-3(α),20(α), *allo*-pregnanediol-3(α),20(α), and *allo*-pregnanediol-3(β),20(α), in approximately one-half the quantities present in human pregnancy urine. β-Equistanol was also isolated, and the presence of α-equistanol was demonstrated. The carbinol fraction upon oxidation gave an acid of the aliphatic series with a molecular formula of $C_{18}H_{36}O_2$. There was also isolated a hydrocarbon of the aliphatic series melting at 63° and having the molecular formula $C_{28}H_{58}$.

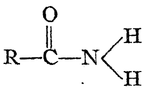
STATE COLLEGE, PENNA. RECEIVED AUGUST 8, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

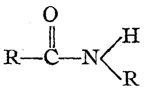
Infrared Absorption Studies. VI. Association in the Acid Amides and Oximes[1]

BY A. M. BUSWELL, W. H. RODEBUSH AND M. F. ROY

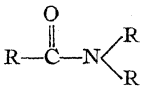
Structure of Acid Amides.—The classical structures assigned to amides and N-substituted amides are



$R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}N\begin{smallmatrix}H\\H\end{smallmatrix}$

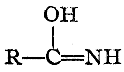


$R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}N\begin{smallmatrix}H\\R\end{smallmatrix}$



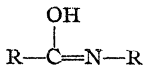
$R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}N\begin{smallmatrix}R\\R\end{smallmatrix}$

However, certain reactions of the amides, *e. g.*, alkylation, indicate that compounds of the first two types above may have the alternative tautomeric structures



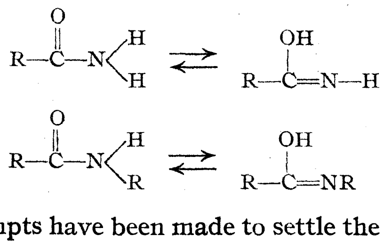
$R{-}\overset{\overset{\displaystyle OH}{|}}{C}{=}NH$

and



$R{-}\overset{\overset{\displaystyle OH}{|}}{C}{=}N{-}R$

in that two isomeric reaction products are obtained in each case. Reactions of this type led to the belief that the amides probably existed in tautomeric equilibria of the two forms.



$R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}N\begin{smallmatrix}H\\H\end{smallmatrix} \rightleftarrows R{-}\overset{\overset{\displaystyle OH}{|}}{C}{=}N{-}H$

$R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}N\begin{smallmatrix}H\\R\end{smallmatrix} \rightleftarrows R{-}\overset{\overset{\displaystyle OH}{|}}{C}{=}NR$

Attempts have been made to settle the question as to which of the two forms prevails by a study of the physical properties. Various authors[2] have found that the ultraviolet absorption spectrum indicates either tautomerism or the enolic form. Most of this work was in alcoholic solution but

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[1] These studies are carried out with the aid of a grant from the Rockefeller Foundation. The main problem is the mechanism of hydration of biological substances ("bound water"). The present paper (VI) presents data on the absorption spectra of relatively simple organic nitrogen compounds whose functional groups resemble those found in proteins. Previous publications from this Laboratory dealing with association are II, *J. Chem. Phys.*, **5**, 501 (1937), and V, THIS JOURNAL, **60**, 2239 (1938).

[2] Ramart-Lucas and Gaunfeld, *Bull. soc. chim.*, [5] **4**, 478 (1937).

TABLE I

ACID AMIDES

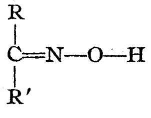
Amide	Molal concn.[a]	Cell length, cm.	Absorption maxima[b] CH μ	CH K	μ	K	NH μ	NH K	μ	K	Others μ	Others K	μ	K
Acetamide	0.001	10.18	3.30	7.5			2.925	27	2.83	27	3.145	10		
CH_3CONH_2	.002 (s)	5.07	3.30	7.5			2.925	27	2.83	29	3.145	17		
n-Valeramide	.002	10.18	3.45	41	3.37	68	2.92	23	2.83	26	3.14	19		
$C_4H_9CONH_2$	.004	5.07	3.45	41	3.37	70	2.92	23	2.83	24	3.14	27		
	.008 (s)	2.53	3.45	43	3.37	67	2.92	22	2.83	25	3.14	40		
	.002	10.18	3.47	46	3.40	73	2.90	19			2.97	7		
n-Cyclohexylacetamide	.008	5.07	3.47	46	3.40	73	2.90	17			2.98	8		
$CH_3CONHC_6H_{11}$	.032	0.640	3.47	46	3.40	73	2.90	16			2.99	23		
	.128	.1582	3.47	47	3.40	72	2.90	13			3.02	64	3.23	18
	.512	.0374	3.47	47	3.40	76	2.90	5			3.04	79	3.23	34
Acetanilide	.001	10.18	3.38	8	3.26	24	2.90	24						
$CH_3CONHC_6H_5$	.008 (s)	1.262	3.38	10	3.26	29	2.90	26			2.97	15		
Benzanilide	.0035 (s)	2.53	3.25	31			2.86	26						
$C_6H_5CONHC_6H_5$														
N,N-Diphenylacetamide	.008	1.262	3.38	4	3.25	29								
$CH_3CON(C_6H_5)_2$														
N,N-Diphenylbenzamide	.008	1.262	3.25	40										
$C_6H_5CON(C_6H_5)_2$														
N,N-Dimethylacetamide	.008	2.53	3.39	52										
$CH_3CON(CH_3)_2$														

[a] (s) indicates a nearly saturated solution.

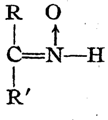
[b] μ is the wave length of the absorption. K is the molal absorption coefficient.

Herzberg and Kölsch[3] have reported that the vapor of formamide shows no absorption characteristic of N—H or C═O. Data upon dipole moments and the Raman spectrum do not appear to offer any conclusive evidence upon this point. It is always possible, of course, to account for the reaction products assuming either formula to be correct. The only chance for a final decision upon the question would appear to be the determination of the characteristic infrared absorption due to hydrogen in the region from 2.6 to 3.6 μ. No report of any work in this region has appeared in the literature. Some results have been obtained in the region of the first overtone, which are however necessarily difficult to interpret.

The situation in regard to the oximes is somewhat similar to that of the amides. There are two structures which are compatible with the chemical evidence.



$$RR'C{=}N{-}O{-}H$$



$$RR'C{=}N(\rightarrow O){-}H$$

There is of course a possibility of tautomerism and the final decision as to structure must be made from a study of physical properties. Here again Freymann and Freymann[4] have studied the infrared absorption in the region of the harmonics with results which indicated the presence of the hydroxyl group.

Experimental

The infrared spectrograph used for this work has been described in previous publications in this series. The compounds used in this work were prepared and carefully purified in this Laboratory by Mr. J. R. Downing. The data in every case represent the ratio of the absorption of a solution in carbon tetrachloride to the absorption of the pure solvent. The molal absorption is calculated as given by the formula

$$\frac{1}{cd}\log\frac{I_0}{I}$$

and the product $c \times d$ is maintained constant for each compound in order to avoid deviations from Lambert's law. The chief difficulty was the low solubility of amides and oximes in carbon tetrachloride. The higher homologs were found to be somewhat more soluble. For those amides for which no curve is shown the data for the principal absorption peaks are included in a table. Curves are given for all of the oximes which were studied.

The Amides.—The high melting and boiling points of the amides have long been recognized as evidence for a high degree of association. Kumler[5] has pointed out that this evidence as well as that of cryoscopic data point to a marked differ-

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[3] G. Herzberg and R. Kölsch, *Z. Elecktrochem.*, **39**, 672 (1933).

[4] M. and R. Freymann, *Bull. soc. chim.*, [5] **4**, 944 (1937).

[5] W. D. Kumler, THIS JOURNAL, **57**, 600 (1935).

ence in the behavior of the amides when the hydrogens attached to the nitrogen are replaced by alkyl groups. This evidence points to hydrogen bonding as the mechanism by which association takes place. Recently Zellhoefer, Copley and Marvel[6] have found that the solubility of chloroform varies in the different amides in such a way as to agree closely with the degree of association to be expected.

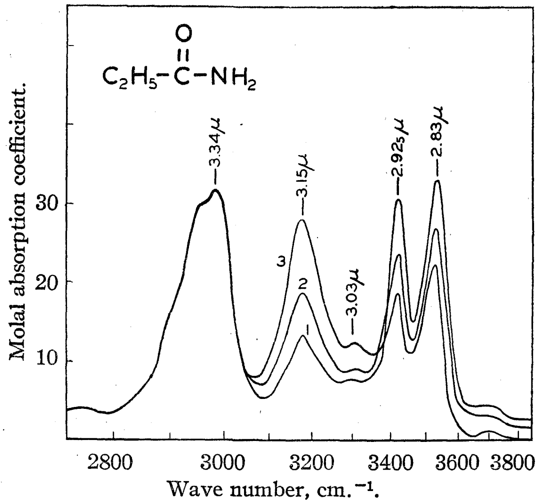
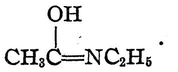


Fig. 1.—Propionamide: (1) 0.002 *M* in 10.18-cm. cell. (2) 0.004 *M* in 5.07-cm. cell. (3) 0.008 *M* in 2.53-cm. cell.

The first curve shown, Fig. 1, is that for propionamide which because of somewhat greater solubility permits a greater range of concentration than acetamide. The C–H absorption at 3.34 μ remains constant over the concentration range while a marked variation with concentration is shown in the region of N–H absorption and there is no indication of any O–H absorption. One may say, therefore, that in the ordinary amides in carbon tetrachloride solution there is no tendency toward enolization. The NH_2 group may be expected to show modes of vibration similar to that of the water molecule.[7] There are two modes involving the stretching of the N–H bonds which are infrared active. One of these is symmetric with respect to the hydrogens and one anti-symmetric. In water these frequencies are at 2.67 and 2.76 μ, respectively. Here we find the N–H frequencies at 2.83 and 2.92 μ. As the concentration is increased the association through hydrogen bonding increases and the absorption at 3.15 μ characteristic of hydrogen bonded N–H increases. The unbonded N–H peaks are reduced in intensity but otherwise unmodified. The solubility is limited so that the association is not complete at the highest concentration obtainable but one cannot doubt that at higher concentrations in another solvent for example, the absorption characteristic of the unbonded N–H would disappear completely.

This behavior is perhaps best accounted for by assuming that when the molecule enters a polymer both hydrogens are involved in the bond formation. Benzamide does not show any particular difference except that the relative intensity of the two peaks in the N–H absorption is altered. The intensities depend indirectly upon the dipole moments associated with the N–H bonds and also the angle between them, and these are evidently slightly altered by the introduction of the phenyl group. The C–H absorption at 3.25 μ which is characteristic of aromatic molecules appears to vary somewhat, but this may be due to the overlapping N–H bond peak. The absorption curves for N-ethyl acetamide in Fig. 3 show interesting variations from those for the unsubstituted amides. The C–H peak is the same as before and only a single peak is to be expected for the N–H absorption and this appears as might be expected intermediate in position between the two peaks of Fig. 1. The peak at 3.22 μ may be assumed to correspond to the peaks at 3.15 μ in the other cases and hence to represent the hydrogen bonded N–H but the peak at 3.03 μ corresponds exactly to that of a hydrogen bonded hydroxyl. Furthermore, the great increase in intensity is strongly suggestive of a hydroxyl which absorbs more strongly than does an N–H group. We believe therefore that this absorption indicates the presence of the enolic form  $\overset{\text{OH}}{\overset{|}{\text{CH}_3\text{C}}}{=}\text{NC}_2\text{H}_5$. This form only exists in the polymer at higher concentrations since there is no absorption in the region 2.8 μ which would be characteristic of unbonded hydroxyl. It may be said therefore that at higher concentrations N-ethylacetamide is largely associated and that a considerable fraction (one-half or more) of the molecules so associated exist in the enolic form. It should be noted of course that N,N-dimethylacetamide shows no absorption except that due to C–H and no physical behavior indicating association.

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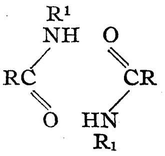
[6] G. F. Zellhoefer, M. J. Copley and C. S. Marvel, This Journal, **60**, 1337 (1938); also an article to appear soon.

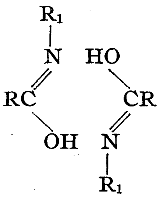
[7] E. F. Barker and W. W. Sleator, *J. Chem. Phys.*, **3**, 660 (1935).

To summarize we may say that while the ordinary amides show a strong tendency toward association (much greater than the alcohols at low concentration) the monosubstituted amides show a smaller tendency, and the disubstituted amides do not associate at all. This conclusion is confirmed by the various physical properties, cryoscopic behavior, behavior as a solvent, etc. In the case of the unsubstituted amides the dielectric constant and other properties suggest the formation of polymers of indefinite molecular weight, similar to those which occur in the alcohols. In the monosubstituted amides the tendency toward association is less strong and one may assume that a considerable fraction of the molecules are associated to form dimers. Dr. M. J. Copley of this Laboratory informs us that the solubility of chloroform in N-ethylacetamide could be accounted for by assuming the pure liquid to consist largely of dimers.

While there are certain well-recognized conditions necessary for enolization to take place in a molecule, we believe that one which has not been sufficiently emphasized is that *the shift of the mobile hydrogen usually involves the formation of a hydrogen bond.* An isolated amide molecule in carbon tetrachloride has no opportunity for forming a hydrogen bond. (The case would of course be different if the solvent were alcohol.) Dr. M. J. Copley has suggested to us that if a dimer is formed with bonds N–H–O similar to the carboxylic acids



then by a shift of hydrogens the structure



is easily obtained and the second structure may easily be the more stable. It must be remembered that our evidence shows that enolization takes place only in the associated molecules and it is only in the dimers with N–H → O bonds that a simple mechanism has been suggested. In a chain polymer, for example, enolization would involve a molecular rearrangement equivalent to ionization of the hydrogen, which is hardly to be expected to take place in a carbon tetrachloride solution. In the absence of other suggestions as to the mechanism of enolization one is forced to assume the existence of dimers in the monosubstituted amides and, as has been said above, this assumption is favored by the other known properties of these substances in the liquid state. Any attempt to explain why the unsubstituted amides do not form dimers or if they do form these, why these dimers do not enolize, would of course be highly speculative. One of course may reason by analogy with formic acid where in the pure liquid the dimers give way to polymers, presumably because of the bonding action of the hydrogen attached to carbon. In an unsubstituted amide the R_1 groups shown above would be replaced by hydrogens and it is easy to suggest ways in which these additional hydrogens might interfere with the formation of stable dimers. It should be noted of course that there is a slight absorption at 3.03 μ in Figs. 1 and 2 suggestive of a slight tendency toward enolization. One may predict that the reactions of the acid amides will under comparable conditions confirm the hypothesis of enolization that has been proposed above.

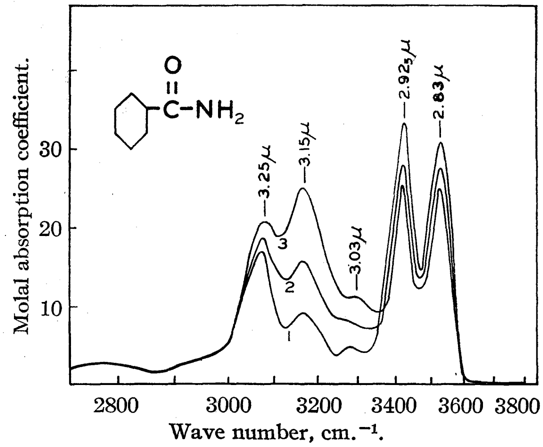
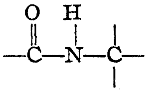


Fig. 2.—Benzamide: (1) 0.0005 *M* in 10.18-cm. cell. (2) 0.001 *M* in 10.18-cm. cell. (3) 0.002 *M* in 5.07-cm. cell.

It should be noted that the essential group in the N-substituted amides is the same as that of the peptide linkage in the proteins, *viz.*



$$\begin{array}{ccccc} & \mathrm{O} & & \mathrm{H} & \\ & \| & & | & | \\ — & \mathrm{C} & — & \mathrm{N} & —\mathrm{C}— \\ & & & & | \end{array}$$

The absorption curve of gelatin[8] shows such

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(8) A. M. Buswell, Karl Krebs and W. H. Rodebush, THIS

striking similarities that one can scarcely doubt that precisely the same type of hydrogen bonding is present in both cases. One would assume, of course, that the hydrogen bonding occurs as a cross linkage between two polymeric chains or perhaps between parts of the same chain.

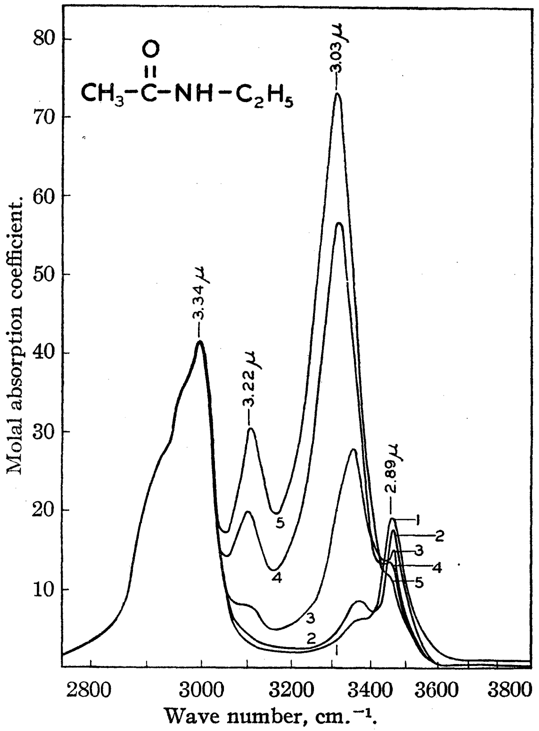
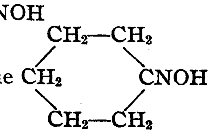


Fig. 3.—N-Ethylacetamide: (1) 0.002 *M* in 10.18-cm. cell. (2) 0.008 *M* in 5.07-cm. cell. (3) 0.032 *M* in 0.640-cm. cell. (4) 0.128 *M* in 0.1582-cm. cell. (5) 0.512 *M* in 0.0374-cm. cell.

The Oximes.—In order to avoid complications which might arise from possible geometrical isomerism, only symmetrical ketoximes were studied. In Figs. 4, 5, 6 and 7 the absorption curves are given at various concentrations for the following compounds.

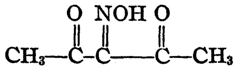
Acetoxime $(CH_3)_2CNOH$

Cyclohexanone oxime



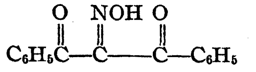
Benzophenone oxime $(C_6H_5)_2CNOH$

The oxime of dimethyl triketone



$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-\overset{\overset{\displaystyle NOH}{\|}}{C}-\overset{\overset{\displaystyle O}{\|}}{C}-CH_3$$

The oxime of diphenyl triketone



$$C_6H_5\overset{\overset{\displaystyle O}{\|}}{C}-\overset{\overset{\displaystyle NOH}{\|}}{C}-\overset{\overset{\displaystyle O}{\|}}{C}-C_6H_5$$

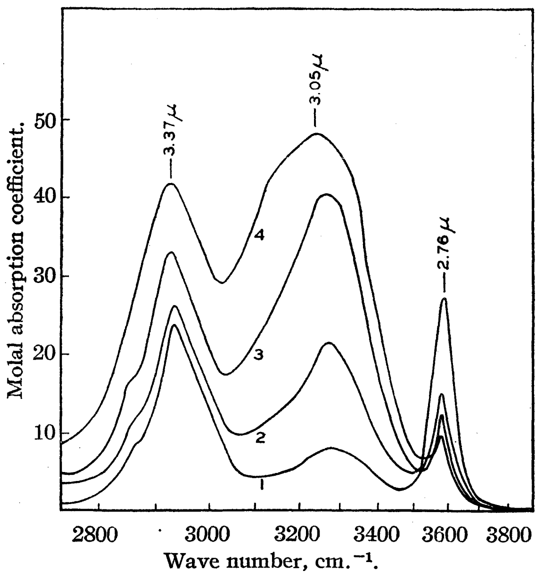


Fig. 4.—Acetoxime: (1) 0.001 *M* in 10.18-cm. cell. (2) 0.004 *M* in 10.18-cm. cell. (3) 0.016 *M* in 2.53-cm. cell. (4) 0.064 *M* in 0.640-cm. cell.

The absorption peak at 2.76 μ in Figs. 4, 5 and 6 is clearly indicative of the hydroxyl group which is to be expected in the usually accepted formula for oximes. There is no indication whatever of an N–H absorption. As the concentration is in-

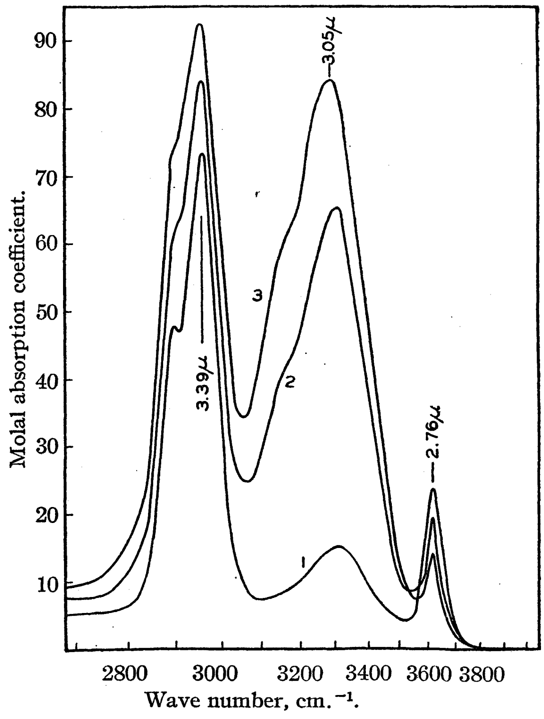


Fig. 5.—Cyclohexanone oxime: (1) 0.0178 *M* in 10.18-cm. cell. (2) 0.0285 *M* in 0.640-cm. cell. (3) 0.1139 *M* in 0.1582-cm. cell.

JOURNAL, **59**, 2603 (1937). One of us (M. F. R.) has called attention to the fact that the enolized dimer should dissociate into enolized monomers. This does not happen and the hypothesis of enolization cannot be considered as fully substantiated until the absence of the enolic form in the monomers is accounted for.

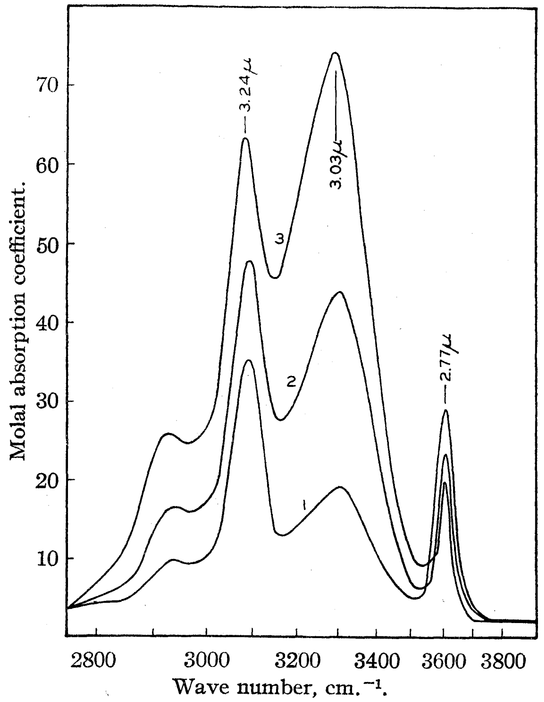


Fig. 6.—Benzophenone oxime: (1) 0.002 *M* in 10.18-cm. cell. (2) 0.008 *M* in 2.53-cm. cell. (3) 0.032 *M* in 0.640-cm. cell.

creased the "association peak" characteristic of hydrogen bonding appears at about 3.0 just as in the alcohols.[9] All this is quite to be expected. The startling thing about these curves is that the molal absorption due to C–H increases with increasing concentration in spite of the fact that the product of concentration times cell length was maintained constant. This behavior has been noted already in the case of benzamide which shows C–H absorption and we are by no means certain how to account for it. There is of course the possibility that the oximes form unsymmetrical dimers so that all C–H vibrations remain active. (In a symmetrical dimer as acetic acid only the anti-symmetric C–H vibrations are active.) Under these conditions because of the augmented dipole moment, the change in moment associated with transition might be increased sufficiently to account for the increased absorption. A simpler explanation of course of the increasing C–H absorption is that the absorption due to the hydrogen bonding overlaps the C–H region. In view of the acidic character of the oximes, this is a reasonable assumption. In the carboxylic acids the absorption extends over a very broad interval. The unbonded hydroxyl frequency of the oximes is at 2.77 μ which is very near the unbonded hydroxyl wave length of acetic acid.

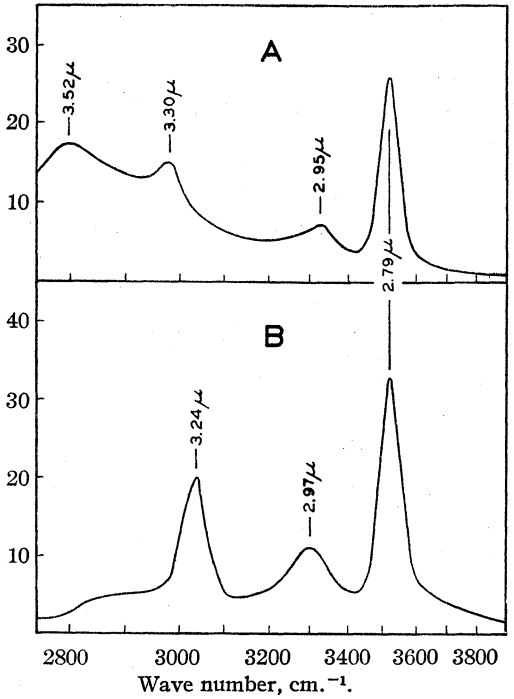


Fig. 7.—A. Oxime of dimethyl triketone: 0.002 *M* in 10.18-cm. cell. B. Oxime of diphenyl triketone: 0.002 *M* in 10.18-cm. cell.

In all of the results so far we have no direct evidence as to whether the bonding is to oxygen or nitrogen (N–H → O or N–H → N) since either is generally possible. In an attempt to distinguish between these possibilities the absorption for the two triketone oximes was measured, Fig. 7. Here while the solubility is too low to permit of much association, there is reason to believe that the absorption at 2.95–2.97 μ is indicative of intermolecular hydrogen bonding which is presumably OH → O. The absorption at 2.79 is of course the unbonded hydroxyl and there is no evidence of chelation.

Summary

Infrared absorption has been studied for a number of acid amides and oximes. Association due to hydrogen bonding is observed and in the case of monosubstituted amides association is accompanied by a considerable amount of enolization. Attention is called to the striking similarity of the absorption due to association in the substituted amides and that due to the peptide group in gelatin.

URBANA, ILLINOIS RECEIVED JULY 11, 1938

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[9] A. M. Buswell, V. Deitz and W. H. Rodebush, *J. Chem. Phys.*, **5**, 501 (1937).

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY, UNIVERSITY OF MISSOURI]

Photo-voltaic Effects in Grignard Solutions

BY ANNA JANE HARRISON,[1] DOROTHY NIGHTINGALE AND R. T. DUFFORD

It has previously been reported that metallic electrodes in ether solutions of Grignard compounds form a voltaic cell and that the potential difference between the electrodes changes when one or both electrodes are illuminated.[2] Both electrodes may be made from the same metal or from different metals. An extensive list of metals and a number of both aliphatic and aromatic Grignard compounds have been investigated.[3] In all cases both the dark voltage and the photovoltaic response were only roughly reproducible or completely non-reproducible. Several cases, however, indicated that the magnitude and direction of the response might be dependent upon the Grignard compound.

This investigation was undertaken in an attempt to obtain reproducible results so that this effect might be used in the study of homologous series of organic groups. Magnesium amalgam electrodes were studied first since these would have a liquid surface which could be changed by shaking and since magnesium would be present to establish equilibrium with the ions of the Grignard compound.

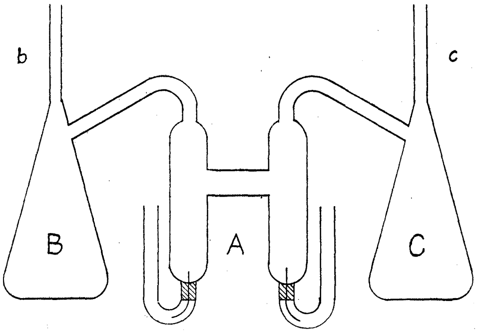

Fig. 1.

Experimental.—Each cell was kept in a separate compartment of a black light-proof box and was illuminated through a small window by a thousand-watt lamp. The temperature was controlled by a water-bath and the voltage was measured by a potentiometer which was sensitive to a few tenths of a millivolt. Ordinary laboratory reagents were used. All organic compounds were dried over calcium chloride and all liquids were distilled. The ether was dried over and distilled from sodium. Freshly sanded magnesium ribbon was used both in the reactions and as electrodes.

The apparatus shown in Fig. 1 was filled with nitrogen and kept closed as much as possible while 15 mg. of fluorenone, 25 cc. of ether and 5 cc. of saturated sodium amalgam were placed in B and 5 cc. of 1% magnesium amalgam and 25 cc. of the Grignard solution in C. The Grignard compound had been synthesized previously in a nitrogen atmosphere. Concentrations ranged from one-half to two molar. The magnesium amalgam had been made in a partial vacuum and the sodium amalgam under dry kerosene. The cell was again filled with nitrogen, evacuated, and openings b and c sealed. After shaking for several hours, the sodium fluorenone produced in B was decanted into the cell, A, and after standing for at least two hours to allow complete drying,[4] was returned to B. After rinsing A several times with ether distilled from B, this side bulb was sealed off. The Grignard solution and the electrode material were transferred to the cell and C sealed off. Electrical connections were made to the magnesium amalgam through very fine platinum ribbon which had been worked into a section of glass tubing at the bottom of each arm of the cell. Mercury contacts were made on the outside. With the exception of the lower part of one arm, the cell was well covered with black friction tape so that only one electrode could be exposed to light.

Similar cells were constructed with metallic magnesium electrodes. These electrodes were suspended by a platinum wire from the platinum connection through the glass at the top of the cell. The platinum–magnesium connection was high enough to be above the solution in the cell. In these cells, the Grignard compound was synthesized in the side bulb after the apparatus had been sealed. In order to avoid any possible reaction between the sodium fluorenone and the magnesium electrodes, the cell was dried with ether distilled from the sodium fluorenone solution rather than by transferring sodium fluorenone into the cell. After the sodium fluorenone side bulb, B, had been removed, a mixture of the Grignard reagent and excess alkyl halide was transferred into the cell to allow the alkyl halide to react with the magnesium electrodes for a short time to ensure a clean electrode surface. The Grignard solution was then returned to its side bulb and ether distilled into the cell to rinse it. The cell was filled with Grignard reagent and the reaction bulb removed. Both types of cells were prepared with phenylmagnesium bromide and with ethylmagnesium bromide.

Results.—Typical results obtained are given in Fig. 2. In this the potential difference in millivolts is plotted against the time in minutes. The sign is that of the electrode in the untaped arm

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(1) Abstract of a dissertation presented by Anna Jane Harrison in partial fulfilment of the requirements for the degree of Master of Arts at the University of Missouri.

(2) Dufford, Nightingale and Gaddum, THIS JOURNAL, **49**, 1858 (1927).

(3) Dufford, *J. Phys. Chem.*, **34**, 1544 (1930); **35**, 988 (1931); **37**, 709 (1933).

(4) Bent and Irwin, THIS JOURNAL, **58**, 2072 (1936).

with respect to the electrode in the taped arm. An arrow pointed upward indicates the beginning and an arrow pointed downward the end of the exposure to light. All cells containing the magnesium amalgam electrodes gave a zero dark voltage with the exception of occasional temporary variations of the order of a millivolt Curve A shows the effect of light on the untaped arm. The illuminated electrode became positive with respect to the dark electrode to the extent of almost 2 mv. and then decreased slightly. Curve B shows the effect produced in the same cell by focusing the light on the taped arm instead of the untaped arm. The latter was unprotected from the large amount of diffused light. The response was in the opposite direction and somewhat larger. These responses must, therefore, be due to heating effects rather than any direct effect of the light. Similar curves of greater magnitude (12 to 20 mv.) were obtained when no water-bath was used. The curves were reproducible and after illumination ceased the voltage became smaller until zero was reached. Similar responses were obtained by placing the two arms of the cell in two water-baths which were not at the same temperature. Cells containing metallic magnesium electrodes gave the same type of results as is shown by curves C and D. In these the heating effect was slightly greater in the untaped arm than in the taped arm. This might be expected, however, since absorption was taking place on the electrode surface in one case and on the cell wall in the other case. Responses of this type will be referred to as no photo-voltaic effect.

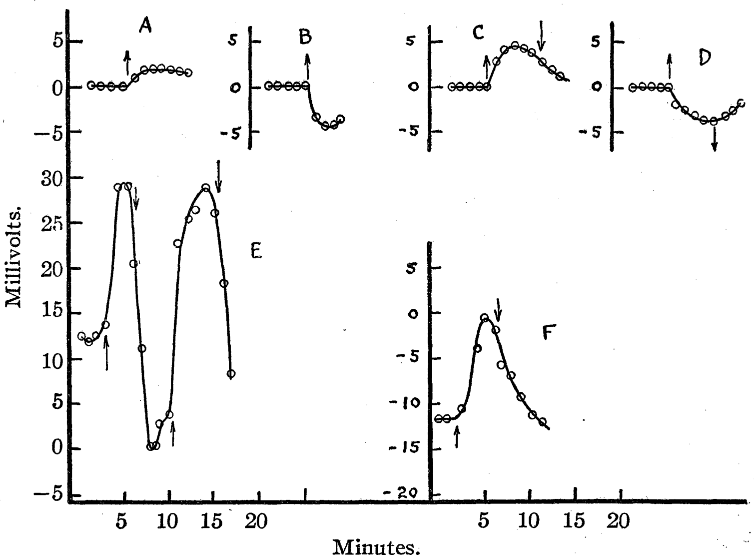

Fig. 2.—Curves A and B show the response of magnesium amalgam electrodes with the light focused on the untaped electrode (A) and on the taped electrode (B). Curves C and D are the same for magnesium electrodes which have been cleaned by the reaction with the organic halide. Curve E shows the response to light obtained with magnesium electrodes which had not been "cleaned." Curve F gives the response to light of cleaned magnesium electrodes which had been exposed to oxygen. An arrow pointed upward indicates the beginning and an arrow pointed downward the end of the exposure to light. In all cells one electrode was protected from light by tape. The sign of the voltage is that of the electrode in the untaped arm with respect to the electrode in the taped arm.

Cells containing magnesium electrodes, which had not been cleaned with the reaction mixture but had been dried with ether distilled from the sodium fluorenone, showed variable dark voltages and variable photo-voltaic responses. For the most part these responses to light were rather large as is shown by curve E. The illuminated electrode always became positive with respect to the dark electrode. Responses of this magnitude could not be produced by temperature changes. Both the dark voltage and the light sensitivity could be destroyed by opening the cell and adding a few drops of the corresponding organic halide or by simply allowing the cell to stand for several days. The phenylmagnesium bromide solutions in two of these cells in which the photo-voltaic sensitivity had been destroyed by adding phenyl bromide were returned to the reaction bulbs. The Grignard solutions were kept cold with dry ice and ether while the cells were filled with oxygen, which had not been dried. After fifteen minutes the apparatus was evacuated and closed. After rinsing with ether distilled from the reaction flasks, the cells were filled. Both cells showed variable dark voltages and photo-voltaic responses. One such response is shown by Curve F. The Grignard solutions were clear and gave no evidence of having been oxidized. The dark voltage and the light sensitivity were destroyed in one cell by the addition of phenyl bromide and in the other by allowing it to stand.

Discussion.—A surface film appears to be necessary for light sensitivity in the case of magnesium electrodes. Presumably, this film is removed by the reaction of the organic halide with the adjacent atoms of magnesium. If the film is magnesium hydroxide its disappearance on standing might be explained by the reaction with the magnesium bromide from the Grignard equilibrium to produce basic magnesium bromide which is soluble in ether.

Summary

(1) Magnesium amalgam electrodes gave zero dark voltage and no light sensitivity with ether solutions of either phenylmagnesium bromide or ethylmagnesium bromide. (2) Magnesium electrodes which had been cleaned by reacting with the organic halide gave the same results. (3) Magnesium electrodes which had not been cleaned in this manner showed variable dark voltages and variable photo-voltaic responses. Both of these could be destroyed by adding the organic halide or by allowing the cell to stand for several days. (4) "Cleaned" magnesium electrodes were made sensitive to light by exposure to oxygen.

COLUMBIA, MO. RECEIVED JUNE 23, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

The Addition of Sulfur, Hydrogen Sulfide and Mercaptans to Unsaturated Hydrocarbons

BY S. O. JONES[1] AND E. EMMET REID

There have been many investigations of the action of sulfur and hydrogen sulfide on unsaturated hydrocarbons[2] and a few on the addition of mercaptans[3] but so many points have not been cleared up that further study seemed desirable.

Curiously enough the end-products are much the same whether an unsaturated hydrocarbon is treated with sulfur, hydrogen sulfide or a mercaptan. Thus with ethylene, sulfur gives hydrogen sulfide which reacts with more ethylene to form ethyl mercaptan which then adds to more ethylene to form ethyl sulfide.

Our results help to explain the presence of ethyl, *i*-propyl and other mercaptans and the corresponding sulfides in petroleum distillates but do not account for the presence of methyl mercaptan and methyl sulfide.

The Action of Sulfur.—Quite different results are obtained from the reaction with sulfur according to the conditions and whether free sulfur or a compound which readily liberates sulfur is used. When ethylene was passed over pyrites at 350° about 1% of thiophene was isolated along with hydrogen sulfide and ethyl mercaptan, while when it was bubbled through sulfur at 325° much hydrogen sulfide was formed along with 3% of ethyl mercaptan and small amounts of carbon disulfide and ethyl sulfide. We found it advantageous to use ethyl tetrasulfide as a sulfur donor. This is a liquid which mixes well with organic compounds and decomposes on heating, giving off what may be assumed to be atomic sulfur. The proportions were calculated on the basis of the tetrasulfide going down to the disulfide. A noteworthy difference is that with it, appreciable yields of the cyclic sulfides were obtained.

When ethylene was bubbled slowly through ethyl tetrasulfide kept at about 150°, the main product isolated was ethyl mercaptan with some ethyl sulfide and in addition some ethylene sulfide. The results of heating several hydrocarbons in a bomb with ethyl tetrasulfide are given in Table I.

TABLE I

Hydrocarbons with Et_2S_4, 10 hrs. at 180°

Hydrocarbon	Yields of products, % Mercaptan	Sulfide	Cyclic sulfide
Ethylene	5	18	1
Propylene	6	20	15
Heptene-1	20	..	..
Octene-1	19	..	..
Cyclohexene	8	..	8

The mercaptans, except from ethylene, and sulfides were all secondary.

The Addition of Hydrogen Sulfide.—The addition of hydrogen sulfide was effected by heating in the bomb for ten hours at 180°. Sulfur was added as a catalyst for without it there was little if any addition. The results are given in Table II. The sulfur is found on the secondary or tertiary carbon atom in accordance with Markownikow's rule.

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[1] Taken from the Ph. D. dissertation of S. O. Jones, R. J. Reynolds Tobacco Co. Fellow, The Johns Hopkins University, June, 1936.

[2] Mailhe and Renaudie, *Compt. rend.*, **195**, 391 (1932); Duffey, Snow and Keyes, *Ind. Eng. Chem.*, **26**, 91 (1934).

[3] Posner, *Ber.*, **38**, 646 (1905); Nicolet, THIS JOURNAL, **57**, 1098 (1935).

TABLE II

Addition of hydrogen sulfide, 10 hrs. at 180°

Hydrocarbon	Yields of products, %	
	Mercaptan	Sulfide
Ethylene	11	80
Propylene	7	90
i-Butylene	23	6
Octene-1	9	35
Cyclohexene	7	5

The addition takes place according to Markownikow's rule. In all cases the mercaptan that is first formed adds to a second molecule of the hydrocarbon to form the sulfide. In the case of the simple unsaturates this second reaction must be rapid as compared to the first addition as little of the mercaptans is left over. *t*-Butyl and cyclohexyl mercaptans evidently do not add so readily to the hydrocarbons.

The Addition of Mercaptans.—The unexpected observation was made in the course of our experiments that peroxides influence the mode of addition of mercaptans to unsaturates just as Kharasch[4] found that they influence the addition of hydrogen bromide. When we heated ethyl mercaptan with propylene we obtained ethyl *i*-propyl sulfide, but with octylene the product was ethyl *n*-octyl sulfide. The propylene had never been exposed to the air while the octylene had been stored for some time in a partly filled bottle and gave a strong test for peroxides. By adding ethyl mercaptan to propylene in the presence of added peroxides, we obtained ethyl *n*-propyl sulfide.

It has been observed by Posner and Nicolet[3] that thiophenol and *p*-thiocresol add to unsaturates contrary to Markownikow's rule. We have verified this in a large number of cases, but by using freshly distilled thiophenol and *p*-thiocresol we were able to reverse the mode of addition. Kharasch[4] observed that *p*-thiocresol was not effective as an anti-oxidant unless it was freshly distilled. It appears that only very small amounts of peroxides such as are usually present in the hydrocarbon or in the *p*-thiocresol itself are sufficient to influence the addition of mercaptans while for hydrogen bromide much larger amounts are required. In the absence of catalysts scarcely any addition takes place even on heating for twenty-four hours at 180°. Sulfur catalyzes the normal addition and peroxides the abnormal. It is difficult to suppress the abnormal addition entirely. Into each of 3 tubes of 2-cc. capacity were placed 0.25 g. of *p*-thiocresol and 0.4 cc. of tridecene. The *p*-thiocresol had been distilled recently *in vacuo* and the tridecene had just been distilled over sodium. To the first tube was added a trace of ascaridole, to the second a trace of sulfur and nothing to the third. After the usual heating the product in the first tube was solid and on recrystallization gave 0.3 g. which melted at 39.9°, the melting point of *p*-thiocresyl *n*-tridecyl sulfide made from *n*-tridecyl bromide in the usual way. From the liquid products in the other two tubes it was possible to isolate 0.01 and 0.08 g., respectively, of the sulfide melting at the same point.

In a number of experiments the products were identified by their boiling points and by oxidation to known solid sulfones but for positive proof of structure unsaturated hydrocarbons[5] and mercaptans were chosen that would give known crystalline sulfides which previously had been prepared from the potassium salt of the mercaptans and the normal alkyl bromides.[6] The tubes were of 2-cc. capacity and the hydrocarbon was in slight excess. The heating was for ten hours and 180°. The results given in Table III show conclusively that the abnormal addition took place with these hydrocarbons which had been exposed to air for some weeks.

In another series tridecylene was added to dimercaptans.[7] The results are given in Table IV.

In one experiment lauryl mercaptan was added to allyl lauryl sulfide $C_{12}H_{25}SCH_2CH{=}CH_2$ and the product was $C_{12}H_{25}S(CH_2)_3SC_{12}H_{25}$, m. p. 47°, proved by melting point and mixed melting point to be identical with that from lauryl bromide and trimethylene mercaptan.

Experimental

Ten moles of ethylene bubbled at the rate of 50 cc. per minute through a 25-cm. layer of sulfur in a vertical tube kept at 325° gave much hydrogen sulfide. The 25 cc. of condensate gave 15 g. of ethyl mercaptan, b. p. 34–37°, $Hg(SEt)_2$, m. p. 76°, 2 g. of carbon disulfide and 3 g. of ethyl sulfide, b. p. 91–92°, $Et_2S{\cdot}HgCl_2$, m. p. 76.5°. Five moles passed at the rate of 20 cc. per minute through a 20-cm. column of ethyl tetrasulfide at 140–150° gave 30 g. of condensate, largely ethyl sulfide but containing 10 g. of ethyl mercaptan $Hg(SEt)_2$, m. p. 76°, and 1.5 g. of ethylene sulfide,[8] b. p. 54–57°, S calcd. 53.36, found 53.09 and 53.12.

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(4) Kharasch and Hannum, THIS JOURNAL, **56**, 712 (1934).

(5) Prepared by Kozacik and Reid, *ibid.*, **60**, 2436 (1938).

(6) The alkyl bromides were those described by Meyer and Reid, *ibid.*, **55**, 1574 (1933).

(7) Hall and Reid, unpublished results.

(8) Delépine, *Bull. soc. chim.*, **733**, 03 (1923).

TABLE III

MELTING POINTS AND ANALYSES OF SULFIDES OBTAINED BY ADDITION COMPARED WITH THOSE OF SYNTHETIC SULFIDES

Mercaptan	Unsaturate	Sulfide	Synthetic M. p., °C.	By addition M. p., °C.	Sulfur, % Calcd.	Sulfur, % Found	
C_6H_5SH	$CH_3(CH_2)_8CH{=}CH_2$	$C_6H_5S(CH_2)_{10}CH_3$	33.8	33.8	12.13	11.90	11.93
p-$CH_3C_6H_4SH$	$CH_3(CH_2)_8CH{=}CH_2$	$CH_3C_6H_4S(CH_2)_{10}CH_3$	29.8	29.8	11.52	11.58	11.49
β-$C_{10}H_7SH$	$CH_3(CH_2)_8CH{=}CH_2$	$C_{10}H_7S(CH_2)_{10}CH_3$	46.8	46.8	10.00	10.01	10.10
$C_{12}H_{25}SH$	$CH_3(CH_2)_8CH{=}CH_2$	$C_{12}H_{25}S(CH_2)_{10}CH_3$	37.2	37.2	8.99	9.14	9.10
C_6H_5SH	$CH_3(CH_2)_{10}CH{=}CH_2$	$C_6H_5S(CH_2)_{12}CH_3$	43.8	43.9	10.95	10.69	10.78
p-$CH_3C_6H_4SH$	$CH_3(CH_2)_{10}CH{=}CH_2$	$CH_3C_6H_4S(CH_2)_{12}CH_3$	40.2	40.2	10.46	10.57	10.40
β-$C_{10}H_7SH$	$CH_3(CH_2)_{10}CH{=}CH_2$	$C_{10}H_7S(CH_2)_{12}CH_3$	54.6	54.5	9.36	9.10	9.21
$C_{12}H_{25}SH$	$CH_3(CH_2)_{10}CH{=}CH_2$	$C_{12}H_{25}S(CH_2)_{12}CH_3$	39.2	39.8	8.35	8.33	8.30
C_6H_5SH	$CH_3(CH_2)_{12}CH{=}CH_2$	$C_6H_5(CH_2)_{14}CH_3$	51.0	51.1	10.07	10.07	10.01
p-$CH_3C_6H_4SH$	$CH_3(CH_2)_{12}CH{=}CH_2$	$CH_3C_6H_4S(CH_2)_{14}CH_3$	48.0	48.8	9.58	9.83	9.60
β-$C_{10}H_7SH$	$CH_3(CH_2)_{13}CH{=}CH_2$	$C_{10}H_7S(CH_2)_{14}CH_3$	61.0	60.9	8.65	8.39	8.45
$C_{12}H_{25}SH$	$CH_3(CH_2)_{12}CH{=}CH_2$	$C_{12}H_{25}(CH_2)_{14}CH_3$	49.2	49.2	7.77	7.60	7.62
C_6H_5SH	$CH_3(CH_2)_{14}CH{=}CH_2$	$C_6H_5S(CH_2)_{16}CH_3$	57.6	57.6	9.20	8.91	8.98
p-$CH_3C_6H_4SH$	$CH_3(CH_2)_{14}CH{=}CH_2$	$CH_3C_6H_4S(CH_2)_{16}CH_3$	56.0	55.8	8.84	8.70	8.65
β-$C_{10}H_7SH$	$CH_3(CH_2)_{14}CH{=}CH_2$	$C_{10}H_7S(CH_2)_{16}CH_3$	66.2	66.2	8.29	8.10	8.19
$C_{12}H_{25}SH$	$CH_3(CH_2)_{14}CH{=}CH_2$	$C_{12}H_{25}S(CH_2)_{16}CH_3$	53.6	52.1	7.25	7.10	7.13
C_6H_5SH	$CH_3(CH_2)_{16}CH{=}CH_2$	$C_6H_5S(CH_2)_{18}CH_3$	62.4	60.5	8.49	8.28	8.35
p-$CH_3C_6H_4SH$	$CH_3(CH_2)_{16}CH{=}CH_2$	$CH_3C_6H_4S(CH_2)_{18}CH_3$	61.0	59.5	8.21	8.08	8.12
β-$C_{10}H_7SH$	$CH_3(CH_2)_{16}CH{=}CH_2$	$C_{10}H_7S(CH_2)_{18}CH_3$	71.2	70.0	7.52	7.32	7.40
$C_{12}H_{25}SH$	$CH_3(CH_2)_{16}CH{=}CH_2$	$C_{12}H_{25}S(CH_2)_{18}CH_3$	..	53.2	6.84	6.80	6.75

TABLE IV

MELTING POINTS AND ANALYSES OF SULFIDES OBTAINED BY ADDITION OF TRIDECENE TO DIMERCAPTANS AND MELTING POINTS OF SYNTHETIC SULFIDES. $R = n\text{-}C_{13}H_{27}$

Mercaptan	Sulfide	Synthetic	By addition	Sulfur, % Calcd.	Sulfur, % Found	
$HS(CH_2)_2SH$	$RS(CH_2)_2SR$	64	63.9	13.98	13.69	13.75
$HS(CH_2)_3SH$	$RS(CH_2)_3SR$	53	53	13.37	13.30	13.36
$HS(CH_2)_4SH$	$RS(CH_2)_4SR$	56.2	56.2	13.17	13.47	13.10
$HS(CH_2)_5SH$	$RS(CH_2)_5SR$	57.4	57.3	12.80	12.70	12.65
$HS(CH_2)_6SH$	$RS(CH_2)_6SR$	59.2	59.2	12.45	12.50	12.40
$HS(CH_2)_7SH$	$RS(CH_2)_7SR$	60.4	60.4	12.13	12.10	12.09
$HS(CH_2)_8SH$	$RS(CH_2)_8SR$	61.2	59.4	11.81	11.91	11.99
$HS(CH_2)_9SH$	$RS(CH_2)_9SR$	63.8	63.8	11.51	11.62	11.44
$HS(CH_2)_{10}SH$	$RS(CH_2)_{10}SR$	64.2	64.2	11.23	11.01	11.19
$HS(CH_2)_{11}SH$	$RS(CH_2)_{11}SR$	66.6	65	10.96	10.80	10.74
$HS(CH_2)_{12}SH$	$RS(CH_2)_{12}SR$	67.0	65.5	10.71	11.01	10.89
$HS(CH_2)_{18}SH$	$RS(CH_2)_{18}SR$	73.6	73	9.31	9.21	9.25

This was identical with a preparation by the method of Delépine.

All other experiments unless otherwise stated were made by heating in a steel bomb for ten hours at 180°. From 30 g. of propylene and 45 g. of ethyl tetrasulfide we obtained: 1 g. of carbon disulfide, 3 g. of i-PrSH, Hg(i-PrS)$_2$, m. p. 62°; 21 g. of i-Pr$_2$S, b. p. 118–121°; oxidized to sulfone, m. p. 36.4°; i-Pr$_2$SO$_2$, m. p. 36°,[9] and 10 g. of cyclic propylene sulfide, S calcd. 43.26, found 43.14. Under the same conditions, substituting sulfur for the ethyl tetrasulfide, the same products were found except that there was none of the cyclic sulfide.

Isobutylene, 14 g., and 23 g. of ethyl tetrasulfide in the bomb eight hours at 160° gave 1 g. of carbon disulfide, 5 g. of ethyl disulfide and a mixture of unsaturated hydrocarbons from which no sulfur compounds could be isolated.

From 27 g. of heptene-1 and 15 g. of Et$_2$S$_4$, we obtained 5 g. of carbon disulfide, 2 g. of ethyl disulfide, and 10.5 g., b. p. 140–170°, from which, by extraction with potassium hydroxide solution, heptane-thiol-2, b. p. 163–165°, n^{25}D 1.4459, was obtained, agreeing with the data in the literature. There was much carbonization.

From 56 g. of octene-1 and 45 g. of Et$_2$S$_4$ 10 g. of octylene was recovered along with 8 g. of carbon disulfide, 5 g. of ethyl disulfide and 30 g. of which half was hydrocarbon and half octanethiol-2. This was identified by treating it with octadecyl bromide, the resulting $C_8H_{17}SC_{18}H_{37}$ had m. p. 24° and was identical with that made from authentic octanethiol-2; n-$C_8H_{17}SC_{18}H_{37}$, m. p. 42.6°. There was much carbonization.

Cyclohexene, 82 g., and 32 g. of sulfur gave 6 g. of carbon disulfide and 15 g. of cyclohexyl mercaptan, b. p. 153–155°, S calcd. 27.60, found by I titration 27.45 and 27.49. Five runs were made using in each the same amount of cyclohexene with 93 g. of ethyl tetrasulfide, equivalent to 32 g. of sulfur. The products, united and fractionated, gave 34 g. of carbon disulfide, 105 g., b. p. 80–84°, of chiefly unreacted cyclohexene, 45 g., b. p. 154–155°, of cyclohexyl mercaptan and 50 g., b. p. 180°, of cyclohexene sulfide. This had d^0_4 0.9466, d^{25}_4 0.9274; n^{25}D 1.4881; S calcd. 28.10, found 28.00 and 28.05%. Besides these there were 15 g. of ethyl disulfide, b. p. 151–154°, and 40 g. of ethyl trisulfide, b. p. 85° at 15 mm.

Addition of Hydrogen Sulfide.—From 28 g. of ethylene and 34 g. of hydrogen sulfide liquefied in the bomb, with 5 g. of sulfur, there were obtained 7 cc. of ethanethiol, b. p. 34–7°, and 77 cc. of ethyl sulfide, b. p. 90.5–93°.

From 21 g. of propylene, 17 g. of hydrogen sulfide and 5 g. of sulfur, we obtained 2.5 g., b. p. 57–60°, which gave Hg(i-PrS)$_2$, melting at 62°, and 25 g., b. p. 117–121°, oxidized to sulfone, m. p. 35.5°, i-Pr$_2$SO$_2$ melting at 36°. This was repeated after thoroughly cleaning the bomb and leaving out the sulfur catalyst. The liquid product was only 3 cc., b. p. 60–180°, and contained mercaptan and sulfide.

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[9] Delépine, *Compt. rend.*, **172**, 158 (1921).

From 14 g. of isobutylene, 8.5 g. of hydrogen sulfide and 3 g. of sulfur we obtained 6 g. of *t*-butyl mercaptan, b. p. 65–67°, S calcd. 35.56, found by I titration 35.48 and 35.44, and 6 g., b. p. 115–160°, of *t*-butyl sulfide. This was refractionated, 1.8 g., b. p. 72° at 71 mm., S calcd. for *t*-Bu_2S 21.92, found 21.63 and 21.76. The remainder was hydrocarbons.

From 46 g. of octene-1, 17 g. of hydrogen sulfide and 3 g. of sulfur were recovered 20 g. of octylene and 5 g., b. p. 89° at 30 mm., identified as octane-thiol-2, $n^{25}D$ 1.4480. Titrated with I, found S, 21.69 and 21.78, calcd. 21.92. With octadecyl bromide it gave a sulfide melting at 24°. The sulfide fraction boiled at 281–283°.

From 82 g. of cyclohexene, 34 g. of hydrogen sulfide and 3 g. of sulfur, 40 g. of cyclohexene was recovered along with 8 g. of the mercaptan, b. p. 153–155°, and 4 g. of the sulfide, b. p. 180° at 50 mm., S calcd. 16.17, found by Br titration 16.08 and 16.01, $n^{25}D$ 1.50473, sulfone m. p. 126°.

Addition of Mercaptans.—All runs were made in a steel bomb for ten hours at 180°. Small samples for Tables III and IV were sealed in glass tubes which were surrounded in the bomb by a liquid of the proper vapor pressure. The solid sulfides from these were recrystallized from alcohol.

From 20 g. of thiophenol, 8 g. of propylene and 1 g. of sulfur were obtained 1 g. of *i*-PrSH, boiling at 57–59°, 2 g. of *i*-Pr_2S boiling at 118–120° and 12 g. of *i*-PrSPh which gave a liquid sulfone, *n*-$PrSO_2Ph$, m. p. 46°.

From 28 g. of ethylene and 62 g. of ethanethiol with 3 g. of sulfur the yield of diethyl sulfide was 93% but without the sulfur catalyst there was no condensation, Propylene and ethyl mercaptan did not combine without the catalyst but from 3 g. of sulfur, 21 g. of propylene and 31 g. of ethanethiol, 44 g. of *i*-PrSEt boiling at 103–104°, 4 g. of PrSEt boiling at 115–117° and 4 g. of *i*-Pr_2S boiling at 120–121° were obtained. From 21 g. of the same propylene mixed with 61 g. of octene-2, 3 g. of ascaridole and 62 g. of ethanethiol the products were: 2 g. of *i*-PrSEt, b. p. 103–110°; 25 g. of *n*-PrSEt, b. p. 115–117°; sulfone, m. p. 25°; and 13 g. of EtSOct, b. p. 102–103° at 11 mm.; sulfone, m. p. 68°.

Starting with 56 g. of octene-1 containing peroxides and 31 g. of ethanethiol we obtained 14 g., b. p. 145–154° at 100 mm., of which 75% was *n*-octyl SEt, and 14 g., b. p. 154–156°, pure *n*-octyl SEt identified as sulfone, m. p. 68°. The same materials with the addition of 4 g. of hydroquinone gave only 4 g. of sulfide which was not increased by twenty-four hours of heating. When the same were heated with 4 g. of sulfur the products were 5 g., b. p. 109° at 70 mm., of octane-thiol-2; 50 g., b. p. 145–147° at 100 mm., of *s*-octyl ethyl sulfide of which the sulfone was a liquid; and 5 g., b. p. 281–283°, 175° at 20 mm. of di-*s*-octyl sulfide; and 5 g., b. p. 281–283°, 175° at 20 mm. of di-*s*-octyl sulfide.

Cyclohexene, 7 cc., and ethanethiol 5 cc. were sealed in a glass tube which was surrounded in the bomb by a like mixture containing hydroquinone. From the sealed tube 5 cc. of cyclohexyl SEt was isolated but there was no reaction in the outside mixture. Two runs were made with half mole each of these reactants. With sulfur as catalyst the yield was 60% and with peroxides 40%.

Ethyl mercaptan, 0.5 mole, and 0.25 mole of *n*-butylacetylene with 2 g. of sulfur were heated. Fractionation of the product gave 4 g., b. p. 133°, and 16 g., b. p. 95–110° at 150 mm. The first of these took up $2Br_2$ and gave 2HBr on hydrolysis, showing the presence of 1 = and 1 S. The other took up $2Br_2$ and gave 4HBr, showing the presence of 2 S. The constitutions of these were not determined.

Summary

1. Sulfur strips hydrogen from unsaturates even to form hydrogen sulfide a part of which adds to the double bond producing a mercaptan which adds to more of the unsaturate to give a sulfide.

2. The addition of hydrogen sulfide takes place readily and follows Markownikow's rule. Sulfur is an effective catalyst.

3. Mercaptans add to double bonds in accordance with Markownikow's rule if peroxides are eliminated or sulfur used as a catalyst. In the presence of peroxides the abnormal addition takes place. The amount of peroxide required is small.

BALTIMORE, MD.

RECEIVED AUGUST 6, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF TEXAS]

Polyazines. II. The Reaction of Hydrazine Hydrate with Acetylacetone, Acetonylacetone, and Benzil[1,2]

BY BERNHARD G. ZIMMERMAN[3] AND H. L. LOCHTE

The reaction between the two bifunctional types of compounds, diketones and hydrazine hydrate, should generally yield polyazines which are formed by continued condensation of ketone and hydrazine. Cyclic compounds are formed directly only in those special cases which lead to the formation of 5- or 6-membered rings.[4,5] Four- and seven-membered rings apparently are formed in such cases only rarely and then in small yield.

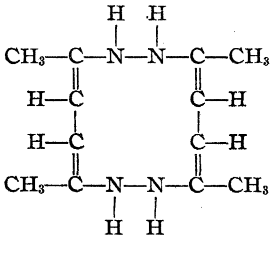
Kinetic theory and probability considerations lead us to predict that in cases in which there is simultaneous formation of both cyclic and open chain compounds, the yield of cyclic products can be increased by working in very dilute solutions.[6]

A previous communication[5] on the reaction between diacetyl and hydrazine hydrate showed that the main product obtained is a polyazine of the type

$$H_2N—N{=}C(CH_3)[C(CH_3){=}N—N{=}C(CH_3)]_nC(CH_3){=}O$$

The present paper presents results obtained with several other diketones.

The reaction between acetonylacetone and hydrazine hydrate was first studied by Gray,[7] who isolated two crystalline products. Equimolecular amounts of the reactants yielded a 12-membered ring compound to which he assigned the formula



while the reaction between two moles of ketone and three of hydrazine hydrate yielded the azine-hydrazone

$$H_2N—N{=}C(CH_3)—CH_2—CH_2—C(CH_3){=}N—N{=}C\text{-}(CH_3)CH_2—CH_2C(CH_3){=}N—NH_2$$

The direct formation of a 12-membered ring in a concentrated solution, as reported by Gray, is unexpected; but Gray gave not only complete analyses which are of no value as a means of differentiating between the cyclic and open chain polymeric structure, but also reported derivatives, solubility in various solvents, and made molecular weight determinations. Gray, however, did not report a melting point for this crystalline 12-membered ring. Molecular weights found agreed closely with those required for the 12-membered ring. Smith and McCoy[8] also obtained the same substances, but gave no additional information.

In view of Gray's results a number of attempts were made to repeat his work, but experiments under conditions reported by Gray, as well as in very dilute solution in which the yield of such a compound should have been better, failed to reveal any crystalline substance that could be identified as Gray's compound.

Gray's directions yielded a viscous oil which remained liquid for months. Analysis of a fraction boiling at 114–115° at 2 mm. agreed with results obtained by Gray, as did cryoscopic molecular weight determinations in benzene. Even after careful fractionation of the liquid, no crystalline 12-membered ring could be isolated.

Dilute solutions yielded in all cases mainly 3,6-dimethylpyridazine which has been prepared in a number of different ways, but Gray,[7] Smith and McCoy,[8] and Paal and Ubber[9] all agreed that it could not be prepared by direct reaction between acetonylacetone and hydrazine hydrate. Apparently, the only essential difference between their experiments and ours lay in the fact that our work was done in very dilute solution. About 3% yield of a crystalline polymer of the type

$$H_2N_2C(CH_3)CH_2[CH_2C(CH_3){=}N—N{=}C\text{-}(CH_3)CH_2]_{n=184}—CH_2C(CH_3)O$$

also could be isolated from the same dilute solution. In benzene solution, the azine-hydrazone

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[1] Based on part of a dissertation submitted by B. G. Zimmerman in partial fulfilment of the requirements for the degree of Doctor of Philosophy at the University of Texas, June, 1937.

[2] Presented at the 95th meeting of the American Chemical Society at Dallas, Texas, April 18–22, 1938.

[3] Present address: General Aniline Works, Inc., Grasselli, N. J.

[4] Carothers, *Chem. Rev.*, **8**, 358 (1931).

[5] Zimmerman and Lochte, THIS JOURNAL, **58**, 948 (1936).

[6] Ruggli, *Ann.*, **392**, 92 (1912).

[7] Gray, *J. Chem. Soc.*, **79**, 682–686 (1901).

[8] Smith and McCoy, *Ber.*, **35**, 2169 (1902).

[9] Paal and Ubber, *ibid.*, **36**, 497 (1903).

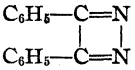
of Gray was obtained in excellent yield. In concentrated solutions, using no solvents and heating on a steam-bath for two weeks, only a black tar, from which no crystalline products could be isolated, was obtained.

The reaction of benzil, diacetyl, and acetylacetone with benzil dihydrazone yielded only mixed polyazine resins. No definite structure could be assigned to these resins.

Two crystalline azines, the mono- and diazine, were isolated from the reaction between benzil monohydrazone and diacetyl.

As expected, acetylacetone and hydrazine hydrate yielded only the 5-membered ring, 3,5-dimethylpyrazole; no polymeric substance could be isolated as a by-product.

According to Curtius,[10] benzil monohydrazone decomposes in an aqueous solution to yield the four-membered ring



All attempts to isolate such a 4-membered ring were unsuccessful.

Experimental

Condensation of Acetonylacetone with Hydrazine Hydrate in Dilute Solution.—Ninety-seven grams of acetonylacetone and 42.5 g. of hydrazine hydrate were dissolved in 5 liters of water, and heated on a steam-bath for six weeks.

The crystals that separated on evaporating most of the water and cooling were filtered off and recrystallized four times from a large volume of 50% alcohol. Except for slight solubility in ethanol, the white crystals were insoluble in all common solvents; m. p., softens at 260° and melts at 276° with decomposition.

Anal. Calcd. for $O{=}C(CH_3){-}CH_2[CH_2{-}C(CH_3){=}N{-}N{=}C(CH_3){-}CH_2]_{184}{-}CH_2C(CH_3){=}N{-}NH_2$: C, 65.41; H, 9.10; N, 25.39; mol. wt., 20,366. Found: C, 65.28; H, 9.08; N, 25.42; mol. wt., micro Rast camphor, 9.314 mg. of product dissolved in 84.40 mg. of camphor showed a depression in the freezing point of 0.200°, mol. wt., 21,836. Check determinations indicated molecular weights from 18,000 to 22,000.

Picrate.—This separated as shiny yellow crystals when a dilute alcoholic solution of picric acid was added to a hot alcoholic solution of the polymer. Recrystallized from much ethanol, it melted at 170–176° with decomposition.

Anal. Calcd. for $n = 184$: N, 20.63. Found: N, 20.62.

Platinic Chloride Salt.—An orange-yellow crystalline salt formed when a 10% solution of platinum chloride was added to a hot alcoholic solution of the polymer. The salt was washed with water, alcohol, ether, and dried; m. p. 260–266° dec.

Anal. Calcd. for $n = 184$: Pt, 31.00. Found: (micro) Pt, 30.89, 30.93.

Hydrochloride.—Five-tenths gram of the polymer was dissolved in hot alcohol and dry hydrogen chloride passed in. The resulting white salt melts at 200–201° with decomposition to a red mass.

Anal. Calcd. for $n = 184$: Cl, 24.10. Found: Cl, 24.07.

The hydrochloride is very soluble in water. Neutralization equivalent (calcd. 146.5, found 146.7) corresponds to the structural unit of the polymer.

Each of these salts has thus resulted from reaction with each structural unit.

3,6-Dimethylpyridazine.—The filtrate from the polymer was fractionated at 40 mm. in a stream of hydrogen. The 40–200° fraction was then fractionated at 37 and 31 mm. The fraction boiling at 119–122° at 31 mm. was then refractionated at 2 mm. The main fraction boiling at 64° at 2 mm. solidified on cooling. After further purification, it melted at 34–35°. Complete analysis of the base as well as the analysis and properties of the picrate, platinic chloride, and hydrochloride agreed with those reported by Paal and Koch.[11] The platinum chloride was found to contain either one or four molecules of water of crystallization.

Gray's Azine-Hydrazone ($C_{12}H_{14}N_6$).—This compound reported by Gray was obtained when 10 cc. of acetonylacetone was dissolved in 300 cc. of benzene and 15 cc. of hydrazine hydrate added with shaking for one hour. After numerous recrystallizations from ethanol it melted at 136–137° (Gray reported 132°).

Benzil Monohydrazone and Diacetyl.—Six and five-tenths grams of benzil and 2.5 g. of diacetyl dissolved in 125 cc. of alcohol were refluxed for eighteen hours. On cooling, the yellow crystals which formed were filtered off and recrystallized from alcohol; m. p., 85.8°.

Anal. Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.94; H, 5.25; N, 9.59; mol. wt., 292. Found: C, 74.01; H, 5.69; N, 9.67; mol. wt. (ebullioscopic in benzene), 285.

On continued refluxing of the filtrate, a second yellow product was isolated. After recrystallization from benzene, the melting point was found to be 238.3° with decomposition.

Anal. Calcd. for $C_{32}H_{26}N_4O_2$: C, 77.07; H, 5.26; N, 11.24; mol. wt., 498. Found: C, 77.29; H, 5.49; N, 11.17; mol. wt. (micro Rast camphor), 505.

3,5-Dimethylpyrazole.—This compound was prepared according to the directions of Rosengarten[12] and Dedichen[13] and the filtrate examined for polymeric by-products, but none could be isolated. This compound was found to be satisfactory as a selective inhibitor for some micro-organisms.[14]

Molecular Weight Determinations.—In the course of attempts to determine the molecular weight of these moderately high molecular weight polyazines, it was observed that the molecular weight appeared to increase with concentration of the polymer in benzene in spite of the fact that the solutions appeared to be perfectly clear up to the

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[10] Curtius, *J. prakt. Chem.*, [2] **39**, 131 (1899).

[11] Paal and Koch, *Ber.*, **37**, 4385 (1904).

[12] Rosengarten, *Ann.*, **279**, 238 (1894).

[13] Dedichen, *Ber.*, **39**, 1848 (1906).

[14] Zimmerman and Lewis, U. of Texas, unpublished results.

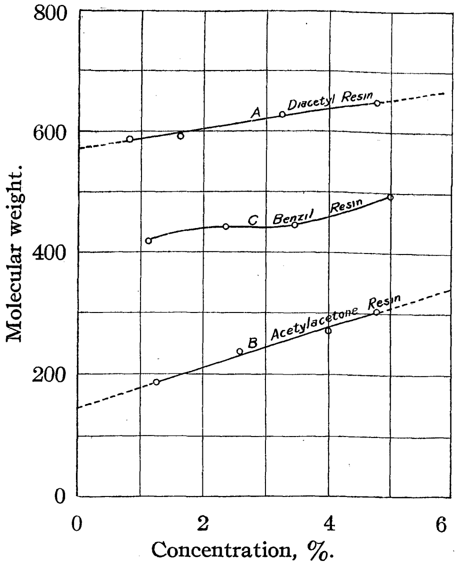

Fig. 1.—Molecular weight–concentration curves.

point at which the benzene started to freeze. Figure 1 shows results obtained with three different resins. Meanwhile Staudinger and co-workers[15] reported similar difficulties with polymers, and offer an explanation for this observed increase in molecular weight with an increase in concentration.

Summary

Acetonylacetone and hydrazine hydrate react to yield 3,6-dimethylpyridazine, the azine-hydrazone of Gray, and an insoluble crystalline polyazine.

The 12-membered ring of Gray could not be isolated under any conditions.

Benzil dihydrazone reacts with benzil, diacetyl, and acetylacetone to yield resins.

The 4-membered ring, formed by the decomposition of benzil monohydrazone, of Curtius could not be isolated.

Acetylacetone and hydrazine hydrate yield 3,5-dimethylpyrazole without polymeric by-product.

Cryoscopic molecular weight determinations of polyazines with benzene as solvent yield values that appear to increase with concentration of polymer.

Austin, Texas Received June 4, 1938

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[15] Staudinger and co-workers, *Ber.*, **68** 2313 (1935).

[Contribution from the School of Chemistry and Physics of the Pennsylvania State College]

The Reducing Action of Primary Grignard Reagents

By Frank C. Whitmore, A. H. Popkin, J. S. Whitaker, K. F. Mattil and J. D. Zech

The reducing action of *t*-butylmagnesium chloride on trimethylacetyl, isobutyryl, *n*-butyryl[1] and *t*-butylacetyl[2] chlorides has been reported already. Similar studies have now been made to find the effect of branching, in both the Grignard reagent and the carbonyl compound, on the yields of the reduction products.

n-Butylmagnesium bromide and trimethylacetyl chloride produced neopentyl alcohol in 27% yield together with a 69% yield of *n*-butyl-*t*-butylcarbinol representing a total yield of 96% of the reduction products. In the case of *t*-butylmagnesium chloride, the yield of neopentyl alcohol was 95% with a 1% yield of di-*t*-butylcarbinol.

Several other reactions of the Grignard reagent were studied next with emphasis on the by-product obtained. Excess *n*-butylmagnesium bromide gave the usual products with acetyl chloride, ethyl acetate, acetaldehyde and 2-hexanone and, in addition, the by-products indicated

$CH_3COCl \longrightarrow 8\%\ CH_3CH_2OH$

$\searrow 13\%\ CH_3CHOHC_4H_9$

$CH_3CO_2C_2H_5 \longrightarrow 3\%\ CH_3CHOHC_4H_9$

$CH_3CHO \longrightarrow 18\%\ CH_3CH_2OH$

$CH_3COC_4H_9 \longrightarrow 9\%\ CH_3CHOHC_4H_9$

The preparation of a series of tertiary carbinols for subsequent dehydration studies involved the addition of methylneopentyl ketone to some primary Grignard compounds. With ethylmagnesium bromide, evidence of a trace of methylneopentylcarbinol was obtained but its identity was not established positively. This reduction product was identified when higher Grignard reagents were used. The yields of methylneopentylcarbinol were 5.5% using *n*-propylmagnesium bromide, 5.7% using *n*-butylmagnesium bromide

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[1] Greenwood, Whitmore and Crooks, This Journal, **60**, 2028 (1938).

[2] Whitmore and Heyd, *ibid.*, **60**, 2030 (1938).

and 3.4% using *n*-amylmagnesium bromide. The conditions of concentration and temperature during the addition of ketone in the preparations of the neopentylcarbinols were approximately identical.

An attempt to isolate neopentyl alcohol from the action of *n*-butylmagnesium bromide on ethyl trimethylacetate was not successful. The only reduction product isolated was *n*-butyl-*t*-butylcarbinol, present in 40% yield. This verified the observation of Leroide.[3] As had been observed previously,[4] the addition of ethyl trimethylacetate to *t*-butylmagnesium chloride in ether produced no reaction, the recovery of the ester being quantitative. There was indication, however, of a reaction at elevated temperatures and studies are now in progress employing di-*n*-butyl ether and benzene as solvents. Because of the unusual stability of ethyl trimethylacetate toward the tertiary Grignard reagent and its reactivity toward *n*-butylmagnesium bromide, an investigation is being made of its behavior toward isopropylmagnesium bromide.

There is the possibility that 2-hexanol might appear as a result of acetaldehyde formation due to peroxidation of the ether.[5,6] Careful studies indicate that this is not the source of the 2-hexanol in the present experiments.

Experimental

Description of Apparatus.—A description of the columns employed is given because of the importance of fractionation in this work. The fractionating columns were of the total condensation, variable take-off type[7] containing single turn, 4-mm. glass helices as packing.[8] The dimensions are reported as length of packing space and internal diameter of the column: Column I, 62 × 0.9 cm.; II, 90 × 1.5 cm.; III, 110 × 1.5 cm.; IV, 68 × 1.5 cm.; V, 58 × 1.1 cm.; VI, 46 × 0.9 cm.; VII, 77 × 1.4 cm.; VIII, 48 × 0.9 cm.; IX, 27 × 0.5 cm.; X, 47 × 0.9 cm.; XI, 64 × 1.2 cm.; XII, indented, 110 × 1.4 cm.

Reaction of *n*-Butylmagnesium Bromide with Trimethylacetyl Chloride.—Trimethylacetyl chloride, b. p. 58° (150 mm.), $n^{20}\text{D}$ 1.4126, was prepared in 87% yield from thionyl chloride (Eastman Kodak "practical") and trimethylacetic acid, b. p. 158° (725 mm.), m. p. 34°. *n*-Butylmagnesium bromide was obtained by treating 97 g. (4 moles) of magnesium with 548 g. (4 moles) of *n*-butyl bromide, b. p. 99–100° (724 mm.), $n^{20}\text{D}$ 1.4400, and 1400 cc. of anhydrous ether. The undiluted acid chloride was added during one hour. The Grignard complex was decomposed with ice, extracted with ether and the ether removed, b. p. 34° (726 mm.), using column IV. The residue was then placed under column VI and fractions 1–5 were collected, 26.2 g., b. p. 42–105° (726 mm.), $n^{20}\text{D}$ 1.3693–1.3718. Fractions 6–12, 24.1 g., b. p. 110–111.5°, were solid at room temperature. Of these, fractions 7 and 12 yielded phenylurethans melting at 112–113° which did not depress the m. p. when mixed with the known phenylurethan of neopentyl alcohol. The yield of neopentyl alcohol based on acid chloride was 27%. Fractions 13 and 14, 2.7 g., 36–71° (16 mm.), $n^{20}\text{D}$ 1.4042–1.4190, were the intermediate fractions between the two reduction products. Fractions 15–25, 99.8 g., b. p. 71° (15 mm.), $n^{20}\text{D}$ 1.4319–1.4321, gave a phenylurethan melting at 64.5–65.5° which gave no depression on mixing with an authentic sample of the same derivative of *n*-butyl-*t*-butylcarbinol. The yield of the secondary carbinol as reduction product was 69%. A residue of 4.5 g., $n^{20}\text{D}$ 1.4329, was pure *n*-butyl-*t*-butylcarbinol, the weight representing the operating hold-up in column VI. A careful search gave no trace of 2-hexanol. It had been suggested that the secondary alcohol might be a product of acetaldehyde formation from peroxide in the ether.

Reaction of *n*-Butylmagnesium Bromide with Acetyl Chloride.—*n*-Butylmagnesium bromide was prepared from 685 g. (5 moles) of *n*-butyl bromide, b. p. 99° (732 mm.), 1450 cc. of dry ether and 122 g. (5 moles) of magnesium. Acetyl chloride ("practical" Eastman Kodak Co. product) was purified by distillation, b. p. 52° (737 mm.), from dry dimethylaniline. The addition of 157 g. (2 moles) of the undiluted acetyl chloride to the above Grignard reagent, concentrated by boiling off one liter of ether, was completed in one hour and twenty minutes. The complex was decomposed with ice, extracted with ether and the ether removed through column IV. The reaction mixture was fractionated through column VI to give: 1, 4.9 g., b. p. 34–64° (736 mm.), $n^{20}\text{D}$ 1.3579; 2–3, 8.9 g., 64–78°, 1.3672–1.3800; 4, 3.2 g., 78–86°, 1.3944; 5, 8.8 g., 79–115° (727 mm.), 1.4011; 6–8, 13.0 g., 115–116.5°, 1.4022–1.4032; 9–10, 10.2 g., 120–134°, 1.4047–1.4118; 11–13, 22.5 g., 134–139.5°, 1.4152–1.4169; 14, 8.6 g., 139.5–145°, 15–20, 53.5 g., 35–74° (14 mm.), 1.4181–1.4278; 21–23, 51.9 g., 85–101° (12 mm.), 1.4351–1.4362; residue 8.2 g.

Fraction 1 was largely ether; 2 and 3 represented an 8% yield of ethyl alcohol as identified through the α-naphthylurethan, m. p. and mixed m. p. with an authentic sample, 78.5–79°. Fractions 4 and 5 contained water layers. Fractions 6–8 were identified as *n*-butyl alcohol by the α-naphthylurethan, m. p. and mixed m. p. with an authentic derivative, 70–71°. Fractions 9 and 10 gave no test for 2-hexanone on treatment with 2,4-dinitrophenylhydrazine. They probably consisted of 2-hexanol and *n*-butyl alcohol. Fractions 11–13 were identified as 2-hexanol by oxidation of a sample to the corresponding ketone with an aqueous acid dichromate solution and the formation of the 2,4-dinitrophenylhydrazone, m. p. and mixed m. p., 106–107°. Fractions 14 and 15 were probably mixtures of 2-hexanol with the decenes formed by the dehydration of some of the methyl-di-*n*-butylcarbinol during the fractionation.

Fractions 16–20 proved to be mainly olefins from the dehydration of methyl-di-*n*-butylcarbinol. They approached the values b. p. 97° (84 mm.) and $n^{20}\text{D}$ 1.4295.

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(3) Leroide, *Ann. chim.*, [9] **16**, 354 (1921).

(4) Conant and Blatt, THIS JOURNAL, **51**, 1227 (1929).

(5) Clover, *ibid.*, **44**, 1107 (1922).

(6) Pierotti and Stewart, *ibid.*, **59**, 1773 (1937).

(7) Whitmore and Lux, *ibid.*, **54**, 3451 (1932).

(8) Wilson, Parker and Laughlin, *ibid.*, **55**, 2795 (1933).

Fractions 21–23 were methyl-di-*n*-butylcarbinol, the constants of a known sample of which were b. p. 100° (24 mm.), n^{20}D 1.4349.

Reaction of *n*-Butylmagnesium Bromide with Ethyl Acetate.—Ethyl acetate was purified by treatment of commercial ethyl acetate (Eastman Kodak Co.) with phosphorus pentoxide and fractionation through column V, b. p. 74° (737 mm.), n^{20}D 1.3722. *n*-Butylmagnesium bromide was prepared using 1465 g. (10.6 moles) of *n*-butyl bromide, 258 g. (10.6 moles) of magnesium and 1750 cc. of dry ether. The addition of the ethyl acetate, 440 g. (5 moles), in 700 cc. of dry ether was completed in ten hours. The products were isolated as usual and fractionated through column IV to give: 1, 17.3 g., 35–55° (737 mm.), n^{20}D 1.3592; 2–4, 88.0 g., 75–76°, 1.3731–1.3688; 5, 8.7 g., 37° (24 mm.), 1.4037; 6, 16.3 g., 58° (24 mm.), 1.4160; 7, 32.8 g., 62.5–100° (24 mm.), 1.4304; 8–17, 513.4 g., 100° (24 mm.), 1.4348–1.4351.

Fractions 1–5 contained ether, ethyl alcohol and unreacted ethyl acetate. Fraction 6 was identified as 2-hexanol (3% yield) by oxidation to the ketone and preparation of a 2,4-dinitrophenylhydrazone, m. p. and mixed m. p., 106–107°. Treatment of fraction 6 with 2,4-dinitrophenylhydrazine before oxidation gave no evidence of the presence of 2-hexanone. Fraction 7 contained methyl-di-*n*-butylcarbinol with some 2-hexanol as impurity. Fractions 8–17 represented a 64% yield of the tertiary carbinol which gave a 90% yield of decenes, b. p. 69° (27 mm.), n^{20}D 1.4294, when refluxed with anhydrous copper sulfate.

Reaction of *n*-Butylmagnesium Bromide with Acetaldehyde.—*n*-Butylmagnesium bromide was made from 685 g. (5 moles) of *n*-butyl bromide, 121.5 g. (5 moles) of magnesium and one liter of dry ether. After boiling off 400 cc. of ether, 88 g. (2 moles) of acetaldehyde, b. p. 22–23° at 720 mm. (purified by distillation of 500 g. of a technical grade Eastman Kodak Co. product to which had been added 4 g. of hydroquinone), was added. The addition complex was decomposed with ice and an excess of sulfuric acid. The layers were separated and the aqueous layer extracted again with ether. The final water layer was distilled through column IV. After the dissolved ether had been collected at 34°, a fraction, 15.4 g., b. p. 75–90°, which yielded an α-naphthylurethan, m. p. and mixed m. p., 78.5–79°, corresponding to that for ethyl alcohol, was obtained. A second fraction 90–99°, on drying, also gave an α-naphthylurethan corresponding to ethyl alcohol. The weight of fractions 1 and 2 after drying was 21.4 g., or approximately 18% yield.

The ether was removed from the ethereal extracts of the reaction products through column IV and the products were fractionated through column V to give: 1, 8.4 g., 42–75° (727 mm.), n^{20}D 1.3622; 2–4, 11.9 g., 75–134°, 1.3940–1.4100; 5–6, 66.4 g., 136°, 1.4144–1.4147; residue 28 g. Fraction 1 contained a small amount of ethyl alcohol as identified by its α-naphthylurethan. Fractions 5 and 6 contained the normal product, 2-hexanol.

Reaction of *n*-Butylmagnesium Bromide with 2-Hexanone.—Dehydrogenation of 3 kg. of Eastman "Technical" 2-hexanol yielded crude 2-hexanone which was fractionated through column II into 67 fractions of approximately 40 g. each. The best fractions were combined and refractionated through column V. Addition of 200 g. (2 moles) of purified 2-hexanone, b. p. 125° (732 mm.), n^{20}D 1.4010 to 4.5 moles of filtered *n*-butylmagnesium bromide in 2 liters of ether was completed in one hour with the liberation of 0.15 mole of olefin. The reaction mixture was decomposed with ice, the ether layer decanted, and the aqueous layer steam distilled. The aqueous layer of the distillate was extracted with ether and the total ethereal solutions combined for removal of ether through column XII. The residual products were then fractionated through column I to give: 1–12, 33.1 g., 45° (125 mm.) –80° (98 mm.), n^{20}D 1.4051–1.4079; 13–16, 18.1 g., 80° (87 mm.) –82° (24 mm.), n^{20}D 1.4138–1.4186; 17–33, 343 g., 95° (20 mm.) –78° (3 mm.), 1.4331–1.4358.

Fractions 1–12 were refractionated through column VI to give: 34–36, 10.1 g., 105–111° (739 mm.), n^{20}D 1.4060–1.4008; 37–41, 19.3 g., 116–118°, 1.4017–1.4030; residue, 5 g. Fractions 37–41 were unreacted 2-hexanone, 2,4-dinitrophenylhydrazone, m. p. and mixed m. p., 106–107°.

Fractions 13–16 were refractionated through column IX to give: 42–44, 3.1 g., 131–133.5° (739 mm.), 1.4068–1.4150; 45–50, 7.8 g., 135–136°, 1.4160–1.4162; residue, 0.9 g.

Fractions 42–50 and the residue of that fractionation were identified as 2-hexanol by oxidation with an acid dichromate solution and formation of a 2,4-dinitrophenylhydrazone for 2-hexanone, m. p. and mixed m. p., 106–107°. A portion of fraction 48, 1.7 g., gave no test for 2-hexanone with 2,4-dinitrophenylhydrazine prior to oxidation.

Reaction of *n*-Butylmagnesium Bromide with Ethyl Trimethylacetate.—Ethyl trimethylacetate, b. p. 116.5° (735 mm.), n^{20}D 1.3912 was prepared by the action of ethyl alcohol on trimethylacetyl chloride. *n*-Butylmagnesium bromide was prepared using 97 g. (4 moles) of magnesium, 548 g. (4 moles) of *n*-butyl bromide and 1600 cc. of ether. On completion of Grignard formation, 400 cc. of ether was distilled off and 130 g. (1 mole) of undiluted ethyl trimethylacetate was added to the concentrated Grignard solution during one-half hour. The complex was decomposed with ice, extracted with ether and after removal of the ether through column IV the products were fractionated through column VI to give: 1–2, 4.3 g., 32–110° (741 mm.); 3–4, 4.2 g., 111–116°; 5–6, 7.9 g., 43–63° (11 mm.), n^{20}D 1.4150–1.4208; 7, 7.2 g., 64.5° (11 mm.), 1.4250; 8–13, 57.5 g., 65.5–67° (11 mm.), 1.4295–1.4310; 14–22, 99.6 g., 105.5–107° (11 mm.), 1.4488.

Fractions 3–4 were identified as *n*-butyl alcohol by the α-naphthylurethan, m. p. and mixed m. p., 70–71°. Fractions 8–13 represented a 40% yield of *n*-butyl-*t*-butylcarbinol which gave a phenylurethan melting at 65–66°. Fractions 14–22 were di-*n*-butyl-*t*-butylcarbinol in 50% yield. Based on a density determination of a representative fraction, d^{20}_4 0.8498, the molecular refraction was found to be 63.16; calcd. 63.76.

Fractions 5–6 were investigated for 2-hexanol as a possible product of peroxide and aldehyde formation in the ether but no α-naphthylurethan was obtained, nor did oxidation with acid dichromate solution yield any evidence of 2-hexanone. Fraction 7 was impure di-*n*-butyl-*t*-butylcarbinol.

Addition of Methyl Neopentyl Ketone to Ethylmagnesium Bromide.—The methyl neopentyl ketone[9] used in this and subsequent reactions had a b. p. range of 122–124° (725–730 mm.) and $n^{20}D$ 1.4035–1.4040. The Grignard reagent was prepared from 121 g. (5 moles) of magnesium, 545 g. (5 moles) of ethyl bromide (Eastman Kodak Co. "practical"), and 1 liter of ether. The addition of 353 g. (3.1 moles) of ketone was completed in four hours. The complex was decomposed with ice, the mixture extracted with ether, and the ether removed through column XII. The products were fractionated through column XI at reduced pressure to minimize dehydration of the tertiary carbinol. A salt–ice trap and a solid carbon dioxide–acetone trap were used in series to condense the low boiling material evolved as gases when the pressure was lowered: 1, 5.2 g., 40–48° (176 mm.); 2, 3.8 g., 42° (93 mm.); 3, 2.9 g., 35° (18 mm.), $n^{20}D$ 1.4284; 4, 6.8 g., 66° (18 mm.), 1.4315; 5–18, 359 g., 44° (4 mm.), 1.4335–1.4375. The trap condensed 29.1 g. of liquid which, on fractionation through column X, gave 26.5 g. of ether and a residue, 19, of 1.9 g. The 23.2 g. collected in the salt–ice trap gave a residue, 20, of 2.1 g. after the ether had been removed through column X. Fraction 4, above, on distilling through column X, gave 21, 3 g., 115° (739 mm.), 1.4240 which was combined with fractions 3, 19 and 20 to give on distillation through a semi-micro fractionating column (43.5 × 0.6 cm.): 22, 1.1 g., 90–115° (744 mm.), 1.4160; 23, 1.0 g., 130–145°, 1.4288; residue, 6 drops. Since no derivative could be made for 23 using α-naphthyl isocyanate, no methylneopentylcarbinol was found.

Fraction 22 gave no indication of the presence of *s*-butyl alcohol as a by-product of peroxide and aldehyde formation in the ether. Fractions 5–18 represented methylethylneopentylcarbinol.[10]

Addition of Methyl Neopentyl Ketone to *n*-Propylmagnesium Bromide.—*n*-Propylmagnesium bromide was prepared from 553 g. (4.5 moles) of *n*-propyl bromide, b. p. 70–71° (735 mm.), $n^{20}D$ 1.4344, 109 g. (4.5 moles) of magnesium and one liter of ether. The addition of 342 g. (3 moles) of methyl neopentyl ketone was completed in three hours. The complex was decomposed with ice, extracted with ether which was then removed through column XII, and the products fractionated through column V to give: 1, 27.1 g., 37–87° (728 mm.), $n^{20}D$ 1.3850; 2, 5.2 g., 20.5° (13 mm.). Dehydration of the tertiary carbinol made fractionation difficult. The remainder was dried with anhydrous potassium carbonate, then fractionated through column XI using a salt–ice trap and a solid carbon dioxide–acetone trap in series to give: 3–7, 101.8 g., 35–56° (14 mm.), 1.4232–1.4260; 8–13, 42.6 g., 62–73° (14 mm.), 1.4280–1.4352; 14–20, 74.1 g., 74–75° (14 mm.), 1.4367–1.4371; 21–23, 32.8 g., 85–97° (14 mm.), 1.4528–1.4590; residue, 26 g.; trap, 2.9 g.

Fractions 8–13, fractions 32–39 and the residue of the refractionation (below) represented 106 g. (0.76 mole) of olefin.

Fractions 14–20 contained 77 g. (0.49 mole) of methyl-*n*-propylneopentylcarbinol.

Fractions 1, 2, 3–7 and the contents of the traps were dried over anhydrous sodium sulfate, and fractionated through column X to give at 741 mm. pressure: 24–28, 33.5 g., 35–132°, 1.3630–1.4130; 29–31, 16.6 g., 132–140°, 1.4170–1.4218; 32–39, 39.4 g., 142–150°, 1.4237–1.4260; residue 25 g. Fractions 29–31, gave the 3,5-dinitrobenzoate of methylneopentylcarbinol, m. p. and mixed m. p., 95°. This was confirmed by the α-naphthylurethan, m. p. 86–87°, which likewise did not depress in m. p. when mixed with the α-naphthylurethan of methylneopentylcarbinol.

Fractions 24–29 were refractionated through column X, in an attempt to isolate possible 2-pentanol. Fractions 40–44, 17.2 g., 35–116° (738 mm.), 1.3655–1.3920; 45–47, 1.8 g., 116–126°, 1.4006–1.4050; 48–52, 15.4 g., 126–145°, 1.4090–1.4245; residue 4.1 g. were obtained. Fractions 45–47 gave no 2-pentanol. The rapid absorption of bromine with liberation of hydrogen bromide in fractions 44–52 indicated the presence of unchanged methylneopentyl ketone.

Based on boiling point and refractive index curves, the total yield of methylneopentylcarbinol was 5.5%.

Addition of Methyl Neopentyl Ketone to *n*-Butylmagnesium Bromide.—The addition of methyl neopentyl ketone, 342 g. (3 moles), to 3.17 moles of *n*-butylmagnesium bromide, was completed in two hours. The products were isolated in the usual fashion and fractionated through column XI, using salt–ice and dry ice–acetone traps, to give: 1–7, 44.9 g., 28° (187 mm.) –78° (9 mm.), 1.3900–1.4354; 8–19, 325 g., 78–79° (9 mm.), 1.4400; 20–23, 40.5 g., 125° (6 mm.), 1.4572–1.4590; residue 8.2 g., wt. in traps, 91 g.

Fractions 8–19 represented a 62% yield of methyl-*n*-butylneopentylcarbinol.

The 91 g. collected in the traps left 10.1 g. after removal of ether. This was combined with fractions 1–7 and refractionated at 739 mm. through column X to give: 24–31, 30.6 g., 48–136°, 1.3820–1.4168; 32–33, 7.1 g., 137°, 1.4180–1.4190; 34, 2.4 g., 145°, 1.4225; residue, 3 g.

Fraction 32 gave a quantitative yield of the α-naphthylurethan of methylneopentylcarbinol, m. p. 86–87°, when treated with α-naphthyl isocyanate indicating the presence of methylneopentylcarbinol as reduction product and the absence of 2-hexanol in detectable quantities. The same fraction gave a 3,5-dinitrobenzoate which, on one crystallization, melted at 95–95.5° corresponding to the derivative of methylneopentylcarbinol, again indicating the purity of the fraction. Both derivatives were confirmed by mixed melting points with authentic samples. Boiling point and refractive index curves showed a 5.7% yield of methylneopentylcarbinol as reduction product.

Addition of Methyl Neopentyl Ketone to *n*-Amylmagnesium Bromide.—The addition of 342 g. (3 moles) of the ketone to 3.75 moles of the Grignard reagent was completed in two and one-half hours. The products were isolated in the usual fashion and fractionated through column XI to give: 1–6, 39.4 g., 55° (31 mm.) –48° (16 mm.), 1.4080–1.4150; 7–8, 12.3 g., 48–49° (16 mm.), 1.4215–1.4245; 9–17, 105 g., 79–81° (16 mm.), 1.4340–1.4350; 18–30, 222 g., 92° (8 mm.), 1.4425; 31–32, 16.4 g., 103–109° (6 mm.), 1.4540–1.4587; residue, 43 g. The traps used in this fractionation condensed 41 g. of low boiling material which

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(9) Methyl neopentyl ketone is one of the products of the chromic acid oxidation of diisobutylene. The experimental details of its preparation will be discussed in a later paper.

(10) Previously prepared by K. C. Laughlin of this Laboratory.

contained 9.6 g. after removal of ether through column X. This was combined with fractions 1–6 to give through column X: 33–36, 14.8 g., 35–122° (750 mm.), 1.3542–1.4040; 37–39, 10.3 g., 122–132°, 1.4040–1.4140; 40–41, 6.6 g., 136°, 1.4158–1.4170; residue, 3.5 g.

The residue above, 37–39, and fractions 7–8 were combined and fractionated through column X to give 5.0 g. of methylneopentylcarbinol, $n^{20}D$ 1.4175–1.4195, which gave an α-naphthylurethan, m. p. and mixed m. p., 86–87°. This was checked with a 3,5-dinitrobenzoate, m. p. and mixed m. p., 95–95.5°. This sample, together with the 6.6 g. of fractions 40–41, represents a 3.4% yield of reduction product. Attempts to find 2-heptanol were unsuccessful. Fractions 9–17 contained dodecenes (0.63 mole) and fractions 18–30 contained methyl-*n*-amylneopentylcarbinol.

Summary

1. The yields of reduction products from the action of *n*-butylmagnesium bromide on acetyl chloride and trimethylacetyl chloride are reported.

2. Reductions involving *n*-butylmagnesium bromide with ethyl acetate, acetaldehyde and 2-hexanone are also described.

3. The reducing actions of ethyl-, *n*-propyl-, *n*-butyl- and *n*-amyl-magnesium bromides with methyl neopentyl ketone are reported.

4. No evidence was found that ether peroxide was the source of the carbinols.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

The Action of Primary Grignard Reagents on *t*-Butylacetyl Chloride

BY FRANK C. WHITMORE, A. H. POPKIN, J. S. WHITAKER, K. F. MATTIL AND J. D. ZECH

The reduction of trimethylacetyl chloride to neopentyl alcohol in 95% yield[1] and *t*-butylacetyl chloride to neopentylcarbinol[2] in 1% yield when treated with *t*-butylmagnesium chloride has been reported. The results of the present investigation agreed with these observations, the action of ethyl-, *n*-propyl-, *n*-butyl- and *n*-amylmagnesium bromides on *t*-butylacetyl chloride giving no evidence for the formation of neopentylcarbinol in detectable quantities. In view of the yields of primary alcohol obtained by the reduction of isobutyryl-, *n*-butyryl-[3] and pivalyl chlorides using *t*-butylmagnesium chloride and of acetyl chloride using *n*-butylmagnesium bromide,[4] it is possible that the primary, secondary or tertiary character of the groups attached to the α-carbon of the acid chloride may have a more pronounced influence on the extent of reduction than has the branching of the chain. This possibility is being studied.

No reduction product was isolated when *t*-butylacetyl chloride was added to ethylmagnesium bromide, but similar addition to *n*-propyl, *n*-butyl and *n*-amylmagnesium bromides produced the corresponding secondary carbinols in 24.4, 20.5 and 19.3% yields. The chief products were the expected tertiary alcohols, although the recognized instability of such higher molecular weight tertiary carbinols was again evidenced in the partial dehydration of di-*n*-propylneopentyl-, di-*n*-butylneopentyl- and the complete dehydration of di-*n*-amylneopentylcarbinols during fractionation at reduced pressure.

Pure *n*-propyl-, *n*-butyl- and *n*-amylneopentylcarbinols were required for identification of the reduction products obtained. The action of aluminum isopropylate in isopropyl alcohol on *n*-propyl, *n*-butyl and *n*-amyl neopentyl ketones produced the desired secondary carbinols in 92, 93 and 89% yields, respectively. The ketones had been prepared in excellent yields by the action of the appropriate Grignard compound on *t*-butylacetamide.[5]

Experimental

Addition of *t*-Butylacetyl Chloride to Ethylmagnesium Bromide.—The Grignard solution was prepared from 545 g. (5 moles) of ethyl bromide, b. p. 36° (730 mm.), $n^{20}D$ 1.4240, magnesium and 1.5 liter of dry ether. Addition of 182 g. (1.3 moles) of *t*-butylacetyl chloride, b. p. 68° (100 mm.), $n^{20}D$ 1.4226, prepared in 86% yield from the action of thionyl chloride on the acid, was completed in seventy-five minutes. The complex was decomposed with ice, extracted with ether and the product, on removal of solvent using column XII, was fractionated through column XI,[6] to give: fraction 1, 2.6 g., b. p. 35–78° (740 mm.), $n^{20}D$ 1.3770–1.4010; 2, 7.7 g., 50° (10 mm.), 1.4370;

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[1] Greenwood, Whitmore and Crooks, THIS JOURNAL, **60**, 2028 (1938).

[2] Whitmore and Heyd, *ibid.*, **60**, 2030 (1938).

[3] Greenwood, Whitmore and Crooks, *ibid.*, **60**, 2028 (1938).

[4] Whitmore, Popkin, Whitaker, Mattil and Zech, *ibid.*, **60**, 2458 (1938).

[5] A detailed description of the synthesis of branched aliphatic ketones from the acid amide and Grignard reagent is in preparation.

[6] The fractionating columns used have already been described, Whitmore, Popkin, Whitaker, Mattil and Zech, THIS JOURNAL, **60** 2458 (1938).

3–12, 89.4 g., 62–64° (10 mm.), 1.4390–1.4400; 13–14, 29.1 g., 76–93° (9 mm.), 1.4440; residue 7.3 g.

Fraction 1 contained ethyl alcohol; 3,5-dinitrobenzoate, m. p. and mixed m. p. 91–92°.

Fractions 3–14 were diethylneopentylcarbinol, d^{20}_4 0.8352, *MR:* calcd. 50.0, obsd. 49.8. Dehydration of the carbinol took place even on standing.

The constants for ethylneopentylcarbinol[7] are b. p. 150–152° (735 mm.), $n^{20}_{\rm D}$ 1.4250. Attempts to find this carbinol in the reaction mixture were not successful. Similar attempts to identify neopentylcarbinol also were unsuccessful.

Addition of *t*-Butylacetyl Chloride to *n*-Propylmagnesium Bromide.—Addition of 228 g. (1.7 moles) of *t*-butylacetyl chloride, b. p. 79° (150 mm.), $n^{20}_{\rm D}$ 1.4212 to 4.5 moles of *n*-propylmagnesium bromide in 1.5 l. of ether was completed in one hour and forty minutes. The addition complex was decomposed with ice, extracted with ether and the product fractionated through column XI to give (using 2 solid carbon dioxide traps): 1–8, 137.3 g., 20° (120 mm.) –62° (13 mm.), $n^{20}_{\rm D}$ 1.4142–1.4230; 9–13, 104.4 g., 62° (13 mm.) –88° (9 mm.), 1.4330–1.4410; residue, 19 g.; traps, 85 g. The trap condensate gave 7.5 g. of residue after removal of ether and this, together with fractions 1–8, through column X gave: 14, 2.4 g., 40–82° (733 mm.), 1.3780; 15–16, 4.1 g., 86–96°, 1.3825–1.3970; 17–19, 4.9 g., 135–172°, 1.4156–1.4200; 20–23, 22.9 g., 172°, 1.4220–1.4290; 24–25, 10.5 g., 172°, 1.4340–1.4345; 26–34, 46.0 g., 58–60° (10 mm.), 1.4300–1.4315; 35–37, 30.0 g., 58–59° (8 mm.), 1.4320–1.4330; residue, 1 g.

Fractions 9–13, on refractionation through column X, gave: 38, 55 g., 62–64° (10 mm.), 1.4325; 39–43, 44.8 g., 64° (10 mm.), 1.4330–1.4332, d^{20}_4 0.7759; 44–46, 18.3 g., 66–90° (10 mm.), 1.4340–1.4385; 47–48, 8.4 g., 94–96° (10 mm.), 1.4429, d^{20}_4 0.8376; 49–50, 5.1 g., 108–110° (10 mm.), 1.4390–1.4400; residue, 3.2 g.

Fractions 15–16 were identified as *n*-propyl alcohol by the m. p. and mixed m. p. of the 3,5-dinitrobenzoate, 74–74.5°.

Fractions 20–23 and 26–34 represented a 24.4% yield of *n*-propylneopentylcarbinol, phenylurethan, m. p. and mixed m. p. 82°.

Fractions 24, 25 and 35–43 were dodecenes obtained by dehydration of the tertiary carbinol. Fractions 47–48 were di-*n*-propylneopentylcarbinol. *Anal.* Calcd. for $C_{12}H_{26}O$: C, 77.4; H, 14.0. Found: C, 77.2; H, 13.9. All attempts to identify neopentylcarbinol failed.

Addition of *t*-Butylacetyl Chloride to *n*-Butylmagnesium Bromide.—The addition of 228 g. (1.7 moles) of *t*-butylacetyl chloride to 4.5 moles of *n*-butylmagnesium bromide in 1.5 l. of ether was completed in one hour and thirty-five minutes. The product was isolated in the usual manner to give through column XI: 1–14, 83 g., 26–82° (14 mm.), 1.4024–1.4352; 15–21, 43 g., 87–112° (8 mm.), 1.4391–1.4400; 22–24, 132.3 g., 112° (8 mm.), 1.4415–1.4424; residue, 9 g. The solid carbon dioxide trap contents, 95.0 g., were largely ether. Fractions 1–21 contained water, indicating dehydration.

The trap condensates, on removal of ether, yielded 17 g. which on combining with fractions 1–14 gave through column X: 25–28, 11.3 g., 35–75° (733 mm.), 1.3540–1.3680; 29–41, 47.2 g., 102–190°, 1.3840–1.4291; 42–49, 31.2 g., 190–200°; 1.4300–1.4390; residue, 3.4 g.

Fractions 15–24 were refractionated through column X to give: 50, 6.7 g., 90° (8 mm.), 1.4385; 51–53, 23.1 g., 90° (8 mm.), 1.4400–1.4403; 54–61, 84.0 g., 101–110° (8 mm.), 1.4415–1.4458; 62–64, 35.8 g., 112–113° (8 mm.), 1.4460; 65, 10.2 g., 113° (8 mm.), 1.4469; residue, 2 g.

Fractions 29–41, on refractionation through column X, gave: 66–69, 6.5 g., 74–108° (735 mm.), 1.3807–1.3980; 70–74, 10.0 g., 109–113°, 1.4010–1.4050; 75–76, 3.2 g., 113–186°, 1.4170–1.4250; 77–81, 19.0 g., 186–190°, 1.4260–1.4300; residue, 1 g.

Fractions 42–49 and 77–81 represented 54.9 g. (0.35 mole), 20.5% yield of *n*-butylneopentylcarbinol, α-naphthylurethan, m. p. and mixed m. p., 70–70.5°.

Fractions 51–53 were olefins obtained by the dehydration of di-*n*-butylneopentylcarbinol, d^{20}_4 of olefins was 0.7824; *MR*, calcd. 66.38; obsd. 66.12.

Fractions 62–64 contained di-*n*-butylneopentylcarbinol d^{20}_4 0.8320; *MR*, calcd. 68.5; obsd. 68.59. Dehydration followed on standing.

Fractions 70–74 were *n*-butyl alcohol, phenylurethan, m. p. and mixed m. p., 62.5–63°. All attempts to identify neopentylcarbinol failed.

Addition of *t*-Butylacetyl Chloride to *n*-Amylmagnesium Bromide.—The addition of 200 g. (1.5 moles) of *t*-butylacetyl chloride to 4.1 moles of *n*-amylmagnesium bromide, completed in one hour and twenty minutes, yielded a crude product which gave through column XI: 1–4, 43.9 g., 42–87° (15 mm.), 1.4140–1.4280; 5–7, 36.5 g., 90° (15 mm.) –92° (10 mm.), 1.4310–1.4316; 8–11, 36.7 g., 92–107° (10 mm.), 1.4340–1.4348; 12–18, 186.3 g., 118–130° (13 mm.), 1.4442–1.4460; residue, 5 g.; trap contents, 59 g. Fraction 1–7 contained water, indicating dehydration.

The trap condensate yielded 5.1 g. which was combined with fraction 1. Repeated fractionation of all the fractions using column X gave: 19, 1.4 g., 35–113° (733 mm.), 1.3530; 20–24, 19.9 g., 113–136°, 1.4132–1.4170; 25, 3.7 g., 50–90° (13 mm.), 1.4260; 26–32, 54.5 g., 90–93° (10 mm.), 1.4302–1.4350; 33, 8.0 g., 90–112° (10 mm.), 1.4410; 34–39, 147.7 g., 118° (10 mm.), 1.4450, d^{20}_4 0.7856, *MR* for the hexadecenes; calcd. 75.62; obsd. 75.70; residue, 12.7 g., 1.4452.

Fractions 20–24 were *n*-amyl alcohol, phenylurethan, m. p. and mixed m. p., 48°.

Fractions 26–32 were *n*-amylneopentylcarbinol, phenylurethan, m. p. and mixed m. p., 60–61°. The yield, estimated from the boiling point and refractive index curves, was 19.3%.

Fractions 34–39 were 0.71 mole of olefins from the dehydration of di-*n*-amylneopentylcarbinol. No evidence was obtained for the presence of neopentylcarbinol.

Preparation of *n*-Propylneopentylcarbinol.—*n*-Propyl neopentyl ketone, 39 g. (0.27 mole), b. p. 111–112° (150 mm.),[8] was heated for twenty-four hours under column VI with 32.6 g. (0.15 mole), of aluminum isopropylate in 300 cc. of dry isopropyl alcohol, the acetone being removed as formed. The reaction mixture was treated with ice and excess hydrochloric acid, extracted with ether and the product, on removal of the solvent, fractionated through VI to give: 1–2, 1.7 g., 80–84.5° (29 mm.), 1.4193–1.4243;

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[7] Prepared by C. I. Noll, this Laboratory.

[8] Prepared by H. C. Crafton, this Laboratory.

3–7, 35.5 g., 85° (29 mm.), 1.4260; residue, 0.8 g. Fractions 3–7 were a 92% yield of *n*-propylneopentylcarbinol. *Anal.* Calcd. for $C_9H_{20}O$: C, 75.0; H, 14.0. Found: C, 74.5; H, 14.5. The phenylurethan had m. p. 82°.

Preparation of *n*-Butylneopentylcarbinol.—*n*-Butyl neopentyl ketone, b. p. 69° (13 mm.), n^{20}_D 1.4204, d^{20}_4 0.8143, was prepared in 77% yield by the action of *n*-butylmagnesium bromide on *t*-butylacetamide, m. p. 132°. Heating of 26.7 g. (0.17 mole) of the ketone with 20.4 g. (0. 1 mole) of aluminum isopropylate in 120 cc. of dry isopropyl alcohol was conducted for twenty-four hours with the removal of acetone, during the course of the reaction, through column VI: 1–2, 3.1 g., 90–99° (30 mm.), 1.4254–1.4300; 3–5, 22.2 g., 95° (24 mm.), 1.4308, d^{20}_4 0.8212; residue, 2.0 g. Fractions 3–5 represented a 93% yield of *n*-butylneopentylcarbinol. *Anal.* Calcd. for $C_{10}H_{22}O$: C, 75.9; H, 13.9. Found: C, 75.7; H, 14.1. The α-naphthylurethan had m. p. 70–70.5°.

Preparation of *n*-Amylneopentylcarbinol.—*n*-Amylneopentyl ketone, b. p. 86° (13 mm.), n^{20}_D 1.4247, d^{20}_4 0.8184, was prepared in 60% yield from *n*-amylmagnesium bromide and *t*-butylacetamide. Heating of 51 g. (0.25 mole) of aluminum isopropylate in 400 cc. of dry isopropyl alcohol with 90 g. (0.53 mole) of the ketone for thirty-three hours gave a crude carbinol which, on fractionation through column VI, gave: 1–2, 3.4 g., 80–94° (12 mm.), 1.4271–1.4326; 3–12, 80.7 g., 96° (13 mm.), 1.4338, d^{20}_4 0.8225. Fractions 3–12 represented an 89% yield of *n*-amylneopentylcarbinol. *Anal.* Calcd. for $C_{11}H_{24}O$: C, 76.7; H, 14.0. Found: C, 76.9; H, 14.0. Phenylurethan, m. p. 60.5–61°; α-naphthylurethan, m. p. 63–63.5°.

Summary

1. The action of *n*-propyl-, *n*-butyl- and *n*-amylmagnesium bromides on *t*-butylacetyl chloride produced, together with the expected tertiary carbinols and olefins, *n*-propylneopentylcarbinol in 24.4% yield, *n*-butylneopentylcarbinol in 20.5% yield, *n*-amylneopentylcarbinol in 19.3% yield, respectively. No reduction product could be isolated when ethylmagnesium bromide was used.

2. The preparation and physical constants of *n*-propylneopentyl-, *n*-butylneopentyl-, and *n*-amylneopentylcarbinols have been reported.

STATE COLLEGE, PENNA.

RECEIVED JUNE 29, 1938

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Studies in the Phenanthrene Series. XXI. Morpholino Alcohols Derived from Phenanthrene[1]

BY ERICH MOSETTIG, FORREST W. SHAVER AND ALFRED BURGER

As part of a systematic search for substances with central narcotic action, which, eventually, might replace morphine, we have synthesized in previous years a large variety of amino alcohols derived from phenanthrene.[2] Dr. N. B. Eddy at the University of Michigan has shown[3] that some of these phenanthryl amino alcohols produce in the cat marked analgesia and a physiological picture very like that of morphine. Furthermore, a distinct interdependence of degree of analgesic action and nature of the tertiary amino group became evident when, in the various groups of amino alcohols, individual members differing only in the basic group were compared. Thus, for example, the diethylamino derivatives of types I and II are superior to the dimethylamino derivatives.[4]

Extension of these studies to morpholino alcohols (I–VI) seemed justified, in order that comparison with the corresponding diethyl and piperidino compounds might be made.

The preparation of the various amino alcohols proceeded quite normally except that in the catalytic hydrogenation of 2-morpholino-1-keto-1,2,-3,4-tetrahydrophenanthrene the two diastereoisomeric forms (A and B) of the corresponding amino alcohol (type III) were formed. We have

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[1] (a) The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, the University of Virginia, and the University of Michigan. (b) Communications XIX and XX of this series have been submitted to the *Journal of Organic Chemistry*.

[2] (a) Mosettig and van de Kamp, THIS JOURNAL, **55**, 3448 (1933); (b) Burger and Mosettig, *ibid.*, **56**, 1745 (1934); (c) van de Kamp and Mosettig, *ibid.*, **57**, 1107 (1935); (d) Mosettig and Burger, *ibid.*, **57**, 2189 (1935); (e) van de Kamp and Mosettig, *ibid.*, **58**, 1568 (1936); (f) Burger and Mosettig, *ibid.*, **58**, 1570 (1936); (g) Burger and Mosettig, *ibid.*, **58**, 1857 (1936); (h) van de Kamp, Burger and Mosettig, *ibid.*, **60**, 1321 (1938); (i) Burger, *ibid.*, **60**, 1533 (1938).

[3] (a) Eddy, *J. Pharmacol.*, **55**, 419 (1935); (b) Eddy, *ibid.*, (*Proc.*) **54**, 140 (1936); (c) Mosettig, Eddy and co-workers, "Attempts to Synthesize Substances with Central Narcotic and, in Particular, Analgesic Action," Supplement 138 to the U. S. Public Health Reports, Government Printing Office, Washington, D. C., in press.

[4] Such regularities have been observed also in the dibenzofuran series [Eddy, *J. Pharmacol.*, **58**, 159 (1936); Mosettig and Robinson, THIS JOURNAL, **57**, 2186 (1935); Robinson and Mosettig, *ibid.*, **58**, 688 (1936)] and in the carbazole series [Ruberg and Small, *ibid.*, **60**, 1591 (1938)].

No.	Derivatives of phenanthrene	Appearance
1	2-(2-Morpholino-1-oxo-ethyl)-[a]	Light yellow plates
2	-Hydrochloride[b]	Light yellow plates
3	2-(2-Morpholino-1-hydroxy-ethyl)-[c]	Colorless
4	-Hydrochloride[d]	Colorless leaflets
5	3-(2-Morpholino-1-oxo-ethyl)-[e]	Light yellow
6	-Hydrochloride	Light yellow needles
7	3-(2-Morpholino-1-hydroxy-ethyl-	Colorless leaflets
8	-Hydrochloride[f]	Colorless leaflets
9	2-(3-Morpholino-1-oxo-propyl)-[g]	Colorless leaflets
10	-Hydrochloride[b]	Colorless leaflets
11	2-(3-Morpholino-1-hydroxy-*n*-propyl)-[h]	Colorless
12	-Hydrochloride[i]	Needles
13	2-(3-Morpholino-1-acetoxy-*n*-propyl)-HCl[j]	Colorless plates
14	3-(3-Morpholino-1-oxo-propyl)-[k]	Colorless leaflets
15	-Hydrochloride[l]	Colorless prisms
16	3-(3-Morpholino-1-hydroxy-*n*-propyl)-	
17	-Hydrochloride[m]	Colorless
18	3-(3-Morpholino-1-acetoxy-*n*-propyl)-HCl[j]	Colorless prisms
19	3-Methoxy-9-(2-morpholino-1-oxo-ethyl)-HCl[n]	Yellow
20	3-Methoxy-9-(2-morpholino-1-hydroxy-ethyl)-HCl[o]	Glittering leaflets
	Derivatives of 1,2,3,4-tetrahydrophenanthrene	
21	2-Morpholino-1-keto-[p]	Yellow clusters
22	-Hydrochloride	Colorless
23	2-Morpholino-1-hydroxy-(A)[q]	Colorless needles
24	-Hydrochloride	Colorless
25	2-Morpholino-1-acetoxy-HCl (A)	
26	2-Morpholino-1-hydroxy-(B)	Stout prisms
27	-Hydrochloride	Colorless
28	2-Morpholino-1-hydroxy-(B_1)	Colorless flat plates
29	2-Morpholino-1-acetoxy-HCl (B_1)	
30	2-Morpholinomethyl-1-keto-	Glittering plates
31	-Hydrochloride[r]	Colorless prisms
32	2-Morpholinomethyl-1-hydroxy-	Colorless prisms
33	-Hydrochloride[s]	Stout prisms
34	3-Morpholino-4-keto-[t]	Colorless needles
35	-Hydrochloride	Colorless
36	3-Morpholino-4-hydroxy-	Colorless prisms
37	-Hydrochloride[u]	Whetstone-shaped
38	3-Morpholino-4-acetoxy-HCl	Colorless needles
39	3-Morpholinomethyl-4-keto-HCl[v]	Prisms
40	3-Morpholinomethyl-4-hydroxy-HCl	Colorless flat plates

Solvent	M. p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
MeOH	154–156	$C_{20}H_{19}O_2N$	78.65	78.49	6.28	6.30
MeOH–Et_2O	268, dec.	$C_{20}H_{20}O_2NCl$	70.25	70.32	5.90	6.05
MeOH	129–131	$C_{20}H_{21}O_2N$	78.13	78.06	6.89	6.67
MeOH–Et_2O	244–245, dec.	$C_{20}H_{22}O_2NCl$	69.84	69.61	6.46	6.35
MeOH	136.5–137.5	$C_{20}H_{19}O_2N$	78.65	78.44	6.28	6.13
MeOH–Et_2O	237, dec.	$C_{20}H_{20}O_2NCl$	70.25	69.95	5.90	6.03
MeOH	115–117	$C_{20}H_{21}O_2N$	78.13	78.18	6.89	6.56
MeOH–Et_2O	214, dec.	$C_{20}H_{22}O_2NCl$	69.84	69.59	6.46	6.32
MeOH	120–130	$C_{21}H_{21}O_2N$	78.95	79.34	6.63	6.39
MeOH	224–226, dec.	$C_{21}H_{22}O_2NCl$	70.86	71.15	6.24	6.19
	98–100	$C_{21}H_{23}O_2N$	78.46	78.30	7.22	7.36
MeOH–Et_2O	177–179, dec.	$C_{21}H_{24}O_2NCl$	70.46	70.18	6.76	6.99
MeOH–Et_2O	253, dec.	$C_{23}H_{26}O_3NCl$	69.05	69.36	6.56	6.84
MeOH	114–116	$C_{21}H_{21}O_2N$	78.95	78.96	6.63	6.75
MeOH–Et_2O	207–208, dec.	$C_{21}H_{22}O_2NCl$	70.86	71.06	6.24	6.22
MeOH	83–86	$C_{21}H_{23}O_2N$	78.46	78.36	7.22	7.32
MeOH–Et_2O	172–174, dec.	$C_{21}H_{24}O_2NCl$	70.46	70.72	6.76	6.80
	226–227, dec.	$C_{23}H_{26}O_3NCl$	69.05	69.44	6.56	6.74
MeOH–Et_2O	240–242, dec.	$C_{21}H_{22}O_3NCl$		Nitrogen,	3.77	3.72
MeOH–Et_2O	217–219, dec.	$C_{21}H_{24}O_3NCl$	67.44	67.04	6.47	6.52

Me_2CO	141–171, dec.	$C_{18}H_{19}O_2N$	76.83	77.04	6.81	6.81
EtOH-Et_2O	230–231, dec.	$C_{18}H_{20}O_2NCl$		Nitrogen,	4.41	4.62
EtOH	179–180	$C_{18}H_{21}O_2N$	76.28	75.90	7.48	7.70
EtOH	245, dec.	$C_{18}H_{22}O_2NCl$	67.57	67.39	6.94	6.68
EtOH–Et_2O	189, dec.	$C_{20}H_{24}O_3NCl$	66.36	66.70	6.69	6.65
EtOH	139–140.5	$C_{18}H_{21}O_2N$	76.28	76.16	7.48	7.52
EtOH–Et_2O	252–253, dec.	$C_{18}H_{22}O_2NCl$	67.57	67.43	6.94	7.33
EtOH	153–154	$C_{18}H_{21}O_2N$	76.28	76.28	7.48	7.71
MeOH–Et_2O	208–210, dec.	$C_{20}H_{24}O_3NCl$	66.36	65.72	6.69	7.10
Dil. MeOH	121	$C_{19}H_{21}O_2N$		Nitrogen,	4.75	4.77
EtOH	182–183, dec.	$C_{19}H_{22}O_2NCl$		Nitrogen,	4.22	4.26
EtOH	120–121	$C_{19}H_{23}O_2N$	76.72	76.82	7.80	7.73
EtOH	230–240, dec.	$C_{19}H_{24}O_2NCl$	68.33	68.36	7.25	6.96
Dil. MeOH	127–128	$C_{18}H_{19}O_2N$		Nitrogen,	4.98	5.08
MeOH–Et_2O	227–228, dec.	$C_{18}H_{20}O_2NCl$	68.00	68.38	6.35	6.21
MeOH	185–186	$C_{18}H_{21}O_2N$	76.28	76.45	7.48	7.36
EtOH	238–240, dec.	$C_{18}H_{22}O_2NCl$	67.57	67.24	6.94	7.52
EtOH–Et_2O	203–204, dec.	$C_{20}H_{24}O_3NCl$		Nitrogen,	3.87	4.00
EtOH–Et_2O	170–172, dec.	$C_{19}H_{22}O_2NCl$		Nitrogen,	4.22	4.40
EtOH–Et_2O	173, dec.	$C_{19}H_{24}O_2NCl$	68.33	68.62	7.25	7.07

[a] To a solution of 5 g. of 2-ω-bromoacetylphenanthrene[2a] in 40 ml. of dry benzene was added 3.5 g. of morpholine (n^{20}D 1.4547), and the mixture was allowed to stand overnight. It was diluted with ether, the solution was washed with water, and the solvent was evaporated under reduced pressure; yield 89%.

[b] The hydrochloride was obtained by adding an ethereal solution of hydrogen chloride to an acetone solution of the free base.

[c] Liberated from No. 4 with sodium hydroxide solution and extracted into ether.

[d] A suspension of 4 g. of No. 2 and 0.16 g. of platinum oxide in 160 ml. of ethanol absorbed the required amount of hydrogen in about ten hours. The catalyst was filtered out and the solvent was evaporated under reduced pressure. The residue was dissolved in acetone, the acetone solution was diluted with ether, and allowed to crystallize; yield 75%.

[e] Obtained like No. 1, by employing 8.3 g. of 3-ω-bromoacetylphenanthrene, 40 ml. of benzene, and 5.6 g. of morpholine. The amino ketone was purified through the hydrochloride; yield 85%.

[f] Prepared like No. 4; yield 70%.

[g] A mixture of 3 g. of 2-acetylphenanthrene,[5] 1 g. of paraformaldehyde, 2 g. of morpholine hydrochloride (prepared by neutralizing morpholine with alcoholic hydrogen chloride and precipitating the salt with ether), and 12 ml. of isoamyl alcohol was boiled under reflux for six minutes. The amino ketone hydrochloride precipitated out within this time, and the precipitation was completed by addition of ether to the cooled reaction mixture. The free base was liberated from the salt with ammonium hydroxide, and extracted into ether. The ether solution was washed with water. The base was purified by sublimation in an oil-pump vacuum, and crystallization; yield 73%.

[h] Prepared from No. 12 and purified by sublimation in an oil-pump vacuum.

[i] Prepared like No. 4; yield 63%.

[j] A suspension of 0.3 g. of the amino alcohol in 5 ml. of dry pyridine and 1 ml. of acetic anhydride was allowed to stand for forty-eight hours. The solvent was evaporated under reduced pressure, the residue was washed with acetone and recrystallized.

[k] Prepared from No. 15.

[l] Prepared like No. 9, except that the hydrochloride, as precipitated from the reaction mixture, was purified by crystallization; yield 76%.

[m] Prepared by catalytic hydrogenation of No. 15; yield 82%.

[n] Ten and two-tenths grams of 3-methoxy-9-ω-bromoacetylphenanthrene[2b] was allowed to react with 7.5 g. of morpholine in 50 ml. of benzene for one hour. The mixture was extracted with water, the benzene solution was dried, evaporated in a vacuum, and the oily residue was converted to the hydrochloride in acetone solution; yield 82%.

[o] Prepared by catalytic hydrogenation of No. 19 (methanol, platinum oxide); yield 70%. The free base could not be obtained crystalline.

[p] Nine grams of 1-keto-2-bromo-1,2,3,4-tetrahydrophenanthrene[2d] and 7.5 g. of morpholine were allowed to react in 30 ml. of benzene for forty-eight hours. The red mixture was extracted with water and a crystalline residue was obtained by evaporation of the benzene layer; yield 55%.

[q] Seventeen and five-tenths grams of No. 22 in 400 ml. of methanol and 0.5 g. of platinum oxide absorbed approximately the calculated amount of hydrogen in a week. The mixture of crystalline hydrochlorides was converted to the bases, m. p. 95–127°; yield 16 g. This mixture was dissolved in 100 ml. of hot ethanol and allowed to crystallize. The first crop (A) was filtered when the temperature of the solution had reached 30°. Another crop (B) was obtained by allowing the filtrate to crystallize slowly. The base A was recrystallized from ethanol three times to the constant m. p. 179–180°; yield 1 g. The hydrochloride was formed from the base in acetone suspension with ethereal hydrogen chloride. The acetyl derivative was obtained by the action of acetic anhydride in pyridine solution. The base B was recrystallized from ethanol three times to the constant m. p. 139–140.5°; yield 1 g. In a second experiment, similarly, two bases were obtained. The one was base A of m. p. 179–180°, the other one melted at 153–154° (B_1). A new determination of the melting point of B showed that this compound had changed, in the meantime, to the higher-melting form.

[r] Prepared by the Mannich reaction, by heating to boiling a solution of the reactants (10 g. of 1-ketotetrahydrophenanthrene, 12 g. of paraformaldehyde, and 7 g. of morpholine hydrochloride) in 50 ml. of isoamyl alcohol for four minutes. The crude hydrochloride was washed with acetone; yield 41%.

[s] Prepared by catalytic hydrogenation of No. 31; yield 94%.

[t] Prepared like No. 21 by allowing 3-bromo-4-keto-1,2,3,4-tetrahydrophenanthrene to react with morpholine in benzene solution; yield 63%.

[u] Prepared by catalytic hydrogenation of No. 35; yield 68%.

[v] Six grams of 4-keto-1,2,3,4-tetrahydrophenanthrene was boiled with 4.2 g. of morpholine hydrochloride, 7.2 g. of paraformaldehyde, and 24 ml. of isoamyl alcohol for twenty-five minutes. The reaction mixture was worked up in the usual manner; yield 30%.

never observed in our previous work the simultaneous formation of diastereoisomeric amino alcohols under analogous conditions. When a noble metal catalyst is employed in the reduction of amino ketones, generally only one of the two possible amino alcohols is formed, while in the sodium amalgam reduction both forms may be obtained.[6]

The possibility that one of the two compounds A or B is a hexahydro derivative cannot be excluded entirely, since, because of lack of material, we did not attempt to demonstrate the isomerism by converting A and B to identical desoxy compounds.

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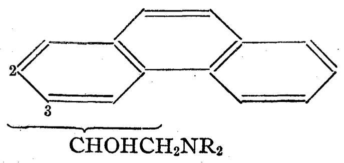
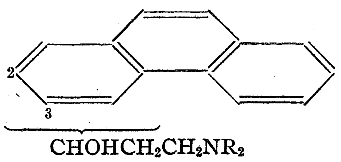
(5) Mosettig and van de Kamp, THIS JOURNAL, **52**, 3704 (1930).

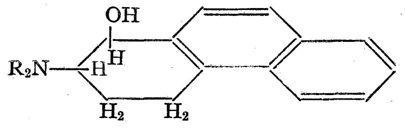
(6) See Hyde, Browning and Adams, *ibid.*, **50**, 2287 (1928), and Mannich, Borkowsky and Wan Ho Lin, *Arch. Pharm.*, **275**, 54 (1937). See also Shriner and Teeters, THIS JOURNAL, **60**, 936 (1938).



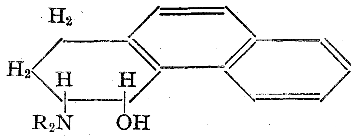
I[2a]



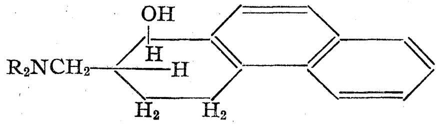
II[2e]



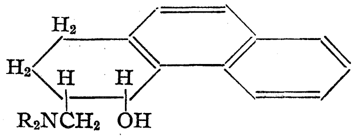
III[2d]



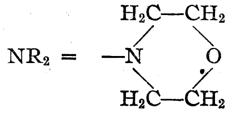
IV[2d]



V[2f]



VI[2f]



All of the amino alcohols that have been tested so far (Nos. 4, 8, 20, 24, 27, 33, 37, 40 of the accompanying table)[7] show only low analgesic action or none at all. In the instances where a comparison with analogous diethylamino and piperidino compounds was possible, it became apparent that replacement of the diethyl or piperidino group by the morpholino group resulted in a decrease of analgesia in the ratio from 2:1 to about 8:1.

Summary

The synthesis of a series of morpholino alcohols from 2-acetylphenanthrene, 3-acetylphenanthrene, 3-methoxy-9-acetylphenanthrene, 1-keto-tetrahydrophenanthrene and 4-keto-tetrahydrophenanthrene is described.

UNIVERSITY, VIRGINIA RECEIVED JULY 9, 1938

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[7] Eddy, unpublished results.

[CONTRIBUTION FROM THE DEPT. OF CHEMICAL ENGINEERING, UNIVERSITY OF CINCINNATI, AND THE RESEARCH LABORATORIES OF THE WM. S. MERRELL COMPANY]

An Investigation of the Effect of Chemical Structure on Local Anesthetic Action of Diothane Analogs[1]

BY ELSIE M. WALTER[2]

Most local anesthetics in general use contain a benzene ring somewhere in their structure. In fact, many early experimenters claimed that a compound must contain a benzoyl group to exhibit anesthetic action. In 1925, Gilman and Pickens[3] studied the effect of various aromatic rings on the anesthetic action of procaine. They prepared the furan, thiophene, and pyrrole analogs of procaine. Their results indicate that the order of decreasing activity is benzene > pyrrole > thiophene > furan > methyl. More recently, however, Phatak and Emerson[4] prepared various alkyl esters of 2-furoic acid where the alkyl varied from methyl to amyl. They found that all of the compounds possess local anesthetic action which increases with the size of the alkyl from methyl to amyl. The amyl furoate has approximately the same activity as cocaine. It was pointed out by the authors that the corresponding benzoates show either incomplete or no anesthetic action.

Since very little work has been done on the effect of substituting various aromatic rings for the benzene ring in the structure of local anesthetics, it was decided to prepare some furan analogs of Diothane (piperidinopropanediol diphenylurethan hydrochloride[5]) and compare their

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[1] From a thesis in partial fulfilment of the requirements for the degree of Chemical Engineer, University of Cincinnati, June, 1938.

[2] Present address: Institutum Divi Thomae, Cincinnati, Ohio.

[3] H. Gilman and R. M. Pickens, THIS JOURNAL, **47**, 245 (1925).

[4] N. M. Phatak and G. A. Emerson, *J. Pharmacol.*, **58**, 174 (1936).

[5] T. H. Rider, THIS JOURNAL, **52**, 2115 (1930); T. H. Rider and E. S. Cook, *J. Pharmacol.*, in press.

physiological action with that of the corresponding benzoyl compounds. The difuroate, dibenzoate, diacetate, dicinnamate, and difuranacrylate of piperidinopropanediol were prepared and tested pharmacologically. The dibenzoate was previously reported by Pyman.[6] The remaining compounds have not been reported before.

Experimental

1-Piperidinopropane-2,3-diol dibenzoate was prepared from 1-piperidinopropane-2,3-diol and benzoyl chloride by the Schotten–Baumann reaction according to the method of Pyman,[6] but it was recrystallized from petroleum ether instead of alcohol. The piperidinopropanediol used in all the reactions was made from the previously described specially purified piperidine.[7] The dibenzoate formed needle-like white crystals, m. p. 64–65°, uncorr., as reported by Pyman.[6] The hydrochloride was prepared by dissolving the free base in ether and introducing gaseous hydrogen chloride. The gummy, white hydrochloride on washing with anhydrous ether became solid and was ground to a fine white powder; m. p. 126–130°, uncorr.

Anal. Calcd. for $C_{22}H_{26}O_4NCl$: Cl, 8.78. Found: Cl, 8.84.

1-Piperidinopropane-2,3-diol difuroate was prepared from piperidinopropanediol and furoyl chloride in the same manner as the dibenzoate. The ester was decolorized with charcoal in ether solution. It was precipitated as a fluffy white solid by evaporating the ether solution to a small volume and adding petroleum ether. It can also be crystallized from ether in white needle-like crystals; m. p. 73–74°, uncorr. The hydrochloride was prepared in the same manner as the dibenzoate hydrochloride; m. p. 163–164.5°, uncorr.

Anal. Calcd. for $C_{18}H_{22}O_6NCl$: Cl, 9.19. Found: Cl, 9.28.

1-Piperidinopropane-2,3-diol diacetate was prepared by slowly adding with stirring 32 g. (0.2 mole) of piperidinopropanediol to 45 g. (0.44 mole) of acetic anhydride kept in an ice-bath. After the addition was completed, the mixture was heated to 75° and then allowed to stand at room temperature for about five hours. After neutralizing with sodium carbonate in an ice-bath, the ester was extracted with ether and the solution was dried over sodium sulfate. After removing the ether, the diacetate remained as a colorless oil which becomes orange upon exposure to light and air. The hydrochloride was prepared in the usual manner and stored in a desiccator, since the ester hydrolyzes readily on exposure to moisture; m. p. 128–133°, uncorr.

Anal. Calcd. for $C_{12}H_{22}O_4NCl$: Cl, 12.68. Found: Cl, 12.80.

1-Piperidinopropane-2,3-diol dicinnamate could not be prepared by the Schotten–Baumann reaction because of the hydrolysis of cinnamoyl chloride. An attempt to produce it from the diacetate by the Perkin reaction failed also. Condensation of the alcohol and acid chloride was successful in benzene but the resulting ester did not crystallize and could not be completely freed of benzene. Condensing the acid chloride and the alcohol without a solvent was the most satisfactory method.

Seven grams (0.044 mole) of cinnamoyl chloride was melted and 3.2 g. (0.02 mole) of piperidinopropanediol were added slowly with stirring. The material formed a clear yellow viscous mass. After cooling and washing with numerous portions of dry ether and standing for several days under ether the crude hydrochloride crystallized. This was purified by neutralizing with the theoretical quantity of 5% sodium hydroxide, extracting with ether, precipitating with 2 *N* hydrochloric acid, and regenerating the free base with sodium hydroxide. The hydrochloride was prepared by treating the free base, in absolute ether, with hydrogen chloride gas, freeing from excess hydrochloric acid by washing with ether, and crystallizing from water; m. p. 159–161°, uncorr.

Anal. Calcd. for $C_{26}H_{30}O_4NCl$: Cl, 7.78. Found: Cl, 8.10.

1-Piperidinopropane-2,3-diol difuranacrylate was prepared similarly to the dicinnamate. Furanacrylic acid was prepared according to the method of Gibson and Kahnweiler[8] and was converted into the acid chloride according to the method of T. Sasaki.[9] Three and two-tenths grams (0.02 mole) of piperidinopropanediol was added slowly with stirring to 6 g. (0.044 mole) of melted furanacryloyl chloride. The crude hydrochloride was a very viscous light brown oil. The free base, obtained by neutralizing the hydrochloride with the theoretical amount of sodium hydroxide, extracting with ether, and decolorizing with charcoal, was also a heavy viscous oil. The purified hydrochloride was obtained similarly to that of the dicinnamate and was a colorless oil when first prepared but became colored in a few hours. It has resisted attempts to crystallize it.

Anal. Calcd. for $C_{22}H_{26}O_6NCl$: Cl, 8.14. Found: Cl, 8.19.

Pharmacological.—The following table roughly evaluates the strength of the compounds as local anesthetics. The tests were made with a solution of the hydrochlorides in distilled water. The time in minutes required for the production of sensory anesthesia in the exposed sciatic nerve of the frog, and the duration of anesthesia after one-minute application of the solution to the cornea of the rabbit are given.

Ester	Concn., %	Frog sciatic onset, min.	Rabbit cornea Onset, min.	Rabbit cornea Duration, min.
Dibenzoate	1	2	2	7
Difuroate	1	4	2.5	4
Diacetate	1	..	..	No action
Dicinnamate	<1	2	2.5	6–7
Difuranacrylate	1		1.5	8–8.5
Difuranacrylate	2	..	1.5	13
Procaine	1			Incomplete

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(6) F. L. Pyman, *J. Chem. Soc.*, **93**, 1793 (1908).

(7) E. S. Cook and T. H. Rider, THIS JOURNAL, **59**, 1739 (1937); T. H. Rider and E. S. Cook, *ibid.*, **59**, 1741 (1937); E. S. Cook, *ibid.*, **59**, 2661 (1937).

(8) H. B. Gibson and C. F. Kahnweiler, *Am. Chem. J.*, **12**, 314 (1890).

(9) T. Sasaki, *Biochem. Z.*, **25**, 272 (1910).

The dibenzoate caused irritation of the eye. The dicinnamate caused a milky film to appear over the cornea, sloughing of the tissue, and about twelve hours later, marked conjunctival irritation and swelling of the eyelids. The difuroate and the difuranacrylate seemed to have a lachrymatory effect, but caused very little, if any, irritation of the eyes. There was considerable difficulty in obtaining a solution of the dicinnamate. A few drops of hydrochloric acid were used to produce the 1% suspension for testing on the cornea, and a 25% solution of propylene glycol was required to produce the 1% solution for testing on the sciatic nerve of the frog.

It will be seen that the dibenzoate was more active than the difuroate, which agrees with the findings of Gilman and Pickens.[3] However, introduction of a double bond appears to reverse this order, the difuranacrylate being more active than the dicinnamate. In the furan series, the introduction of the double bond gave an expected increase in activity, the furanacrylate being twice as active as the furoate. A similar increase in activity is not found on comparing the dicinnamate with the dibenzoate, but this may have been due to the low solubility of the dicinnamate and the precipitation on application to the eye. The dicinnamate showed rapid penetration when applied to the nerve. As was expected, the diacetate was inactive. The furan compounds have the advantage over the benzene analogs of being more soluble and less irritating.

Acknowledgment.—The author wishes to express her sincere appreciation for the advice, criticism and assistance given her by Drs. Elton S. Cook of the Institutum Divi Thomae, Robert S. Shelton of the Wm. S. Merrell Co., and E. F. Farnau of the University of Cincinnati. The author wishes to thank Mr. N. M. Phatak for the pharmacological tests.

Summary

The diacetate, dibenzoate, difuroate, dicinnamate, and difuranacrylate of piperidinopropanediol were prepared. The results of the pharmacological tests indicate that the furan ring has a favorable effect on anesthetic action. It apparently increases the solubility and decreases the irritation in this series of compounds.

CINCINNATI, OHIO RECEIVED JULY 23, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BARNARD COLLEGE]

Addition Reactions of Unsaturated Alpha-Ketonic Acids. V

BY MARIE REIMER AND ELIZABETH CHASE

Earlier papers in this series[1] have shown that the behavior of the unsaturated side-chain of benzalpyruvic acid is influenced strongly by methoxyl groups in different positions in the benzene ring: the stability of the dibromo addition products, the tendency to formation and the stability of hydrates, the color of the compounds alone and in solution in concentrated sulfuric acid show decided variation in the different compounds. Most striking is the fact that a methoxyl group in the para position entirely inhibits the photochemical reaction so conspicuous a characteristic of benzalpyruvic acid and its esters[2] and noticeable to a less degree with the *o*- and the *m*-methoxy-substituted acids. Because of the prevalence of methoxyl groups in natural products and because of differences in activity noticed when methoxyl replaces hydrogen in several different classes of compounds,[3] it becomes of interest to determine whether the blocking of the sunlight reaction is a function of the *p*-methoxyl group, as such, or whether and to what extent other groups in the para position in the benzene ring have the same effect. Such studies are now under way in this Laboratory.

The present paper deals with benzalpyruvic acid in which there is a methyl group in the para position. The methyl group was chosen because of certain well-known similarities in the influence of methyl and methoxyl: the effect on orientation in the benzene ring, on ease of substitution and on the coupling reaction,[4] for example. These, however, are influences of these groups on hydrogen of the ring. In reactions involving a side-chain wide differences have been described, not-

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[1] No. IV, Reimer, Tobin and Schaffner, THIS JOURNAL, **57**, 211 (1935).

[2] Reimer, *ibid.*, **46**, 783 (1924).

[3] *Cf.* Reimer, *ibid.*, **48**, 2454 (1926).

[4] V. Auwers and Borsche, *Ber.*, **48**, 1716 (1915).

ably the greater effect of the methoxyl over that of the methyl group on dissociation into free radicals of hexaarylethanes[5] and of phenylated hydrazines[6] and the increased "migration aptitude" of the anisyl group.[7] In the case here studied differences have been noted. The *p*-methylbenzalpyruvic acid adds bromine readily to form a dibromide more stable than that of the *p*-methoxy compound but less so than that of the unsubstituted acid. It forms an unstable hydrate: that of benzalpyruvic acid is stable while the *p*-methoxy acid forms no hydrate. The methyl substituted acid is slowly affected by sunlight. The color changes with sulfuric acid are not so marked as with the methoxy acid. In all these reactions the effect of the methyl group is seen to be intermediate between that of methoxyl and of hydrogen in the para position.

Experimental Part

4-Methylbenzalpyruvic acid was prepared by mixing 17.6 g. (0.2 mole) of pyruvic acid with 24 g. (0.2 mole) of toluic aldehyde and adding slowly, with stirring, 55 cc. (0.23 mole) of a 25% solution of potassium hydroxide in methyl alcohol. The temperature was kept at about 10°. Toward the end of the reaction a yellow color developed and the yellow condensation product crystallized out. After standing overnight, this was filtered and washed with methyl alcohol and with ether; yield of pure product, 95%. From a cooled, saturated aqueous solution of this potassium salt, hydrochloric acid precipitated an acid which crystallized from boiling benzene in bright canary yellow plates melting at 127°. The acid is fairly soluble in boiling water, more soluble in the usual organic solvents.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.47; H, 5.26. Found: C, 69.86; H, 5.37.

If the acid is allowed to crystallize slowly from dilute aqueous solution it separates in long shining yellow needles which soften about 80° and melt 100–110°. The needles rapidly become opaque and then melt at 127°. This loss of water is so rapid that no significant analyses could be obtained.

On exposure of the pure acid to the sunlight, the odor of *p*-tolualdehyde is at once apparent showing oxidation of the acid at the ethylenic linkage. The yellow color of the acid fades slowly. After several weeks' exposure the pale tan amorphous product was dissolved in benzene, the sirupy solution filtered and allowed to evaporate at room temperature. From the dark shellac-like mass which resulted none of the original acid nor any other crystalline product could be separated. It is undoubtedly a mixture of oxidation and polymerization products. The acid is perfectly stable in the dark.

The methyl ester of *p*-methylbenzalpyruvic acid, prepared readily by dissolving the acid in a small volume of cold methyl alcohol saturated with hydrochloric acid, crystallized from boiling methyl alcohol in slender pale yellow needles melting at 81°.

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.56; H, 5.88. Found: C, 70.70; H, 6.16.

After long exposure of the ester to bright sunlight about one-half was regained unchanged. The residue was a heavy reddish oil, evidently a mixture of products like that obtained from the acid.

The ethyl ester, prepared in the same way, did not crystallize from the alcohol–acid mixture. When the reaction mixture was poured into iced sodium carbonate solution an oil separated which quickly solidified. The solid separates from a slightly warmed concentrated solution of ethyl alcohol to which a few drops of water have been added in light yellow shining plates melting at 44–46°. From a more dilute solution it crystallizes slowly in stiff yellow needles of the same melting point.

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.56; H, 6.42. Found: C, 71.22; H, 6.53.

Reactions with Bromine

4-Methylbenzalpyruvic Acid Dibromide, $CH_3C_6H_4CHBr-CHBrCOCOOH$.—To the pyruvic acid dissolved in iced, dry chloroform, one molecular proportion of bromine was added drop by drop. The decolorization was rapid. Toward the end of the reaction the dibromo addition product separated out as a nearly white, granular solid, which, after washing with cold chloroform, melted at 145–147°. A further quantity was obtained from the filtrates; yield 84%. The compound can be crystallized from benzene but a purer product is obtained by adding an equal volume of low boiling ligroin to the warm benzene solution.

Anal. Calcd. for $C_{11}H_{10}O_3Br_2$: C, 37.71; H, 2.86. Found: C, 37.76; H, 3.73.

The methyl ester of the dibromo acid may be prepared by dissolving the acid in the smallest possible quantity of methyl alcohol, saturated with hydrogen chloride or with an ethereal solution of diazomethane. It separates from methyl alcohol in shining plates melting at 86–87°.

Anal. Calcd. for $C_{12}H_{12}O_3Br_2$: C, 39.56; H, 3.29. Found: C, 39.64; H, 3.53.

β-Bromo-4-methylbenzalpyruvic Acid, $CH_3C_6H_4CH{=}CBrCOCOOH$.—On boiling the dibromo acid for a few minutes with water and allowing the filtered solution to cool, crystals of the unsaturated acid separated in colorless needles. The compound does not crystallize with water as do the corresponding bromo-*p*-methoxyl- and the unsubstituted bromobenzalpyruvic acids. It separates from boiling benzene in fine, colorless needles melting at 182°.

Anal. Calcd. for $C_{11}H_9O_3Br$: C, 49.07; H, 3.34. Found: C, 48.90; H, 3.28.

The methyl ester cannot be prepared by action of methyl alcohol and hydrogen chloride. This is also the case with all other β-bromobenzalpyruvic acids so far studied. It is obtained readily by action of diazomethane in ethereal solution. It separates from boiling methyl alcohol in colorless crystals melting at 77°.

Anal. Calcd. for $C_{12}H_{11}O_3Br$: C, 50.88; H, 3.88. Found: C, 50.91; H, 3.75.

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(5) Gomberg and Buchler, THIS JOURNAL, **45**, 207 (1923).

(6) Wieland and Lecher, *Ann.*, **381**, 206 (1911); *Ber.*, **45**, 2600 (1912).

(7) Bachmann and Moser, THIS JOURNAL, **54**, 1124 (1932).

Oxidation of β-bromo-4-methylbenzalpyruvic acid in dilute alkaline solution with a slight excess of hydrogen peroxide gave in good yield the corresponding bromomethylcinnamic acid. The acid separates from hot ethyl alcohol or from benzene in long, fine, shining needles with a characteristic asbestos-like texture. After repeated crystallization the substance melts at 192°. This is the melting point of the bromo-4-methylcinnamic acid described by Gattermann[8] and listed in Beilstein[9] as α- or β-bromo-4-methylcinnamic acid. The acid prepared as just described from the β-bromo ketonic acid must be α-bromo-4-methylcinnamic acid. In order to test its identity with Gattermann's acid the latter was prepared from *p*-methylcinnamic acid.

4-Methylcinnamic acid was obtained readily by hydrogen peroxide oxidation of 4-methylbenzalpyruvic acid dissolved in a 1% solution of sodium carbonate. After standing overnight the yellow color of the ketonic acid had disappeared and dilute acid precipitated from the solution an almost quantitative yield of the methylcinnamic acid. It crystallized from methyl alcohol in colorless, stocky crystals melting at 198–199° and readily formed a methyl ester melting at 58°. When bromination was carried out in boiling carbon bisulfide solution, as described by Gattermann, a dibromo addition product separated on cooling. This melted with decomposition at 192°, and, on treatment with a 25% solution of potassium hydroxide in methyl alcohol, yielded an unsaturated bromo acid melting also at 192°, all as described by Gattermann. This acid crystallized from benzene in shining silky needles with an asbestos-like texture. A mixed melting point determination proved the acid identical with that obtained by oxidation of β-bromo-4-methylbenzalpyruvic acid. This acid, therefore, described in Beilstein as α- or β-bromo-4-methylcinnamic acid, is the α-bromo acid.

Its methyl ester, prepared by use of diazomethane, separates slowly from ether in large flat plates melting at 36–37°.

Anal. Calcd. for $C_{11}H_{11}O_2Br$: C, 51.76; H, 4.31. Found: C, 51.66; H, 4.54.

The methyl ester of the 4-methylcinnamic acid dibromide (192°) separates from methyl alcohol in shining prisms melting at 101°.

Anal. Calcd. for $C_{11}H_{12}O_2Br_2$: C, 39.28; H, 3.57. Found: C, 39.62; H, 3.88.

When the bromination of 4-methylcinnamic acid was carried out slowly in iced chloroform in the usual way, about one-third of the product had crystallized out by the time the last drops of bromine were added. This product, after washing with cold chloroform, consisted of fine shining crystals melting with slow decomposition at 180–182°. Repeated analyses of samples from different preparations showed the substance to contain a little more than one-half the amount of bromine for the dibromo addition compound so that it was thought to be impure α-bromo-4-methylcinnamic acid. Heating the substance with potassium acetate in methyl alcohol, however, yielded an oil with a strong odor of bromostyrene, and, as the only acid product, the original unbrominated 4-methylcinnamic acid. The substance, melting 180–182°, is then a mixture of 4-methylcinnamic acid and a dibromo addition product which is decomposed completely by treatment with potassium acetate. As Gattermann's 4-methylcinnamic acid dibromide, melting at 192°, gives a quantitative yield of α-bromo-4-methylcinnamic acid under the same treatment and even when warmed with a 25% solution of potassium hydroxide, this substance formed by reaction of bromine in cold chloroform must be an isomeric dibromide. Such a compound was postulated by Gattermann to account for his poor yield of dibromide. We have been no more successful than he in obtaining the substance in pure condition.

The chloroform filtrates from this reaction deposited about a 50% yield of the 192° dibromo addition product.

Reactions with Excess of Bromine

When *p*-methoxybenzalpyruvic acid[3] was treated with bromine in methyl alcoholic solution for the purpose of forming the methyl hypobromite addition product, no such reaction took place. The products were found to be β-bromoanisalpyruvic acid accompanied by its methyl ester brominated in the ring. For purposes of comparison this experiment was repeated with 4-methylbenzalpyruvic acid. The products were in large yield β-bromo-4-methylbenzalpyruvic acid. A small amount of impure residues on oxidation in hot solution of potassium permanganate gave terephthalic acid. There had been, then, no bromination in the ring.

By direct action of excess of bromine in boiling carbon bisulfide solution or on long standing at room temperature, there was also no ring substitution. These experiments show a very definite resistance to bromination in the ring when methyl instead of methoxyl is present in the para position to the unsaturated side-chain.

Reaction with Concentrated Sulfuric Acid.—The yellow color of 4-methylbenzalpyruvic acid and of its methyl and ethyl esters changes rapidly in solution in concentrated sulfuric acid to a reddish-orange then to deep red and finally to a dark brown color. The bromine compounds, all colorless, change to a greenish-yellow and finally to a faint violet. None of the colored products compare in brilliancy with those of the methoxy-substituted compounds.

Summary

For purposes of comparison with other para-substituted benzalpyruvic acids, the para methylbenzalpyruvic acid has been studied.

NEW YORK, N. Y. RECEIVED JULY 12, 1938

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[8] Gattermann, *Ann.*, **347**, 358 (1906).

[9] Beilstein, (ed. IV), Vol. IX, p. 617.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

The Use of Added Protein in the Determination of the Activity of Tyrosinase

BY MARK H. ADAMS AND J. M. NELSON

Tyrosinase is generally defined as the enzyme which catalyzes the aerobic oxidation of certain monohydric phenols such as tyrosine and *p*-cresol, and ortho-dihydric phenols such as catechol and its derivatives. In attempting to isolate the enzyme in a highly purified form, or to determine its relative amounts in tissues, a satisfactory method for its quantitative estimation becomes necessary.

Two principal methods have been used in the past to determine its activity. One involves the determination by chemical means of either the rate of disappearance of the substrate, or the rate of formation of some of the reaction products. The other depends on manometric measurements of the rate of oxygen uptake by the enzyme–substrate system. The latter is the simpler and is sufficiently accurate if conditions are such that the rate of oxygen absorption remains constant for about half an hour. Due to its simplicity the manometric appears to be the favored method. As substrate catechol has been used by Richter,[1] Kubowitz,[2] and Keilin and Mann.[3] Graubard and Nelson[4] preferred to use *p*-cresol in place of catechol, because the rate of oxidation is slower and tends to remain constant over a longer period of time. They used the Warburg form of respirometer[5] with flat-bottomed 50-cc. reaction flasks, the apparatus being run at about 90 complete oscillations per minute; temperature 25°. The reaction mixtures consisted of 4 cc. of 0.1% *p*-cresol, a desired volume of the enzyme solution, 2 cc. of phosphate (0.2 *M*)–citrate (0.1 *M*) buffer, and sufficient water to make the final volume in the reaction flask 8 cc.; *p*H of the reaction mixture was 6.2. The unit of enzyme activity was defined as the amount of enzyme needed to induce the above system to absorb oxygen at the rate of 10 cu. mm. per minute. Their best preparations of tyrosinase had a dry weight of about 0.1 mg. per unit of activity. With preparations of this degree of purity, they found that the rate of oxygen uptake was directly proportional to the amount of enzyme used, provided the latter was in the range of 0.5 to 2 units.

Since then methods of purifying tyrosinase preparations have been improved greatly so that preparations are now available having a dry weight of 0.0015 mg. per unit of activity. In the case of these highly purified preparations of tyrosinase the Graubard and Nelson method was found to be no longer satisfactory, due to the occurrence of considerable inactivation of the enzyme.

In working with highly active preparations of tyrosinase it also was observed that inactivation often occurred when the solutions were diluted. Saul and Nelson[6] observed a similar loss in activity when highly purified preparations of yeast invertase, having a *p*H value on the acid side of the optimum *p*H 4.5, were diluted. When, however, a little protein was added to the enzyme solution, either before or after dilution, this abnormal decrease in activity almost vanished. With this influence of added protein in mind, gelatin was added to dilute solutions of highly purified tyrosinase preparations, and large increases, often several hundred per cent., in activity were noted. When sufficient *p*-cresol was used in the reaction mixture the new value for the activity remained constant throughout a wide range of dilutions.

It will be noticed by means of curves IV and V in Fig. 2 that an increase in added gelatin from 1 to 5 mg. furnishes no additional protection to the enzyme against inactivation. Since in both instances only half (600 cu. mm.) of the theoretical total oxygen uptake (3 atoms, 1244 cu. mm.) occurred it is evident that it is not possible to overcome the inactivation entirely by adding gelatin, and if the oxidation of the *p*-cresol is to be carried to completion, more enzyme would have to be used. The protein contained in the enzyme preparation seems also to exert to some extent an influence on the activity similar to that exerted by gelatin. Thus the data for curve VI in Fig. 2 were obtained by using 2.5 times as much tyrosinase preparation (no gelatin added) as in the experiment represented by Curve I. Yet the ac-

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[1] D. Richter, *Biochem. J.*, **28**, 901 (1934).

[2] Kubowitz, *Biochem. Z.*, **292**, 221 (1937).

[3] D. Keilin and T. Mann, *Proc. Roy. Soc.* (London), **125B**, 187 (1938).

[4] M. Graubard and J. M. Nelson, *J. Biol. Chem.*, **112**, 135 (1935).

[5] M. Dixon, "Manometric Methods," University Press, Cambridge, 1934.

[6] Saul and Nelson, *J. Biol. Chem.*, **111**, 95 (1935).

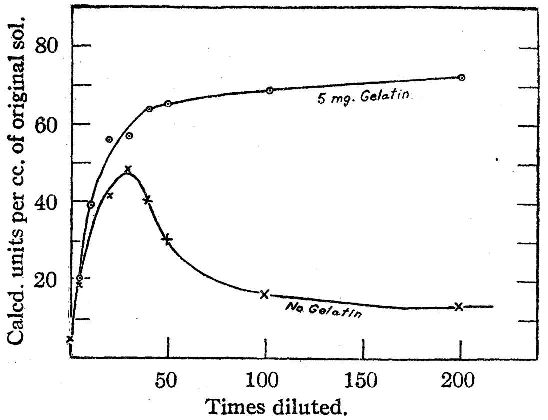

Fig. 1.—Showing change in activity of a tyrosinase preparation (*Psalliota campestris*) on dilution, and the influence on the activity when 5 mg. of gelatin was added to the reaction mixtures (modified Graubard and Nelson method). The increase in activity up to a dilution of 30 times the original volume was probably due to lack of sufficient oxygen. The activity was determined by taking manometric readings of the oxygen uptake at five-minute intervals. Usually a lag occurred in the rate of oxygen uptake at the beginning of the reaction. This was especially true in the case of more highly purified preparations. For this reason the rate of oxygen uptake was allowed to increase gradually until a maximum value was reached. The maximum rate remained practically constant for thirty to sixty minutes and was used in the calculation of the activity in terms of units, as defined by Graubard and Nelson. Temperature 25°. *p*H of reaction mixture 7.0. 1 unit of preparation used had a dry weight of 0.005 mg.

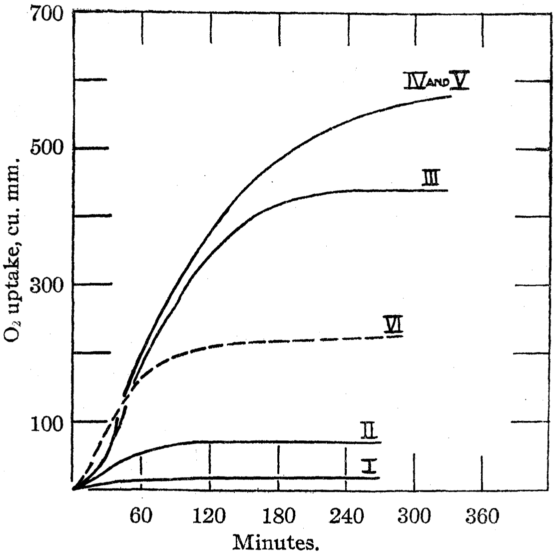

Fig. 2.—Showing the effect of different amounts of gelatin on the activity of tyrosinase. Mg. of gelatin present in the reaction mixtures contained in Warburg flasks: I, 0.0; II, 0.01; III, 0.1; IV, 1.0; V, 5.0. All reaction flasks contained same amount of enzyme, 4 mg. of *p*-cresol, *p*H 7.0 and amounts of gelatin indicated. Total volume 8 cc. Temperature 25°. Activity determined as described in legend of Fig. 1. Theoretical oxygen uptake for 4 mg. of *p*-cresol (3 atoms of oxygen) = 1244 cu. mm. Curve VI differs from Curve I in that twice as much enzyme preparation was used, but no gelatin just as in the case of Curve I.

tivity calculated on the basis of Curve VI was 0.3 unit compared to roughly 0.05 unit when calculated by means of Curve I. In other words, by using 2.5 times as much enzyme the activity was increased about 6 times. Likewise, Curve VI shows a total oxygen uptake (220 cu. mm.) which is about 10 times the total oxygen uptake in the case of Curve I (18 cu. mm.), thereby indicating less inactivation when more enzyme was used. The addition of 0.1 mg. of gelatin (Curve III) brought the initial rate of oxygen uptake nearly up to the maximum value, obtained when 1 mg. of gelatin was used (Curve IV). This explains why Graubard and Nelson were able to get activities roughly proportional to the concentration of enzyme used, since their most active preparation had about 0.1 mg. of protein per unit.

TABLE I

Protein	Activity units per cc.
No protein	0.18
Gelatin 5 mg.	.70
Egg albumin 5 mg. (before dialysis)	.40
Egg albumin 5 mg. (after dialysis)	.70
Serum albumin 5 mg.	.69
Hemoglobin 5 mg.	.74
Casein (saturated soln.)	.73
Oxglobin 5 mg. (before dialysis)	.05
Oxglobin 5 mg. (after dialysis)	.69
Catalase (concd. preparation)	.67
Ivory soap 5 mg.	.23
Gum arabic 50 mg.	.67
Agar-agar 1 mg.	.30

Just why gelatin exerts a protective action on the activity we are unable to state. Almost any protein, in the native or denatured condition, seems to have much the same effect as shown in Table I.

A comparison of four different brands of gelatin gave similar results. Ivory soap had very little effect on the enzyme's activity, whereas agar-agar did cause a noticeable increase of about 0.12 unit. It was not possible to use a greater amount of agar due to its tendency to form a gel. Gum arabic in amounts of 0.1 mg., which is comparable to the amount of protein necessary for maximum protection, exerted practically no influence on the enzyme's activity. Only by using large amounts, 50 mg., was it possible to obtain an effect comparable to that of 0.1 mg. of protein.

TABLE II

SHOWING THE INFLUENCE OF *p*H ON THE ACTIVITY OF TYROSINASE (*Psalliota campestris*) IN THE PRESENCE OF 5 MG. OF GELATIN, TEMPERATURE 25°

*p*H of reaction mixture	4.0	4.5	5.0	5.5	6.0
Activity, units per cc.	0.0	0.20	0.55	0.69	0.76
*p*H of reaction mixture	6.5	7.0	7.5	8.0	
Activity, units per cc.	0.81	0.88	0.90	0.88	

From the data in Table II it will be observed that the change in rate of oxygen uptake is quite marked in the more acid range of *p*H but approaches a maximum around *p*H 7. Beyond *p*H 7 there is danger of autoxidation and for this reason *p*H 7 is the better hydrogen ion concentration for determining activity of tyrosinase toward *p*-cresol, rather than *p*H 6.2 originally used by Graubard and Nelson. Furthermore, the above data indicate no optimum *p*H value for the enzymatic oxidation of *p*-cresol, which is not in line with results reported by Graubard and Nelson. Due to an oversight the last-named investigators failed to mention the use of borate buffer in the more alkaline range. Since then this buffer has been shown to exert a retarding influence on the rate of oxygen uptake, and thus explains the apparent optimum *p*H. Narayanamurti and Ramaswami Ayyar[7] also reported an optimum *p*H value of 6.5 in the oxidation of tyrosine by tyrosinase (from the bean *Dolichos lab lab*). They also used borate buffer for the more alkaline *p*H range.

The data in Table III show that there is a gradual increase in oxygen uptake with increase in concentration of *p*-cresol used. Changing the rate of oscillation of the Warburg apparatus to more than 90 complete oscillations did not influence the rate of oxygen uptake.

TABLE III

SHOWING THE INFLUENCE OF CONCENTRATION OF *p*-CRESOL ON THE RATE OF OXYGEN UPTAKE

Temperature 25°. *p*H of reaction mixture 7.0. Same amount of enzyme used in all experiments. 5 mg. gelatin. Reaction volume 8 cc.

p-Cresol, mg.	0.0	1.0	2.0	3.0	4.0	5.0
Activity, units per cc.	.0	0.36	0.58	0.72	0.83	0.94

In the light of the results obtained in this study it was decided to modify the method of Graubard and Nelson as follows. Reaction mixture: 1 cc. of an aqueous solution containing 4 mg. of *p*-cresol, added to the reaction mixture from the side-arm of the reaction flask at zero time; 2 cc. of (0.1 *M*) citrate–(0.2 *M*) phosphate buffer solution (*p*H of reaction mixture, 7.0); 1 cc. of an aqueous solution containing 5 mg. of gelatin; 1 cc. of enzyme solution and sufficient volume of water to make total reaction volume 8 cc.

Summary

1. The importance of protein concentration in the determination of the activity of highly purified preparations of tyrosinase has been pointed out.

2. The method of Graubard and Nelson for determining the activity of tyrosinase toward *p*-cresol has been modified to conform to the influence of protein.

NEW YORK, N. Y.

RECEIVED JUNE 25, 1938

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[7] D. Narayanamurti and Ramaswami Ayyar, *J. Indian Inst. Science*, **12**, 109 (1929).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

On the Nature of the Enzyme Tyrosinase

BY MARK H. ADAMS AND J. M. NELSON

In the literature on oxidases from the time of Bourquelot to the present, tyrosinase has been generally considered capable of performing two quite distinct oxidative functions: one, the introduction of a hydroxyl group ortho to the already existing hydroxyl in certain monohydric phenols; and two, the oxidation of certain ortho-dihydric phenols to the corresponding ortho-quinones. Several theories have been proposed to account for these two types of activity. Onslow[1] favored the view that tyrosinase is really a catechol oxidase, and that the oxidation of the monohydric phenols is due to a secondary reaction in which *o*-quinones serve as the oxidizing agent. Richter[2] states "The oxidation of *p*-cresol therefore appears to be essentially a secondary oxidation in which the formation of an *o*-quinone is involved, rather than a direct oxidation of the cresol." Keilin and Mann[3] also believe that the monophenolase activity is due to the catechol oxidase (polyphenolase) plus some "factor" probably of the *o*-quinone type as suggested by Onslow.

Against Onslow's theory may be cited the

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[1] M. W. Onslow, "The Principles of Plant Biochemistry," University Press, Cambridge, 1931, p. 138.

[2] D. Richter, *Biochem. J.*, **28**, 901 (1934).

[3] D. Keilin and T. Mann, *Proc. Roy. Soc.* (London), **125B**, 187 (1938).

experience of Pugh,[4] who obtained from slugs (*Arion ater*) an oxidase which catalyzes the oxidation of catechol but not *p*-cresol. If the oxidation of *p*-cresol is dependent on *o*-quinones, then a mixture of this enzyme and homoquinone should bring about the oxidation of the *p*-cresol. This however, was found not to be the case. Workers in these Laboratories have had similar experience. When the oxidase from sweet potatoes (*Batatas batatas*), which also brings about the oxidation of catechol but not *p*-cresol, was added to a mixture of catechol and *p*-cresol, only the catechol was oxidized.

The oxidation of catechol when catalyzed by tyrosinase is very rapid, and when the rate of oxygen uptake is measured by means of the Warburg form of respirometer, difficulty is often encountered in securing accurate readings. If the rate of oxidation is reduced by using less enzyme, then considerable inactivation of the enzyme is apt to occur, especially in the case of the more highly purified preparations. Richter and Kubowitz[5] as well as others have ascribed the inactivation of the enzyme to presence of *o*-benzoquinone formed in the oxidation of the catechol. To avoid inactivation, Richter carried on the oxidation of the catechol in the presence of reagents such as aniline which react with the quinone as it formed and thereby prevent its action on the enzyme. Kubowitz, on the other hand, oxidizes the catechol in the presence of a reducing system, thereby changing the quinone as it is formed back to catechol. An objection to Kubowitz's reducing system, which consists of hexosemonophosphate, Negelein's Zwischen Ferment and Coferment II, is that very few laboratories have it on hand. Richter's use of aniline is not satisfactory since Wagreich and Nelson[6] have shown that even in the presence of aniline considerable inactivation is apt to occur.

Graubard and Nelson (unpublished) have shown that although tyrosinase is without action on hydroquinone, it can be made active if a small amount of catechol is added. This is readily understood since the oxidation–reduction system of catechol–*o*-benzoquinone has a higher potential than the system hydroquinone–*p*-benzoquinone. The *o*-benzoquinone being reduced by the hydroquinone back to catechol, causes the latter to play the role of an oxygen carrier. In a sense the hydroquinone can be looked upon as serving the same purpose as the reducing system used by Kubowitz, but having the advantage of being more generally available. Furthermore, the enzyme seems to suffer less inactivation when the catechol–hydroquinone system is used. Judging from Kubowitz's data, his rates of oxygen uptake remained constant for only ten to fifteen minutes, while when catechol–hydroquinone is used the rates remain constant for over half an hour.

The activity of tyrosinase preparations with respect to catechol was determined by the use of the Warburg form of respirometer[7] using 50-cc. flasks and 90 complete oscillations per minute; temperature 25°. Reaction mixtures consisted of 1 cc. of an aqueous solution containing 5 mg. of hydroquinone and 0.1 mg. of catechol (added from the side-arm of the flask at zero time). In the flask were: 2 cc. of (0.1 *M*) citrate–(0.2 *M*) phosphate buffer (*p*H of reaction mixture 7.0); 1 cc. of aqueous solution containing 5 mg. of gelatin; enzyme solution and sufficient water to make the total volume equal to 8 cc. The amount of enzyme required to cause the rate of oxygen uptake to equal 10 cu. mm. per minute was defined as one "catechol unit." The rate of oxygen uptake was usually directly proportional to the amount of oxidase used, provided the enzyme had been purified sufficiently to remove the naturally occurring substrates, and the amount of enzyme was less than two catechol units. As would be expected, the amount of catechol used affects the rate of oxygen uptake. The data represented in Fig. 1 were obtained by using 5 mg. of hydroquinone and amounts of catechol varying from 0.01 to 0.3 mg. It will be noted that beyond 0.1 mg. of catechol the increase in the rate of oxygen uptake tends toward a maximum, and explains why the mixture of 0.1 mg. of catechol and 5 mg. of hydroquinone was selected for use in the method described above.

When a tyrosinase preparation also contains laccase, then obviously this method for determining the activity of tyrosinase toward catechol is no longer applicable. The presence of laccase can be detected readily since such preparations catalyze the oxidation of hydroquinone when no catechol is present.

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(4) C. E. M. Pugh, *Biochem. J.*, **24**, 1442 (1930).

(5) Kubowitz, *Biochem. Z.*, **292**, 221 (1937).

(6) H. Wagreich and J. M. Nelson, *J. Biol. Chem.*, **115**, 459 (1936).

(7) M. Dixon, "Manometric Methods," University Press, Cambridge, 1934.

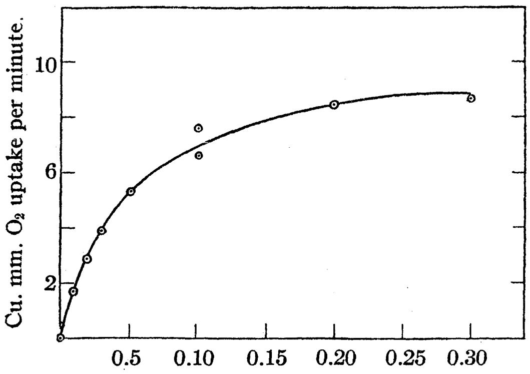


Fig. 1.—Showing the change in rate of oxygen uptake when varying amounts of catechol were used in the presence of 5 mg. of hydroquinone.

The addition of gelatin was found to be necessary in measuring the activity of tyrosinase preparations toward catechol, just as it was found necessary in the *p*-cresol method described in the previous paper. In one instance the addition of gelatin caused a 50% increase in the rate of oxidation of the catechol–hydroquinone reaction mixture. The effect of the gelatin varies with the purity and concentration of the enzyme.

Since the use of the catechol–hydroquinone mixture as a substrate depends on the oxidation of catechol, while the method described in the previous paper involves the oxidation of *p*-cresol, it was decided to compare the activities of different tyrosinase preparations with respect to the two substrates. In Table I are given the relative catechol and *p*-cresol activities for preparations of tyrosinase obtained from different sources. The activities toward catechol were obtained by using that amount of tyrosinase solution equal to 1 unit when *p*-cresol served as the substrate.

TABLE I

Source	Activity toward *p*-cresol	Activity toward catechol–hydroquinone
Lactarius piperatus	1 unit	0.08 unit
Irish potato	1 unit	.67 unit
Puff ball	1 unit	.05 unit
Psalliota campestris	1 unit	.64 unit
Sweet potato	0.0 unit	1.00 unit

It is evident from the values given in the table that the tyrosinases from the various sources are not identical. On the basis of one *p*-cresol unit, the potato and *Psalliota campestris* enzymes are roughly eight to ten times as active toward catechol as are the enzymes of the puff ball and *Lactarius piperatus*.

Several possible explanations for these differences in activities toward the two substrates suggest themselves: first, that each source yields a tyrosinase which is unique (if this were the case then the relative activity of the enzyme toward *p*-cresol as compared with that toward catechol should remain unchanged during any number of purification processes); second, that the tyrosinase preparations in reality consist of a mixture of two enzymes, one acting on *p*-cresol, or perhaps on both *p*-cresol and catechol, the other acts exclusively on catechol; third, that some accompanying substance, non-enzymatic in nature, as suggested by Keilin and Mann, enables the catechol oxidase to bring about the oxidation of the *p*-cresol.

To test the first and third possibilities a tyrosinase preparation (*Psalliota campestris*) was subjected to series of purification operations: precipitation with acetone, precipitation with ammonium sulfate, adsorption to kaolin and alumina, foreign proteins removed by gentle heat, and thorough dialysis against distilled water at frequent stages during the process. The activities with respect to the catechol–hydroquinone mixture and to *p*-cresol were measured at the different stages of purification and the ratios of the two activities are given in Table II.

TABLE II

Showing loss in catechol activity in contrast to loss in *p*-cresol activity when a tyrosinase preparation from the common mushroom was subjected to the following purification.

Stage of purification	Catechol units/ *p*-cresol units
After first acetone precipitation	3.2
After second acetone precipitation	2.2
After ammonium sulfate precipitation	2.5
After adsorption to kaolin	1.6
After adsorption to alumina	1.5
Highly purified preparation	0.64

The data in Table II show that by this particular method of purification it is possible to increase relatively the ratio of the *p*-cresol activity to the catechol activity about five times. Keilin and Mann, on the other hand, using a somewhat different procedure in purifying their tyrosinase (polyphenolase) preparation (also from *Psalliota campestris*), obtained a highly purified preparation very low in *p*-cresol activity compared to its catechol activity.

In adsorbing the tyrosinase to alumina, mentioned above, an insufficient amount of the latter was used, thereby leaving some of the enzymatic activity still remaining in the residual solution.

The activity in the latter solution was found to have five catechol units to each *p*-cresol unit, instead of 1.5 catechol to one *p*-cresol unit in the case of the material adsorbed to the alumina. In other words, the activity toward the *p*-cresol appears to be more readily adsorbed to the alumina than the part which brings about the oxidation of the catechol. By repeating the treatment with insufficient alumina, it was possible to obtain, as shown by the data in Table III, preparations very high in catechol activity compared to the activity toward *p*-cresol.

TABLE III

Showing the preferential adsorption of the activity toward *p*-cresol by alumina at *p*H 5.

		p-Cresol units per cc.	Catechol units per cc.	Catechol units / *p*-cresol units
Orig. crude prepn.		43	53	1.3
After adsorptions	first	13.5	30	2.2
	second	5.3	22.5	4.3
	third	2.0	17.4	8.7
	fourth	0.58	5.4	9.3

Likewise, it was possible to increase the activity toward *p*-cresol more than toward catechol by eluting that part of the tyrosinase preparation which was adsorbed to alumina. For this purpose a series of adsorptions, followed by elutions by means of secondary sodium phosphate, were performed and solutions were obtained having as high as 3 *p*-cresol units to one catechol unit, whereas the original solution contained about 4 *p*-cresol units to 5 of the catechol units. Furthermore, the substance responsible for the *p*-cresol activity did not pass through a dialyzing membrane, and was completely precipitated from solution when the latter was made 0.6 saturated with ammonium sulfate.

The facts that the activity toward *p*-cresol can be concentrated by absorption techniques relatively more rapidly than the activity toward catechol, that it does not dialyze through semipermeable membranes, and that it is completely precipitated by ammonium sulfate, all point toward the probability that the aerobic oxidation of *p*-cresol is catalyzed by an enzyme different from the one which brings about the oxidation of catechol.

As further support for this view may be cited the effect of gentle heat. A tyrosinase preparation containing 73 catechol units and 11.5 *p*-cresol units, or 6.4 catechol to 1 *p*-cresol unit, was heated for five minutes at 60°. The catechol activity dropped to 6.5 units and the *p*-cresol activity to 0.3 unit, making the ratio of the two activities 22 catechol units to 1 *p*-cresol unit, thus showing that activity toward *p*-cresol suffered more inactivation than the activity toward catechol.

If the catalytic activity toward *p*-cresol were due to some non-enzymatic factor plus catechol oxidase, as is believed to be the case by some, then the addition of catecholase to a solution of tyrosinase preparation from the wild mushroom, *Lactarius piperatus*, which is rich in *p*-cresol activity and poor in catechol oxidase, thereby containing a relatively high concentration of the factor, should cause an increase in the *p*-cresol activity greater than the sum of *p*-cresol activities of the two preparations. The data given in Table IV, however, show that the activities of the two preparations were just additive and mutually independent.

TABLE IV

Units	1 cc. *Lactarius piperatus* prepn.	1 cc. *Psalliota campestris* prepn.	1 cc. each prepn.
Catechol	0.10	1.47	1.56
p-Cresol	1.05	0.23	1.26

To make certain that the lack of increase in the *p*-cresol activity could not be ascribed to the *Lactarius piperatus* preparation containing a "factor" not suitable for enabling the catechol oxidase, obtained from *Psalliota campestris*, to oxidize *p*-cresol, experiments like those corresponding to the data in Table IV, were repeated using two preparations both from *Psalliota campestris*. Again the two activities were additive and independent of each other.

TABLE V

Units	1 cc. *Psalliota campestris* No. L	1 cc. *Psalliota campestris* No. 70	1 cc. of each prepn.
Catechol	0.52	1.44	1.90
p-Cresol	1.03	0.24	1.22
	Prepn. No. L heated at 60° for 5 min.		
Catechol	0.27	1.44	1.65
p-Cresol	.15	0.24	0.43
	Prepn. No. L acidified to below *p*H 3.5 for 5 min.		
Catechol	0.0	1.44	1.40
p-Cresol	.0	0.24	0.28

Furthermore, if the activity toward *p*-creso is due to some "factor" plus catechol oxidase then a preparation that had been inactivated should regain its activity toward *p*-cresol on the addition of some active catechol oxidase. To test this possibility preparation No. L was inactivated both by heat and with acid, after which it was added to preparation No. 70 and the activities again measured. In neither instance was there any indication of a non-enzymatic factor which operated with the catechol oxidase in bringing about the oxidation of *p*-cresol.

If there is a "factor" which together with catecholase catalyzes the aerobic oxidation of monohydric phenols, such as *p*-cresol, it is not nonenzymatic, since it has so many properties common to enzymes. Thus it is adsorbable to alumina and kaolin, completely precipitated by ammonium sulfate, does not pass through semipermeable membranes, is heat labile, readily inactivated by acid, and by methods generally employed in the purification of enzymes it has been possible to separate it partially from catechol oxidase.

It should be mentioned that so far the adsorption to alumina and kaolin has failed to affect the ratio of catechol oxidase to the activity responsible for the oxidation of *p*-cresol in the case of tyrosinase preparations obtained from the wild mushrooms, *Lactarius piperatus* and the common pasture puff ball, *Calvatia cyathiformis*. Both of these preparations were rich in activity toward *p*-cresol and poor in catechol oxidase.

Summary

1. The ratio of the activities toward catechol and *p*-cresol in tyrosinase preparations from the common mushroom, *Psalliota campestris*, can be varied by adsorption of the enzymes to alumina and kaolin.

2. By means of partial adsorption it is possible to obtain preparations in the residual solution rich in catechol oxidase and poor in activity toward *p*-cresol.

3. The ratio of the activity toward *p*-cresol to that toward catechol was greater in the elutate from the adsorption than in the original solution.

4. The activity toward *p*-cresol possesses properties common to enzymes in general. It is heat labile, inactivated by dilute acids, does not pass through semi-permeable membranes, and can be precipitated from solution by ammonium sulfate.

5. The catechol activity and the activity toward *p*-cresol are mutually independent.

6. So far attempts to affect the ratio of the catechol and *p*-cresol activities of tyrosinase preparations from the mushroom, *Lactarius piperatus* and the puff ball, *Calvatia cyathiformis*, have been unsuccessful.

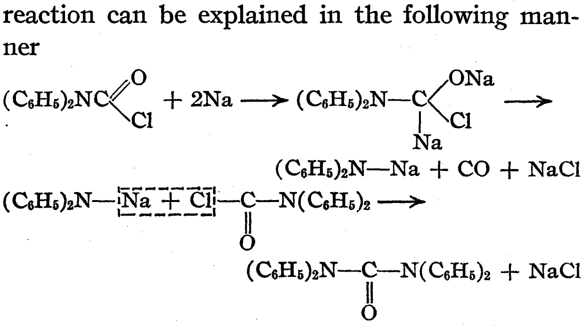
NEW YORK, N. Y. RECEIVED JUNE 25, 1938

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF WASHINGTON]

Reactions of Sodium and Potassium on Acid Chlorides

BY IRWIN A. PEARL, THEODORE W. EVANS AND WILLIAM M. DEHN

In a prior article[1] it was reported that diphenylcarbamine chloride treated with sodium in boiling toluene yielded tetraphenyloxamide. Further work now has shown conclusively that the reaction follows the more interesting course to form tetraphenylurea and carbon monoxide.[2] That tetraphenyloxamide was not first formed in the reaction was proved by the following experiments. Tetraphenyloxamide, prepared from diphenylamine and oxalyl chloride by the method of Stolle,[3] was treated with atomized sodium in boiling toluene under the same conditions as was the diphenylcarbamine chloride. No tetraphenylurea could thus be found, or from tetraphenyloxamide by heating for two hours at 195°. The reaction can be explained in the following manner



$$(C_6H_5)_2NC<^{O}_{Cl} + 2Na \longrightarrow (C_6H_5)_2N{-}\underset{\underset{Na}{|}}{C}<^{ONa}_{Cl} \longrightarrow$$

$$(C_6H_5)_2N{-}Na + CO + NaCl$$

$$(C_6H_5)_2N{-}\boxed{Na + Cl}{-}\underset{\underset{O}{\|}}{C}{-}N(C_6H_5)_2 \longrightarrow$$

$$(C_6H_5)_2N{-}\underset{\underset{O}{\|}}{C}{-}N(C_6H_5)_2 + NaCl$$

Proof of this type of mechanism was obtained by treating diphenylcarbamine chloride with an excess of sodium in toluene and obtaining sodium diphenylamine in the residue. These observa-

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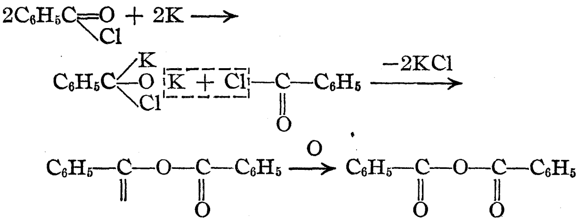
(1) Evans and Dehn, THIS JOURNAL, **52**, 3645 (1930).

(2) Hammerich [*Ber.*, **25**, 1826 (1892)] reported the reaction of ditolylcarbamine chloride with sodium in ether to give the oxamide derivative.

(3) Stolle, *ibid.*, **46**, 3916 (1913).

tions led to a study of the reaction of sodium and potassium on other acid chlorides.

Sodium reacts with benzoyl chloride in anhydrous ether solution to give ethyl benzoate as the main product. This reaction, with other metals, was reported by Varvoglis.[4] However, sodium or potassium reacts with benzoyl chloride in dry xylene to give benzoic anhydride and sodium chloride. This unique reaction, in which oxygen is obtained from the atmosphere, can be explained in the following simple manner



In like manner phthalyl chloride and succinyl chloride react with potassium or sodium in dry xylene to give phthalic anhydride and succinic anhydride in 70 and 60% yields, respectively. *p*-Toluenesulfonyl chloride reacts with potassium to give di-*p*-tolyldisulfone and potassium chloride according to the following

$$2CH_3—C_6H_4—SO_2Cl + 2K \longrightarrow CH_3—C_6H_4—SO_2—SO_2—C_6H_4—CH_3 + 2KCl$$

Experimental

Preparation of Tetraphenylurea.—To a mixture of atomized sodium in toluene was added one mole of diphenylcarbamine chloride and this mixture was boiled for a short time. The precipitated sodium chloride was filtered off and large, jewel-like crystals, in 66% yield, separated from the cooled filtrate. Recrystallization from toluene gave crystals melting at 182–183°. A mixed melting point with pure tetraphenylurea, prepared by the method of Michler and Zimmermann,[5] showed no depression. The gas evolved during the reaction was collected and analyzed. It proved to be carbon monoxide. Further proof that this compound is the urea and not the oxamide was obtained by the analytical data. In the prior paper there was given only the nitrogen value, which agreed equally well with either compound.

Calcd. % for	$(C_6H_5NCO)_2$	$(C_6H_5N)_2CO$	Found
C	79.6	82.4	82.3
H	5.1	5.5	5.9
N	7.1	7.7	7.5
O	8.2	4.4	4.3 diff.

Reaction of Diphenylcarbamine Chloride with Excess of Sodium.—Diphenylcarbamine chloride was added to an excess of atomized sodium in boiling toluene for thirty minutes. The mixture was filtered and well washed with toluene. The filtrate and washings were evaporated to a small volume and, upon cooling, yielded crystals of tetraphenylurea melting at 182–183°. Part of the sandy precipitate from the original filtration was treated with water. Diphenylamine melting at 50–52° separated. The rest of this sandy precipitate was treated with benzoyl chloride and, after warming, washed well with dilute sodium carbonate solution; recrystallizing from alcohol yielded crystals of benzoyldiphenylamine melting at 176–177°. When potassium was substituted for sodium in this experiment, the same results were obtained.

Reaction of Benzoyl Chloride and Sodium in Anhydrous Ether.—A mixture of 1.1 g. of atomized sodium in 50 cc. of dry xylene was decanted and after washing with absolute ether the sodium was covered with 50 cc. of absolute ether. To this mixture was added 7 g. of benzoyl chloride. The flask was stoppered and allowed to stand for ten days with occasional shaking. The contents were then filtered and the ethereal filtrate was evaporated. A residue of 6.5 g. of ethyl benzoate boiling at 210–213° was obtained.

That ethyl benzoate was not formed by the reaction of benzoyl chloride with absolute ether was proved by a mixture of the two without sodium. The benzoyl chloride was recovered quantitatively with no trace of ethyl benzoate.

Reaction of Benzoyl Chloride and Potassium in Anhydrous Xylene.—Two grams of potassium was atomized in 50 cc. of dry xylene and allowed to cool. To this was added 7 g. of benzoyl chloride and the mixture was heated occasionally for two days. After disappearance of all the potassium, the potassium chloride was filtered off and the xylene filtrate was evaporated on the steam-plate. A heavy oil was obtained and, on standing, this yielded light colored crystals. After drying on a porous plate and recrystallizing from ether, they melted at 41–42°. A mixed melting point with pure benzoic anhydride showed no depression.

Reaction of Phthalyl Chloride and of Succinyl Chloride with Potassium and Sodium.—A mixture of 10.1 g. of phthalyl chloride and 4.0 g. of atomized potassium in 100 cc. of xylene was heated to boiling and allowed to stand for three weeks. The potassium chloride was filtered off and the filtrate yielded 5.3 g. (70%) of phthalic anhydride. Recrystallization from benzene gave white needles melting at 130–131°. A mixture with pure phthalic anhydride melted at the same temperature.

Six grams of succinyl chloride and 2 g. of sodium were treated in the same manner for eight weeks. A yield of 2.5 g. (60%) of succinic anhydride melting at 116–118° was obtained. Recrystallization from absolute alcohol yielded crystals melting at 118–119°. A mixture with pure succinic anhydride melted at the same temperature.

Reaction of *p*-Toluenesulfonyl Chloride with Potassium or Sodium.—To a mixture of 4 g. of atomized potassium and 100 cc. of warm xylene was added gradually 19 g. of *p*-toluenesulfonyl chloride. The vigorous reaction taking place after each addition was allowed to subside before the next addition. After all the chloride was added the

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[4] Varvoglis, *Ber.*, **70**, 2391 (1937). This author treated acid chlorides in absolute ether with a large number of metals. Of all the metals tried, only iron and zinc were effective, and these yielded ethyl esters of the respective acids. On the basis of this work, potassium and sodium probably would have been predicted to be without action.

[5] Michler and Zimmermann, *ibid.*, **12**, 1166 (1879). These authors prepared the urea by treating diphenylcarbamine chloride with diphenylamine.

mixture was allowed to cool. All the potassium had disappeared and the reaction mixture was thick with precipitate. The mixture was filtered and the precipitate was dried. The precipitate was treated with water and extracted with ether. The ethereal extraction upon evaporation yielded 3 g. of crude di-*p*-tolyldisulfone melting at 214–218°. Recrystallization from benzene yielded crystals melting at 220–221°.

Summary

1. Diphenylcarbamine chloride and sodium or potassium yield tetraphenylurea and carbon monoxide with the intermediate formation of sodium or potassium diphenylamine.

2. Benzoyl chloride and sodium or potassium in anhydrous ether yield ethyl benzoate.

3. Acyl chlorides with sodium or potassium in xylene yield acid anhydrides.

4. *p*-Toluenesulfonyl chloride yields di-*p*-tolyldisulfone when treated with sodium or potassium in xylene.

SEATTLE, WASHINGTON RECEIVED JULY 11, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ST. PETER'S COLLEGE]

The Catalytic Properties of Charcoal. II. Further Studies on the Indophenol Reaction

BY JAMES F. O'BRIEN, VINCENT TKAC AND CLAUDE SCHWOB

The unusual factors encountered in a previous study of the activity of charcoal in catalyzing the hydrogen peroxide oxidation of a mixture of α-naphthol and *p*-phenylenediamine at *p*H 4.5 to form indophenol[1] prompted us to continue our studies of this interesting reaction.

Two aspects of this oxidation particularly suggest further investigation. What is the cause of the decrease in yield of the indophenol after one-half minute? What is the role of the charcoal in these oxidative reactions? In the present paper we attempt to give a partial answer to the first question. The third paper of this series will treat of certain findings relative to the second question.

We first repeated the original work[1] under carefully controlled conditions, using a so-called "pure" sucrose charcoal. At both 30 and 40° we confirmed our former findings, the yield being at a maximum at one-half minute and then decreasing to a value which remained constant after seven minutes. As before, the indophenol was found to be strongly adsorbed by the charcoal so that the latter and the filtrate were analyzed separately. Figure 1 shows the amount of indophenol present at various times. The charcoal furnished the bulk of the indophenol (curve 1), but a definite peak at one-half minute shows in the filtrate curve (curve 2).

TABLE I

Time, min.	Temp. coeff.	*E*, cal.
0.25	1.083	1400
.5	1.138	2300
1	1.198	3300
2	1.238	3900
4	1.239	3900
7	1.239	3900
14	1.241	3900
28	1.245	4000

The ratio of the total yields of the reaction at 40° to those of the reaction at 30° at corresponding times gives us a series of numbers which are akin to temperature coefficients (Table I). It will be noticed that these ratios increase linearly with time until, after two minutes, they approach a constant value. A rough calculation of the apparent energies of activation for these reaction times was made by substituting these coefficients in the Arrhenius equation. It is to be emphasized that Hinshelwood[2] and others have pointed out that such a substitution cannot give the true energy of activation for a heterogeneous reaction. It is interesting to note, however, that the values obtained for E as well as for the temperature coefficients show that two distinct processes are going on in this reaction, one predominating in the first two minutes, the second one after that. The energy of activation was likewise determined for the uncatalyzed formation of indophenol at 30 and 40° (Fig. 1, curves 5 and 6), and found to be approximately 5000 cal.

The progressive increase in the value of E for the catalyzed reaction suggests either of two possibilities: the charcoal suffers poisoning as the

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[1] Paper I, Schwob, THIS JOURNAL, 58, 1115 (1936).

[2] Hinshelwood, "The Kinetics of Chemical Change in Gaseous Systems," The Clarendon Press, Oxford, 1933, p. 348, *et seq.*

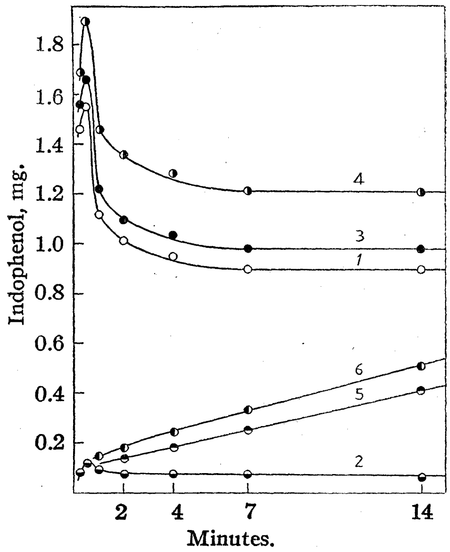

Fig. 1.—Curve 1, indophenol obtained from charcoal at 30°; curve 2, indophenol in the filtrate (30°); curve 3, total yield at 30°; curve 4, total yield at 40°; curve 5, yield at 30° in the absence of charcoal; curve 6, yield at 40°, no charcoal. The maximum yield in curve 4 is approximately 5% of the theoretical.

reaction progresses, or the indophenol is destroyed by a secondary reaction. Were the former true it seems likely that the amount of indophenol present would not decrease with time but, rather, would increase owing to the uncatalyzed reaction. The gradual destruction of indophenol remains as the only possibility consistent with the experimental facts, and we believe, on the strength of the following work, that this destruction not only takes place, but that the presence of charcoal is necessary. If this last is true, the addition of some charcoal-inhibiting agent when the reaction has proceeded one-half minute should prevent any subsequent falling off in yield.

The inhibitors tested were amyl alcohol and potassium cyanide, added when the reaction had progressed exactly one-half minute. As seen in Fig. 2, curve 2, the addition of amyl alcohol poisoned the charcoal to some extent, resulting in a constant yield much greater than that of the uninhibited reaction. The addition of potassium cyanide (Fig. 2, curve 3) completely stopped the destruction of indophenol and permitted a gradual increase in yield. This indicates that the removal of the charcoal from the field of action by means of cyanide not only prevents the destruction of indophenol but allows its formation to proceed at the same rate as the uncatalyzed reaction (compare the latter portion of this curve with Fig. 1, curve 5).

What is the nature of this catalyzed destruction of indophenol? Recently, other investigators,[3] working on the catechol–tyrosinase reaction, obtained results similar to ours when insufficient enzyme was used to promote the oxidation of catechol, an effect which they attributed to secondary reactions between catechol and quinone. We felt it necessary to determine whether a similar condition would account for our results, that is, whether the reaction which destroys the indophenol involves excess reagents. Reducing the substrate concentration to one-quarter of the value used in former experiments, a curve was constructed for the reaction at 30° (Fig. 2, curve 4). The filtrate yields were negligible. Multiplying the constant value (1.38 mg.) obtained here by four to permit direct comparison with the other curves gives a constant yield value of 5.5 mg. This shows that in the presence of sufficient charcoal we have the apparent anomaly of lessened indophenol destruction. This can only be interpreted as proof that excess reagents are involved in the destruction of indophenol. Conversely, with substrate concentrations double those of the original experiments, final indophenol yields were obtained which were much lower than those formerly obtained.

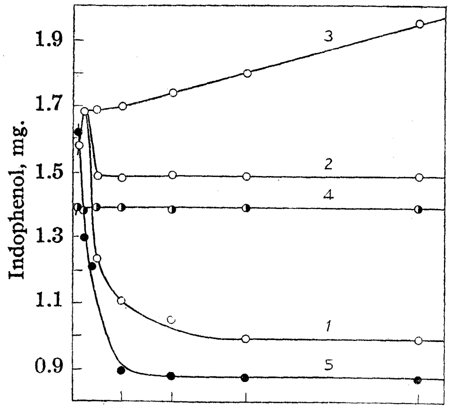

Fig. 2.—Curve 1, same as curve 3, Fig. 1; curve 2, effect of amyl alcohol; curve 3, effect of potassium cyanide; curve 4, one-quarter concentrations; curve 5, double concentrations.

Hence, we are led to believe that the indophenol destruction is catalyzed by charcoal and in-

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[3] Dawson and Nelson, THIS JOURNAL, 60, 250 (1938).

volves a reaction with excess reagents (α-naphthol, *p*-phenylenediamine, and/or hydrogen peroxide). In fact, we found that indophenol adsorbed on charcoal is destroyed more rapidly when suspended in dilute hydrogen peroxide containing either α-naphthol or *p*-phenylenediamine than in the presence of peroxide solution only. Although, due to the difficulty of obtaining a sufficiently concentrated solution of pure indophenol in water, these experiments are at best qualitative, they are in good agreement with the above work.

What is the role of the peroxide? The catalytic effect of charcoal in promoting the oxidation by air or oxygen of many chemical individuals is well known. It was thought desirable to investigate the indophenol reaction in the absence of hydrogen peroxide, using air as the oxidant. This is analogous to the action of the enzymes known as oxidases as distinguished from peroxidases, and we consequently favor the use of the name "oxidase action" to denote this particular catalytic role of charcoal.

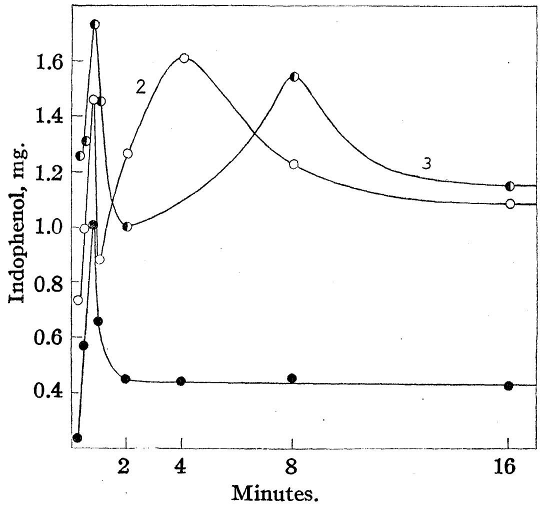

Fig. 3.—Curve 1, total indophenol yield at *p*H 4.5; curve 2, *p*H 6.5; curve 3, *p*H 7.5.

We first performed an experiment at *p*H 4.5 and 20°. The curve obtained (Fig. 3, curve 1) bears a striking resemblance to the peroxidase curves. Hence, we are inclined to think that the same factors predominate whether hydrogen peroxide or oxygen be the oxidant. Among these factors, the disappearance of indophenol is especially interesting. If peroxide is one of the substances involved in the disappearance of the dye, air must be an equally good reagent. However, if we consider the results of the quarter concentration peroxidase experiment (Fig. 2, curve 4), it becomes evident that neither peroxide nor oxygen is of as great importance in the destruction of indophenol as the other reagents. In that experiment, reducing the amount of α-naphthol and *p*-phenylenediamine without reducing the quantity of peroxide and having the reaction mixture fully exposed to air, resulted in comparatively little destruction of indophenol.

Variation in the hydrogen-ion concentration in the oxidase experiments led to results which are worth noting. The data concerning *p*H changes presented here apply only to oxidase action since it is probable that, due to the well-known catalase properties of charcoal, some oxidase action is likely to take place during the peroxidase reaction,[4] resulting in data difficult of interpretation. Moreover, the peroxidase reaction at *p*H's higher than 4.5 does not lend itself readily to kinetic study due to its rapidity.

A decrease in acidity to *p*H 6.5 in the oxidase reaction led, as was expected, to an increased yield of indophenol (Fig. 3, curve 2). More important, however, is the shape of the curve, two maxima now being evident, one at three-quarters of a minute, the other at four minutes. These results prompted us to increase further the *p*H to 7.5. Again an increased yield was noted, and again a second maximum appeared, but at eight minutes instead of four (Fig. 3, curve 3).

While performing these experiments, it was noted that ten or twelve seconds after the start of the reaction a deep red color (indophenol) appeared throughout the reaction mixture, only to disappear in three or four minutes. The presence of charcoal in suspension tends to obscure this color, but it is plainly visible by means of transmitted light.

These observations, while scarcely sufficient as a basis for theorizing, nevertheless have tempted us to formulate the following explanation as a working hypothesis to guide further experimentation.

We believe that each oxidase curve is of the same type, and is the resultant of two actions, reaching a maximum simultaneously or nearly so at *p*H 4.5, but successively at a higher *p*H. Let us consider the latter curves. The charcoal in some way activates the oxygen in solution,[5]

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[4] That this combined catalase–oxidase action is not the sole catalytic effect in the peroxidase reaction has been pointed out previously,[1] and will be discussed more fully in Paper III of this series.

[5] This activation of oxygen by charcoal is suggested by experiments to be described in the next paper of this series.

and perhaps one or more of the reagents, so as to make possible a fast reaction in the body of the solution. This reaction, as evidenced by the red color, reaches a peak in a few seconds, at which point the indophenol produced is adsorbed by the charcoal, and begins to undergo degradation by reacting with the excess reagents under the catalytic influence of the charcoal. A second reaction on the charcoal surface now becomes dominant and the indophenol produced is adsorbed quickly. This second reaction, sensitive to hydrogen-ion concentration, produces the second rise in the curve. However, as the indophenol accumulates, the rate of destruction increases and the curve drops again.

We have, as yet, no explanation which we feel we can offer for the constancy of the final indophenol yield in all the above reactions. It is interesting to note that this value remains constant for at least twenty-four hours in every case.

Experimental

The charcoal used in this investigation was prepared from reagent-grade sucrose. It was carbonized in porcelain casseroles and activated at red heat in silica crucibles for fifteen minutes. The ash content was found to be less than 0.02%. Constant temperature baths maintained the system at 30 or 40 ± 0.03 or 20 ± 0.4°. In general, the method described in the previous paper[1] was used for determining the catalytic activity of the charcoal. It was noted that the filtrate was not appreciably colored upon filtration, but, rather, that the indophenol color appeared only after a few minutes. Although a mild vacuum was used to provide an increased filtering speed, we attribute most of the filtrate yield to a reaction between excess reagents after and during filtration. Another modification of the original procedure consisted in using 36 cc. (six 6-cc. portions) of toluene to extract the charcoal.

In the oxidase experiments we simply omitted the hydrogen peroxide. All buffers were of the citrate type, checked by means of a glass electrode.

In the reactions involving inhibitors either 2.0 cc. of a 2% solution of amyl alcohol in water, or 0.7 cc. of a 2% aqueous solution of potassium cyanide was added one-half minute after the start of the reaction. For curves 4 and 5 in Fig. 2, only the concentrations of the α-naphthol and *p*-phenylenediamine were altered.

A concordance of results of 4 to 5% was consistently obtained, and each point on the curves represents the average of at least three determinations. Near the region of each maximum in the curves the time was varied slightly so as to fix the point of greatest yield.

Summary

1. The peroxidase activity of charcoal in catalyzing the formation of indophenol has been reinvestigated.

2. It now appears that the observed destruction of indophenol after one-half minute is due to a reaction involving excess reagents and catalyzed by charcoal.

3. The oxidase activity of charcoal in the indophenol reaction has been investigated. This action is very similar to the peroxidase action. It is suggested that the formation of indophenol takes place both in solution and on the surface of the charcoal.

JERSEY CITY, N. J.

RECEIVED MAY 9, 1938

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, ST. PETER'S COLLEGE]

The Catalytic Properties of Charcoal. III. A Comparison of the Oxidative Properties of Various Charcoals. The Effect of Charcoal Hydrosols on Hydrogen Peroxide and Oxygen

BY JOSEPH F. KEEGEL, WILLIAM A. SURUDA AND CLAUDE SCHWOB

1. A Comparison of the Properties of Various Charcoals.—This Laboratory has been investigating the properties of charcoal for several years.[1] We have used mainly purified animal charcoal and sucrose charcoal. The findings of several investigators[2] have suggested the possibility that other charcoals might be more suitable as catalysts. Moreover, it is one of the aims of this series of investigations to attempt a standardization in the use of charcoal as a catalyst, a need which we believe pressing since, in so far as we have noticed, no two investigators have used exactly the same charcoal.

Hence, in this phase of the investigation we endeavored to find conditions under which charcoals of various kinds may be prepared in a manner easily duplicated without special equipment. Next, we tested these charcoals for catalytic activity in decomposing hydrogen peroxide (cata-

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[1] I, (a) Schwob, THIS JOURNAL, **58**, 1115 (1936); II, (b) O'Brien, Tkac and Schwob, *ibid.*, **60**, 2480 (1938).

[2] (a) Rideal and Wright, *J. Chem. Soc.*, 1813 (1926); (b) Zylbertal, *Biochem. Z.*, **236**, 131 (1931).

lase action), in promoting oxidations with hydrogen peroxide (peroxidase action) and with oxygen (oxidase action). For purposes of comparison, the same charcoals were tested in standard adsorption experiments.

Because we wished that the preparation of our charcoals be simple, a temperature of only 590 to 600° was chosen for activation. While this is a rather low and certainly not optimum temperature,[3] it gave some excellent charcoals.

Four kinds of charcoal were prepared as suggested by the work of Rideal and Wright.[2a] These were made (a) from pure sucrose (yielding a charcoal designated as "C–C" charcoal), (b) from a sucrose–urea mixture (C–N charcoal), (c) from a sucrose–ferric chloride mixture (C–Fe charcoal), and (d) from sucrose with the addition of both the iron salt and urea (Fe–C–N charcoal).

Catalase activity was determined by measuring the rate of evolution of oxygen from an 0.25 molar solution of hydrogen peroxide in the presence of 100 mg. of charcoal. The specific reaction rate was calculated from the data by assuming a unimolecular reaction.

The oxidase activity was determined according to the method of O'Brien, Tkac and Schwob,[1b] the results reported being the final constant yield of indophenol.[4] The peroxidase activity, reported similarly, was also obtained by methods developed in this Laboratory.[1a,b]

In the adsorption experiments two substrates were employed, benzoic acid and acetic acid. The former was used in the method of Miller,[5] and the latter was used in determining the familiar Freundlich adsorption isotherm. Table I summarizes our results.

TABLE I

Charcoal	Miller test, %	Isotherm[a]		Catal.	Oxid.	Peroxid.
		K	n	$K \times 10^4$	mg.	mg.
C–C	8.17	0.17	0.48	9.0	0.063	0.15
C–N	5.96	.076	.51	23	.12	0.45
C–Fe	16.9	.41	.39	21	.69	1.35
Fe–C–N	10.9	.11	.60	170	.72	3.4

[a] In $x/m = Kc^n$, where c = molar concentration at equilibrium.

A second set of charcoals was then prepared in order to test the reproducibility of the charcoals. Tests showed agreement within 4 to 9% for most of the properties with the notable exception of the catalase activities of the C–N and C–Fe charcoals, which were approximately 25% greater for the second batch, and the peroxidase activity of the C–Fe charcoal which was 15% higher than that of the original batch. However, these deviations were not large enough to disturb the relations between the various properties.

It is evident from Table I that the C–Fe charcoal is the best adsorbent and the C–N one is the poorest for both substrates. There seems to be no direct relation between adsorptive power and catalytic effect since the Fe–C–N charcoal is the most active catalyst with the C–Fe one second and the unpromoted C–C charcoal poorest. What is especially striking is that the various charcoals show very much the same order of activity for all three catalytic processes. The one exception is the standing of the C–N and C–Fe charcoals as regards catalase action. The difference, however, is very small.

We cannot legitimately theorize with such limited data at hand, but we readily are led to think that there is some process common to all three catalytic actions. On thermodynamic grounds we should expect a catalyst good for the decomposition of hydrogen peroxide to be equally good for its formation. Does this indicate that oxidase action involves the formation of a peroxide as postulated by Lamb and Elder?[6] Then what is the function of charcoal in influencing reactions in the presence of peroxide? This question we attempt to answer in the second part of this paper.

2. The Effect of Charcoal Sols on the E. m. f. Produced by Hydrogen Peroxide Solutions. The Function of Charcoal in Oxidative Reactions.—In order to gain some idea of the role of charcoal in the so-called peroxidase reactions it is necessary to find some method which will enable us to estimate the relative oxidizing power of hydrogen peroxide in the presence and absence of charcoal. This immediately suggests the use of oxidation–reduction potentials. However, it has been pointed out that the oxidation–reduction potential of peroxide cannot be measured directly by the usual means.[7] Ort and his collaborators[8] have found that the voltages

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[3] King, *J. Chem. Soc.*, 889 (1935).

[4] The detailed analysis of the oxidase and peroxidase curves obtained with these charcoals will be made the subject of a separate investigation.

[5] Miller, *J. Phys. Chem.*, **30**, 1168 (1926), method (a).

[6] Lamb and Elder, THIS JOURNAL, **53**, 137 (1931).

[7] Bancroft and Murphy, *J. Phys. Chem.*, **39**, 337 (1935).

[8] Ort and Bollman, THIS JOURNAL, **49**, 805 (1927); Ort, *ibid.*, **50**, 420 (1928); *J. Phys. Chem.*, **33**, 825 (1929); Clifton and Ort, *ibid.*, **34**, 855 (1930); Roepke and Ort, *ibid.*, **35**, 3596 (1931); Ort and Roepke, *ibid.*, **38**, 1061 (1934).

developed in peroxide–sugar solutions are greatly affected by certain amino acids. The results of this investigation led these workers to the conclusion that an active, easily oxidized form of glucose exists in such solutions, but no conclusion was drawn as to the effect of the amino acid on the hydrogen peroxide.

In the first paper of this series[1a] we attempted a measurement of the voltages developed in hydrogen peroxide solutions in the presence of charcoal sols in order to determine whether the presence of colloidal charcoal had any influence upon the peroxidase reaction. Although the hypothesis involving the presence of colloidally dispersed charcoal has not been found necessary to explain our more recent results, the method seemed a suitable one for leading us to at least a partial answer to the question: what is the function of charcoal in oxidative processes?

By measuring the potentials developed across a bright platinum electrode and a saturated calomel electrode immersed in peroxide solutions with and without the addition of charcoal sols of various kinds, we can determine the specific effect of the charcoal upon the peroxide alone, as distinguished from any effect upon the reagents or products of any reaction we may choose to employ to test charcoal activity. The need for such work was felt especially in this Laboratory when we had to postulate the existence of an active form of oxygen in solution in order to explain the shape of the oxidase curves obtained in a previous study.[1b]

When we attempted to measure the potentials of peroxide solutions of different concentrations, we obtained widely varying results which were not duplicable. The voltages as read directly ranged from 0.56 to 0.45 v. for peroxide solutions varying between 0.5 and 0.05%. In the presence of charcoal sols, however, the voltage was easily measured and reproduced. This effect may be due to a speeding up of the attainment of equilibrium in a manner analogous to the effect of charcoal on the oxygen electrode.[6] Another effect is noted when the amount of charcoal sol added is varied and the concentration of the peroxide kept constant at 0.2%. The voltage progressively decreases as shown in Fig. 1, which also illustrates the irreproducibility of peroxide potentials in the absence of sufficient charcoal. Similar results were obtained with charcoal sols prepared in various ways from a wide variety of "pure" and commercial activated charcoals. In every case (some 150 experiments) the same type curve was obtained.

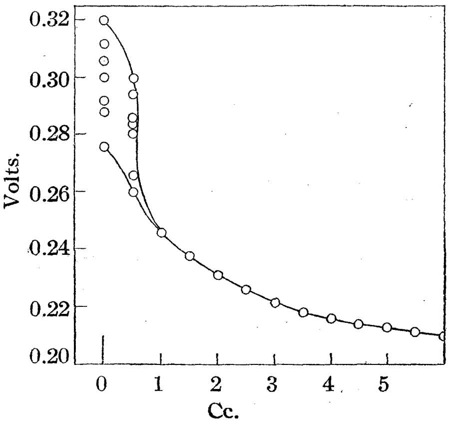

Fig. 1.—Voltage obtained from 0.2% hydrogen peroxide in the presence of varying amounts of charcoal hydrosol. With less than one cc. of sol the voltages were not duplicable.

In order to prove that it was the charcoal surface which produced this effect we studied the action of various charcoal poisons. Amyl alcohol prevented any dropping off of the voltage, and showed marked stabilizing power, giving an unvarying and reproducible voltage reading of 0.216 ± 0.0004 v. in the presence of varying amounts of charcoal. Potassium cyanide produced the same pair of results, but at a reduced voltage (0.027 v.). These findings indicate that it is an easily poisoned surface of charcoal which activates the hydrogen peroxide.

The explanation proposed for the shape of some of the oxidase curves obtained in this Laboratory[1b] is based upon experiments which indicate that charcoal will have the same effect upon oxygen. If air or oxygen is bubbled through distilled water a constant voltage is obtained between platinum and calomel electrodes after about fifty minutes (0.300 v. for oxygen, 0.260 v. for air). When the water is replaced by charcoal sol the voltages obtained are lower and become constant in a shorter time (0.250 v. for oxygen, 0.220 v. for air, in thirty-five minutes).

In view of these findings we believe that charcoal, independently of its possible effects upon the other reagents, has a definite effect upon hydrogen peroxide and oxygen, an effect which may be made to account in part for the oxidase and peroxidase properties of charcoal.

It may be objected that the peroxidase properties of charcoal are due solely to a combination of catalase and oxidase properties. This cannot be the case in the oxidation of uracil by hydrogen peroxide in the presence of charcoal[9] as shown in a previous paper.[1a] There we also stressed the fact that colloidal charcoal has definite peroxidase activity while lacking marked catalase activity. The latter property has now been investigated for a large number of charcoal sols. While 44 cc. of a 0.25 molar solution of hydrogen peroxide in a 100-cc. Pyrex flask liberated 3.0 cc. of oxygen in twenty minutes, when the water was replaced by a wide variety of charcoal sols, the yield of oxygen varied between 3.1 and 4.3 cc., a very small increase.

Experimental

Preparation of the Charcoals.—Approximately 190 g. of reagent-grade sucrose was suspended in 200 cc. of water in a porcelain vessel and heated until charring was complete. After grinding in an agate mortar, the product was activated for one hour in porcelain crucibles at 590 to 600°. Urea was added in the proportion of 5 parts to 95 of sucrose, while ferric chloride was added to the extent of 3%. The charcoals containing iron were washed repeatedly with distilled water until free from chloride before being activated.

Catalase Activity.—This was measured in a 100-cc. Pyrex flask, containing 100 mg. of the charcoal to be tested, 24 cc. of water, and 20 cc. of *p*H 7.5 citrate buffer. In a side-arm 1 cc. of superoxol was placed so that tilting the flask introduced it into the solution. The oxygen was measured in a 10-cc. gas buret while the flask was shaken 90 times per minute. In testing the charcoal hydrosols, the buffer and charcoal were omitted, and either 44 cc. of water or of charcoal hydrosol and 1 cc. of superoxol were used.

Preparation of the Charcoal Hydrosols.—Two general methods were used, the one described in the first paper of this series,[1a] and a new one involving the use of no diluent or foreign substance.[10] Some of the sols were stabilized with gelatin. In all cases the results were qualitatively the same as shown in Fig. 1, which represents the data for a gelatin protected sol obtained by the sodium chloride-grinding method. These sols contained in the neighborhood of 0.003 mg. of charcoal per cc.

Electrometric Measurements.—This work was performed as described originally[1a] except that only 4 cc. of 0.5% hydrogen peroxide was used. The results were duplicable within 3 mv. if one or more cc. of sol was present.

Summary

1. Several charcoals have been prepared and compared in catalase, peroxidase, oxidase and adsorptive properties.

2. The charcoals tested stand in the same order of activity for all three catalytic processes.

3. By electrometric means charcoal sols have been found to cause some activation of hydrogen peroxide and oxygen.

4. The catalase activity of the charcoal hydrosols prepared has been found to be very slight.

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[9] Schwob and Cerecedo, THIS JOURNAL, **56**, 2771 (1934).

[10] Schwob and Shea, unpublished research.

JERSEY CITY, N. J. RECEIVED MAY 9, 1938

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF INORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, No. 69]

Studies in Organo-silicon Synthesis. I. The Wurtz Reaction with Silicon Chlorides

BY WALTER C. SCHUMB, JOSEPH ACKERMAN, JR., AND CHARLES M. SAFFER, JR.

Although numerous alkyl and aryl silanes have been prepared, and the field of organo-silicon chemistry has been explored extensively by Kipping and other investigators, it seemed worth while in the opinion of the writers to make a comparative study of compounds containing the linkages Si–C, Si–Si, and Si–X, leading to further knowledge of the stability of these bonds and of the reactivity of substituent groups as affected by the nature of the environment of the silicon atom.

The preparation of compounds of the type R_4Si and $R_3Si–SiR_3$, where R may be either alkyl or aryl, is generally effected by the Wurtz synthesis from SiX_4 and R_3SiX, where X is halogen. In some unpublished work[1] it had been determined that the Wurtz reaction, when applied to *p*-chlorobiphenyl and Si_2Cl_6, did not lead to the formation of hexaxenyldisilane but splitting of the Si–Si linkage occurred, and good yields of tetraxenylsilane were obtained. It was thought of interest, therefore, to determine whether this synthesis would be applicable to the preparation of other hexasubstituted disilanes, or whether cleavage of the Si–Si bond invariably would result.

The first synthesis tried was the preparation of hexaethyldisilane, $(C_2H_5)_3Si–Si(C_2H_5)_3$, which previously had been prepared by Friedel and Laden-

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[1] J. Ackerman, Jr., S. B. Thesis, M. I. T., 1936.

burg[2] by the interaction of hexaiododisilane with diethylzinc in a sealed tube. Kraus and Nelson[3] also prepared it by the action of sodium on $(C_2H_5)_3SiBr$. By the reaction of sodium and hexachlorodisilane, Si_2Cl_6, with ethyl bromide the only product we obtained was tetraethylsilane, $(C_2H_5)_4Si$; no hexaethyldisilane could be isolated. With *n*-amyl chloride, Si_2Cl_6 and sodium, tetra-*n*-amylsilane was formed, a compound hitherto undescribed in the literature, which proved to be identical with the compound formed from $SiCl_4$, sodium and *n*-amyl chloride.

As aryl examples, the reaction of Si_2Cl_6 and sodium with chlorobenzene and with *p*-chlorobiphenyl gave tetraphenylsilane and tetraxenylsilane (a new compound), respectively, but no hexa-substituted disilanes. Hence it was concluded that hexaalkyl- and hexaaryldisilanes cannot be prepared from Si_2Cl_6 by this method of synthesis, since the Si–Si bond invariably is ruptured, leading to the formation of tetrasubstituted monosilanes. It may be argued that under gentler conditions of reaction, such as the avoidance of excess alkali metal, or lower temperatures, fission of the Si–Si bond might not occur; but we have observed no such cleavage when hexaphenyldisilane was treated with excess sodium in boiling xylene or benzene for ten hours with or without the addition of chlorobenzene, indicating that excess of sodium is not the cause of the splitting of the Si–Si linkage. At lower temperatures the reaction studied merely failed to proceed at a noticeable rate.

It seemed of considerable interest to determine the effect of employing a compound containing the more stable Si–O–Si configuration in the Wurtz synthesis. For this purpose, the reaction of Si_2OCl_6 with sodium and chlorobenzene was investigated. Somewhat unexpectedly, tetraphenylsilane was found to be the product formed. With ethyl bromide, Si_2OCl_6 and sodium, tetraethylsilane alone was isolated. Thus the Si–O–Si configuration likewise is broken up when it is subjected to the Wurtz reaction with alkyl or aryl halides.

Further studies in the synthesis of these compounds with the Grignard reagent are in progress.

Experimental

I. Reactions with $SiCl_4$. Tetraxenylsilane.—This substance was prepared according to the method employed in the preparation of tetraphenylsilane by Polis[4] from 45 g. of *p*-chlorobiphenyl, 10 g. of silicon tetrachloride and 12 g. of sodium wire in 250 cc. of anhydrous ether. A yield of about 90% of crude tetraxenylsilane was obtained when the ether was evaporated and the remaining solids extracted with hot benzene. The tetraxenylsilane was recrystallized several times from benzene in the form of long, glistening, colorless needles with 2 mols of benzene of crystallization. At 80° the needles lost benzene and became opaque. The benzene-free product melts at 274° (corr.). It is insoluble in water, alcohol, ether, and cold benzene. Its solubility in boiling benzene is 5 g. per liter, and it is more soluble in hot xylene. When rubbed in a mortar it becomes electrified.

Anal. Calcd. for $Si(C_{12}H_9)_4$: C, 89.9; H, 5.67; Si, 4.39; mol. wt., 640. Found: C, 90.0; H, 5.80; Si, 5.0; mol. wt. (camphor s. p.), 630.

Tetra-*n*-amylsilane.—This compound was prepared by the interaction of 85 g. of *n*-amyl chloride, 34 g. of silicon tetrachloride and 38 g. of sodium wire in 200 cc. of anhydrous ether. The general method followed was that employed by Taurke[5] in the preparation of tetraisoamylsilane. When the crude product was distilled, the largest fraction came over between 290 and 320°, corresponding to a yield of 80%, and after repeated distillation boiled at about 305°. The sample was washed with concentrated sulfuric acid to remove any silicols or silicones,[6] then with water, and finally dried with calcium chloride. It then boiled at 318° (corr.), $d^{32}{}_4 = 0.8252$, $n^{25}{}_D = 1.4510$. The purified material is a colorless, odorless oil, soluble in benzene, ether, absolute alcohol, cyclohexane, and xylene. It is practically insoluble in reagent alcohol and in water. It is not hydrolyzed in contact with water.

Anal. Calcd. for $Si(C_5H_{11})_4$: C, 76.8; H, 14.2; Si, 9.0; mol. wt., 312. Found: C, 76.4; H, 14.3; Si, 8.9; mol. wt. (cyclohexane s. p.), 309, 320.

II. Reactions with Si_2Cl_6.—These reactions were carried out in a dry atmosphere with 14 g. of Si_2Cl_6 and 20 g. of sodium wire in 300 cc. of anhydrous ether, together with the desired alkyl or aryl halide. The Si_2Cl_6 used boiled at 90° at 125 mm. and melted from −1 to 0°; the absence of any silicon tetrachloride was thus assured. In the case of the alkyl silanes the reaction product was extracted with ether and, after evaporation of the ether, the liquids were vacuum distilled to hinder formation of the corresponding silicones (trialkylsilicyl oxides).

Reaction with Ethyl Bromide.—Forty-nine grams of the alkyl halide was used with the reactants as described above. No reaction was noted even after several hours of refluxing. However, on addition of a few drops of ethyl acetate a gentle reaction ensued and was allowed to continue with warming for three days. (Kipping and Lloyd[7] report similar difficulty in the preparation of tetraethylsilane from silicon tetrachloride, by sodium and ethyl bromide, obtaining only a small yield.) The ether extract, after treatment with water to destroy excess hexachlorodisilane and evaporation of the ether, gave 2 cc. of a colorless oil. After two fractionations 0.8 cc. was obtained boil-

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[2] Friedel and Ladenburg, *Ann.*, **203**, 251 (1880).

[3] Kraus and Nelson, THIS JOURNAL, **56**, 194 (1934).

[4] Polis, *Ber.*, **18**, 1540 (1885).

[5] Taurke, *ibid.*, **38**, 1661 (1905).

[6] Friedel and Crafts, *Ann. chim. phys.*, **19**, 337 (1870).

[7] Kipping and Lloyd, *J. Chem. Soc.*, **79**, 456 (1901).

ing at 150° (Emich method)[8] (b. p. of tetraethylsilane, 150–152°). Mol. weight, calcd., 144; found (cyclohexane s. p.), 135, 139. The substance therefore was concluded to be tetraethylsilane. No material boiling higher than 160° was observed, which excludes the formation of hexaethyldisilane, b. p. 250°.

Reaction with *n*-Amyl Chloride.—Thirty-five grams of *n*-amyl chloride was used, and a vigorous reaction gave a 60% yield of a crude oil. On purification this proved to be identical with the tetra-*n*-amylsilane prepared above from silicon tetrachloride and *n*-amyl chloride; b. p. 305–312°; mol. wt. calcd., 312; found (cyclohexane s. p.), 302.

Reaction with Chlorobenzene.—Thirty-five grams of chlorobenzene was used. The solid reaction products were extracted with xylene, the melting points of each crystallization fraction rising from 218 to 229 and 231° (corr.) for the highly purified product. The recorded melting point of tetraphenylsilane is 233° (corr.). A yield of about 60% was obtained. A mixed melting point of the product with some pure tetraphenylsilane gave no depression (231°), while known mixtures of tetraphenylsilane and hexaphenyldisilane gave marked depressions: mol. wt. calcd. for $Si(C_6H_5)_4$, 336; found (camphor s. p.), 340, 343.

Reaction with *p*-Chlorobiphenyl.—Eighty grams of *p*-chlorobiphenyl, used in a manner similar to the reaction of this substance with silicon tetrachloride, gave a 60% yield of tetraxenylsilane in the form of glistening needles, melting at 270° after repeated crystallization. A mixed melting point with a known sample of tetraxenylsilane gave no depression. The compound was, therefore, characterized as tetraxenylsilane.

Anal. Calcd. for $Si(C_{12}H_9)_4$: C, 89.9; H, 5.67. Found: C, 89.7, 89.9; H, 5.63, 5.87.

III. Reactions with Si_2OCl_6.—The Si_2OCl_6 had been prepared by Mr. A. B. Levine in this Laboratory by the simultaneous action of chlorine and oxygen upon heated silicon, followed by a series of careful fractional distillations. The purified substance, melting at −35°, was analyzed for chlorine and silicon, the results being in good agreement with the theory. 16.5 g. of Si_2OCl_6 and 20 g. of sodium wire were used in each of the following experiments.

Reaction with Chlorobenzene.—Forty-five grams of chlorobenzene was used. The purified needles obtained by repeated crystallization from xylene and benzene gave a product melting at 227° (uncorr.). A yield of approximately 60% was obtained. A mixed melting point (227°) with tetraphenylsilane, m. p. 228° (uncorr.), gave no depression.

Anal. Calcd. for $Si(C_6H_5)_4$: C, 85.71; H, 6.01; mol. wt., 336. Found: C, 85.74; H, 6.17; mol. wt. (camphor s. p.), 339, 346, 330.

Thus it is to be concluded that the main product of the reaction is tetraphenylsilane. A small amount of material from the ether washings of the product gave a melting point of 148°, corresponding exactly with the recorded melting point of triphenylsilicol, $(C_6H_5)_3SiOH$.

Reaction with Ethyl Bromide.—The same sluggish reaction was observed as in the case of hexachlorodisilane and with silicon tetrachloride. Fifty grams of ethyl bromide was used. One cc. of an oil, boiling between 150 and 158° (Emich method),[8] was obtained. No material boiling above 165° was found. Molecular weight, calcd. for $Si(C_2H_5)_4$, 144; found, 150, 154. The compound therefore was characterized as tetraethylsilane.

IV. Molecular Weight Determinations with Cyclohexane and Camphor.—Cyclohexane, because of its large cryoscopic constant and miscibility with alkyl silanes, was used in the usual Beckmann freezing point apparatus. The molecular weights of the solid compounds (aryl silanes) were determined using camphor, in a modification of the Rast method.[9] A few milligrams of the compound was mixed with ten times as much camphor in a small Pyrex test-tube. The tube was then sealed off and the substances melted together in an oil-bath. The solidification point can be determined directly, *i. e.*, by observing the mixture in the original oil-bath, or by observing the solidification point of the substance in a melting point tube. The second method was checked to determine whether or not sublimation of a small amount of camphor from the melting point tube affected the results. The same results were obtained in both cases.

V. Silicon Analysis.—The percentage of silicon in the compounds was determined by a modification of the method described by Marvin and Schumb:[10] 0.5 gram of the sample was introduced from a weighed pipet into a nickel crucible half full of a fusion mixture, consisting of sodium peroxide and sugar charcoal. More of the mixture was added and, after ignition in the usual manner, the sodium silicate present in the fusion product was then analyzed, the silicon being determined as silicon dioxide.

Summary

1. Hexasubstituted alkyl and aryl disilanes and hexasubstituted silicyl oxides could not be prepared from hexachlorodisilane and trichlorosilicyl oxide, respectively, by the Wurtz synthesis. Instead, the Si–Si linkage invariably was broken, leading to the formation of tetrasubstituted monosilanes.

2. The Wurtz reaction was carried out with hexachlorodisilane and ethyl bromide, *n*-amyl chloride, chlorobenzene and *p*-chlorobiphenyl yielding, respectively, the tetrasubstituted silanes, $Si(C_2H_5)_4$, $Si(n\text{-}C_5H_{11})_4$, $Si(C_6H_5)_4$ and $Si(C_{12}H_9)_4$. No substituted disilanes could be detected.

3. Likewise the Wurtz reaction, applied to trichlorosilicyl oxide and ethyl bromide or chlorobenzene, resulted in the breaking of the Si–O–Si linkage, giving tetrasubstituted silanes.

4. Tetraxenylsilane and tetra-*n*-amylsilane were prepared from both tetrachlorosilane and hexachlorodisilane.

CAMBRIDGE, MASS. RECEIVED JULY 22, 1938

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[8] Emich, *Monatsh.*, **38**, 219 (1917).

[9] Rast, *Ber.*, **55**, 1051, 3727 (1922).

[10] Marvin and Schumb, THIS JOURNAL, **52**, 574 (1930).

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

The Ethane Equilibrium

BY R. N. PEASE AND A. M. BYERS, JR.

Storch and Kassel[1] have suggested that the experimental data on the position of equilibrium in the reaction

$$C_2H_4 + H_2 \rightleftarrows C_2H_6$$

are in error because of the occurrence of side-reactions in general, and particularly because the alleged presence of propylene has interfered with the analytical determination of ethylene. As to the latter, a correction would decrease the calculated ethylene concentration, and increase the value obtained for the equilibrium constant. This would lead to better agreement with quantum-statistical calculations in which free rotation about the C–C band in ethane is assumed.

As a matter of fact, Travers and Hockin[2] state explicitly that no C_3 hydrocarbons are found on fractionation of the products. Nevertheless, in view of the interest attaching to the question of free rotation in ethane, an additional test seemed desirable. We have, therefore, carried out a series of experiments in which ethane–ethylene–hydrogen mixtures were circulated through a reaction tube at 600°, and the mixture subsequently fractionated in a modified Podbielniak still.

The net result was that in no case was a fraction obtained condensing between −88° and room temperature which contained more than 10% of the total olefin. Moreover, since the paraffin hydrocarbon accompanying this was shown by combustion analysis to be ethane, it is more than likely that at least a part of this residuum was ethylene. We therefore feel safe in saying that considerably more than 90% of the total olefin is certainly ethylene. Similarly we can say that no appreciable amount of volatile paraffin higher than ethane is present. This holds equally for starting material consisting of either ethane alone, or ethylene plus hydrogen, or of a near-equilibrium mixture of all three.

Although we were not especially interested in adding to the already numerous data on the equilibrium constant, the results that were obtained may be reported. These appear in Table I. Our final runs were made at 600° (with close temperature control and measurement). There is one run starting with pure ethane, one run with a 50% ethylene–hydrogen mixture and four runs with near-equilibrium mixtures. The times given are the total times of circulation. We are not prepared to convert these to actual heating times, since the method of circulation consisted of "thermal siphoning" (flow due to difference in density between hot and cold gas) and the constants of the apparatus were not accurately determined. Judging from other equilibrium data, our longest time (one hundred and eighty minutes) is equivalent to something less than thirty minutes of actual heating. About 400 cc. of gas was used in each experiment.

TABLE I

EQUILIBRIUM MEASUREMENTS AT 600°

Time, min.	Final press., atm.	Composition, % C_2H_6	C_2H_4[a]	H_2	CH_4	N_2	"K_P," atm.
		Ethane side					
180	0.602	67.9	15.3	14.4	1.0	1.4	51.2
		Ethylene–hydrogen side					
180	0.734	28.5	20.6	43.9	6.4	0.6	4.3
		Near-equilibrium mixtures (C_2H_4–H_2 side)					
30	0.858	58.2	19.5	20.6	0.7	1.0	16.9
60	.968	60.2	16.8	16.5	5.4	1.0	22.4
120	.902	64.8	15.2	17.3	2.1	0.6	27.3
180	.952	63.2	13.8	16.1	5.1	1.7	29.9

[a] "C_2H_4" = total olefin.

The results for the "near-equilibrium" mixture indicate a value somewhat greater than 30 for the equilibrium constant at 600°. This is in good agreement with previous determinations (see below).

It is perhaps not generally appreciated that the experimental data for the equilibrium constant of this reaction are in excellent agreement not only among themselves, but also with Third Law calculations based on thermal data alone (except for the entropy of hydrogen). Kemp and Pitzer[3] have, to be sure, emphasized the latter point by a calculation of the entropy of ethane based on a single value of the equilibrium constant. However, the concordance goes far beyond this.

We may calculate the equilibrium constant from thermal data as follows. For ΔH°_{298}, Kistiakowsky finds −32,575 cal. by direct measure-

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[1] Storch and Kassel, THIS JOURNAL, **59**, 1240 (1937).

[2] Travers and Hockin, *Proc. Roy. Soc.* (London), **136A**, 1 (1932).

[3] Kemp and Pitzer, THIS JOURNAL, **59**, 276 (1937).

ment,[4] whereas Rossini obtains −32,783 cal. from heats of combustion.[5] We take $\Delta H^\circ_{298} = -32{,}675 \pm 100$ cal. as the average value. Heat capacities of the three gases between 250 and 400° A.[6] are in agreement with the equation

$$\begin{aligned}\Delta C_P &= \Delta\Gamma_0 + \Delta\Gamma_1 T\\ &= -6.77 + 0.0074T\end{aligned}$$

The "conventional" value of ΔH°_0 is then −30,986 cal.

Recent experimental measurements of the entropies of ethylene[7] and ethane,[8] together with the statistical value for hydrogen,[9] give

$$\begin{aligned}C_2H_4\colon S^\circ_{298} &= 52.48 \pm 0.10 \text{ e. u.}\\ H_2\colon S^\circ_{298} &= 31.23 \pm 0.01 \text{ e. u.}\\ C_2H_6\colon S^\circ_{298} &= 54.85 \pm 0.20 \text{ e. u.}\\ \Delta S^\circ_{298} &= -28.86 \pm 0.20 \text{ e. u.}\end{aligned}$$

Then

$$\Delta F^\circ_{298} = -24{,}072 \text{ cal.}$$

The estimated error in this quantity is ± 150 cal.

For the integration constant, I, in the equation

$$\Delta F^\circ = \Delta H^\circ_0 - \Delta\Gamma_0 T \ln_e T - {}^1/_2\, \Delta\Gamma_1 T^2 + I\,T$$

one then obtains

$$I = -14.274$$

Thus

$$\Delta F^\circ = -30986 + 6.77T \ln_e T - 0.0037T^2 - 14.274T$$

and

$$\log_{10}K = +\frac{6774}{T} - 3.408 \log_{10}T + 0.000809T + 3.120$$

Experimental equilibrium data have been obtained by Frey and Huppke[10] at 400, 450 and 500° using a chromium oxide catalyst; by Videnski and Vinikova[11] at 500°, also using a chromium oxide catalyst; by Travers and Pearce[12] between 550 and 620°; and by Pease and Durgan[13] at 600, 650 and 700°.

These data represent altogether about 150 individual measurements over a 300° temperature range, and a range of pressures from about 0.5 to 2 atm. Among the experiments are some in which equilibrium was approached from either side, and also with varying ratios of ethylene to hydrogen. As already mentioned, it cannot be maintained that the analytical measurements are in serious error. There is admittedly the possibility that all measured equilibria are displaced by the side-reactions yielding methane and liquid products. However, it would be extraordinary if under all the conditions studied (especially in the work of Travers and Pearce), the displacement should have been of the same magnitude. All things considered, therefore, it is difficult to see how the experimental determinations can be seriously in error.

The comparison of experimental and theoretical values is given in Table II. The agreement is very satisfactory. A somewhat better fit would be obtained by decreasing slightly the integration constant of the free energy equation. However, any such change would fall well within the estimated uncertainty of ± 150 cal. in ΔF^0_{298}.

TABLE II

EXPERIMENTAL AND CALCULATED VALUES OF THE EQUILIBRIUM CONSTANT

$$K_P = \frac{x_{C_2H_6}}{x_{C_2H_4}x_{H_2}}\,\frac{1}{P_{\text{atm.}}}$$

Temp. °C.	°Abs.	K_P Exptl.	Calcd.	Observer
400	673	12000	12530	F
450	723	1800	2162	F
500	773	420	465	F
		320	465	V
550	823	135	121	T
570	843	65.4	73.8	T
590	863	41.0	45.7	T
600	873	32.2	36.6	P
610	883	27.9	29.2	T
620	893	22.4	23.5	T
650	923	12.2	12.6	P
700	973	5.0	4.8	P

(F = Frey; V = Videnski; T = Travers; P = Pease)

It may be recalled that the entropy data on which the free energy equation is based favor a high potential barrier against internal rotation in ethane.[3] The assumption of a low barrier (or free rotation) leads to values of K_P at 600° which are two to three times larger than the experimental.[14] As already indicated, there is no obvious reason why the experimental data should be in error by anything like this amount.

The question as to whether some gross error has been made in the assignment of the seventeen normal modes of vibration and the corresponding

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[4] Kistiakowsky, *et al.*, THIS JOURNAL, **57**, 65 (1935).

[5] Rossini, *J. Research Natl. Bur. Standards*, **17**, 629 (1936).

[6] H_2: Davis and Johnston, THIS JOURNAL, **56**, 1045 (1934). C_2H_4 and C_2H_6: Eucken and Parts, *Z. physik. Chem.*, **20B**, 184 (1933).

[7] Egan and Kemp, THIS JOURNAL, **59**, 1264 (1937).

[8] Witt and Kemp, *ibid.*, **59**, 273 (1937).

[9] Giauque, *ibid.*, **52**, 4816 (1930).

[10] Frey and Huppke, *Ind. Eng. Chem.*, **25**, 54 (1933).

[11] Videnski and Vinikova, *J. Gen. Chem.* (*Moscow*), **4**, 120 (1934).

[12] Travers and Pearce, *J. Soc. Chem. Ind.*, **53T**, 321 (1932). See also Travers and Hockin, *Proc. Roy. Soc.* (London), **136A**, 1 (1932).

[13] Pease and Durgan, THIS JOURNAL, **50**, 2715 (1928).

[14] Smith and Vaughan, *J. Chem. Phys.*, **3**, 341 (1935); Teller and Topley, *J. Chem. Soc.*, 876 (1935).

frequencies for the ethane molecule is one which the authors are not prepared to discuss. If such an error has not been made, there would seem to be a flat contradiction between the thermodynamic data (including heat capacity measurements for gaseous ethane[15]) on the one hand, and on the other, the spectroscopic data as analyzed by Bartholomè and Karweil.[16] In addition, there is the difficulty in accounting theoretically for the high potential barrier apparently demanded by the thermodynamic data.[17]

However this contradiction may be resolved, the authors wish to emphasize that in dealing with the problem the experimental data on the ethane equilibrium cannot be ignored.

Summary

Additional experiments on the ethane–ethylene–hydrogen equilibrium have been carried out to determine whether the presence of volatile hydrocarbons higher than ethylene and ethane could have invalidated previous analytical work, as suggested by Kassel and Storch.[1] The evidence is that the error is certainly less than 10%, confirming the conclusion of Travers and Hockin.[2]

A comparison of all experimental values with values based on the Nernst Heat Theorem (and the Third Law) emphasizes the internal consistency of the data.

It is concluded that there is no good ground for ignoring the experimental data on the ethane equilibrium in dealing with the question of free rotation in the ethane molecule.

PRINCETON, N. J.

RECEIVED JULY 14, 1938

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[15] Kistiakowsky, *et al.*, *J. Chem. Phys.*, **6**, 407 (1938). See, however, Hunsman, *Z. physik. Chem.*, **39B**, 23 (1938).

[16] Bartholomè and Karweil, *ibid.*, **39B**, 1 (1938).

[17] Eyring, THIS JOURNAL, **54**, 3191 (1932).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AT THE OHIO STATE UNIVERSITY]

Fluorinated Derivatives of Propane. II

BY ALBERT L. HENNE AND ELBERT C. LADD

Three chlorinated derivatives of propane (C_3Cl_8, $CHCl_2CCl_2CCl_3$ and $CCl_3CHClCCl_3$) have been synthesized and subjected to fluorination. Three monofluorides, three difluorides and two trifluorides have thus been made. These new compounds are described, their structural formulas established and the course of the fluorination thereby demonstrated.

Extending to the propane series the investigations which have covered methane and ethane compounds is not a mere expansion, because the propane molecule offers a new position on its center carbon atom, and because the increased distance between its ends affects the course of the fluorination. As the ultimate purpose is the synthesis of fluorinated derivatives of much greater length, it is essential to learn the effect that the position and the distance of the fluorinated groups exert upon the molecule as a whole.

Synthesis.—The heptachloropropanes were synthesized by condensing chloroform with tetrachloroethylene, or carbon tetrachloride with trichloroethylene, in the presence of aluminum chloride. From asymmetrical heptachloropropane, a treatment with potassium hydroxide gave hexachloropropylene, and the latter combined with chlorine to yield octachloropropane. This method, originated by Prins,[1] has been improved, as described in the experimental part, but it cannot be extended to the condensation of fluorinated molecules of methane and ethylene, for the reasons previously reported.[2]

The chlorinated propanes were thoroughly purified before subjecting them to fluorination. This precaution was taken because fluorination gives only one of the possible isomers at each stage, and the isolation of the fluorinated compounds in a pure state is much facilitated by starting from well-defined material. The fluorination was performed as indicated in the experimental part, but the isolation, purification, analysis and description of the new compounds followed the methods of preceding papers[3] and the results have been tabulated.

The reason for describing the fluorination procedures in detail is that chlorinated propanes may split into one molecule of chlorinated methane and one of chlorinated ethylene, which is merely the reverse of the condensation reaction by means of

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[1] Prins, *J. prakt. Chem.*, [2], **89**, 416 (1914).

[2] I, Henne and Newman, THIS JOURNAL, **60**, 1697 (1938).

[3] *Ibid.*, **56**, 1726 (1934); **58**, 402, 404, 882, 884, 887, 889 (1936); **59**, 1200, 1400, 2434 (1937).

which they have been synthesized. Consequently, the fluorination products contain compounds resulting from the fluorination of the split products, which complicate the separation and affect the yields. The fluorinated methane derivatives are volatile and escape the field of reaction; the other by-products are $CCl_2{=}CCl_2$ and products derived therefrom, namely, CCl_3CCl_3, CCl_3CCl_2F, CCl_2FCCl_2F and CCl_2FCClF_2, on the one hand, and $CHCl{=}CCl_2$ and its derivatives, namely, $CHCl_2CCl_3$, $CHCl_2CCl_2F$ and $CHCl_2CClF_2$ on the other hand. It should be emphasized that this splitting is quite important with the chlorinated propanes, but vanishes rapidly with increasing fluorination of the molecules, as is evident from the fact that the by-products are related to the starting materials, and not to their fluorinated derivatives.

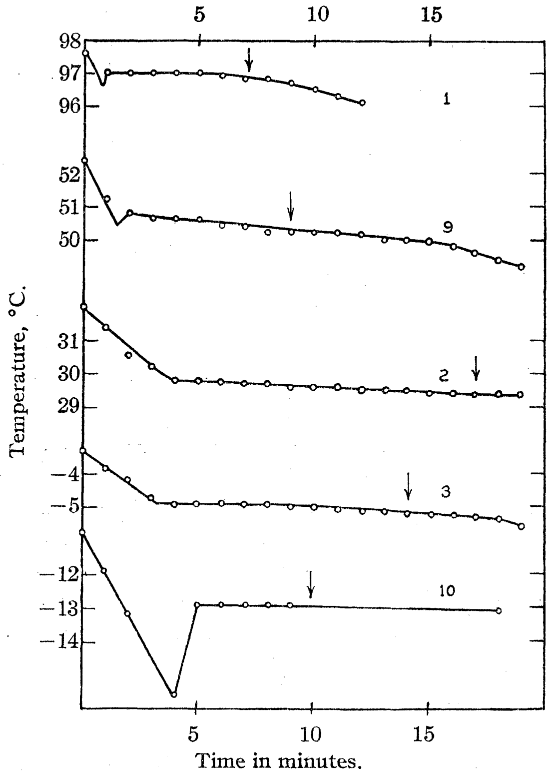

Fig. 1.—Freezing curves. Numbers refer to compounds in Table I. Arrows denote end of stirring.

Determination of Structure.—In the determination of the structural formulas advantage was taken of the fact that fully halogenated compounds are crystalline, in contrast with compounds which have hydrogen in the molecule. Even with only one hydrogen atom present, the compounds are liquids, and become glassy at very low temperatures only. It was, therefore, practical to substitute the hydrogen by chlorine and isolate the resulting fully halogenated compound in a state of high purity by alternating fractional distillation and fractional crystallization. A second step of the determination consisted in synthesizing three derivatives, $CCl_3CCl_2CCl_2F$, $CCl_3CCl_2CClF_2$ and $CCl_3CF_2CCl_3$, as described elsewhere.[4] The third step was the reaction with zinc in alcohol. This, however, requires qualification.

In general, when a polyhalogenated compound is treated with zinc in alcohol, two atoms of halogen are removed and a derivative of ethylene is formed. It has, so far, been an inflexible rule that the heavier halogens are removed preferentially, and an analysis of the zinc salts produced is then sufficient to establish the nature of the removed halogens. However, in the present case, the situation was complicated by the fact that all the resulting ethylenic compounds proved unstable, some of them exceedingly so; therefore, the procedure had to be modified in order to retain its significance. When the zinc reactions were performed, the tests for chloride and fluoride ions were made at repeated intervals, as soon as the reaction started, and it was found that at that stage zinc chloride only was produced. Conversely, when the reaction was allowed to proceed to completion, it was always found that some fluorine had been removed from the organic molecules, and also that much less fluorine than chlorine had combined with the zinc; therefore, it was held that significance would be attached only to the tests performed in the early stages of the zinc reaction, when the concentration of reaction products in the alcohol was still small, and the decomposition of the ethylenic compounds minimized.

Results of the Structure Determination.—Synthetic $CCl_3CCl_2CCl_2F$ melts at 97° and is identical with the product obtained by fluorinating C_3Cl_8 (No. 1 in table).

The monofluoride (No. 7) formed from *s*-C_3HCl_7 yields zinc chloride only in a treatment with zinc in alcohol, and by chlorination in sunlight it gives the compound melting at 97°. Moreover, it gives a mixture of ethylenic compounds boiling over a 3° range, after treatment with alcoholic potassium hydroxide, and this mixture treated with chlorine yields the compound melting at 97°, exclusively. Its formula is therefore $CCl_3CHClCCl_2F$.

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[4] THIS JOURNAL, 59, 2434 (1937), and paper now presented for publication.

TABLE I

No.	Compounds	M. p., °C.	B. p., °C.	t	d^t_4	n^t_α	n^t_D	n^t_β	MR_D	AR_F	Cl/F		Mol. wt.	
											Obsd.	Calcd.	Obsd.	Calcd.
1	$CCl_3CCl_2CCl_2F$	97.0	236.8								6.76	7.00	300	303
2	$CCl_2FCCl_2CCl_2F$	29.8	194.2	35.0	1.79151	1.47191	1.47418	1.48052	45.02	0.98	2.96	3.00	289	287
3	$C_3Cl_5F_3$	− 4.9	152.3	20.0	1.77023	1.43738	1.43959	1.44510	40.21	1.04	1.65	1.67	268	270
4	$CHCl_2CCl_2CCl_2F$	Glass	210.0	20.0	1.77384	1.50024	1.50311	1.51012	44.80	0.64	5.78	6.00	272	269
5	$CHCl_2CCl_2CClF_2$	Glass	168.4	20.0	1.73162	1.45995	1.46241	1.46853	40.09	.95	2.54	2.50	256	252
6	*a*-$C_3HCl_4F_3$	Glass	129.8	20.0	1.69124	1.41767	1.41967	1.42466	35.27	1.10	1.30	1.33	233	236
7	$CCl_3CHClCCl_2F$	Glass	207 dec.	20.0	1.76188	1.49836	1.50105	1.50814	44.94	0.78	6.1	6.0	265	269
8	$CCl_2FCHClCCl_2F$	Glass	167.4	20.0	1.71720	1.45745	1.45972	1.46585	40.22	1.02	2.50	2.50	252	252
9	$CCl_3CCl_2CClF_2$	50.8	193.4								3.05	3.00	285	287
10	$CCl_3CF_2CCl_3$	−12.9	194.2	20.0	1.8105		1.47996		45.00	0.98	3.00	3.00	287	287
11	$CCl_3CF_2CCl_2F$	<−80	154.5	20.0	1.7590		1.43939		40.46	1.12	1.67	1.67	267	270

The monofluoride (No. 4) obtained from asymmetrical C_3HCl_7, treated in the same ways, yields $ZnCl_2$ only, is transformed into the compound melting at 97° by chlorination, gives, with potassium hydroxide, a single ethylenic derivative boiling over a 0.2° range, the chlorination of which yields again the derivative melting at 97°. Therefore its formula can only be $CHFClCCl_2$-CCl_3 or $CHCl_2CCl_2CCl_2F$ and a choice can be based only on analogy with preceding cases. In view of the fact that CCl_3 groups have always been much more easily fluorinated than $CHCl_2$ groups, and of the fact that the experimental conditions used are regarded as inadequate to attack the $CHCl_2$ group, the second formula is adopted.

The difluorides are, without exception, identical whether obtained directly, or from the monofluorides. Therefore, one of their fluorine atoms is located on an end carbon. By chlorination in sunlight, the difluoride (No. 5) from *a*-C_3HCl_7 gives a compound melting at 51°, identical with synthetic $CCl_3CCl_2CClF_2$. Its formula is therefore either $CHF_2CCl_2CCl_3$ or $CHCl_2CCl_2CClF_2$, and the latter is chosen for the reasons given in discussing the monofluoride. These reasons become even more convincing when comparing the plausibility of a $CClF_2$ group in contrast to a CHF_2 group.

The difluoride (No. 8) obtained from *s*-C_3HCl_7 must be $CCl_2FCHClCCl_2F$, because it yields zinc chloride only, in a zinc treatment, and because its chlorination yields a compound melting at 30°, identical with the difluoride (No. 2) obtained from C_3Cl_8. The latter must therefore be CCl_2FCCl_2-CCl_2F.

The structure of the trifluorides (Nos. 3 and 6) is not demonstrated, but can be predicted with plausibility. From C_3Cl_8, the trifluoride (No. 3) should be written $CCl_2FCCl_2CClF_2$, mostly because it has a relatively high melting point (−4°) and the only other possible formula, $CCl_2FCClFCCl_2F$ would call for a much lower melting point. From *s*-C_3HCl_7, the trifluoride should be $CCl_2FCHClCClF_2$, mostly because the fluorination of a —CHCl— group has never been performed with antimony fluoride. It is expected that by chlorination in sunlight this trifluoride will yield the compound melting at −4°, and thereby prove the structure proposed for the trifluoride obtained from C_3Cl_8. Finally, from *a*-C_3HCl_7, the trifluoride (No. 6) could be either $CHCl_2CClFCClF_2$ or $CHClFCCl_2CClF_2$ though the ease with which it is obtained miligates somewhat against the latter formula. By chlorination in sunlight, a compound should be obtained with a melting point somewhere between −10 and −15°, as would befit a compound written $CCl_3CClFCClF_2$. This is confirmed by a preliminary experiment which gave a melting point of −13 to −12°.

The above experiments, which are slow and depend on intense sunlight, are under way and will be reported together with the preparation of the tetrafluorides, which is also under way. It is not intended to fluorinate further, as this would merely make new compounds, but shed no additional light on the fluorination course.

Discussion.—The criterion for purity was the freezing curve, whenever possible. These curves are given and speak for themselves. When the compounds formed glasses instead of crystals, the Engler distilling range was used, and found to be 0.2° or less, except in the case of No. 7, which decomposed when distilled at normal pressure and gave a 3° range.

The analyses gave rise to the difficulties reported before, which forced the use of the chlorine/fluorine ratio, instead of the customary percentages. The use of this ratio has the disadvantage that it is much more affected by small experimental errors than are the percentages. Nevertheless, the results leave no doubt as to the identity of the compounds.

The molecular weights, taken by freezing point depression in benzene, gave particularly good values. The molecular refraction was computed by means of the Lorentz–Lorenz formula. The atomic refraction *AR*F was obtained by subtracting from the molecular refraction the required number of carbon increments (2.418), chlorine increments (5.967) and hydrogen increments (1.100), and dividing by the number of fluorine atoms in the compound considered. The atomic refraction increases always with the degree of fluorination; it is much more steady in fully halogenated compounds than in hydrogen bearing derivatives.

Experimental

Preparation of $CHCl_2CCl_2CCl_3$.—Ten gram molecules of tetrachloroethylene, 20 gram molecules of chloroform and 50 g. of aluminum chloride were placed in a 5-liter round-bottomed flask equipped with a reflux condenser and heated to gentle boiling during twenty hours. The reaction mixture was cooled and poured into water, washed, decanted and dried. A fractional distillation yielded, besides the unreacted material recovered, 6.8 gram molecules of *a*-heptachloropropane, boiling at 163–166° at 90 mm.

Fluorination of $CHCl_2CCl_2CCl_3$.—Two procedures were used, the first to obtain a mixture rich in mono- and difluorides, the second a product rich in di- and trifluorides.

First Procedure.—In a one-liter flask 1160 g. of *a*-C_3HCl_7 and 740 g. of SbF_3Cl_2 were placed and vigorously stirred so that the temperature of the mixture would never exceed 50°. After the mixture had cooled to 30°, it was heated slowly to 130–140° and held there for five hours. It was then cooled, poured into water, washed with hydrochloric acid to remove the antimony salts, then with water and dried. These operations gave 907 g. of reaction products containing approximately 60 g. of trifluoride, 315 g. of difluoride and 435 g. of monofluoride.

Second Procedure.—In a 3-liter flask 1970 g. of heptachloride mixed with 1245 g. of SbF_3Cl_2 was heated to 140–150° and held at this temperature for eight hours. The subsequent operations were identical with those of the first procedure and yielded 1740 g. of crude product which separated into 400 g. of trifluoride, and 1000 g. of difluoride, approximately. The remainder of the material was composed of ethylenic derivatives, and of fluorinated compounds of ethane, resulting from the splitting of the propane molecule. The more abundant by-products were $CCl_2{=}CCl_2$, CCl_3CCl_2F, CCl_2FCCl_2F and C_2Cl_6.

Preparation of C_3Cl_8.—Ten gram molecules of $CHCl_2CCl_2CCl_3$ was placed in a 5-liter flask, equipped with an efficient stirrer, and a solution of 600 g. of potassium hydroxide in methanol was added dropwise. The heat evolved is considerable, and the addition of the hydroxide should be slow to avoid splitting the propane molecule. After completion of the addition the mixture was stirred during an additional hour and then washed with water. The hexachloropropylene thus obtained (2300 g.) was treated with a slow current of chlorine, in sunlight, and with the temperature constantly kept below 50°. When crystals of octachloropropane prevented further passage of the chlorine, the mixture was allowed to stand in sunlight until it became snow white. It could then be separated by filtration under suction, but this was not done, on account of the high vapor tension of C_3Cl_8. Fractional distillation was used instead. The unchlorinated product was then returned for a further treatment with chlorine. When the operations were conducted with care, and without localized heating, the yields were quantitative.

Fluorination of C_3Cl_8.—Three procedures have been used, to obtain mixtures rich in mono-, di- and trifluoride, respectively.

First Procedure.—In a round-bottomed flask equipped with an air-cooled reflux condenser, 960 g. of C_3Cl_8, 180 g. of SbF_3 and 40 g. of $SbCl_5$ were heated for eight hours at 140°. The following day 30 g. of SbF_3Cl_2 was added and the heating was continued at 140° for another six hours. During this treatment, the lower layer containing most of the SbF_3 gradually liquefied and dissolved in the upper layer of organic material. The liquid reaction mixture was poured into commercial hydrochloric acid while still hot, and washed free of antimony salt. The crude product, amounting to 910 g., solidified at room temperature. By fractional distillation at 90 mm. it was separated into one-half of monofluoride and one-half of unreacted C_3Cl_8.

Second Procedure.—In a round-bottomed flask equipped with an air-cooled reflux condenser 1500 g. of C_3Cl_8, 560 g. of SbF_3 and 75 g. of $SbCl_5$ were mixed and heated for five hours on a steam-bath. A further quantity of 100 g. of $SbCl_5$ was then added in small portions, and the heating continued for twenty hours. The reaction mixture, which had become progressively homogeneous, was allowed to cool before it was poured into aqueous acid, then washed and dried. The crude product amounted to 1092 g., from which about 750 g. of difluoride was obtained by fractional distillation at 90 mm.

Third Procedure.—In a round-bottomed flask equipped with an air-cooled reflux condenser 1220 g. of C_3Cl_8, 500 g. of SbF_3 and 75 g. of $SbCl_5$ were heated on a steam-bath for twelve hours. A further portion of 80 g. of $SbCl_5$ was added and heating continued on the steam-bath for two hours. The mixture was then cooled, and the liquid layer decanted from the crystalline antimony salts into a flask equipped with a water-cooled reflux condenser, and 400 g. of SbF_3Cl_2 was added. The reaction was then heated to 140° without haste, because the fluorination reaction is quite active at the start. It is advisable to have a pan of ice water ready to chill the mixture if it threatens to escape control. After the temperature of 140° had been reached, the heating was continued for two hours. Then, after complete cooling, the washing, drying and distillation were performed as in the preceding cases. The crude product amounted to 700 g., and contained about 300 g. of trifluoride.

Preparation of $CCl_3CHClCCl_3$.—Trichloroethylene (520 g.), carbon tetrachloride (1220 g.) and aluminum chloride (50 g.) were stirred in a 2-liter flask at 20–30° for forty-eight hours. Access of moisture was prevented by thorough drying at the start, by using a mercury seal on the stirrer, and by protecting the vent with a calcium chloride tube. The reaction mixture was poured cautiously into ice water, vigorously shaken, decanted, washed with water, dried over calcium chloride and subjected to distillation at atmospheric pressure to recover the unreacted materials. As soon as this nears completion, the distillation is pursued at reduced pressure, with a carbon dioxide trap to stop the light boiling compounds. The distillation at 20 mm. gave 551 g. of chlorinated propane, boiling from 126 to 132°; this was a 49% conversion yield. The tar formation amounted to 5%, and the remainder of the ingredients was recovered unreacted. The reaction did not take place at lower temperatures, and resinification increased rapidly at higher temperatures. At 70°, resinification was complete. Consequently, the lower conversion yield was accepted, and the recovered materials were repeatedly re-treated.

Fluorination of $CCl_3CHClCCl_3$.—Two procedures were employed, to obtain products rich in mono- and in difluoride, respectively.

First Procedure.—In a 1-liter round-bottomed flask 500 g. of *s*-heptachloropropane, 120 g. of SbF_3 and 20 g. of $SbCl_5$ were placed, stirred vigorously for three hours and then heated to 70–80° for one hour, with stirring continued. The mixture was cooled, and its liquid layer, after pouring into hydrochloric acid, was washed, dried and distilled at 90 mm. The crude product amounted to 427 g., of which a little more than one-third was monofluoride.

Second Procedure.—Heptachloropropane (916 g.), SbF_3 (520 g.) and $SbCl_5$ (100 g.) were placed in a 1-liter round-bottomed flask and stirred overnight at room temperature. The mixture was then heated for ten hours on a steam-bath, cooled to separate most of the antimony chloride, decanted into acid, washed, dried and distilled at 90 mm. The crude product amounted to 630 g., of which a little more than one-half was the difluoride.

Summary

The syntheses of C_3Cl_8, $CHCl_2CCl_2CCl_3$ and $CCl_3CHClCCl_3$ have been improved. From these compounds, the mono-, di- and trifluorides have been obtained by replacement of chlorine atoms by fluorine. The formulas of the new derivatives have been established experimentally for the mono- and difluorides, and reasoned out for the trifluorides. The properties have been tabulated, together with those of three additional fluorochloropropanes which were synthesized independently for identification purposes. The course of the fluorination has thus been established.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UNIVERSAL OIL PRODUCTS COMPANY]

Reaction of Isobutene and Diisobutene with Phenol, with and without Scission of C–C Linkages

BY V. N. IPATIEFF, HERMAN PINES AND B. S. FRIEDMAN

In previous papers[1] it was shown that when diisobutene reacts with benzene in the presence of sulfuric acid, *t*-butyl-, *p*-di-*t*-butyl-, and tri-*t*-butylbenzene are formed. In view of the fact that Niederl and Natelson and co-workers[2,3] failed to notice analogous products observed by others[4] when phenol was treated with diisobutene in the presence of sulfuric acid, it was decided to investigate this reaction.

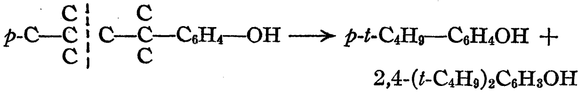
When Natelson's[3] directions were followed closely, the product contained no butylphenol. A compound not previously reported, which appears to be 2,4-di-*t*-octylphenol [2,4-di-($\alpha,\alpha,\gamma,\gamma$,-tetramethobutyl)-phenol], was isolated in addition to the expected *p*-*t*-octylphenol [*p*-(α,α,-γ,γ,-tetramethobutyl)-phenol].

When, however, phenol and diisobutene were treated with a large excess of sulfuric acid and the temperature allowed to rise to 85%, the product was found to contain some *p*-*t*-butylphenol.

The alkylation of phenol with diisobutene in the presence of phosphoric acid required a temperature of 150°; and the yield of *p*-*t*-octylphenol was quite low. *p*-*t*-Butylphenol was isolated and identified.

The production of the *p*-*t*-butylphenol could have taken place by either of two series of reactions

$$\text{Diisobutene} \longrightarrow 2\ i\text{-}C_4H_8 \qquad (A)$$
$$i\text{-}C_4H_8 + C_6H_5OH \longrightarrow t\text{-}C_4H_9\text{-}C_6H_4OH$$
$$\text{Diisobutene} + C_6H_5OH \longrightarrow t\text{-}C_8H_{17}\text{-}C_6H_4OH \qquad (B)$$



$$p\text{-}C{-}\overset{C}{\underset{C}{C}}\ \vdots\ C{-}\overset{C}{\underset{C}{C}}{-}C_6H_4{-}OH \longrightarrow p\text{-}t\text{-}C_4H_9{-}C_6H_4OH + 2,4\text{-}(t\text{-}C_4H_9)_2C_6H_3OH$$

The possibility that reaction could take place by (B) is evidenced by the fact that *p*-*t*-octylphenol heated under pressure to 140° in the presence of 90% phosphoric acid was cleaved to pro-

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[1] (a) Ipatieff and Pines, THIS JOURNAL, **58**, 1056 (1936); (b) Ipatieff and Pines, *J. Org. Chem.*, **1**, 464 (1936).

[2] (a) Niederl and Natelson, THIS JOURNAL, **55**, 2571 (1933); (b) Niederl, Natelson and Beekman, *ibid.*, **53**, 272 (1931).

[3] Natelson, *ibid.*, **56**, 1584 (1934).

[4] British Patent, 453,335, Aug. 20, 1936; *C. A.*, **31**, 485 (1937). *Cf.* Smith and Rodden, THIS JOURNAL, **59**, 2353 (1937), who used aluminum chloride.

duce both *p-t*-butylphenol and 2,4-di-*t*-butylphenol. Cleavage also took place at the point of attachment of the octyl group to the nucleus, yielding phenol and octenes.

The alkylation of phenol with isobutene and phosphoric acid at 100° gave good yields of the expected products, *p-t*-butylphenol and 2,4-di-*t*-butylphenol.

Nitration of *p-t*-butylphenol with hot acetic–nitric acids yielded the expected 2,6-dinitro-4-*t*-butylphenol,[5] but the same reagent effected a cleavage of one of the butyl groups in 2,4-di-*t*-butylphenol to form 4,6-dinitro-2-*t*-butylphenol. The structure of the latter compound was established by its synthesis from *p*-nitrophenol by alkylation with isobutene in the presence of phosphoric acid, followed by nitration.

The replacement of a tertiary alkyl group by a nitro group corresponds to the conversion of *t*-amylphenol[6a] and *t*-butylphenol[6b] into picric acid by use of concentrated and fuming nitric acids, respectively.

Experimental Part

Phenol and Diisobutene

Experiment A. Small Quantities of Sulfuric Acid.[3]—To a rapidly stirred mixture of one mole each of phenol and diisobutene in a flask surrounded by an ice-water bath, was added dropwise 2 cc. of 96% sulfuric acid. After the mixture had become viscous, the contents of the flask were heated to 65° and stirred at that temperature for fifteen minutes.

The reaction product was placed along with 4 g. of sodium carbonate in a modified Claisen flask and the various fractions separated by vacuum distillation. The fraction (8 cc.) boiling at 210–215° (29 mm.), n^{20}D 1.5040, failed to crystallize, was soluble in a solution composed of equal parts of methanol and 50% aqueous potassium hydroxide. It yielded an oil when nitrated. It probably is di-*t*-octylphenol.

Anal. Calcd. for $C_{22}H_{38}O$: C, 83.02; H, 11.94; mol. wt., 318. Found: C, 82.53; H, 12.02; mol. wt., 314.

No trace of *p-t*-butyl- or 2,4-di-*t*-butylphenols was found.

Experiment B. Large Quantities of Sulfuric Acid.—A mixture of two moles each of phenol and diisobutene was placed in a flask surrounded with an ice-bath. To this was added with stirring 78 g. of 96% sulfuric acid. The time of addition was one minute; the temperature inside of the flask rose to 85°. After fifteen minutes of stirring the temperature fell to 0°. The product was washed with water, dried over anhydrous sodium sulfate, and separated by vacuum distillation. The fraction (8 cc.) boiling at 141–152° (26 mm.) consisted chiefly of *p-t*-butylphenol, m. p. 100° after recrystallization from heptane. Mixed melting point with authentic sample was 99–100°.

Nitration.—One-half gram of *p-t*-butylphenol was treated with 2 cc. of a mixture of equal volumes of concentrated nitric acid and glacial acetic acid. After five seconds the vigorously reacting mixture was poured onto crushed ice. The solid product was separated by filtration, washed with water; recrystallized from dilute ethanol it yielded 2,6-di-nitro-4-*t*-butylphenol, m. p. 95–96°.

Experiment C. Phosphoric Acid.—Ninety-two grams of phenol, 57 g. of diisobutene, and 50 g. of 90% phosphoric acid were placed in the glass liner provided with a capillary[7] and heated at 150° for six hours in an Ipatieff type rotating bomb. The bomb was charged with 20 atmospheres of nitrogen in order to keep the material within the glass liner during the run. The product was washed with water, dried, and upon distillation in vacuum yielded, besides phenol, 22 g. of unreacted diisobutene, 16 g. of *p*-($\alpha,\alpha,\gamma,\gamma$-tetramethobutyl)-phenol (b. p. 169–181° (28 mm.), m. p. 84–85°) and 4 g. of *p-t*-butylphenol.

Phenol and Isobutene with Phosphoric Acid.—Isobutene was passed into a rapidly stirred mixture of 94 g. of phenol and 30 g. of 89% phosphoric acid kept at 100° until 100 g. was absorbed. The product after being washed with water, dried, and distilled under reduced pressure, yielded 84 g. (40% yield based on phenol) of *p-t*-butylphenol, m. p. 99–101°, and 62 g. (30% yield based on phenol) of 2,4-di-*t*-butylphenol 143–147° (20 mm.), n^{20}D 1.5080. The latter solidified only after being seeded with some authentic (Eastman) 2,4-di-*t*-butylphenol; m. p. and mixed m. p. 55°.

Nitration of the dialkylated phenol with acetic–nitric acid yielded 4,6-dinitro-2-*t*-butylphenol, yellow plates from dilute ethanol; m. p. 123–124°; mixed m. p. with specimen prepared from *p*-nitrophenol (see below) by alkylation and nitration was 122–123°.

Calcd. for $C_{10}H_{12}O_5N_2$: C, 50.00; H, 5.00; N, 11.66. Found: C, 50.11; H, 5.13; N, 11.35.

***p*-($\alpha,\alpha,\gamma,\gamma$-Tetramethobutyl)-phenol with Phosphoric Acid. (A) At 200°.**—One hundred and twenty-two grams of *p*-($\alpha,\alpha,\gamma,\gamma$-tetramethobutyl)-phenol, b. p. 170–175° (28 mm.), and 25 g. of 90% phosphoric acid were heated for five hours at 200° under nitrogen pressure (20 kg./sq. cm.) in an Ipatieff rotating bomb equipped with a glass liner. The product was washed with a small quantity of saturated sodium sulfate solution, dried over anhydrous sodium sulfate, and distilled under reduced pressure.

The fraction (9 g.) boiling at 62–130° (30 mm.) was extracted with alkali and found to contain 4 g. of phenol and 7.5 cc. of hydrocarbons. The identity of the phenol was established by converting it to 2,4,6-tribromophenol, m. p. and mixed m. p. with authentic sample 91–92°. The hydrocarbons were separated by distillation into the following fractions: 1, 4.3 cc., 100–115°, n^{20}D 1.4189; 2, 1.0 cc., 115–125°, 1.4233; 3, 0.8 cc., 126–165°, 1.4300; 4, 1.0 cc., 165–185°, 1.4446. Fraction No. 1 is probably a mixture of octenes.

Anal. Calcd. for C_8H_{16}: C, 85.63; H, 14.37. Found: C, 85.74; H, 14.15.

The fraction (32 g.) boiling at 135–143° (28 mm.) was extracted with 10% potassium hydroxide. The alkali in-

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(5) Henry and Sharp, *J. Chem. Soc.*, 2434 (1926).

(6) (a) Anschütz and Rauff, *Ann.*, **327**, 211 (1903); (b) Jedlicka, *J. prakt. Chem.* (2) **48**, 98 (1909).

(7) Grosse, THIS JOURNAL, **60**, 212 (1938).

soluble material (12 g.) consisted chiefly of 2,4-di-*t*-butylphenol identified by conversion into the nitro derivative described in the preceding experiment. The alkali soluble material, recrystallized from heptane, melted at 101°. Mixed with an authentic sample of *p*-*t*-butylphenol, it melted at 100–101°.

(B) **At 140°.**—One hundred grams of *p*-($\alpha,\alpha,\gamma,\gamma$-tetramethobutyl)-phenol and 25 g. of 90% phosphoric acid heated six hours at 140° in an autoclave under 20 atmospheres of initial nitrogen pressure yielded 2 g. of phenol, 5.6 cc. of hydrocarbons, a 6-g. fraction containing 2,4-di-*t*-butylphenol, and a 12-g. fraction containing *p*-*t*-butylphenol.

Synthesis of 4,6-Dinitro-2-*t*-butylphenol.—Fifteen grams (0.107 mole) of *p*-nitrophenol, 18.6 g. (0.33 mole) of isobutene and 17.5 g. of 90% phosphoric acid was placed in a glass liner and heated at 100° for four hours in an Ipatieff type rotating bomb. All of the isobutene reacted to yield a product containing, besides unreacted *p*-nitrophenol, a tarry substance. The reaction mixture was diluted with water and extracted with ether. The ether solution was treated with 10% potassium hydroxide; the 2-*t*-butyl-4-nitrophenol was precipitated by bubbling carbon dioxide through the yellow alkali solution. The precipitate was separated by filtration and washed with water. When purified by recrystallization from dilute alcohol (norite), it formed colorless flakes, m. p. 138.5–139.5°, yield 15%.

Anal. Calcd. for $C_{10}H_{13}NO_3$: N, 7.17. Found: N, 7.22.

Forty milligrams of the 2-*t*-butyl-4-nitrophenol was heated on a water-bath for two minutes with 0.5 cc. of concentrated nitric acid and 1.0 cc. of acetic acid. The reaction mixture was diluted with crushed ice and water, and the product taken up with ether. The ether solution was washed with water and evaporated on a water-bath. The residue, recrystallized from dilute alcohol, formed yellow plates, m. p. 122–123°; mixed m. p. with a specimen formed by nitration of 2,4-di-*t*-butylphenol was 122–123°. Mixed m. p. with picric acid was 95°.

Summary

4-*t*-Butylphenol and 2,4-di-*t*-butylphenol have been obtained in the alkylation of phenol with diisobutene at higher temperatures either with phosphoric acid or a large excess of sulfuric acid as catalyst.

When *p*-($\alpha,\alpha,\gamma,\gamma$-tetramethobutyl)-phenol was heated under pressure with phosphoric acid, the side chain was cleaved to produce phenol, octenes, *p*-*t*-butylphenol, and 2,4-di-*t*-butylphenol.

Phenol was readily alkylated by isobutene in the presence of phosphoric acid at 100° to produce *p*-*t*-butylphenol and 2,4-di-*t*-butylphenol in 40 and 30% yields, respectively.

RIVERSIDE, ILL. RECEIVED JULY 8, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTH CAROLINA]

Preparation of Some Lower Alkyl Chlorides from the Corresponding Alcohols Using Zinc Chloride and Concentrated Hydrochloric Acid

BY ATHERTON M. WHALEY AND J. E. COPENHAVER

Because of the importance of the alkyl chlorides, this study was undertaken to determine the best procedure for the zinc chloride and hydrochloric acid method. This paper deals principally with *n*-propyl, *n*-butyl and *s*-butyl chlorides. Excellent reviews of the preparation of alkyl chlorides by this method are given by Dehn and Davis,[1] Norris and Taylor[2] and Clark and Streight.[3] The procedure of Norris and Taylor generally has been used and requires six to seven hours to produce 64–66% yield of butyl chloride, for example, from three moles of butyl alcohol. By the method described below, the yield was raised to 76–77% and the time shortened to one hour.

The above investigators, as well as Guyer, Bieler and Hardmier,[4] have found that approximately two moles of zinc chloride for each mole of alcohol, which conclusion was confirmed in this investigation. It was found that long contact of the alkyl chlorides with the zinc chloride–hydrochloric acid mixture caused decomposition and polymerization, and better results were obtained by removing them from the reaction flask as soon as formed. Many catalysts have been tried by other workers but none seemed to be more effective than zinc chloride, hence it has been used throughout this investigation.

Experimental

The reaction flask for a one-mole run was a one-liter round-bottomed, short-necked flask, attached to an up-

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[1] Dehn and Davis, THIS JOURNAL, **29**, 1328 (1907).

[2] Norris and Taylor, *ibid.*, **46**, 753 (1924); *Org. Syntheses*, **5**, 27 (1925).

[3] Clark and Streight, *Trans. Roy. Soc. Can.*, [3] **23**, Sec. 3, 77 (1929).

[4] Guyer, Bieler and Hardmier, *Helv. Chim. Acta.*, **20**, 1462 (1937).

right water-jacketed condenser, which acted as a fractionating column. This must be efficient and long enough to give ease of control of the reflux. The top of this carried a thermometer and a goose-neck connecting an efficient downward condenser. This condenser was attached to a 200-cc. trap, surrounded by an ice–salt mixture, from which the hydrogen chloride escaped into a water absorber. A second trap, similarly cooled, increased the yield from 3–5%. Rubber stoppers were used throughout.

Two moles of zinc chloride was dissolved completely in two moles of concentrated hydrochloric acid, cooling if necessary to prevent the loss of hydrogen chloride. This solution and one mole of alcohol were mixed thoroughly in the reaction flask and heated on a paraffin-bath. It usually required from ten to fifteen minutes for the reaction to start, which was determined by vigorous boiling. The best average bath temperatures for the three chlorides were as follows: *n*-propyl, 138–140°; *n*-butyl, 150–155°; *s*-butyl, 125–130°. This temperature was kept as low as possible to reduce polymerization. By the water in the jacket, the reflux temperature was controlled so that it was approximately the boiling point of the alkyl chloride and never allowed to rise higher than 1–2° above that point. For the three chlorides, these temperatures were respectively: 45–50, 68–80 and 65–69°. When evolution of the chlorides slackened, the temperature of the bath was raised to 160°. The reaction time averaged from fifty to sixty minutes for *n*-propyl and *n*-butyl and thirty minutes for *s*-butyl chloride.

The crude alkyl chloride, which averaged from 90–95% yield, was washed with cold water, repeatedly with small portions of concd. sulfuric acid[5] and finally with very dilute sodium carbonate, the latter being added very little at a time to prevent emulsions. The alkyl chlorides were dried over calcium chloride.[6]

Distillation was made from a 200-cc. flask with a 23-inch (58 cm.) punched-in column, at a rate of one to two drops per second and the product collected at a maximum over a 2° range. The foreshot usually contained some unsaturated derivatives and a slight residue remained in the flask. The yields averaged as follows: *n*-propyl, 70–72%; *n*-butyl, 76–77% and *s*-butyl, 83%.

Discussion

Our results agree with those of Dehn and Davis, that all of the zinc chloride must be dissolved before the reaction is started and with Norris,[7] that more than 1.25 moles of zinc chloride per mole of alcohol is necessary, and, further, that too large an excess of hydrochloric acid decreases the yield. Too much zinc chloride causes polymerization and less prolongs the reaction time. Dry-Ice around the receivers produces larger crude yields, due principally to dissolved hydrogen chloride. *i*-Butyl alcohol was used in one experiment but excessive rearrangement and polymerization cut the yield to 10%, the bath being held at 130° and the reflux temperature at 60–70°. The crude product boiled from 55–180°. One three-mole run with *n*-butyl alcohol gave the same consistent percentage yield. It was shown that the mechanical loss from washing and distilling averaged from 5–8% by running a blank on known quantities of propyl alcohol, propyl chloride and water. This loss was less for butyl chloride because of its lower vapor pressure.

The authors wish to express their sincere appreciation to Dr. E. Emmet Reid, Research Advisor at the University of South Carolina, for his valuable suggestions and help in the course of this investigation.

Summary

A procedure is given for the preparation of *n*-propyl, *n*-butyl and *s*-butyl chlorides, by the zinc chloride–hydrochloric acid method, in better yields and in a much shorter time than has been reported previously.

COLUMBIA, S. C. RECEIVED AUGUST 8, 1938

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[5] McCullough and Cortese, THIS JOURNAL, **51**, 225 (1929); Sherrill, *ibid.*, **52**, 1982 (1930).

[6] "Org. Syntheses, John Wiley and Sons, New York, N. Y., Vol. I, 1921, p. 11.

[7] Norris, *Ind. Eng. Chem.*, **16**, 184 (1924).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

The Alkylation of Naphthalene with Alcohols and Boron Fluoride. The Mechanism of the Reaction

BY CHARLES C. PRICE AND JOSEPH M. CISKOWSKI

The alkylation of benzene by alcohols in the presence of boron fluoride has been reported by McKenna and Sowa[1] to yield, in addition to monoalkylated benzene derivatives, disubstituted products in which the second alkyl group entered the ring para to the one already present. Since this orientation differed from that usually reported for Friedel–Crafts alkylation, the present investigation was undertaken to determine whether a difference in orientation might exist in the case of naphthalene as well. It was of particular interest to investigate this possibility since it might lead to a method for preparing the α-alkylnaphthalenes, in contrast to the readily available β-isomers prepared by the Friedel–Crafts reaction.

Naphthalene was alkylated smoothly and rapidly on passing boron fluoride into a suspension of the hydrocarbon in isopropyl, cyclohexyl, *t*-butyl, or benzyl alcohol. The reaction was usually quite rapid, exothermic and accompanied by the development of a color characteristic of the alcohol used. This color always faded on washing with dilute alkali to remove the catalyst. The reaction is superior to the Friedel–Crafts reaction in these instances in that a cleaner product is obtained with a larger yield, frequently in a much shorter time.

The monoalkylated material, however, consisted chiefly of the β-isomer except in the case of benzyl alcohol, in which case α-benzylnaphthalene was the chief product, accompanied by a small amount of the β-isomer. Roux[2] has reported the preparation of β-benzylnaphthalene from the hydrocarbon and benzyl chloride at 160°. Even in this case, however, the α-isomer results when the reaction is carried out at 90° for only a very short time.

Sowa[3] has proposed that the mechanism for alkylation reactions using boron fluoride as a catalyst, with esters and ethers as well as alcohols, consists primarily in the formation of an olefinic hydrocarbon to which the aromatic compound then adds under the influence of the catalyst. In support of the view is the fact that olefins may be condensed with aromatic compounds to form the corresponding alkylated product. Slanina, Sowa and Nieuwland[4] have reported this reaction but the boron fluoride was always used in conjunction with a co-catalyst, the most effective of which was sulfuric acid. This acid, of course, could readily convert the olefin to the alcohol or its sulfate.

Naphthalene was therefore treated with an olefin, cyclohexene, in the presence of boron fluoride alone. A moderately good yield of β-cyclohexylnaphthalene was obtained, indicating that direct, catalytic addition of an aromatic compound to an olefin is possible in the presence of this catalyst.

Two experimental facts, however, cannot be accounted for on the basis of the olefin mechanism. In the first place, it has been found that cyclohexanol, which reacts with naphthalene readily, can be recovered quantitatively after treatment with boron fluoride under conditions considerably more drastic than those required for alkylation. Not even traces of the olefin were detected.

Secondly, the formation of an olefin as an intermediate is impossible in the case of the benzyl group, which may be introduced as readily as any secondary or tertiary alkyl groups.

It therefore seems quite apparent that the ease of reaction is dependent not on the ease of olefin formation but on the frequently parallel activity of the alcoholic hydroxyl group. It is a well-known fact that benzyl and allyl alcohols, the only primary alcohols condensing readily with aromatic compounds, behave in a manner similar to secondary and tertiary alcohols in reactions involving replacement of the hydroxyl group.

Therefore, a much more likely mechanism for the catalytic effect of the boron fluoride may be still further weakening of the carbon–oxygen bond in the association complex formed between the catalyst and the oxygen-containing organic

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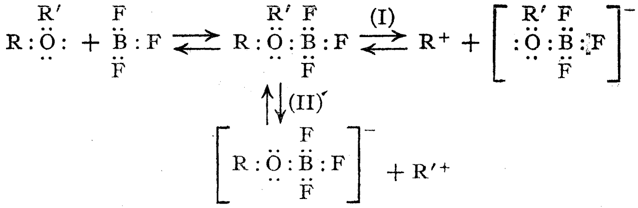
[1] McKenna and Sowa, THIS JOURNAL, **59**, 470 (1937).

[2] Roux, *Ann. chim. phys.*, [6] **12**, 330 (1887).

[3] (a) McKenna and Sowa, THIS JOURNAL, **59**, 470 (1937); (b) McKenna and Sowa, *ibid.*, **59**, 1204 (1937); (c) O'Connor and Sowa, *ibid.*, **60**, 125 (1938).

[4] Slanina, Sowa and Nieuwland, *ibid.*, **57**, 1547 (1935).

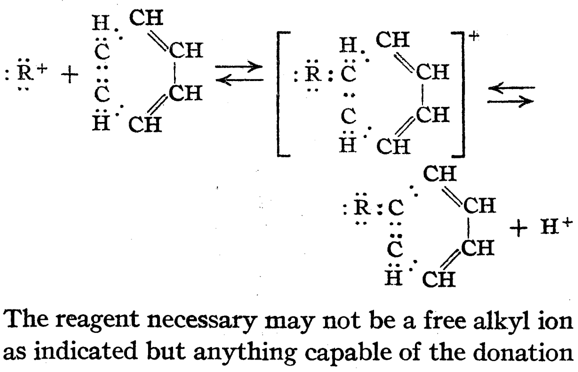
molecule. This may be represented by the following scheme in which R represents an alkyl group while R′ may be a hydrogen atom, an alkyl group or an acyl group.



That the bonds to the oxygen are actually weakened in this complex is demonstrated by the fact that the boron fluoride–alcohol complexes are strong acids, the hydrogen–oxygen bond having been weakened so as to become almost entirely ionic. Since this bond has been weakened enough to ionize it does not seem unreasonable that the carbon–oxygen bond might also ionize at least to a limited extent.

With mixed ethers the mode of ionization will depend on the two alkyl groups present. For instance, benzyl ethyl ether would be expected to ionize more readily to give the benzyl ion than the ethyl ion. In the case of esters apparently the only dissociation is according to (I) since esters in the presence of boron fluoride have been reported as alkylating agents but not acylating agents.[3b]

The positive carbonium ion thus produced may then be considered to be the active alkylating agent. Actually, of course, a free alkyl ion need exist only momentarily in the mixture just as a free hydrogen ion may have only a fleeting existence. For convenience, however, we may write the reaction using the free ion.[4a]



The reagent necessary may not be a free alkyl ion as indicated but anything capable of the donation of such an ion to the aromatic nucleus. The equations are written as reversible since, at least in the case of the Friedel–Crafts reaction, the reversibility is well known.

The ionic nature of this latter reaction seems to be a well-established fact. Dougherty[5] suggested that ionization of the alkyl halide was a portion of the catalytic effect of aluminum chloride.

$$:\ddot{\underset{..}{R}}:\ddot{\underset{..}{X}}: + AlCl_3 \rightleftarrows :\ddot{\underset{..}{R}}^+ - [XAlCl_3]^-$$

Wertyporoch,[6] however, did not believe, as Dougherty had proposed, that any further activation of the aromatic nucleus was necessary. Substantiation of this modification of Dougherty's views on the reaction is obtained from the kinetic study of a Friedel–Crafts alkylation by Ulich and Heyne.[7] They found definite evidence for the formation of the complex between alkyl and metal halides and, in fact, were able to derive the equilibrium constant for its formation.

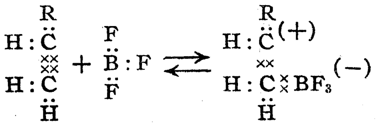
$$C_3H_7Cl + MCl_3 \rightleftarrows C_3H_7Cl{\cdot}MCl_3$$

The rate of the alkylation was directly proportional to the concentration of this complex and of the hydrocarbon, indicating that any further function of the catalyst in activating the latter is negligible.

$$dx/dt = K'[C_3H_7Cl{\cdot}MCl_3][C_6H_6]$$

The rearrangements taking place in the alkyl radical during either the Friedel–Crafts reaction or alkylation with boron fluoride offer no difficulties on the basis of the reaction scheme as outlined. The products are always those predicted by Whitmore's theory of molecular rearrangements,[8] since in every case the electron deficiency in the alkyl ion has migrated from a primary to a secondary or from a secondary to a tertiary carbon atom.

The reaction of the olefins themselves may also be accounted for on the basis of the electron affinity of boron fluoride or aluminum chloride.



This complex, like the alkyl cation, has a carbon atom deficient in a pair of electrons and could react with the unsaturation of the benzene ring in a similar manner, even though in this case the active intermediate has no resultant charge.

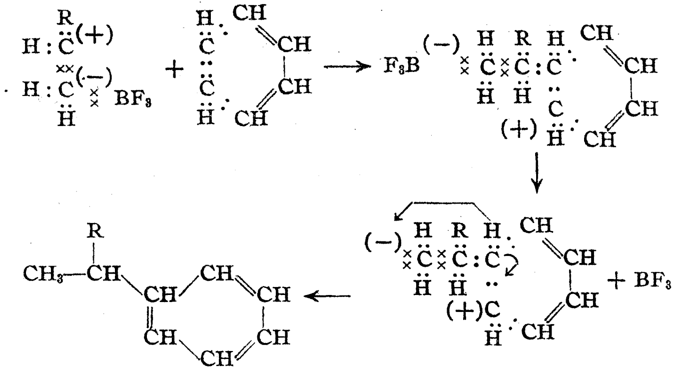
[4a] Since the preparation of this paper for publication Dilthey [*Ber.*, **71**, 1350 (1938)] has suggested this same mechanism for acylation by the Friedel–Crafts reaction.

[5] Dougherty, THIS JOURNAL, **51**, 576 (1929).

[6] Wertyporoch and Firla, *Ann.*, **500**, 287 (1933).

[7] Ulich and Heyne, *Z. Elektrochem.*, **41**, 509 (1935).

[8] Whitmore, THIS JOURNAL, **54**, 3274 (1932).

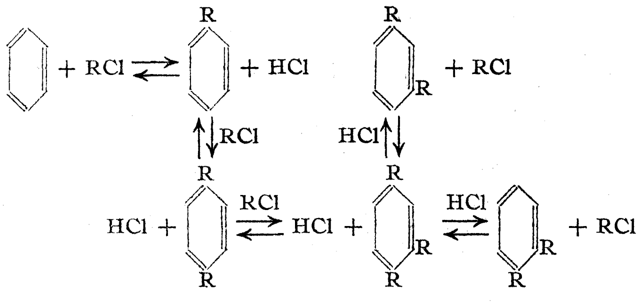


The final step, after the dissociation of the boron fluoride, is merely the α,γ-shift of a proton. Experimental confirmation of the reversible association of boron fluoride with one pair of electrons of an olefinic linkage is anticipated.

This same general mechanism may be used to account for the catalytic polymerization of olefins with boron fluoride or aluminum chloride. In this case the olefin–metal halide complex would associate with the double bond of a second olefin molecule rather than one of an aromatic ring as above.

The mechanism for alkylation and acylation of aromatic compounds is thus analogous to that for bromination[9] which also takes place through the intermediate addition of an electron deficient ion, the bromine cation, followed by elimination of a proton.

It is necessary, however, to account for the fact that aluminum chloride leads to the formation of predominantly meta as well as ortho and para dialkylated material from benzene whereas with boron fluoride the para isomer is formed almost exclusively. This difference may be due to the fact that the Friedel–Crafts reaction is reversible. When alcohols rather than alkyl halides are used, however, the water formed may hydrolyze the catalyst and thus prevent reversibility. The formation of a meta-dialkylbenzene in spite of the ortho–para-directing influence of the first group to enter may then be accounted for by the reaction scheme shown.[10]



Actually the reversal of the alkylation may be considered to be the substitution of hydrogen in place of an alkyl group. In 1,3,4-trialkylbenzene the 1- and 3-groups both orient the incoming hydrogen to the 4-position so this is the alkyl group which would most easily be replaced, thus forming, of course, the meta-dialkylbenzene. Replacement of the 1-alkyl group, taking place to a lesser extent, would be the source of the ortho-isomer, which is not reported in the case of the boron fluoride–alcohol reaction.

Experimental

Alkylation of Naphthalene.—Since the procedures used were quite similar, the results for the various alcohols have been summarized in Table I. In each instance naphthalene (50 g.) was suspended in the alcohol and boron fluoride gas[11] was passed in until two layers separated (fifteen to thirty minutes). The reaction mixture was allowed to stand for periods varying from five minutes to two days and then washed with dilute alkali, filtered from any starting material which may crystallize (5–10 g.), dried and fractionally distilled. The reaction mixtures always developed a color dependent on the alcohol used. With cyclohexyl the color was red, with tertiary butyl purple, with isopropyl green, and with benzyl blue. It always faded on addition of alkali to hydrolyze the catalyst.

That the triisopropylnaphthalene should have the same boiling point as the β-isopropyl derivative seems quite astonishing but this point was checked several times.

Attempted Dehydration of Cyclohexanol.—Cyclohexanol was saturated with boron fluoride and kept at 100° for an hour and a half but no cyclohexene was formed although the temperature was above that required for the alkylation of naphthalene in one-third this time. The alcohol–boron fluoride complex was decomposed with dilute alkali and the alcohol recovered quantitatively. Its identity was checked by the preparation of the phenylurethan deriva-

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(9) (a) Pfeiffer and Wizinger, *Ann.*, **461**, 132 (1928); (b) Price and Arntzen, THIS JOURNAL, **60**, in press (1938).

(10) Baddeley and Kenner [*J. Chem. Soc.*, 303 (1935)], have suggested this mechanism but claimed their experimental work was not in agreement. From 1,2,4-tri-*n*-propylbenzene, on treatment with aluminum chloride, they obtained a considerable quantity (35–40%) of *m*-di-*n*-propylbenzene as well as the symmetrical trisubstituted derivative. The results were interpreted against the mechanism, however, since the authors claimed (apparently with little experimental evidence) that the migrating alkyl group had undergone no isomerization. Nightingale and Smith (96th Meeting of the American Chemical Society, Milwaukee, Sept. 5, 1938) have reported that such isomerization does occur during the migration of the butyl groups in rearrangements of 1,3-dimethyl-4-butylbenzenes. *m*-Xylene was one of the products in each case. The experimental evidence, therefore, seems entirely in agreement with this mechanism.

(11) The compressed gas was obtained from the Harshaw Chemical Co., Cleveland, Ohio, and found most convenient and satisfactory.

TABLE I

ALKYLATION OF NAPHTHALENE WITH BORON FLUORIDE AND ALCOHOLS

Alcohol	Product (yield[a])	B. p. °C.	B. p. Mm.	$n^{20}D$	d^{25}_{25}	MD Calcd.	MD Found	Picrate, m. p., °C.
Cyclohexyl (1.2 moles)	β-Cyclohexyl- (63%)	190–195	15	1.5973[d]	1.020[d]	69.95	69.7	100[d]
	Dicyclohexyl-[b] (9%)	215–225	7					
Tertiary butyl (2.3 moles)	β-*t*-Butyl- (62%)	140–145	13	1.5685	0.979	60.1	58.3	99[e]
	Di-*t*-butyl- (5%)	180–185	13					154[g]
Isopropyl (1.5 moles)	β-Isopropyl- (35%)	265–270	760	1.5775	.974	55.5	57.5	..
Isopropyl (4 moles)	Triisopropyl-[c] (57%)	265–270	760	1.5566	.946	87.15	86.6	..
Benzyl (1.1 moles)	α-Benzyl- (28%)	200–205	9	(m. p. 58°)[f]				100[f]
	β-Benzyl- (2%)							93[f]
	Dibenzyl- (15%)	265–275	9					
	Tribenzyl- (20%)	320–330	9					

[a] Yield calculated on the basis of naphthalene consumed. [b] Mol. wt. calcd. 292; mol. wt. found (ebullioscopically in benzene), 291. [c] Mol. wt. calcd. 254; mol. wt. found 255, 246. *Anal.* Calcd. for $C_{19}H_{26}$: C, 89.76; H, 10.24. Found: C, 89.93; H, 10.62. [d] Bodroux, *Ann. chim. phys.*, [10] **11**, 536 (1927). [e] Barbot, *Bull. soc. chim.*, [4] **47**, 1314 (1930). [f] Roux, *Ann. chim. phys.*, [6] **12**, 330 (1887). [g] Fieser and Price, THIS JOURNAL, **58**, 1842 (1936).

tive, m. p. 82°. This seems to prove that under conditions of rapid and easy alkylation no olefin formation occurred.

Cyclohexylnaphthalene from Cyclohexene.—That olefins will react with naphthalene in the presence of boron fluoride alone, however, was demonstrated by bubbling this catalyst through 50 g. of naphthalene in 48 cc. of cyclohexene for an hour and a half. No layers separated in this case. After standing for a day the mixture was washed with water and alkali, 15 g. of naphthalene was recovered and the mixture dried and distilled. A yield of 20 g. (35%) of β-cyclohexylnaphthalene was obtained. It was identified by its physical constants and the melting point of its picrate.

Summary

The alkylation of naphthalene with alcohols using boron fluoride as a catalyst leads to the formation of the β-alkyl derivatives, with the exception of benzyl alcohol which yields largely α-benzylnaphthalene.

A mechanism for the catalytic effect of boron fluoride in aromatic alkylation is proposed involving the formation of alkyl cations which may then react with the aromatic nucleus.

A mechanism is suggested for the formation of meta-dialkylbenzene from the alkylation of benzene by the Friedel–Crafts reaction.

URBANA, ILLINOIS RECEIVED JULY 5, 1938

[CONTRIBUTION FROM RÖHM & HAAS COMPANY, INC.]

Friedel-Crafts Condensation with Arylalkylene Ether Chlorides

BY HERMAN ALEXANDER BRUSON AND JOHN W. EASTES

While attempting to treat β-phenoxy-β′-chlorodiethyl ether with anhydrous aluminum chloride so as to form a possible chain condensation product by the elimination of hydrogen chloride from a plurality of molecules according to equation (A)

$$C_6H_5—O—C_2H_4—O—C_2H_4Cl \xrightarrow{AlCl_3} C_6H_5—O—C_2H_4—O—C_2H_4(—C_6H_4—O—C_2H_4—O—C_2H_4)_x—C_6H_4—O—C_2H_4—O—C_2H_4\ldots + HCl \quad (A)$$

it was observed that practically no reaction occurred at temperatures as high as 70°, and that the starting material could be recovered substantially unchanged.

The unusual resistance of the ether linkages to splitting by the aluminum chloride, and the failure of the terminal aliphatically bound chlorine atom to react with the phenyl nucleus at temperatures of about 50–60°, where Friedel–Crafts reactions ordinarily take place with ease, suggested the possibility that other typical alkylating or acylating agents would condense probably with the benzene ring according to the customary synthesis, so as to alkylate or acylate the phenyl nucleus without affecting the ether linkages or the terminal chlorine atom.

Such compounds, where the alkyl group is of sufficient chain length and of the proper configuration, are intermediates for the synthesis of newer detergents and wetting agents, and are of interest also in other fields of organic research.[1]

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(1) Bruson, U. S. Patents (a) 2,097,441; (b) 2,098,203; (c) 2,107,366; (d) 2,107,367; (e) 2,115,250; (f) 2,115,192.

It was therefore of interest to try various alkylating and acylating agents upon aryloxyalkylene ethers of the type $R{-}O{-}CH_2CH_2Cl$ and $R{-}O{-}CH_2CH_2{-}O{-}CH_2CH_2Cl$ where R is an aryl nucleus.

It was found that aromatic ether chlorides of this type condensed with acid anhydrides, acyl halides, alkyl halides or olefinic compounds in the presence of anhydrous aluminum chloride to yield the corresponding nuclear acyl or alkyl derivatives without any appreciable scission of the ether linkages or elimination of the terminal chlorine atom.

Phthalic anhydride, for example, condensed with β-phenoxy-β′-chlorodiethyl ether to give β-chloroethoxyethoxybenzoyl-*o*-benzoic acid (I). Similarly, β-phenoxyethyl chloride yielded the corresponding acid (II). Both are crystalline compounds. Attempts to obtain the next higher homolog (III) by the use of β-phenoxyethoxy-β′-chlorodiethyl ether yielded a sirupy acid.

$$\mathrm{C_6H_4(COOH){—}CO{—}C_6H_4{—}O{—}CH_2{—}CH_2{—}O{—}CH_2CH_2Cl} \quad \mathrm{(I)}$$

$$\mathrm{C_6H_4(COOH){—}CO{—}C_6H_4{—}O{—}CH_2CH_2Cl} \quad \mathrm{(II)}$$

$$\mathrm{C_6H_4(COOH){—}CO{—}C_6H_4{—}O{—}CH_2CH_2{—}O{—}CH_2{—}CH_2{—}O{—}CH_2CH_2Cl} \quad \mathrm{(III)}$$

The tendency for these compounds to form is so great that they may be obtained even when benzene is employed as an "inert" solvent for the reactants since no appreciable quantity of benzoyl-*o*-benzoic acid is formed under the conditions used.

The introduction of an ortho substituent, namely, a chloro, methyl, or methoxy group in the phenyl radical of the chloro alkylene ether used, did not prevent the condensation from taking place, the corresponding compounds IV, V and VI being obtained in crystalline form. However, the presence of a para alkyl substituent (methyl) prevented the condensation under the same conditions. It is believed therefore that the para position to the phenol ether link, is the position occupied by the entering phthaloyl group.

$$\mathrm{C_6H_4(COOH){—}CO{—}C_6H_3(Cl){—}O{—}CH_2CH_2{—}O{—}CH_2CH_2Cl} \quad \mathrm{(IV)}$$

$$\mathrm{C_6H_4(COOH){—}CO{—}C_6H_3(CH_3){—}O{—}CH_2CH_2{—}O{—}CH_2CH_2Cl} \quad \mathrm{(V)}$$

$$\mathrm{C_6H_4(COOH){—}CO{—}C_6H_3(OCH_3){—}O{—}CH_2CH_2{—}O{—}CH_2CH_2Cl} \quad \mathrm{(VI)}$$

The condensation of β-(2-naphthoxy)-β′-chlorodiethyl ether with phthalic anhydride likewise yielded the corresponding chloroethoxyethoxy naphthoyl-*o*-benzoic acid (VII) in crystalline form.

In a similar manner, succinic anhydride and maleic anhydride each were condensed with β-phenoxy-β′-chlorodiethyl ether to form the corresponding chloroethoxyethoxybenzoylpropionic acid (VIII) and chloroethoxyethoxybenzoylacrylic acid (IX), respectively.

$$\mathrm{ClCH_2CH_2{—}O{—}CH_2CH_2{—}O{—}C_6H_4{—}CO{—}CH_2CH_2COOH} \quad \mathrm{(VIII)}$$

$$\mathrm{ClCH_2CH_2{—}O{—}CH_2CH_2{—}O{—}C_6H_4{—}CO{—}CH{=}CH{—}COOH} \quad \mathrm{(IX)}$$

Finally, β-phenoxy-β′-chlorodiethyl ether condensed with acetic anhydride or acetyl chloride to yield chloroethoxyethoxyphenyl methyl ketone (X) and with *n*-butyl chloride to give butylphenoxyethoxyethyl chloride (XI), both of which were oils.

The unusual stability of the linkages and the terminal chlorine atom in the beta-aryloxy ether chlorides of the type $R{-}O{-}CH_2CH_2Cl$ and $R{-}O{-}CH_2CH_2{-}O{-}CH_2CH_2Cl$ was still more striking when attempts were made to alkylate the aromatic nucleus by means of olefins or alcohols.

Diisobutylene condensed readily with β-phenoxy-β′-chlorodiethyl ether in the presence of concentrated sulfuric acid to give the corresponding β-(*p*-*t*-octylphenoxy)-β′-chlorodiethyl ether (XII), which was identical with the product obtained by the half etherification of β,β′-dichlorodiethyl ether and *p*-α,α,γ,γ-tetramethylbutylphenol.[1b]

Furthermore, even at temperatures as high as 180° it was possible to alkylate the aromatic nucleus of these ethers with a long chain higher alcohol, in the presence of surface-active siliceous clays ("Tonsil") without appreciable splitting off of hydrochloric acid or scission of the ether linkages. In this manner, octanol-2 condensed with β-phenoxy-β′-chlorodiethyl ether to yield *s*-octyl phenoxyethoxy-ethyl chloride (XIII); and lauryl alcohol condensed with β-phenoxyethyl chloride to yield dodecylphenoxyethyl chloride (XIV). In these compounds the position and the configuration of the alkyl groups has not been determined.

Experimental

(I) β-Chloroethoxyethoxybenzoyl-*o*-benzoic Acid.—(a). To a mixture of 50 g. of phthalic anhydride, 90 g. of anhydrous powdered aluminum chloride and 250 cc. of carbon disulfide in a 1-liter 3-necked flask fitted with a sealed stirrer and reflux condenser, there was added gradually 68 g. of β-phenoxy-β′-chlorodiethyl ether[2] while stirring the reaction mixture. The temperature was maintained at gentle refluxing during the addition and for five hours

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(2) Cretcher, Koch and Pittenger, THIS JOURNAL, **47**, 1174 (1925).

thereafter, during which time hydrogen chloride was evolved copiously. The carbon disulfide was then distilled off on a water-bath and the residue decomposed with 250 cc. of 3 *N* hydrochloric acid on ice, giving a white precipitate which was filtered off and dried. It was purified by dissolving in 10% soda solution, filtering and extracting the oil impurities from the filtrate with ether. After removal of the ether by boiling, the clear, alkaline solution obtained was acidified with hydrochloric acid. The waxy precipitate which at first formed gradually solidified to a hard white mass; yield 72 g., after recrystallization from glacial acetic acid. The compound formed colorless crystals, m. p. 123–124°.

Anal. Calcd. for $C_{18}H_{17}O_5Cl$: C, 62.00; H, 4.91; Cl, 10.18. Found: C, 62.44; H, 4.58; Cl, 10.16.

(b). By adding 45 g. of aluminum chloride in small portions at a time to a solution of 67 g. of β-phenoxy-β′-chlorodiethyl ether and 49 g. of phthalic anhydride in 400 cc. of dry benzene while stirring and cooling with tap water, stirring thereafter for eight hours at 25–30°, and decomposing with ice and hydrochloric acid in the usual manner followed by steaming off the benzene, there was obtained 40 g. of the above chloroethoxyethoxybenzoyl-*o*-benzoic acid, m. p. 124°, and containing 10.09% Cl, indicating that no appreciable quantity of benzoyl-*o*-benzoic acid was formed.

(II) β-Chloroethoxybenzoyl-*o*-benzoic Acid.—A mixture consisting of 49 g. of phthalic anhydride and 90 g. of anhydrous aluminum chloride in 200 cc. of carbon disulfide was treated with 52 g. of β-phenoxyethyl chloride as described in (Ia) above and worked up in the same manner. The product crystallized from benzene in colorless crystals, m. p. 145°.

Anal. Calcd. for $C_{16}H_{13}O_4Cl$: C, 63.05; H, 4.30; Cl, 11.65. Found: C, 62.69; H, 4.18; Cl, 10.05.

(IV) 4-(β-Chloroethoxyethoxy)-3-chlorobenzoyl-*o*-benzoic Acid.—Seventy-eight grams of β-(2-chlorophenoxy)-β′-chlorodiethyl ether was added slowly to a mixture of 49 g. of phthalic anhydride and 90 g. of anhydrous aluminum chloride in 200 cc. of carbon disulfide. The reaction mixture was stirred and heated for five hours on a steam-bath under reflux and then worked up as described in (I). The product crystallized from glacial acetic acid in colorless crystals, m. p. 85°.

Anal. Calcd. for $C_{18}H_{16}O_5Cl_2$: C, 56.38; H, 4.20; Cl, 18.52. Found: C, 56.46; H, 4.37; Cl, 17.5.

(V) 4-(β-Chloroethoxyethoxy)-3-methylbenzoyl-*o*-benzoic Acid.—Seventy-one grams of β-(2-methylphenoxy)-β′-chlorodiethyl ether was added slowly to a mixture of 49 g. of phthalic anhydride and 90 g. of aluminum chloride in 200 cc. of carbon disulfide and after heating for five hours the product worked up as above; crystals, m. p. 87–88.5° (from acetic acid).

Anal. Calcd. for $C_{19}H_{19}O_5Cl$: C, 62.89; H, 5.29; Cl, 9.79. Found: C, 62.31; H, 5.33; Cl, 10.00.

(VI) 4-(β-Chloroethoxyethoxy)-3-methoxybenzoyl-*o*-benzoic Acid.—Seventy-seven grams of β-(2-methoxyphenoxy)-β′-chlorodiethyl ether was added gradually to a mixture of 49 g. of phthalic anhydride and 90 g. of anhydrous aluminum chloride in 200 cc. of carbon disulfide. After four hours of boiling on a steam-bath while stirring under reflux, the product was worked up as above; colorless crystals, m. p. 188–190° (from acetic acid).

Anal. Calcd. for $C_{19}H_{19}O_6Cl$: C, 60.25; H, 5.07; Cl, 9.37. Found: C, 60.13; H, 4.90; Cl, 9.40.

(VII) (2-β-Chloroethoxyethoxy)-naphthoyl-*o*-benzoic Acid.—Seventy-six grams of β-2-naphthoxy-β′-chlorodiethyl ether was added slowly to 49 g. of phthalic anhydride and 90 g. of aluminum chloride in 200 g. of carbon disulfide. The mixture was stirred and boiled for six hours under reflux and worked up in the usual manner. The product was crystallized first from benzene and then from glacial acetic acid; colorless crystals, m. p. 125°.

Anal. Calcd. for $C_{22}H_{19}O_5Cl$: C, 66.25; H, 4.82; Cl, 8.91. Found: C, 66.22; H, 4.63; Cl, 8.84.

(VIII) 4-(β-Chloroethoxyethoxy)-benzoyl-β′-propionic Acid.—To a gently refluxing mixture of 33 g. of succinic anhydride, 90 g. of aluminum chloride and 200 cc. of carbon disulfide there was added gradually 67 g. of β-phenoxy-β′-chlorodiethyl ether while stirring. Refluxing was continued for five hours thereafter. The product was then decomposed with ice and hydrochloric acid. After two crystallizations from benzene and three recrystallizations from ethylene dichloride, the pure compound was obtained in colorless crystals, m. p. 97–98°.

Anal. Calcd. for $C_{14}H_{17}O_5Cl$: C, 55.91; H, 5.69; Cl, 11.81. Found: C, 55.94; H, 5.60; Cl, 11.63.

(IX) 4-(β-Chloroethoxyethoxy)-benzoyl-β′-acrylic Acid.—Sixty-seven grams of β-phenoxy-β′-chlorodiethyl ether was treated with a mixture of 33 g. of maleic anhydride and 90 g. of aluminum chloride in 250 cc. of carbon disulfide for five hours. The product was decomposed with ice and hydrochloric acid and the crude waxy acid obtained purified by dissolving in a *cold* solution of 50 g. of sodium carbonate in 1200 cc. of water and filtering. The clear filtrate upon acidification with dilute hydrochloric acid gave a yellow precipitate of the crude product. This was recrystallized from benzene giving pale yellow crystals, m. p. 100°.

Anal. Calcd. for $C_{14}H_{15}O_5Cl$: C, 56.30; H, 5.06; Cl, 11.88. Found: C, 56.24; H, 5.05; Cl, 11.45.

(X) β-(4-Acetylphenoxy)-β′-chlorodiethyl Ether.—(a). A solution consisting of 34 g. of acetic anhydride and 67 g. of β-phenoxy-β′-chlorodiethyl ether was added slowly to a well-stirred mixture of 90 g. of aluminum chloride and 200 cc. of carbon disulfide cooled in an ice-bath. Stirring was continued for one hour in the ice-bath and then for two hours at room temperature with occasional cooling when the temperature tended to rise. The reaction mixture was decomposed with iced 3 *N* hydrochloric acid and the carbon disulfide distilled off. The residual oil was washed and distilled under vacuum. The product came over at 210–222° (10 mm.) as a yellow oil.

Anal. Calcd. for $C_{12}H_{15}O_3Cl$: C, 59.36; H, 6.23; Cl, 14.63. Found: C, 60.04; H, 6.09; Cl, 14.30.

(b). The same compound was obtained from 50 g. of aluminum chloride in 200 cc. of carbon disulfide treated with a mixture of 16.5 g. of acetyl chloride and 67 g. of β-phenoxy-β′-chlorodiethyl ether.

(XI) β-Butylphenoxy-β′-chlorodiethyl Ether.—A solution of 31 g. of *n*-butyl chloride and 67 g. of β-phenoxy-β′-chlorodiethyl ether was added slowly to a stirred mixture of

45 g. of aluminum chloride and 200 cc. of carbon disulfide. The mixture was then refluxed on the steam-bath for sixteen hours, after which the carbon disulfide was removed by distillation. The residue was decomposed with iced dilute hydrochloric acid, the oil layer separated, washed, and distilled *in vacuo*. The product distilled over at 170–185° (9 mm.) as a colorless oil.

Anal. Calcd. for $C_{14}H_{21}O_2Cl$: C, 65.45; H, 8.27; Cl, 13.83. Found: C, 66.44; H, 8.02; Cl, 13.35.

(XII) **β-(*p*-(α,α,γ,γ-Tetramethylbutylphenoxy))-β′-chlorodiethyl Ether.**—To a solution of 100 g. of β-phenoxy-β′-chlorodiethyl ether and 56 g. of diisobutylene (b. p. 100–104°) there was added dropwise during forty-five minutes while stirring and occasionally cooling, 20 g. of 98% sulfuric acid. The mixture was then stirred for seven hours at room temperature and allowed to stand for eighteen hours. The thick oil obtained was warmed with 145 cc. of 10% sodium hydroxide solution, the oil layer separated, washed and distilled *in vacuo*. The fraction of b. p. 157–167° (1 mm.) was the desired product; yield 107.5 g. or 68%.

Anal. Calcd. for $C_{18}H_{29}O_2Cl$: Cl, 11.34. Found: Cl, 11.68.

(XIII) **β-(*s*-Octylphenoxy)-β′-chlorodiethyl Ether.**—A mixture consisting of 180 g. of β-phenoxy-β′-chlorodiethyl ether, 117 g. of octanol-2 and 20 g. of "Tonsil" clay was heated with stirring for four hours at 160–175° under reflux attached to a water trap. The clay was then filtered off and the *s*-octylphenoxyethoxyethyl chloride, b. p. 175–185° (3 mm.), isolated by vacuum distillation; yield 60%.

Anal. Calcd. for $C_{18}H_{29}O_2Cl$: Cl, 11.34. Found: Cl, 10.78.

(XIV) **β-Dodecylphenoxyethyl Chloride.**—A mixture consisting of 56 g. of β-phenoxyethyl chloride, 66.5 g. of lauryl alcohol and 15 g. of "Tonsil" clay was boiled with rapid stirring for three and one-half hours under a reflux condenser attached to a water trap. The temperature gradually rose from 165 to 195° during this period. Heating was continued for sixteen hours at 180–195°. The mixture was then cooled, diluted with toluene and filtered hot by means of a Büchner funnel. The filtrate was fractionated under reduced pressure. Dodecylphenoxyethyl chloride distilled over at about 185–195° (1 mm.) as a colorless oil, the chlorine analysis of which indicated a purity of 97.5%.

Summary

Aromatic alkylene ether chlorides or polyalkylene ether chlorides of the type R–(O-alkylene)$_n$Cl readily undergo Friedel–Crafts nuclear alkylation or acylation reactions without splitting the ether links, loss of the terminal chlorine atom, or appreciable polymeric intercondensation. A number of acylations with phthalic, succinic, maleic and acetic anhydrides and alkylations with butyl chloride, capryl alcohol, diisobutylene and lauryl alcohol are described.

PHILADELPHIA, PENNA. RECEIVED AUGUST 5, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IOWA STATE COLLEGE]

The Effect of the Composition of the Medium upon the Growth of Yeast in the Presence of Bios Preparations. II. The Response of Several Strains of Saccharomyces Cerevisiae[1]

BY JAMES B. LESH, L. A. UNDERKOFLER AND ELLIS I. FULMER

In a previous communication from these Laboratories[2] data were presented showing that, for the one strain of yeast employed, the presence of magnesium sulfate markedly increased the growth of the yeast in the presence of Bios II or a mixture of Bios II and Bios I (*i*-inositol). The present paper deals with the response of several strains of *Saccharomyces cerevisiae* to the above-mentioned reagents. While 23 strains of yeast were studied during the present investigation, data are presented here for only the 13 of these which can be obtained readily from standard sources: these strains are listed in Table I.

Lucas,[3] Williams, Warner and Roehm,[4] Williams and Saunders,[5] Stantial[6] and Farrell[7] have noted significant differences among various strains of yeast as to their response to various Bios preparations, but the effect of magnesium sulfate had not been considered previously. Magnesium sulfate is a customary ingredient of most media used for growing yeast. However, the media developed in these Laboratories by Fulmer, Nelson and Sherwood[8] for the growth of yeast in the

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(1) This work was supported in part by a grant from the Industrial Science research funds of the Iowa State College for studies on the fermentative utilization of agricultural products.

(2) E. I. Fulmer, L. A. Underkofler and J. B. Lesh, THIS JOURNAL, **58**, 1356 (1936).

(3) G. H. W. Lucas, *J. Phys. Chem.*, **28**, 1180 (1924).

(4) R. J. Williams, M. E. Warner and R. R. Roehm, THIS JOURNAL, **51**, 2764 (1929).

(5) R. J. Williams and D. H. Saunders, *Biochem. J.*, **28**, 1887 (1934).

(6) Helen Stantial, *Trans. Roy. Soc. Can.*, **26**, Sec. III, 163 (1932).

(7) Leone N. Farrell, *ibid.*, **29**, Sec. III, 167 (1935).

(8) E. I. Fulmer, V. E. Nelson and F. F. Sherwood, THIS JOURNAL, **43**, 191 (1921).

TABLE I

KEY TO STRAINS OF *Saccharomyces cerevisiae*

(ATCC = American Type Culture Collection)

Strain		
5	(Hansen)	ATCC No. 4360
6	(Type Frohberg)	ATCC No. 2334
7	(Type Saaz)	ATCC No. 2352
9	(I Hansen)	ATCC No. 2368
10		ATCC No. 765
11	(Berlin RII)	ATCC No. 4099
16		ATCC No. 764
18		ATCC No. 4132
19		ATCC No. 4109
22	(Hansen)	Univ. Ill. No. 2235
26	(Hansen)	ATCC No. 4923
41		ATCC No. 4226
42	(Gebrüde Mayer)	Fleischmann No. 21.4–40

absence of bios do not contain this salt since it was found to be of no advantage. The marked difference in the response of yeast to bios preparations added to Clark's medium (used by Miller and co-workers) which contains magnesium sulfate, and to Medium C or Medium D, which do not, led to the study reported in the previous paper.[2]

The basal medium used in the present investigation was Medium C, developed by Fulmer, Nelson and Sherwood,[8] and contained per 100 cc., 0.188 g. of ammonium chloride, 0.100 g. of dipotassium phosphate and 5 g. of sucrose. Preliminary tests showed the optimum *p*H (after sterilization) to be 6.2. In order to assure the proper *p*H, the medium was made 0.0025 *N* with hydrochloric acid before sterilization. All media were sterilized at 15 lb. (1 atm.) pressure for fifteen minutes. In all experiments, 25 cc. of medium was used in 125-cc. Erlenmeyer flasks. The basal medium was made up in concentrations five-fourths of that given above. Twenty cc. was placed in each flask and made up to 25 cc. by the addition of solutions to be tested or of distilled water. The concentration of *i*-inositol (Bios I) was 0.032 mg., and that of magnesium sulfate 100 mg. (0.008 *M*) per 100 cc. of medium. The Bios II, per 100 cc. of medium, was equivalent to 4.0 cc. of the original extract which had been prepared from malt sprouts by the method of Lucas.[3]

In order to make direct comparisons of the cultures it was necessary to standardize the method of preparing the inoculum. Since several of the strains grew slowly, or not at all, in Medium C, the technique of Miller, Eastcott and Maconachie[9] was adopted. The cultures were transferred daily, for four days, in a medium containing 2% dextrose and 0.5% peptone. The twenty-four-hour culture, from the fourth transfer, was filtered rapidly on a small sterile filter. The yeast was then washed three or four times with sterile distilled water and a portion suspended in sufficient sterile Medium C so that 1 cc. contained the proper number of cells for inoculation of each experimental flask. The yeast count in the various media was determined by means of a Thoma–Zeiss counting chamber after twenty-four hours of incubation at 30°. When the count = 1 there are 250,000 cells per cc. Inoculations were made such that the initial count was one.

In Table II are given the actual counts in the Control (Medium C), together with the relative counts in the control medium and the control to which had been added (a) Bios II, (b) Bios II and *i*-inositol, (c) Bios II and magnesium sulfate and (d) Bios II, inositol and magnesium sulfate. Growth was also determined in the control to which had been added magnesium sulfate, inositol and both magnesium sulfate and inositol; since no increased growth was obtained over the controls the values are not included in the table.

TABLE II

Relative growth of various strains of *Saccharomyces cerevisiae* in Medium C (control) and in the control to which Bios II, inositol and magnesium sulfate had been added. (When the count = 1 there are 250,000 cells per cc.).

Medium strain	Actual count in control	Control	Bios II control	Inositol Bios II control	$MgSO_4$ Bios II control	$MgSO_4$ inositol Bios II control
5	3	1	15	22	10	14
6	2	1	3	5	1	10
7	1	1	11	15	14	19
9	2	1	2	2	4	4
10	5	1	14	21	19	88
11	6	1	4	4	8	19
16	4	1	21	21	25	38
18	10	1	1	2	2	13
19	3	1	1	4	22	27
22	1	1	21	40	46	100
26	12	1	2	2	15	25
41	5	1	3	4	6	14
42	7	1	5	7	4	51

It is at once evident that the various strains of yeast show wide differences in response to the different media. For convenient comparison the various strains may be divided into the following three groups:

Group I. The addition of magnesium sulfate with Bios II does not give increased growth. This group includes strains Nos. 5, 6 and 42. With these strains the counts were actually de-

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[9] W. L. Miller, Edna V. Eastcott and J. E. Maconachie, THIS JOURNAL, 55, 1502 (1933).

creased by the addition of the magnesium sulfate.

Group II. The addition of inositol with Bios II does not give increased growth. This group includes strains Nos. 9, 11, 16 and 26.

Group III. Growth is increased under the conditions given for Groups I and II. These include Nos. 7, 10, 18, 19, 22 and 41.

The above data and groupings show that discrepancies in published results of bios studies may be due largely to differences in the strains of yeast employed and in the composition of the medium. For example, if a strain of yeast belonging to Group I were grown in a medium containing magnesium sulfate, Bios II would give increased counts in the presence of Bios I (inositol); that is, the complementary effect of Bios I and Bios II, as described by Miller and co-workers, would be demonstrated. If, however, a strain of Group II or Group III were employed under the same conditions, the Bios II would be potent in the absence of Bios I and their complementary effect would not be apparent.

Summary

The effect of Bios II, inositol (Bios I) and magnesium sulfate alone and in combinations on the growth of thirteen strains of *Saccharomyces cerevisiae* is reported. On the basis of the marked differences in response to the different media by the various yeast strains they are separated into three distinct groups.

AMES, IOWA RECEIVED JULY 15, 1938

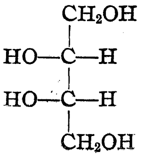
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IOWA STATE COLLEGE]

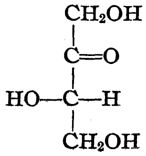
The Production of *l*-Erythrulose by the Action of Acetobacter suboxydans upon Erythritol

BY ROY L. WHISTLER AND L. A. UNDERKOFLER

The use of microörganisms for the production of ketose sugars has made possible the extension of carbohydrate investigations to include several of the rare ketoses which are now easily obtainable in pure form. *l*-Erythrulose was first produced from *meso*-erythritol by Bertrand[1] who employed the "sorbose bacterium" or *Acetobacter xylinum*. Müller, Montigel and Reichstein,[2] using the same organism, recently have converted erythritol to *l*-erythrulose in approximately 60% yield, and have isolated in pure form 50% of the sugar produced.

The present communication deals with the optimum conditions for the production of *l*-erythrulose by the action of *Acetobacter suboxydans* upon *meso*-erythritol, and for the isolation of the erythrulose produced. This organism has been found to effect practically quantitative conversion of the alcohol to the sugar in a short time. It is of interest to note that, although the configuration of the *meso*-erythritol, I, is such that the formation of both *d*- and *l*-erythrulose might be expected, only the *l*-erythrulose, II, is produced by the organism. No organism yet studied has been found to oxidize *meso*-erythritol to *d*-erythrulose.


I


II

It was found that Bertrand's[1] method of purification of the *l*-erythrulose by passage through the bisulfite addition compound was not accomplished easily since complete removal of the sodium bisulfite and recovery of pure unaltered sugar was very difficult. Purification by precipitating the sugar from alcoholic solution through the addition of ether and then distilling the sirup in a molecular still was found most suitable.

Experimental

Methods.—The culture of *Acetobacter suboxydans*, listed as No. 621, was secured from the American Type Culture Collection, and is the same culture previously used in studies reported from these Laboratories.[3,4] The stock cultures are carried on yeast extract–glycerol–agar slants. The cultures used for inoculations in the present experi-

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[1] G. Bertrand, *Compt. rend.*, **130**, 1330 (1900); *Bull. soc. chim.*, [3] **23**, 681 (1900); *Ann. chim. phys.*, [8] **3**, 181 (1904).

[2] H. Müller, C. Montigel and T. Reichstein, *Helv. Chim. Acta*, **20**, 1468 (1937).

[3] E. I. Fulmer, J. W. Dunning, J. F. Guymon and L. A. Underkofler, THIS JOURNAL, **58**, 1012 (1936).

[4] L. A. Underkofler and E. I. Fulmer, *ibid.*, **59**, 301 (1937).

ments were kept active by transfer each twenty-four hours into a medium containing 0.5 g. of yeast extract (Difco powdered product) and 3 g. of erythritol per 100 ml. All media were sterilized in the autoclave for twenty minutes at fifteen pounds (1 atm.) steam pressure, and all cultures were incubated at the optimum temperature of 28°. Preliminary studies were made using 10 ml. of medium in 50-ml. Erlenmeyer flasks. In each case the inoculum consisted of 3 ml. of the twenty-four hour culture of the organism per 100 ml. of fresh medium, measured from a sterile pipet. All fermentations were run in duplicate, and the values reported are the averages for the duplicate determinations. The course of the conversion of the erythritol into erythrulose was followed by determination of copper reduction values by means of the Shaffer–Hartmann[5] sugar titration method.

After isolation of erythrulose had been accomplished, an equation was derived experimentally which permitted calculation of the yields of erythrulose from the copper reduction values previously obtained. This equation was obtained as follows: weighed samples of the sirupy erythrulose were diluted and aliquots of 50 ml. heated with 50 ml. of mixed Fehling's solutions in 500-ml. uncovered Erlenmeyer flasks. The flames were so adjusted as to bring the mixtures to a boil in exactly four minutes, boiling was continued for exactly two minutes and the flasks were then cooled promptly in running water. The cuprous oxide was titrated by the Shaffer–Hartmann method. All reagents, including the Fehling's solutions, were made up exactly as directed by Shaffer and Hartmann.[5] The copper reduction values so obtained were plotted against weight of erythrulose, giving a straight line for amounts of the sugar between 20 and 100 mg. The equation for this line is

$$E = 0.831\ R + 4.380$$

where E represents mg. of erythrulose corresponding to R mg. of copper. This equation provides a convenient method for the calculation of erythrulose from analytical data. Since the erythrulose was recovered as a sirup which did not crystallize, the purity was based on the optical rotation given by Müller, Montigel and Reichstein.[2] Any inaccuracy involved here would mean a corresponding error in the above equation, which must therefore be considered subject to revision if a purer product be secured.

The Development of the Medium.—Employing the proportion of yeast extract which previously had been found optimum for the production of sorbose from sorbitol and of dihydroxyacetone from glycerol,[3,4] *i. e.*, 0.5 g. per 100 ml., media were prepared in which the concentrations of erythritol were varied. After inoculation and incubation, duplicate flasks of each medium were analyzed and the yields ascertained after intervals of three, four, seven and thirty days. The maximum yields were obtained after four to seven days, a slight decrease being sometimes observed after thirty days. The yields after seven days with 3, 4.5, 6, 9, 12, 15 and 18 g. of erythritol per 100 ml. were, respectively, 96, 99, 92, 61, 42, 30 and 18% of erythrulose.

An investigation on the influence of surface–volume ratio on the yield of erythrulose was made, employing different volumes of medium containing 4.5 g. of erythritol and 0.5 g. of yeast extract per 100 ml. in 125-ml. Erlenmeyer flasks. Incubation was for four days. When 10, 20, 30 and 40 ml. of medium were used, the respective surface–volume ratios (sq. cm. area per 1 cc. volume) were 3.18, 1.59, 1.06 and 0.80, and the yields were 98, 97, 93 and 92% of erythrulose.

From the data it may be concluded that the optimum concentration of erythritol in the medium is about 4.5 g. per 100 ml., and that maximum yields are obtained when the ratio of surface to volume of medium is high. Since the conversion of the erythritol to erythrulose was found to be practically quantitative in four days under these conditions when the medium contained 0.5 g. of yeast extract per 100 ml., no attempt was made to improve the medium by variation of the concentration of yeast extract, by addition of salts or by adjustment of the *p*H of the medium (*p*H 6.1 for the medium as prepared).

The Recovery of *l*-Erythrulose.—Thirty-five grams of yeast extract and 335 g. of *meso*-erythritol were dissolved in distilled water to make 7000 ml. of medium which was distributed in quantities of 200 ml. in 2-l. Erlenmeyer flasks. The sterilized medium in each flask was inoculated with 6 ml. of a twenty-four hour culture of *Acetobacter suboxydans* in similar medium, and incubated for nine days at 28°. According to the Shaffer–Hartmann titration, 95% of the erythritol had been converted to *l*-erythrulose.

To each 2000 ml. of the fermented medium were added 15 g. each of Norite, calcium carbonate and infusorial earth and the mixture was well shaken. The liquid was then separated by means of a supercentrifuge. To the recovered liquid was added 10 g. of Norite, the mixture passed through the supercentrifuge and the recovered liquid again passed through the centrifuge for the third time. The light yellow liquid, which was almost free of bacteria or other suspended material, was evaporated under reduced pressure at 35° to a volume of 200 ml. Six hundred ml. of absolute alcohol was added with stirring and the mixture filtered. The filtrate was evaporated under reduced pressure at 30° to a thick sirup of light yellow color, $[\alpha]^{30}\text{D}$ +10.0 (*c*, 2.4 in water). The sirup was taken up in alcohol and a small quantity of ether added. On standing in the refrigerator 2% of the original erythritol separated. On the addition of a little more ether a small quantity of a sirup having a low positive optical rotation separated. Further addition of ether precipitated erythrulose as a light yellow sirup. This sirup was taken up repeatedly in alcohol and precipitated with ether. The resulting sirup was distilled in a molecular still at 90–95° to produce a colorless sirup, $[\alpha]^{30}\text{D}$ +11.31 (*c*, 4.0 in water). By this procedure 87.4% of the erythrulose present in the original fermented liquid, as determined by the Shaffer–Hartmann titration, could be recovered as a sirup.

Summary

A procedure has been given for the production of *l*-erythrulose by the action of *Acetobacter suboxydans* upon *meso*-erythritol and for the isolation of the sugar from the fermented medium.

Ames, Iowa Received July 23, 1938

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[5] P. A. Shaffer and A. F. Hartmann, *J. Biol. Chem.*, **45**, 365 (1920).

[CONTRIBUTION FROM THE DIVISION OF AGRICULTURAL BIOCHEMISTRY AND THE DEPARTMENT OF BOTANY, UNIVERSITY OF MINNESOTA]

Analyses of Glacial and Preglacial Woods[1]

BY WILLIS A. GORTNER

Minnesota has been subjected to five glaciations. The Nebraskan glaciation (*ca.* 700,000–1,000,000 years ago),[2] the Kansan glaciation (*ca.* 500,000 years ago), the Illinoian glaciation (*ca.* 175,000 years ago), the Iowan glaciation (*ca.* 75,000 years ago) and the Wisconsin glaciations. The late Wisconsin ice sheet probably retreated from the middle part of Minnesota about 20,000 years ago. The advance must have taken place considerably earlier and the Peorian interglacial period probably came to an end in northern Minnesota 40,000–50,000 years ago.

In each of the interglacial periods forests developed only to be overridden by the ensuing ice sheets. In certain instances the wood from the interglacial or preglacial forests has been so preserved in the underlying clays as to be readily identifiable as to species and to be truly "wood," *i. e.*, fossilization had not taken place. The present communication deals with the chemical analyses of certain such specimens and supplements and extends similar analyses by Mitchell and Ritter[3] on three fossil woods from gravels of Miocene age in California.

Experimental

Materials. Specimen A—Pre-Nebraskan Spruce Wood.—This wood was secured *in situ* in the Nebraskan glacial till exposed in a highway cut 1.8 miles east of St. Charles, Minnesota. Figure 1 shows the specimens which were selected for analysis. All samples selected for analysis floated on water and after washing free of clay were dried and ground.

Specimen B—Pre-Nebraskan Spruce Wood.—This specimen was found in 1932 at a depth of 55 feet on the south bank of the Cottonwood River near New Ulm, Minnesota. It is shown in Fig. 2.

Specimen C—Peorian (last interglacial) Age Spruce Wood.—This was found at the bottom of a well sunk through 17 feet of lacustrine "clay" which formed in the bed of glacial Lake Agassiz and 70 feet of glacial till (ground moraine of late Wisconsin) in southeastern Kittson County near Bronson, Minnesota. It is shown in Fig. 2.

Specimen D—Peorian Age Spruce Wood.—This specimen was part of a larger "log" found beneath the Wisconsin gravel stratum at a depth of eleven feet, three miles north of Bottineau, North Dakota. It is shown in Fig. 2.

Methods.—The methods used are for the most part those recommended by Bray[4] with such modifications as were necessitated by the nature of the samples. All woods were reduced in a Wiley mill to pass a 40-mesh screen. Ash was determined on 3-g. samples. The alcohol–benzene soluble portion, pentosans, lignin (72% sulfuric acid method), and Cross and Bevan cellulose techniques followed procedures previously described.[5]

Certain of the glacial woods did not respond to the Cross and Bevan cellulose methods, since the lignin chloride formed a jelly-like mass. Mitchell and Ritter also noted this phenomenon in their fossil woods. In the present series of analyses the cellulose content of such woods was determined by a "hypochlorite method" in which the sample was extracted with a sodium hypochlorite solution in a centrifuge tube followed by extracting with 3% sulfurous acid, then with water, then with 2% sodium sulfite solution with repeated extractions, washing and centrifuging until a pure white fiber mat of cellulose was obtained. As an alternative method the cellulose was hydrolyzed with sulfuric acid and the resulting glucose determined volumetri-

TABLE I

SHOWING THE AVERAGE ANALYSES OF THE DIFFERENT WOOD SAMPLES

All Calculations on Basis of Oven-Dry Material

	Wood analyzed				
Approximate age in years	Modern white spruce 0 %	Peorian age (Specimen D) 40,000 %	Peorian age (Specimen C) 40,000 %	Preglacial (Specimen B) 800,000 %	Preglacial (Specimen A) 800,000 %
Ash	0.24	2.98	2.37	5.97	10.47
Lignin	29.73	39.03	53.38	79.23	66.41
Pentosans	9.63	7.21	7.77	2.23	2.10
Alcohol–benzene soly.	1.38	0.71	1.49	1.07	2.91
Cross and Bevan cellulose	60.70	42.30	[a]	[a]	[a]
"Hypochlorite" cellulose	....	35.07	27.10	[b]	
"Sugar" cellulose	65.50	54.75	31.45	4.01	12.21
Holocellulose	70.92	53.79	44.88	13.30	23.68
Total of lignin + ash + holocellulose	100.89	95.80	100.63	98.50	100.56

[a] Not run for these three woods, due to formation of a lignin–chloride jelly which prevented chlorination or washing.

[b] No further determinations by this method; lignin–chloride jelly formed.

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[1] Presented before the Division of Cellulose Chemistry at the General Meeting of the American Chemical Society, Cleveland, Ohio, September, 1934.

[2] (a) G. F. Kay, *Bull. Geol. Soc. Amer.*, **42**, 425–466 (1931); (b) F. Leverett, U. S. Geol. Survey, Professional Paper 161, 5–39 (1932).

[3] R. L. Mitchell and G. W. Ritter, THIS JOURNAL, **56**, 1603–1605 (1934).

[4] W. M. Bray, *Paper Trade J.*, **87**, 59–68 (1928).

[5] S. I. Aronovsky and R. A. Gortner, *Ind. Eng. Chem.*, **22**, 264–274 (1930).

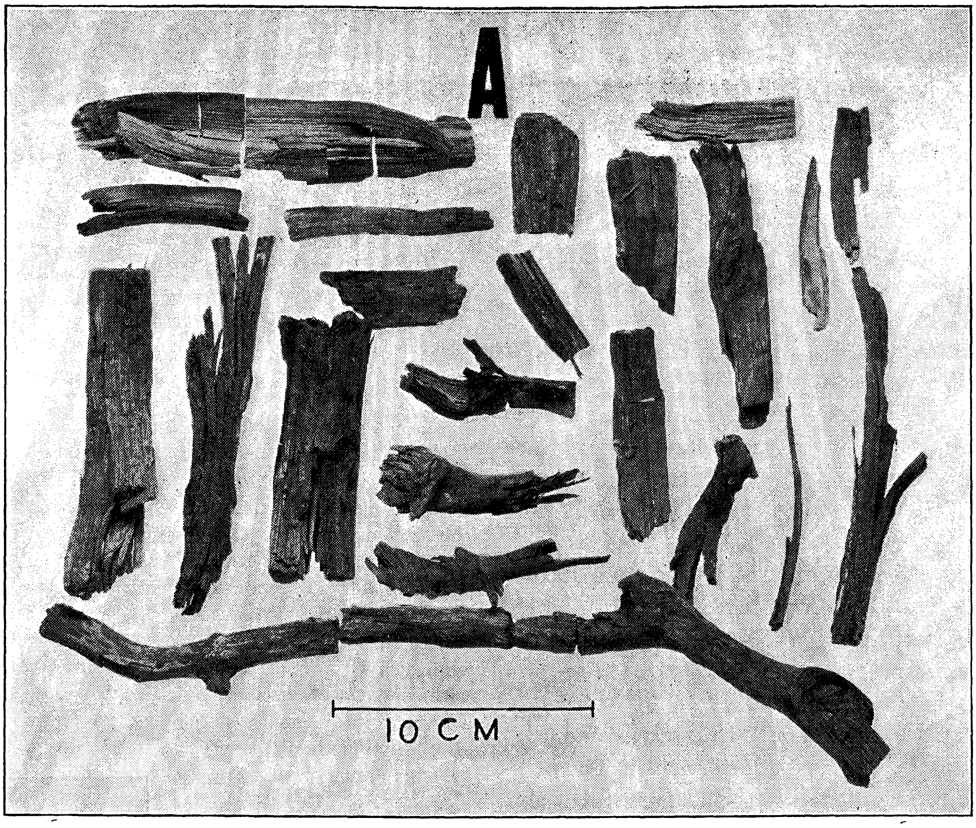

Fig. 1.—Specimen A, preglacial spruce wood.

cally.[6] This value was converted to "cellulose" by the appropriate factor. All woods were also analyzed for total carbohydrates by the "holocellulose" method of Ritter and Kurth.[7]

The Experimental Data.—Table I shows the analytical data and includes for comparison purposes parallel analyses of wood from a recently cut white spruce. These data represent the averages of closely agreeing triplicate or duplicate determinations. The range in duplicate or triplicate analyses for the glacial woods was within the limits allowable for comparable analyses in the pulp and wood-using industries.

Discussion

Ash.—The ash content increases with the age of the wood. This is probably due to the infiltration of mineral matter during the long periods that the wood was buried in the earth.

Cellulose.—The trends in "holocellulose" and "sugar" cellulose are essentially parallel, although no explanation is available for the marked decrease of "sugar" cellulose (4–12%) for the preglacial woods which show a holocellulose content of 13–23%. Possibly the reducing sugars titrated were not glucose, or some other change had taken place so that other compounds than reducing sugars were formed by hydrolysis of the "cellulose" residue. In general, there is a parallelism in the trends shown by all the "cellulose" methods, although the absolute values for any particular sample are not exactly alike.

Pentosans.—Pentosans decrease with age in about the same ratio as cellulose decreases. Possibly these residual "pentosans" are in reality uronic acids which are calculated as pentosans in the methods of analysis. In any event both cellulose and pentosan-like compounds have shown remarkable stability.

Lignin.—There is an apparent increase in lignin. This is probably largely the result of a loss of other wood constituents and is probably not due to an actual increase in lignin *per se*. Assuming a constant lignin value (no change in lignin with age of burial) of 30%, there would remain in the preglacial woods only 7–15% of the holocelluloses and only 9–10% of the pentosans which were present when the glacier overthrew and buried

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[6] J. J. Willaman and F. R. Davison, *J. Agr. Research*, **28**, 479–488 (1924).

[7] G. F. Ritter and E. F. Kurth, *Ind. Eng. Chem.*, **25**, 1250–1253 (1933).

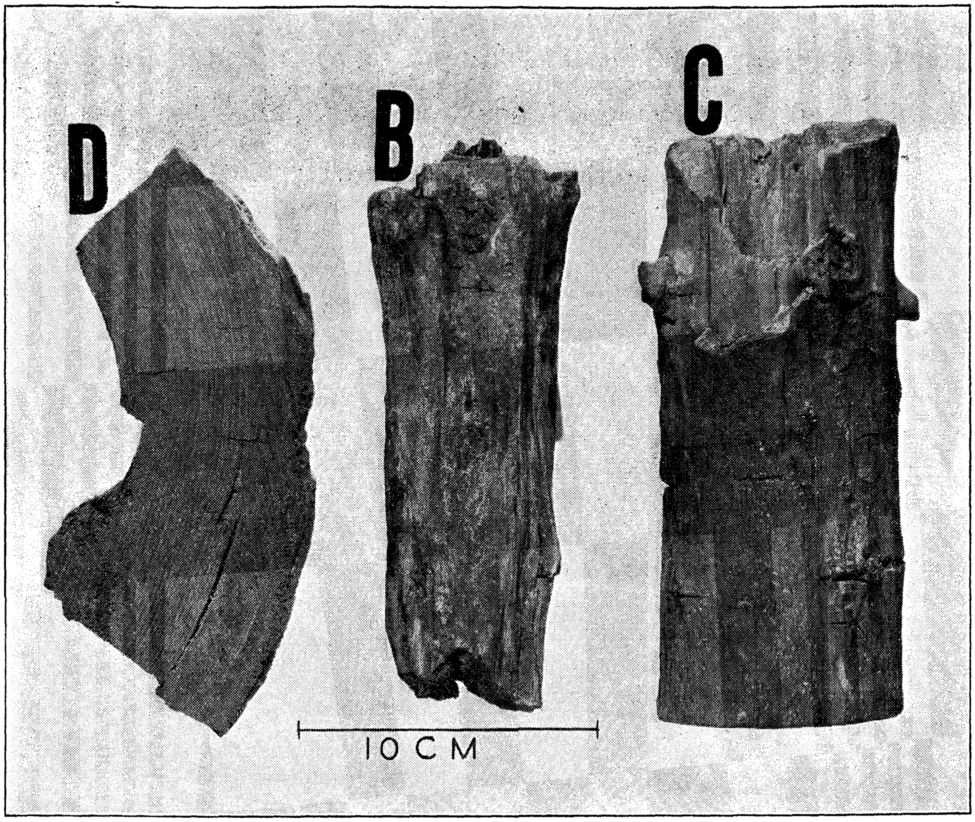

Fig. 2.—Specimen B, preglacial spruce wood; specimens C and D, Peorian age spruce wood.

the forest. It is therefore evident that lignin, or lignin-like complexes, are much more stable than are the cellulose–pentosan complexes.

The above analyses and conclusions parallel in a remarkable degree the analyses and conclusions of Mitchell and Ritter[3] in their studies of the fossil pine and cedrus woods of Miocene age. Apparently after being buried for a few hundreds of thousands of years wood reaches somewhat of an equilibrium with its environment, so that subsequent changes take place extremely slowly. Our analyses of wood of Peorian age indicate an intermediate degree of alteration.

Acknowledgment.—The writer wishes to thank Dr. C. O. Rosendahl, of the Department of Botany, University of Minnesota, for providing and identifying all samples of wood, and for assisting in the planning and executing of these experiments. Sincere thanks are also due Dr. S. I. Aronovsky for outlining appropriate laboratory techniques and for supervising the analytical operations.

Summary

Two samples of preglacial spruce wood (Pre-Nebraskan) and two samples from the Peorian interglacial period were analyzed in comparison with modern white spruce.

The analyses show an increased ash content with age of burial, presumably due to the infiltration of inorganic salts from the earth. The pentosans and cellulose decrease with increase in age of the wood, with lignin showing an apparent increase. It is believed that this lignin increase is only apparent and is due to the decrease in the cellulosic constituents. Correcting to a constant lignin basis, there still remain in the wood which has been buried in the earth for 700,000–1,000,000 years approximately 7–15% of the original "holocelluloses" and 9–10% of the original "pentosans."

ST. PAUL, MINN. RECEIVED MARCH 24, 1938

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE INSTITUTE OF TECHNOLOGY, UNIVERSITY OF MINNESOTA]

The Relation between Equilibrium Constants in Water and in Other Solvents

BY I. M. KOLTHOFF, J. J. LINGANE AND W. D. LARSON

The equilibrium constants, in two different solvents, of a reaction

$$aA + bB + \cdots \rightleftharpoons dD + eE + \cdots \qquad (1)$$

are related to the distribution coefficients of the various components between the phases by the equation

$$K''/K' = D_{\mathrm{A}}^{\mathrm{a}}D_{\mathrm{B}}^{\mathrm{b}}\cdots/D_{\mathrm{D}}^{\mathrm{d}}D_{\mathrm{E}}^{\mathrm{e}}\cdots \qquad (2)$$

In this equation, which was first derived by Nernst,[1] K' and K'' are the equilibrium constants in the first and second solvents, respectively, and D is the distribution coefficient between the two phases of a given reaction component.[2]

The distribution coefficient of a given component is defined as the ratio of the activities of the component in the two phases at distribution equilibrium. For example, the distribution coefficient of component A is defined by

$$D_{\mathrm{A}} = (a'_{\mathrm{A}}/a''_{\mathrm{A}})_{\mathrm{equil.}} \qquad (3)$$

in which the superscipts (′) and (″) refer to the first and second phases, respectively.

If reaction (1) involves only *uncharged* substances the various distribution coefficients can be determined accurately by classical methods, and hence an experimental test of eq. (2) can be made easily. However, if the reaction involves *ionic* components, such an experimental test is much more difficult, because it is impossible to determine unambiguously the *absolute* value of the distribution coefficient of a single species of ion.

The transfer of a single ionic species between two phases would involve a certain amount of electrical work in addition to purely mechanical work (difference in chemical potential between the two phases). The amount of electrical work will depend on the difference in the electrical potentials of the two phases (phase boundary potential), and since this potential difference cannot be determined in an exact way, the absolute value of the distribution coefficient of a single ionic species never can be evaluated unambiguously. Detailed discussions of this subject have been given by Guggenheim,[3] Brönsted[4] and Donnan and Guggenheim.[5]

In an ingenious study of the ionization constants of various acids in water and ethanol, Bjerrum and Larsson[6] attempted to determine the distribution coefficients of individual ionic species by measuring the e. m. f. of cells comprised of an indicator electrode for the ion in question in water and in ethanol. They tried to eliminate the potential at the junction of the two solvents by the use of concentrated salt bridges. Values obtained in this way are approximate only, because it is impossible to eliminate completely the liquid junction potential.

Fortunately, a knowledge of the absolute values of individual ionic distribution coefficients is not essential, because it is possible to determine the products and quotients of individual ionic distribution coefficients in an exact way and these suffice for the purpose.

From the solubilities s_1 and s_2 of a uni-univalent salt AB in two solvents we find

$$D_{\mathrm{A}}D_{\mathrm{B}} = \left(\frac{s_1}{s_2}\right)^2 \frac{\gamma'_{\mathrm{A}}\gamma'_{\mathrm{B}}}{\gamma''_{\mathrm{A}}\gamma''_{\mathrm{B}}} \qquad (4)$$

in which γ denotes the activity coefficient.

From the values of the standard electrode potentials of an ion i in two solvents, the ratio of the distribution coefficient of that ion to the distribution coefficient of the hydrogen ion between the two solvents is given by the relation

$$E^{0\prime} - E^{0\prime\prime} = \frac{RT}{F}\ln\frac{D_{\mathrm{H}}}{D_{\mathrm{i}}} \qquad (5)$$

in which $E^{0\prime}$ and $E^{0\prime\prime}$ represent the standard electrode potentials of the ion i in solvents 1 and 2, respectively.

In the present study the ionization constants of several weak acids in water, methanol and ethanol are compared. If pK represents the negative logarithm of the ionization constant, it can be shown from equation (2) that

$$pK'' - pK' = \Delta pK = \log D_{\mathrm{H}}D_{\mathrm{A}} - \log D_{\mathrm{HA}} \qquad (6)$$

The single primes refer to water, and the double primes to alcohol, while the subscripts H, A and

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[1] W. Nernst, *Z. physik. Chem.*, **9**, 137 (1892); **13**, 531 (1894); *Ann. Physik*, [4] 8, 600 (1902).

[2] A. E. Hill, in Taylor's "Treatise of Physical Chemistry," D. Van Nostrand Co., Inc., New York, N. Y., 1936, p. 483.

[3] E. A. Guggenheim, *J. Phys. Chem.*, **33**, 842 (1929); **34**, 1540 (1930).

[4] J. N. Brönsted, *Z. physik. Chem.*, **143**, 301 (1929).

[5] F. G. Donnan and E. A. Guggenheim, *ibid.*, **A162**, 346 (1932).

[6] N. Bjerrum and E. Larsson, *ibid.*, **127**, 368 (1927).

HA refer to hydrogen ion, the anion of the weak acid and undissociated part of the acid, respectively. The product $D_H D_A$ was found as follows. The solubility of the silver salt of the acid was determined in water and in the two alcohols. These data gave $D_{Ag} D_A$ for water–ethanol and water–methanol, using equation (4). By means of the values of the standard electrode potentials of the silver ion in water, methanol and ethanol[7] the value of the ratio D_H/D_{Ag} was calculated by equation (5). The product of $D_{Ag} D_A$ by D_H/D_{Ag} is $D_H D_A$. The value of D_{HA} was calculated from the solubility ratios of the uncharged acid, allowing for the ionized part if necessary, and assuming that the saturated solutions behave ideally.

Experimental

Ethanol and methanol (anhydrous commercial products) were refluxed over silver oxide, distilled and dehydrated with magnesium by the method of Lund and Bjerrum.[8]

The density of each lot of alcohol treated in this way was determined in a 100-ml. pycnometer with which the density of a given sample could be checked to within ±3 units in the fifth decimal place. The water content of our methanol samples ranged from 0 to 0.03%, while that of ethanol varied from 0.01 to 0.07%. The specific conductance at 25° of the methanol varied from 2.9 to 5.0 × 10^{-6} cm.$^{-1}$ ohm^{-1}; the range in the corresponding values for ethanol was from 0.4 to 1.2 × 10^{-7} cm.$^{-1}$ ohm^{-1}. The conductance of the alcohol was subtracted from the observed specific conductance where necessary.

The acids used in this study were recrystallized and tested for purity.

The silver salts of the acids were precipitated from solutions of the corresponding sodium salts with a slight excess of silver nitrate. These precipitates were washed thoroughly and recrystallized from hot water. The coarsely crystalline products obtained in this way were washed with water, then with ethanol, and air dried.

Saturated solutions of these silver salts were prepared in conductance cells through which a stream of previously dried nitrogen, saturated with the vapor of the solvent, was led to provide stirring. When the conductance had become constant, samples of the saturated aqueous solutions were withdrawn and analyzed for silver by the Volhard method except in the case of salicylate and picrate, where the potentiometric method was used. The solubilities in ethanol and methanol were determined by the conductance method, except in the case of silver picrate solutions which were titrated potentiometrically with thiocyanate. The conductance cells were of the type used by Kolthoff and Willman.[9] Their cell constants were determined in the usual way.

Results

The solubilities of the silver salts in methanol and ethanol were computed from the specific conductances of the saturated solutions by the successive approximation method. For these computations it was necessary to know the equivalent conductance of the ions of each silver salt at the concentrations in the saturated solutions. These values were obtained from the equivalent conductances of the corresponding alkali salt, of silver nitrate or perchlorate, and of the alkali nitrate or perchlorate by means of the Kohlrausch relation

$$\Lambda_{AgA} = \Lambda_{NaA} + \Lambda_{AgNO_3} - \Lambda_{NaNO_3}$$

The required values for the alkali salts in ethanol were taken from the work of Goldschmidt,[10] and those for silver nitrate, silver perchlorate, alkali nitrates, and alkali perchlorates in ethanol from the data of Barak and Hartley.[11] The necessary data for the alkali nitrates and silver nitrate in methanol were taken from the results of Frazer and Hartley,[12] and those for sodium salicylate in methanol from the measurements of Goldschmidt and Aas.[13]

There are no data in the literature for the conductances of the alkali nitrobenzoates and benzoates in methanol; accordingly, they were measured in this study. These results are given in Table I.

TABLE I

EQUIVALENT CONDUCTANCE OF SOME ALKALI SALTS IN METHANOL AT 25°

Concn. $m \times 10^4$	Potassium *o*-nitrobenzoate	Potassium *m*-nitrobenzoate	Potassium *p*-nitrobenzoate	Sodium benzoate
2.00	89.6	79.3	82.5	..
4.00	88.5	78.7	81.6	78.2
6.00	87.7	78.3	81.0	77.9
8.00	87.1	77.9	80.5	77.6
10.0	86.5	77.5	80.1	77.0
12.0	..	..	..	75.8
14.0	..	..	..	75.4
16.0	85.0	76.7	78.7	75.1
20.0	84.1	75.8	77.9	74.4

The solubilities of the silver salts were computed by assuming, as a first approximation, that the equivalent conductances of the ions in the saturated solutions were the same as at infinite dilution. Using the approximate value of the solubility so obtained, the values of the equivalent

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[7] A. Macfarlane and H. Hartley, *Phil. Mag.*, **13**, 425 (1932); **20**, 611 (1935).

[8] H. Lund and J. Bjerrum, *Ber.*, **64**, 210 (1931).

[9] I. M. Kolthoff and A. Willman, THIS JOURNAL, **56**, 1008 (1934).

[10] H. Goldschmidt, *Z. physik. Chem.*, **99**, 116 (1921).

[11] M. Barak and H. Hartley, *ibid.*, **A165**, 272 (1933).

[12] J. E. Frazer and H. Hartley, *Proc. Roy. Soc.* (London), **A109**, 351 (1925).

[13] H. Goldschmidt and F. Aas, *Z. physik. Chem.*, **112**, 423 (1924).

Table II

Solubilities of Several Silver Salts in Water, Methanol, and Ethanol at 25°

	Sp. cond. × 10^5		Solubility			$D_{Ag}D_A$	
Silver salt	Methanol	Ethanol	Water	Methanol	Ethanol	Water–Methanol	Water–Ethanol
Benzoate	5.77	0.79	0.0162[a]	0.000723	0.000237	259	2410
o-Nitrobenzoate	15.9	2.05	.0426	.00204	.000653	437	4260
m-Nitrobenzoate	4.21	0.72	.00500	.000567	.000197	77	645
p-Nitrobenzoate	8.07	1.46	.00894	.00108	.000438	69	416
Salicylate	5.08	1.10	.00442	.000569	.000310	61	205
Picrate	..	73.4	.0475	.0354	.0349	1.80	1.85
(Iodate)	..	(0.0015)	.000177[b]	..	($< 10^{-6}$)	...	...

[a] I. M. Kolthoff and W. Bosch, *J. Phys. Chem.*, **36**, 1685 (1932).

[b] I. M. Kolthoff and J. J. Lingane, *ibid.*, **42**, 133 (1938).

conductances of the ions at that concentration were computed with the aid of the Kohlrausch rule. Successive approximations were made in this way until a constant value for the solubility was obtained. A summary of the results is given in Table II. The solubilities are given in moles per liter.

In order to compute the ionization constants of the acids in methanol and ethanol from those in water by means of equation (6), it was necessary to know the distribution coefficients of the uncharged acids. Also, for comparison of the calculated and observed values of the ionization constants in the alcohols, it was necessary to have directly determined values of these constants in the alcohols. The required data are available in the literature, except the solubilities and dissociation constants of the three nitrobenzoic acids in methanol.

These solubilities were determined by titrating samples of the saturated solutions, after dilution with water, with standard baryta solution, using phenolphthalein as indicator.

Bright and Briscoe[14] determined the acidity constants of the nitrobenzoic acids in water–methanol mixtures, and extrapolated the values to 100% methanol. These constants given by Bright and Briscoe, together with the value of the ionization constant of benzoic acid in Table IV, give 7.4, 8.0, and 8.1, respecitvely, for the values of *pK* for *o*-, *m*- and *p*-nitrobenzoic acids. Since the extrapolation involves an uncertainty, and the measurements involve an interphase potential, the ionization constant of *o*-nitrobenzoic acid was determined by us by the conductivity method. The calculation was made in the classical way by means of the Ostwald dilution formula. Since the ionic strength of the solutions was very small, no correction was applied for the activity of the ions.[15]

For the calculation of the degree of dissociation, α, values of the equivalent conductance of the acid at infinite dilution were calculated in the usual way from conductance data for the potassium salt of the acid (Table I), hydrochloric acid,[16] and potassium chloride.[17] The values obtained are given in Table III. The average value of K of 6×10^{-8} or a pK of 7.22 corresponds reasonably well with the value 7.4 computed from the acidity data of Bright and Briscoe. In Table III, κ is the specific conductance, Λ the equivalent conductance, and α the degree of dissociation.

Table III

Ionization Constant of *o*-Nitrobenzoic Acid in Methanol at 25°

Concn. (molar)	$\kappa \times 10^5$	Λ	$\alpha \times 10^4$	$K \times 10^8$
0.1520	1.76	0.116	6.4	6.2
.1025	1.44	.140	7.7	6.1
.0755	1.19	.158	8.7	5.8
			Average	6.0

A summary of the solubility and ionization constant data for the various acids at 25° in water, methanol, and ethanol is given in Table IV. The solubilities, s, are given in moles per liter of solution. K represents the ionization constant.

With these data it is possible to compute pK values for the several acids in methanol and ethanol by means of equation (6), and to compare them with the experimental values. The results are given in Table V. The data needed for the calculations are given in the previous tables. The distribution coefficients of the un-ionized part of

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(14) W. L. Bright and H. T. Briscoe, *J. Phys. Chem.*, **37**, 787 (1933).

(15) (a) M. S. Sherrill and A. A. Noyes, This Journal, **48**, 1861 (1926); (b) M. Randall and C. F. Failey, *Chem. Rev.*, **4**, 291 (1927).

(16) D. M. Murray-Rust and H. Hartley, *Proc. Roy. Soc.* (London), **A126**, 84 (1929).

(17) G. Carrara, *Gazz. chim. ital.*, **26**, I, 119 (1896).

TABLE IV

IONIZATION CONSTANTS AND SOLUBILITIES OF SEVERAL ACIDS IN WATER, METHANOL, AND ETHANOL AT 25°

Acid	Water		Methanol		Ethanol	
	S	$K \times 10^4$	S	$K \times 10^9$	S	$K \times 10^9$
Benzoic	0.0279[a]	0.661[a]	3.16[f]	0.379[h]	2.91[e]	0.037[h]
o-Nitrobenzoic	.0442[a]	61.2[a]	2.99[g]	60[g]	2.81[b]	3.8[b]
m-Nitrobenzoic	.0204[b]	3.38[b]	3.46[g]	10[k]	3.50[b]	0.673[h]
p-Nitrobenzoic	.0016[b]	3.98[b]	0.200[g]	7.95[k]	0.138[b]	1.2[b]
Salicylic	.0160[a]	10.6[a]	2.57[f]	13.2[h]	2.31[b]	2.2[h]
Picric	.0578[c]	1600[d]	0.628[g]	155000[i]		175000[j]

[a] Ref. 15b. [b] Ref. 6. [c] "International Critical Tables," Vol. IV, 1928, p. 253. [d] I. M. Kolthoff, "Säure–Basen Indicatoren," Verlag von J. Springer, Berlin, 1932. [e] A. Seidell, "Solubilities of Inorganic Compounds," Vol. I, D. Van Nostrand, New York, N. Y., 1919, p. 134. [f] Results obtained by L. S. Guss in this Laboratory. [g] Results obtained by the authors. [h] Goldschmidt and Mathiesen, *Z. physik. Chem.*, **119**, 439 (1926). [i] Goldschmidt and Aarflot, *ibid.*, **117**, 312 (1925). [j] Goldschmidt, *Z. physik. Chem.*, **91**, 46 (1916). [k] Computed from the measurements of Bright and Briscoe, ref. 14. L. S. Guss in the laboratory found 25×10^{-9} for the ortho-, 5.0×10^{-9} for the meta- and 4.0×10^{-8} for the *p*-nitrobenzoic acid.

TABLE V

IONIZATION CONSTANTS IN METHANOL AND ETHANOL FROM DISTRIBUTION DATA

Acid	$D_H D_A$	D_{HA}	pK'	pK'' calcd.	pK'' exptl.
		Ethanol			
Benzoic	17350	0.00914	4.2	10.4	10.4
o-Nitrobenzoic	30600	.0109	2.2	8.7	8.4
m-Nitrobenoic	4640	.00500	3.5	9.5	9.2
p-Nitrobenzoic	2990	.00720	3.4	9.0	8.9
Salicylic	1475	.00537	3.0	8.4	8.7
Picric	13.3		0.8		3.8
		Methanol			
Benzoic	1050	0.00841	4.2	9.3	9.4
o-Nitrobenzoic	1770	.0103	2.2	7.4	7.2–7.6
m-Nitrobenzoic	315	.00514	3.5	8.3	8.0–8.3
p-Nitrobenzoic	280	.00480	3.4	8.1	8.1–8.4
Salicylic	247	.00482	3.0	7.7	7.9
Picric	7.3	.0210	0.8	3.5	3.8

the acids, D_{HA}, were computed from the solubility data for the acids, assuming that the activity coefficients for the uncharged molecules were unity in all three solvents. The values of D_{HA} in water were corrected for the amount of dissociation. The values of $D_H D_A$ needed for these calculations were obtained by multiplying the values of $D_{Ag} D_A$ given in Table II by D_H/D_{Ag}. These latter values were computed from the standard electrode potentials of silver in the three solvents by means of equation (5). In water, the value 0.7996 v.[18] for the electrode potential of silver and the values 0.764[7] v. and 0.749[7] v. in methanol and ethanol, respectively, were used. The values 3.99 and 7.15 for D_H/D_{Ag} were found for water–methanol and water–ethanol, respectively.

Discussion.—From the results in Table V it is seen that the calculated values of *pK* are in fair agreement with the experimentally determined ones. The differences between the two are no larger than the uncertainties in the experimentally determined constants and in the various assumptions and approximations which have been made. The agreement is of the same order as that obtained by Bjerrum and Larsson[6] in ethanol.

Acknowledgment.—We are indebted to the Graduate School of the University of Minnesota for a grant which enabled us to carry out this investigation.

Summary

It has been pointed out that the product and the quotient of the distribution coefficients of ions between two solvents can be determined in an exact way. When these values are known it is possible to calculate equilibrium constants in one solvent from the known values in water.

The ionization constants of six acids in methanol and ethanol were calculated from distribution data and the values of the constants in water. The values calculated in this way were found to be in fair agreement with the experimentally determined ionization constants in methanol and ethanol.

MINNEAPOLIS, MINN.

RECEIVED MAY 4, 1938

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(18) J. J. Lingane and W. D. Larson, THIS JOURNAL, **58**, 2647 (1936).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE INSTITUTE OF TECHNOLOGY OF THE UNIVERSITY OF MINNESOTA]

Ionization Constants of Acid–Base Indicators in Methanol

BY I. M. KOLTHOFF AND L. S. GUSS[1]

The equilibrium constant in a buffer system containing a small amount of an acid–base indicator is given by the expression

$$K' = \frac{(aI_b)(aA)}{(aI_a)(aB)} = \frac{cI_b\ cA}{cI_a\ cB}\,\frac{f_{Ib}\,f_A}{f_{Ia}\,f_B} = K\,\frac{f_{Ib}\,f_A}{f_{Ia}\,f_B} \quad (1)$$

in which a denotes the activity of the component, c the concentration, I_b the basic form and I_a the acid form of the indicator, A and B the acid and basic forms of the buffer, K' the thermodynamic equilibrium constant, while K is the corresponding and experimentally determinable concentration "constant," the value of which varies with the ionic strength of the solution. By extrapolating the values of K found at small ionic strengths to an ionic strength of zero, the value of K' is found. This method of evaluation of K' is similar to that used by Guggenheim and Schindler[2] in aqueous solutions.

In sufficiently dilute solution, the limiting Debye–Hückel expression gives the relation between activity coefficient and ionic strength. In methanol at 25°, this becomes

$$-\log f_{\text{ion}} = 2.0z^2\sqrt{\mu} \quad (2)$$

In the range in which the limiting expression is applicable, equation 1 gives us

$$pK' = pK - \log\frac{f_{Ib}\,f_A}{f_{Ia}\,f_B} = pK - 4.0(z_{Ia} - z_A)\sqrt{\mu} \quad (3)$$

where z_{Ia} and z_A are the charges of the indicator acid and the buffer acid, respectively. If the values of pK are plotted against the square root of the ionic strength, the slope of the curve should be $4(z_{Ia} - z_A)$ in the range where the limiting expression holds. Table I lists values of this slope for various types of indicator and buffer acids.

TABLE I

VALUES OF $4.0(z_{Ia} - z_A)$

Type of buffer acid	Type of indicator acid Cation	 Uncharged	 Anion
Cation	0.0	−4.0	−8.0
Uncharged	4.0	0.0	−4.0
Anion	8.0	4.0	0.0

Having obtained by extrapolation the value of pK, the thermodynamic ionization constant, K_I, of the indicator can be calculated if the dissociation constant of the acid, K_A, is known since

$$pK_I = pK' + pK_A$$

Although there are many data in the literature on the acidity constants and concentration ionization constants of acids in methanol, only few studies have been carried out at sufficiently small ionic strengths to allow the determination of the thermodynamic ionization constant. In the present work, the values of Goldschmidt and coworkers,[3] who determined the constants by the conductivity method, have been adopted as the most reliable values. The constant of veronal, which is not given in the literature, has been determined by the colorimetric procedure described in this paper, using the pK_I value which has been found previously in another buffer. In a similar way, the ionization constants of other acids in methanol have been determined.

Experimental

Reagents.—A good grade of synthetic methanol free of aldehydes was dehydrated by the method of Lund and Bjerrum[4] followed by distillation over sulfanilic acid to remove traces of alkaline impurities. The density of the final product was measured with a 100 ml. pycnometer. Freshly distilled products gave values of d^{25}_4 0.78651. No sample whose density was above 0.78661^{25}_4 was used, the latter value corresponding to less than 0.04% water. The presence of a trace of water has a negligible effect on indicator equilibria in buffered solutions.

The sulfonphthaleins were furnished through the courtesy of Hynson, Westcott and Dunning and were used without further purification. Thymolbenzein was obtained from a collection of the late Dr. W. R. Orndorff of Cornell University. Other indicators were purified by conventional methods.

Lithium chloride was precipitated from a saturated solution in methanol by hydrogen chloride, then fused in platinum in an atmosphere of hydrogen chloride. Sodium bromide and sodium nitrate were recrystallized from water and dried to constant weight at 110°. All other reagents were purified by conventional methods.

Sodium methoxide solutions were prepared by dropping pure sodium into methanol and, after solution was complete, diluting up to the desired strength. Solutions of acids were prepared by weight and checked by titration with sodium hydroxide. Solutions of lithium chloride and

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[1] From the dissertation submitted by L. S. Guss to the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Doctor of Philosophy, May, 1938.

[2] E. A. Guggenheim and T. D. Schindler, *J. Phys. Chem.*, **38**, 543 (1934).

[3] H. Goldschmidt and H. Aarflott, *Z. physik. Chem.*, **117**, 317 (1925); H. Goldschmidt and E. Mathiesen, *ibid.*, **119**, 453 (1926); H. Goldschmidt and F. Aas, *ibid.*, **112**, 429 (1924).

[4] H. Lund and J. Bjerrum, *Ber.*, **64B**, 210 (1931); see also N. Bjerrum and L. Zechmeister, *ibid.*, **56B**, 894 (1923).

sodium bromide were prepared similarly and checked by titration with silver nitrate.

Method.—Accurately measured volumes of a solution of the suitable buffer acid and of sodium methoxide were introduced into a test-tube to give an intermediate color to the indicator investigated. If desired, a certain amount of a neutral salt was added to obtain a certain ionic strength, then 0.05 ml. of 0.04% indicator solution and the mixture made up to 5.0 ml. with methanol. The fraction of the indicator in the alkaline form was then measured by the method of Gillespie[5] and the value of pK calculated from the ratio of the concentration of acid and basic forms of the indicator and the composition of the buffer. These values were then plotted against the square root of the ionic strength, and extrapolated to zero concentration, using the limiting Debye–Hückel expression for the final extrapolation.

Results.—For example, a solution was 0.02 N in benzoic acid, 0.0199 N in sodium benzoate, 0.20 M in lithium chloride and 0.01% in brom cresol green (added as the sodium salt). The ratio of cI_b/cI_a was found to be 0.96 and the ratio of cB/cA in the buffer was 0.99. Hence

$$K = 0.96/0.99 = 0.975$$

and $pK = 0.01$.

As an illustration, in Table II are listed the data obtained in a study of the behavior of brom phenol blue in salicylate buffers. The results of other determinations have been summarized in Table III. The values of pK given were obtained by interpolation from curves in which pK was plotted against the square root of the ionic strength. The first column gives the values obtained on extrapolating to zero ionic strength. The superscripts refer to neutral salts in the solution, 1 referring to lithium chloride, 2 to sodium bromide and 3 to sodium nitrate.

TABLE II

BROM PHENOL BLUE IN SALICYLATE BUFFER

$c_{\text{Salicylate}}$	Salt added	c_{Salt}	$\sqrt{\mu}$	cB/cA	cI_b/cI_a	pK
0.00036			0.019	3.34	0.43	0.89
.00036			.019	5.9	.725	.91
.0005			.022	3.34	.43	.89
.0009			.030	3.34	.47	.85
.0009			.030	5.9	0.82–0.73	0.86–0.91
.0022			.047	3.34	0.54	0.79
.0022			.047	5.9	.925	.80
.0056			.075	3.34	.61	.74
.0056			.075	5.7	1.00–1.08	0.76–0.72
.012			.11	2.03	0.54–0.59	.58–.54
.014			.12	3.34	0.67	0.70
.014			.12	5.9	1.38	.63
.016			.13	8.4	2.33	.56
.006	$NaNO_3$	0.003	.095	2.04	0.43	.68
.006	$NaNO_3$	.006	.11	2.04	.49	.62
.006	$NaNO_3$	.015	.145	2.04	.54	.58
.006	$NaNO_3$	.024	.175	2.04	.615	.52
.006	$NaNO_3$	.030	.19	2.04	.67	.49
.006	$NaNO_3$	.045	.225	2.04	.67	.49
.006	$NaNO_3$	.060	.26	2.04	.67	.49
.006	$NaNO_3$	.090	.31	2.04	.725	.45
.006	LiCl	.014	.14	2.04	.47	.64
.006	LiCl	.027	.18	2.04	.54	.58
.006	LiCl	.041	.22	2.04	.67	.49
.006	LiCl	.069	.275	2.04	.67	.49
.006	LiCl	.137	.38	2.04	.695	.47
.006	LiCl	.274	.53	2.04	.725	.45

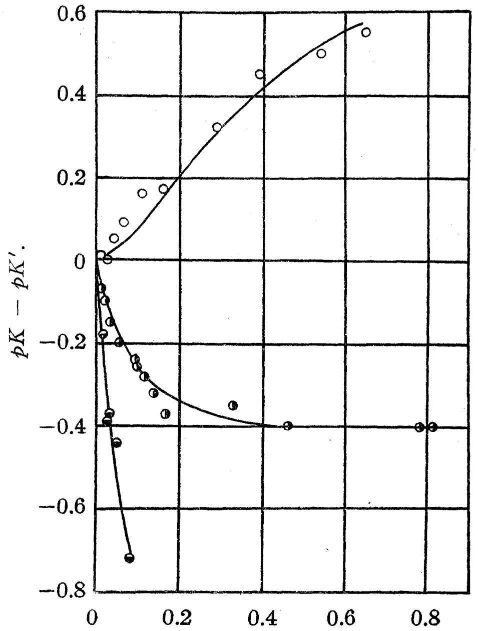

Fig. 1.—Brom cresol green in ○, tartrate, ◑, benzoate, and ◒, ammonium buffers.

The behavior of various indicator–buffer systems is shown more clearly in the figures. Figure 1 shows the behavior of brom cresol green in its alkaline range in various types of buffers. This behavior is typical of the sulfonphthaleins. For convenience, $pK - pK'$ has been plotted against the square root of the ionic strength. In Fig. 2, the behavior of the azo indicators, methyl yellow and methyl orange is illustrated. Figure 3 shows the behavior of methyl red in its two color change intervals. Figure 4 illustrates the two color changes of thymolbenzein and of thymol blue in its acid range.

Discussion

1. The sulfonphthaleins in their alkaline range approach the behavior predicted on the basis of the limiting Debye–Hückel expression, as the ionic strength approaches zero. This is evidenced by the slope of the lines given in Fig. 1. With increasing ionic strength, the pK values vary in some regular way. With buffers of the type A–B$^-$ (A is an uncharged acid, B$^-$ is the

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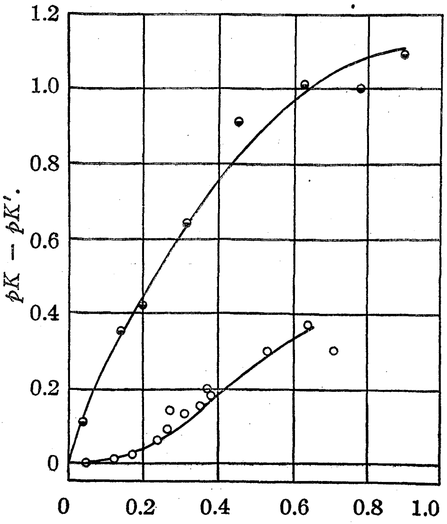
(5) L. J. Gillespie, THIS JOURNAL, 42, 742 (1920).

TABLE III

VALUES OF *pK* IN VARIOUS INDICATOR–BUFFER SYSTEMS

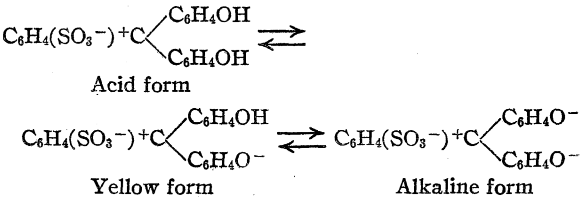
Indicator	Buffer	Ionic strengths 0.0	0.002	0.005	0.01	0.02	0.05	0.1	0.2	0.3	0.5
Brom phenol blue	Salicylate	1.0	0.8	0.75	0.7	0.65^{1} $.6^{3}$	0.5^{13}	0.45^{13}	0.45^{13}		
Brom phenol blue	*o*-Nitrobenzoate	1.3	1.1	1.0	1.0	.9	.85	$.8^{1}$	$.75^{1}$	0.75^{1}	
Brom phenol blue	*m*-Nitrobenzoate	0.6	0.45	0.35	0.3	.25	$.1^{1}$	$.05^{1}$	$.0^{1}$	$.0^{1}$	
Brom phenol blue	*p*-Nitrobenzoate	.5	.3	.25	.2	.1	$.0^{1}$	$-.05^{1}$	$-.1^{1}$	$-.1^{1}$	
Brom cresol green	Benzoate	.4	.25	.2	.15	$.1^{12}$	$.05^{12}$	$.0^{12}$	$.0^{12}$	$.0^{12}$	0.0^{12}
Brom cresol green	Acetate	.15	.0	− .1	− .15	$-.2^{12}$	$-.2^{12}$	$-.25^{1}$ $-.3^{2}$	$-.3^{12}$	$-.35^{12}$	$-.35^{12}$
Brom cresol green	Stearate	− .2	− .35	− .4	− .45	$-.5^{2}$	$-.55^{2}$	$-.55^{2}$	$-.6^{2}$	$-.6^{2}$	$-.6^{2}$
Brom cresol purple	Benzoate	1.9	1.7	1.65	1.6	1.55	1.45^{2}	1.4^{2}	1.4^{2}	1.4^{2}	1.45^{2}
Brom cresol purple	*p*-Aminobenzoate	1.05	0.9	0.85	0.8	0.7	0.65^{2}	0.6^{2}	0.6^{2}	0.6^{2}	0.6^{2}
Brom thymol blue	Veronalate	−0.3	− .45	− .5	$-.6^{2}$ $-.65^{1}$	$-.65^{2}$ $-.75^{1}$	$-.7^{2}$ $-.75^{1}$	$-.7^{2}$ $-.8^{1}$	$-.7^{2}$ $-.85^{1}$	$-.65^{2}$ $-.85^{1}$	$-.5^{2}$ $-.85^{1}$
Phenol red	Veronalate	.1	− .05	− .15	− .2	− .3					
Thymol blue	Veronalate	1.3	1.2	1.1	1.05	1.0	$.95^{1}$	$.9^{1}$	$.85^{1}$	$.85^{1}$	$.85^{1}$
Thymol blue	Phenolate	0.0	−0.15	−0.25	−0.35	−0.45	$-.55^{1}$	$-.65^{1}$			
Thymol blue	Trichloroacetate	− .2	− .2	− .2	− .2	− .2	-0.2^{1}	-0.2^{1}			
Brom thymol blue	Succinate	1.0	1.05	1.05	1.05	1.1	1.15^{2} 1.25^{1}	1.2^{2} 1.3^{1}	1.25^{2} 1.35^{1}	1.25^{2} 1.35^{1}	1.3^{2} 1.4^{1}
Brom cresol green	Tartrate	−0.1	−0.05	0.0	0.05	0.1	0.15^{1}	0.25^{1}	0.35^{1}	0.4^{1}	
Brom cresol green	Ammonium	−0.9	−1.3	−1.55							
Brom phenol blue	Anilinium	2.9	2.5	2.3	2.15	1.95^{1}	1.75^{1}	1.5^{1}	1.3^{1}	1.15^{1}	
Methyl orange	Trichloroacetate	−1.1	−1.1	−1.1	−1.1	-1.1^{1}	-1.05^{1}	-1.0^{12}	-0.85^{12}	-0.8^{12}	-0.75^{12}
Methyl red	Benzoate	−0.2	−0.2	−0.2	−0.2	−0.2	-0.15^{1}	-0.05^{2}	$.0^{12}$	$.1^{12}$	$.25^{12}$
Methyl red	Trichloroacetate	− .8	− .7	− .65	− .6	− .55	$-.45^{1}$	$-.3^{1}$	$-.1^{1}$	$.0^{1}$	$.15^{1}$
Methyl yellow	Trichloroacetate	−1.5	−1.35	−1.3	−1.25	-1.15^{1}	-1.0^{12}	$-.95^{1}$ $-.75^{2}$	$-.75^{1}$ $-.55^{2}$	$-.65^{1}$ $-.45^{2}$	$-.5^{1}$ $-.4^{2}$
Neutral red	Salicylate	0.3	0.45	0.55	0.6	0.75	0.95^{12}	1.2^{12}	1.45^{1} 1.55^{2}	1.6^{2}	1.75^{2}
Methyl yellow	*o*-Chloroanilinium	.0	.0	.0	.0	$.0^{1}$	$.0^{1}$	$.0^{1}$	0.0^{1}	0.0^{1}	0.0^{1}
Methyl orange	*o*-Chloroanilinium	− .15	− .15	− .15	− .15	− .2	− .2	$-.2^{2}$	$-.25^{2}$	$-.2^{2}$	$-.2^{2}$
Thymolbenzein	Trichloroacetate	−1.4	−1.25	−1.1	-1.0^{2}	$-.9^{2}$	$-.7^{2}$	$-.55^{2}$			
Thymolbenzein	Veronalate	0.45	0.45	0.45	0.45^{1}	$.5^{1}$	$.6^{1}$	$.75^{1}$	$.75^{1}$		

corresponding univalent anion base), a limiting slope of −4 is obtained. With increasing ionic strength, the *pK* values decrease less than demanded by the limiting expression. This is to be expected as the latter in methanol will only be valid at very small ionic strengths. When the ionic strength has become of the order of 0.06, the *pK* values remain practically constant with increasing ionic strength. This behavior is typical of all of the sulfonphthaleins and can be interpreted on the basis of the structures of the sulfonphthaleins as originally proposed by Lund[6] and supported by the work of Schwarzenbach.[7] According to Lund, the structural changes of a sulfonphthalein in its various color change intervals is represented by



Square root of ionic strength.

Fig. 2.—○, Methyl orange and ⊖, methyl yellow in trichloroacetate buffer.



$$C_6H_4(SO_3^-)^+C\begin{matrix}\nearrow C_6H_4OH\\ \searrow C_6H_4OH\end{matrix} \rightleftarrows$$

Acid form

$$C_6H_4(SO_3^-)^+C\begin{matrix}\nearrow C_6H_4OH\\ \searrow C_6H_4O^-\end{matrix} \rightleftarrows C_6H_4(SO_3^-)^+C\begin{matrix}\nearrow C_6H_4O^-\\ \searrow C_6H_4O^-\end{matrix}$$

Yellow form Alkaline form

Thus, the yellow form is a hybrid ion with one extra negative charge and the alkaline form a hybrid ion with two extra negative charges. Bjerrum[8] postulated that the charges on a hybrid ion are sufficiently displaced that, in a fairly concentrated solution, it behaves as two ions. Güntel-

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[6] H. Lund, *J. Chem. Soc.*, 1844 (1930).

[7] G. Schwarzenbach, *Helv. Chim. Acta*, **20**, 490 (1937), *et seq.*

[8] N. Bjerrum, *Z. physik. Chem.*, **104**, 147 (1923).

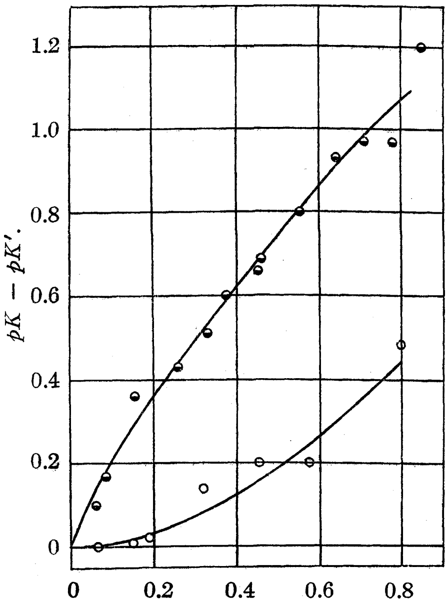

Fig. 3.—Methyl red in ○, benzoate and ◒, trichloroacetate buffers.

berg and Schiödt[9] showed that the behavior of methyl orange with varying ionic strength could be explained by such a hypothesis. The same reasoning should apply to any highly charged ion, with widely displaced charges. Thus, we might assume that at higher ionic strengths the electrical work required to build up n individual charges will be n times as great as that required to build up a single charge. In the yellow form of the sulfonphthaleins, n is equal to 3 and in the alkaline form, equal to 4. At high ionic strengths, we then may write the following relation for the activity coefficient

$$-\log f_n = -n \log f_1 \qquad (4)$$

in which f_1 is the activity coefficient of a univalent ion.

For univalent ions in fairly concentrated solutions, the Debye–Hückel expression might be written

$$-\log f_1 = f(\sqrt{\mu}) + B \qquad (5)$$

where B is some function of the ionic strength. It seems fair to assume that B will be of the same magnitude for ions of a conjugate acid–base system. Applying the above to the sulfonphthaleins in buffers of the type A–B$^-$ at higher ionic strength, we find

$$\begin{aligned} pK &= pK'' - \log f_{\overset{=}{-}} + \log f_{\overset{=}{=}} - \log f_- + \log f_0 \\ &= pK'' - 3\log f_1 + 4\log f_1 - \log f_1 = pK'' \qquad (6) \end{aligned}$$

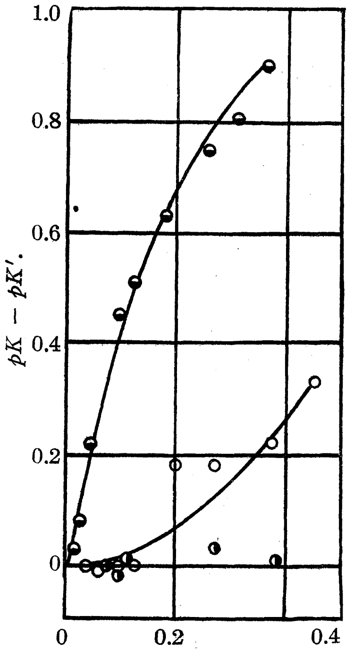

Fig. 4.—Thymolbenzein in ○, veronalate, and ◒, trichloroacetate and ◑, thymol blue in trichloroacetate.

in which pK'' is not the true thermodynamic constant since the relation in equation 4 will not permit extrapolation down to infinite dilution. According to the above interpretation, pK becomes constant at relatively high ionic strengths, which is in agreement with experimental results.

The above considerations are also of practical importance. If the pK values of sulfonphthaleins in various alcohols are determined in buffer solutions of the type A–B$^-$ with an ionic strength of about 0.1, the result of a 5- to 10-fold dilution will be a very small effect upon the pK measured. Extrapolation of those data to an ionic strength of zero, however, would lead to an erroneous result. Kolthoff,[10] who investigated the sulfonphthaleins in ethanol, has applied such an extrapolation. From this discussion, it is clear that his data need correction.

In buffers of the type A$^-$–B$^=$, the pK values of the sulfonphthaleins should become constant and independent of the ionic strength when the latter is very small. Actually, this was found to be the case with brom cresol green in bitartrate–tartrate buffers at ionic strengths below 0.001. When the ionic strength becomes greater than

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[9] E. Güntelberg and E. Schiödt, *Z. physik. Chem.* **135**, 393 (1928).

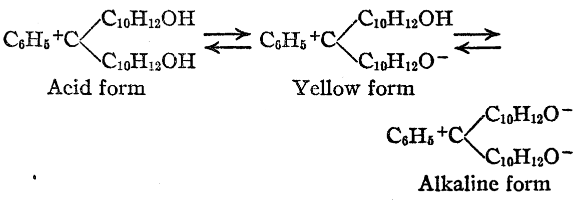
[10] I. M. Kolthoff, *J. Phys. Chem.*, **35**, 2732 (1931).

this, the pK values increase. This is in agreement with the above considerations.

The tremendous effect of the ionic strength upon the pK values in buffers of the type A^+–B is also in agreement with the predictions based on the above discussion. At low ionic strengths, the curve has the slope of -8 required by equation 3 (see Fig. 1). At higher ionic strengths, the theory of individual charges seems again applicable.

The behavior of thymol blue in its acid range is in agreement with the structure proposed by Lund. The pK values found in trichloroacetate buffer were found to be constant up to an ionic strength of 0.1.

2. In connection with what has been said of the sulfonphthaleins, the behavior of thymolbenzein in its two color changes is of interest. On the basis of the work of Lund and Schwarzenbach, the structural changes may be represented by


$$C_6H_5{}^+C\begin{cases}C_{10}H_{12}OH\\C_{10}H_{12}OH\end{cases} \rightleftarrows C_6H_5{}^+C\begin{cases}C_{10}H_{12}OH\\C_{10}H_{12}O^-\end{cases} \rightleftarrows C_6H_5{}^+C\begin{cases}C_{10}H_{12}O^-\\C_{10}H_{12}O^-\end{cases}$$

In its acid range, in a buffer of the type A–B^-, we would have

$$pK = pK'' - \log f_+ + \log f_\mp - \log f_- + \log f_0$$

At small ionic strengths, this leads to

$$pK = pK' + 4\sqrt{\mu}$$

The slope of 4 actually was observed in trichloroacetate buffers. At high ionic strengths, we would expect to find $pK = pK''$ and independent of μ. Although the slope did increase, it still had a positive value at an ionic strength of 0.126.

In the alkaline range, with the same type of buffer, the following relation should hold at higher ionic strengths

$$pK = pK'' - \log f_\mp + \log f_\mp - \log f_- + \log f_0 = pK''$$

Actually the pK was found to be constant up to an ionic strength of about 0.01. Above this, pK increased. More work should be done in order to interpret the behavior of the benzeins at higher ionic strengths.

3. The behavior of azo indicators and of neutral red in buffers of the type A–B^- is in agreement with the postulates given in the introduction of this paper. The slope of the pK line of methyl yellow against the square root of the ionic strength in trichloroacetate buffers and of neutral red in salicylate buffers approaches the value calculated on the basis of the limiting Debye–Hückel expression (Table I and Fig. 2). At greater ionic strengths, the pK values of both indicators increase less than calculated on the basis of the limiting expression, which is to be expected since the latter disregards ionic diameter. With both indicators, the deviations are greater with lithium chloride than with sodium bromide.

The behavior of methyl orange in trichloroacetate buffer (Fig. 2) is explained readily by the hybrid character of the acid form of the indicator. At small ionic strengths, the pK values become constant, but pK increases at greater ionic strengths. In the latter case we have

$$pK = pK'' - \log f_\mp + \log f_- - \log f_- + \log f_0 = pK'' - 2 \log f_1$$

While the behavior of methyl yellow in *o*-chloroanilinium buffer is quite normal, the behavior of methyl orange in the same buffer is abnormal. A limiting slope of pK against the square root of the ionic strength of 4 was expected, but as seen from the data in Table III, the pK was found to be sensibly independent of ionic strength. Whether this result is to be attributed to a specific interaction between methyl orange and the buffer has not been investigated.

Methyl red has two color changes, in the acid range from red to orange and in the alkaline range from orange to yellow. The latter corresponds to the color change in water from so-called Red II to yellow, but is less pronounced in methanol. In the acid range (trichloroacetate buffer), the change of the pK at small ionic strengths is similar to that of methyl yellow and neutral red (see Fig. 3), but at higher ionic strengths the pK does not increase as much as that of other indicators. In the alkaline range (benzoate buffers), the pK becomes constant at small ionic strengths and increases at larger ionic strengths. The salt effect is almost identical with that of methyl orange in trichloroacetate buffer. The salt effects in the acid and alkaline ranges are best explained on the assumption that the orange form (comparable with Red II in water) is present as a neutral amino acid and not as a hybrid ion. This behavior is in agreement with the change of the indicator constant, pK_I, on going from water to methanol. The pK_I of methyl red in water is 5.0, and in methanol ($pK_{I(2)}$), 9.2. The change of 4.2 cor-

TABLE IV

EFFECT OF WATER ON INDICATOR EQUILIBRIA IN BUFFER SOLUTIONS

Buffer	Indicator	cI_b/cI_a In pure methanol	 With 1% water
Trichloroacetate	Methyl yellow	2.33	2.33
Trichloroacetate	Methyl orange	1.50	1.55
Benzoate	Brom cresol green	1.13	1.22
Veronalate	Brom thymol blue	0.64	0.615
Veronalate	Brom cresol purple	0.43	0.41
Veronalate	Phenol red	1.00	1.00
Succinate	Brom cresol purple	0.92	0.82

TABLE V

DISSOCIATION CONSTANTS OF INDICATORS IN METHANOL

Indicator	Buffer	pK_A	pK'	$pK_{I(MeOH)}$	$pK_{I(H_2O)}$
Tropeoline 00	Hydrogen chloride			2.2	2.0
Methyl yellow	Trichloroacetate	4.9	−1.5	3.4	3.25
Thymolbenzein (1)	Trichloroacetate	4.9	−1.4	3.5	
Methyl orange	Trichloroacetate	4.9	−1.1	3.8	3.45
Methyl red (1)	Trichloroacetate	4.9	−0.8	4.1	2.3
Thymol blue (1)	Trichloroacetate	4.9	− .2	4.7	1.65
Neutral red	Salicylate	7.9	− .3	8.2	7.4
Neutral red	Acetate	9.65	−1.4	8.25	7.4
Brom phenol blue	Salicylate	7.9	1.0	8.9	4.1
Brom phenol blue	Benzoate	9.4	−0.4	9.0	4.1
Methyl red (2)	Benzoate	9.4	− .2	9.2	5.0
Brom cresol green	Benzoate	9.4	.4	9.8	4.9
Brom cresol purple	Benzoate	9.4	1.9	11.3	6.4
Brom thymol blue	Veronalate	12.7	−0.3	12.4	7.3
Phenol red	Veronalate	12.7	+ .1	12.8	8.0
Thymolbenzein (2)	Veronalate	12.7	.45	13.15	
Thymol blue (2)	Veronalate	12.7	1.3	14.0	9.2

TABLE VI

DISSOCIATION CONSTANTS OF SOME ACIDS IN METHANOL

Acid	Indicator	pK_I	pK'	pK_A	$pK_A(H_2O)$
o-Nitrobenzoic	Brom phenol blue	8.9	1.3	7.6	2.2
m-Nitrobenzoic	Brom phenol blue	8.9	0.6	8.3	3.5
p-Nitrobenzoic	Brom phenol blue	8.9	.5	8.4	3.4
Acetic	Brom cresol green	9.8	.15	9.65	4.75
Stearic	Brom cresol green	9.8	− .2	10.0	
p-Aminobenzoic	Brom cresol purple	11.3	1.05	10.25	4.8
Veronal	Brom cresol green	9.8	−2.8	12.6	7.4
Veronal	Brom cresol purple	11.3	−1.4	12.7	7.4
Phenol	Thymol blue	14.0	0.0	14.0	9.9
o-Chloroanilinium	Methyl yellow	3.4	.0	3.4	3.25
o-Chloroanilinium	Methyl orange	3.8	− .15	3.95?	3.25
Anilinium	Brom phenol blue	8.9	2.9	6.0	4.6
Ammonium	Brom cresol green	9.8	−0.9	10.7	9.25
Bitartrate	Brom cresol green	9.8	− .1	9.9	4.55
Bisuccinate	Brom cresol purple	11.3	− .1	11.4	5.6
Bisuccinate	Brom thymol blue	12.4	1.0	11.4	5.6
Biphthalate	Brom cresol purple	11.3	−0.35	11.65	5.4

responds to that of an uncharged carboxylic acid. On the other hand, the behavior of methyl orange in this respect (3.5 in water, 3.8 in methanol) indicates conclusively the hybrid ion structure of the acid form. From their work on the indicator constants in water–ethanol mixtures, Baggesgaard-Rasmussen and Reimers[11] arrived at the conclusion that the Red II form of methyl red or the orange form in alcohol has the amino acid and not the hybrid ion structure. Kolthoff[12] and Thiel[13] came to the opposite conclusion from a consideration of the salt effect in water. In agreement with the former conclusion is the fact that the temperature has hardly any effect on the intermediate color of methyl red in a benzoate buffer in water or in methanol. If the orange form had a hybrid structure the color should shift to a yellow on increasing the temperature.

4. The effect of small amounts of water

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[11] H. Baggesgaard-Rasmussen and F. Reimers, *Dansk. Tidsskr. Farm.*, **7**, 225 (1933).

[12] I. M. Kolthoff, *Rec. trav. chim.*, **44**, 68 (1925).

[13] A. Thiel, A. Dassler and F. Wülfken, *Ber.*, **56**, 1667 (1923).

should be negligibly small as long as the concentration of the water is not great enough to affect the properties of the solvent appreciably. From a large number of experiments, a few examples of which are listed in Table IV, it is seen that the presence of 1% water in a buffer solution hardly affects the indicator–buffer equilibrium.

In Table V is given a summary of the values of the negative logarithms of the ionization constants of indicators, pK_{I}, at an ionic strength of zero. The values, naturally, are no more reliable than the pK_{A} values from which they were calculated. The pK_{I} of Tropeoline 00 has been obtained from experiments in dilute hydrochloric acid solutions in methanol, which will be reported in a subsequent publication.

In Table VI is given a list of the pK_{A} values of various acids at $\mu = 0$, which were calculated from the extrapolated pK' values and the pK_{I} values of Table V.

Summary

1. Thermodynamic ionization constants of a number of indicators and of acids have been determined in methanol, and the effect of ionic strength studied.

2. The behavior of the sulfonphthaleins and thymolbenzein is in agreement with modern views of their structures.

3. In agreement with Baggesgaard-Rasmussen and Reimers, it was found that the behavior of methyl red is best explained on the basis of the existence of the free amino acid form, and not of the hybrid form, although the salt effect is not entirely accounted for by this interpretation.

4. The behavior of other indicators is in agreement with present concepts. At very small ionic strengths, the salt effect can be accounted for quantitatively by the limiting Debye–Hückel expression.

MINNEAPOLIS, MINN. RECEIVED AUGUST 5, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

Specific Heats and Heat of Fusion of Tellurium Tetrachloride

BY K. J. FREDERICK AND J. H. HILDEBRAND

A calculation of the internal pressure of tellurium tetrachloride by the senior author[1] shows that this tetrachloride differs from all others in the magnitude of its molecular field, which is near to that of iodine. It is to be expected, therefore, that solutions of these two substances with each other should be nearly ideal, provided that they do not react and that the former does not have a more or less ionic field, which may prove to be the case. The freezing point diagram for this system is now being constructed in this Laboratory. In order to evaluate the data, however, it is necessary to have reliable figures for the specific heats and heats of fusion. Data for iodine recently have been reported by us[2] and this paper presents similar results for tellurium tetrachloride, for which no determinations of the quantities are to be found in the literature.

Preparation and Purification of Sample.—The material used was purified by fractional distillation, the final fraction distilling at a mean temperature of 390° under atmospheric pressure. Its melting point was 224.1°. The purified material was enclosed in small Pyrex glass capsules, evacuated before sealing. The capsules had an external diameter of 12 mm., an internal diameter of 10 mm., and a length of approximately 6 cm. The ratio of weight of tellurium tetrachloride to weight of glass was about 1.4. Two different capsules were prepared and each one was used in a considerable number of the runs. The average free space in the capsules was 1.7 cc. Calculations indicate that the tellurium tetrachloride vapor in the capsules was a negligible factor.

Method.—The apparatus and method used in these determinations were the same as described in the account of the work with iodine. The higher melting point of the tellurium tetrachloride necessitated further calibration of the thermocouple in the furnace and the melting point of tin was used for this purpose.

Results and Discussion.—The value of the heat capacity of the calorimeter was 11.3 ± 0.4 cal. per degree. Runs on the Pyrex glass used in making the capsules showed that its specific heat for the interval 25–250° could be

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[1] J. H. Hildebrand, "Solubility of Non-Electrolytes," Reinhold Publishing Corp., New York, N. Y., 1936.

[2] Frederick and Hildebrand, THIS JOURNAL, **60**, 1436 (1938).

expressed within ± 0.3% by the equation

$$c_p = 0.186 + 5.5 \times 10^{-5}(t - 25) + 1.15 \times 10^{-6}(t - 25)^2$$

The results of the runs made on solid and liquid tellurium tetrachloride are given in Table I. The column headed $H-H_{298.1}$ represents the number of calories evolved in cooling one mole from the temperature in the other column down to 25°. The data listed in the tables are plotted in Fig. 1.

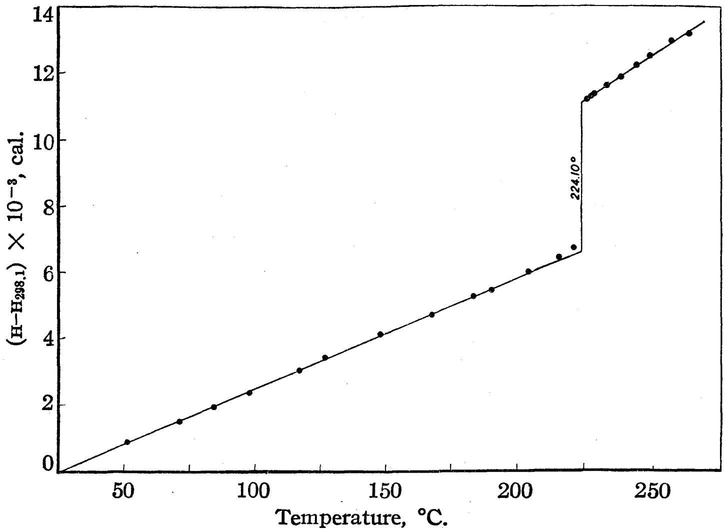

Fig. 1.

The two values obtained for the solid just below the melting point are abnormally high due to some pre-melting. If these two are neglected, the rest of the results for the solid range follow a linear relationship within experimental error. The slope of this line is the molal heat capacity of solid tellurium tetrachloride in the interval 25–224.1° and is 33.1 ± 0.3 cal. per mole. A straight line was also found to fit the data for liquid tellurium tetrachloride within experimental error. This gives a molal heat capacity of liquid tellurium tetrachloride of 55.0 ± 0.5 cal. per mole for the interval 224.1–265°.

TABLE I

Temp., °C.	$H-H_{298.1}$, cal./mole Solid	Temp., °C.	$H-H_{298.1}$, cal./mole Liquid
51.06	847.3	226.20	11,204.7
71.10	1491.3	227.80	11,312.9
84.32	1920.6	229.03	11,366.3
97.91	2331.3	233.28	11,604.4
116.94	3010.3	238.63	11,879.1
126.72	3399.8	244.40	12,224.1
148.36	4110.5	249.36	12,510.4
168.10	4705.5	256.85	12,964.7
184.63	5263.8	263.10	13,169.2
190.65	5466.3		
204.82	5980.5		
216.10	6410.3		
221.60	6720.0		

The heat of fusion of tellurium tetrachloride at the melting point is 4510 ± 30 cal. per mole. The entropy of fusion is 9.07 cal. per degree. This agrees excellently with the entropies of fusion of silicon tetrachloride, 9.08; titanium tetrachloride, 9.00; tin tetrachloride, 9.11; obtained by Latimer.[3]

Summary

Employing the method of mixtures, the heat of fusion of tellurium tetrachloride at the melting point was found to be 4510 ± 30 cal. per mole, the molal heat capacity of solid tellurium tetrachloride in the interval 25–224.1°, 33.1 ± 0.3 cal. per mole, and the molal heat capacity of liquid tellurium tetrachloride in the interval 224.1–265°, 55.0 ± 0.5 cal. per mole.

BERKELEY, CALIF. RECEIVED MAY 31, 1938

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(3) W. M. Latimer, THIS JOURNAL, **44**, 90 (1922).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

The Distribution of Minute Amounts of Material between Liquid Phases

BY D. C. GRAHAME AND G. T. SEABORG

It frequently happens in chemical investigations that a knowledge of the behavior of very small amounts of material in solution, either alone or accompanied by larger amounts of other substances, becomes of considerable importance. Particularly in the use of radioactive substances as indicators for chemical investigations or in the identification of newly discovered artificially prepared radioactive isotopes is it desirable to know what chemical behavior may be expected of minute quantities of radioactive matter in the absence of appreciable amounts of its inactive isotopes. The work of Fajans, Paneth, Hahn and others[1] has led to the formulation of rules concerning the adsorption or coprecipitation of minute amounts of material upon precipitates formed under various conditions. Studies of this sort lead to qualitative conclusions only and do not permit any very accurate prediction as to the behavior of untried substances. It seemed likely, on the other hand, that minute amounts of material would distribute themselves between liquid phases in a simple manner owing to the absence of adsorption phenomena so characteristic of the solid phase. It could not be foretold, of course, whether the walls of the containing vessel or the dust particles inevitably present in the solution would exhibit sufficient adsorption of the microcomponent to influence the experimental results.

I. Partition of Gallium Chloride between Ether and Hydrochloric Acid

Experimental Details.—Ether (99.5%) was dried with anhydrous calcium chloride and metallic sodium, then distilled in an all-glass still (b. p. 34.4 ± 0.2°). Hydrochloric acid, 6 *N*, was distilled in an all-glass still and shaken with ether to remove possible traces of gallium chloride. Chemically pure zinc chloride was dissolved in 6 *N* hydrochloric acid and freed from gallium by repeated extractions of gallium chloride with fresh ether prepared as above. The solution so prepared was evaporated to remove hydrochloric acid, redissolved in doubly-distilled water and electrolyzed between a carbon cathode and platinum anode to give a thin deposit of gallium-free zinc. The zinc was bombarded in air with 8.0 Mev deuterons from the Berkeley cyclotron to form, among other things, radioactive isotopes of gallium. From the intensity of the radioactivity produced ($\sim 10^{-2}$ millicuries of sixty-eight minute gallium) we estimate that the amount of gallium formed was about 10^{-12} g.[2] The sample of zinc containing this gallium was dissolved in 6 *N* hydrochloric acid (prepared as above) and shaken with 25 cc. of ether, whereby most of the radio-gallium was extracted as gallium chloride.

This ether extract was shaken several times with 6 *N* hydrochloric acid (saturated with ether) to remove traces of zinc chloride from the ether solution after which the distribution ratio of the gallium chloride remaining in the ether was determined in the following manner. To the ether solution in a cylindrical separatory funnel an approximately equal volume of 6 *N* hydrochloric acid (saturated with ether) was added. The mixture was brought to a temperature of 20.0 ± 0.1° in a water thermostat and shaken thoroughly to establish equilibrium between the liquid phases. After the volumes had been marked, the aqueous layer was drawn off very carefully into a second separatory funnel and shaken again at 20° with an equal volume of ether already in equilibrium with 6 *N* hydrochloric acid. The two ether extracts thus obtained were evaporated to dryness on shallow copper trays of identical size and shape which could be placed in a reproducible manner under a Lauritsen type quartz fiber electroscope or under a thin-walled Geiger–Müller counter. In order to obtain a fairly uniform deposit on the copper trays, a few drops of alcohol were added to the ether during the evaporation process and the solution was rocked back and forth by hand during the final stages of the evaporation. Gentle heating hastened the evaporation, but the solution was not boiled.

The ratio of the intensities of the radiations from the radioactive gallium on the trays gave a measure of the relative amounts of gallium chloride present in the two ether extracts. From this ratio and a knowledge of the volumes of the ether and aqueous phases, it was possible to calculate by a method of successive approximations the distribution ratio of the gallium chloride between the two liquid phases. Because of the extreme thinness of the deposits on the trays self-absorption of the radiation by the body of the sample did not need to be considered in most instances. In certain experiments, however, the amount of material present in the trays was sufficient to absorb an appreciable fraction of the β-particles emitted by the sample. In such cases the relative intensities were estimated with a Geiger counter under conditions such that only γ-rays were detected. The counting rate was then practically independent of the thickness of the samples over the range of thicknesses used.

Results.—There are two known isotopes of gallium formed by the bombardment of zinc with deuterons, with half-lives of sixty-eight minutes

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[1] A summary and discussion of these investigations is found in Hahn's "Applied Radiochemistry," Cornell University Press, Ithaca, N. Y., 1936.

[2] This estimate also takes into account the fact that other isotopes of gallium (radioactive and non-radioactive) are formed during the bombardment.

and eighty-three hours, respectively. Both were observed in these experiments (in addition to another which will be mentioned later), and since a distribution coefficient for gallium chloride could be obtained from either, measurements were made with one or the other or both. The results obtained are presented in Table I. Column 2 gives the approximate molal concentration of gallium chloride in the ether phase of the first extract. Column 3 gives the half-life of the radioactive body on which the experiment was conducted, and column 4 gives the distribution coefficient, K, expressed as the ratio of the molal concentration in the ether phase to that in the aqueous phase in equilibrium at 20°. The probable error in the distribution coefficient, estimated from the internal consistency obtained in duplicate runs, is about ±10%. Experiment 4 differed from the others in that 7 mg. of gallium chloride was added to the radioactive sample at the beginning of the experiment. The result so obtained indicates that the distribution of gallium chloride between ether and hydrochloric acid is the same at extremely low concentrations of gallium chloride as at ordinary concentrations.

TABLE I

DISTRIBUTION RATIO OF GALLIUM CHLORIDE BETWEEN ETHER AND HCl ($\sim 6\ N$)

Expt.	Initial concn. of $GaCl_3$	Half-life	Distribution ratio K
1	$\sim 10^{-12}$	68 min.	18.1
2	$\sim 10^{-12}$	83 hr.	19.0
3	$\sim 10^{-12}$	68 min.	17.5
4	0.0016	83 hr.	16.9

II. Distribution of Manganous Chloride between Ether and Hydrochloric Acid

Experimental Details.—A solution in ether of manganese-and-cobalt-free ferric chloride was prepared by dissolving sublimed ferric chloride in ether and extracting manganese and cobalt by repeatedly shaking the solution with fresh, triply-distilled (in Pyrex) 6 N hydrochloric acid. The experiments to be described show that such a procedure really does reduce the concentration of manganous chloride and cobalt chloride to extremely low values. The purified ether solution was irradiated with fast neutrons from the Berkeley cyclotron to form, among other things, very small amounts ($\sim 10^{-15}$ g.) of radio-manganese. This ether solution (volume, 82 cc.) was then shaken with two 13-cc. samples of triply-distilled 6 N hydrochloric acid, and great care was exercised to avoid contaminating the second hydrochloric acid extract with any of the first extract that may have escaped removal from the separatory funnel. From the behavior of manganese chloride in ordinary amounts, one would expect that 99.97% of the radio-manganese would appear in the first hydrochloric acid extract. To test this, the hydrochloric acid extracts were purified as follows, and their activity measured with a Geiger counter. Ferric chloride was removed from the two extracts by shaking with ether. Manganese chloride and monosodium hydrogen phosphate were added to each solution to serve as carriers for the subsequent precipitations and concentrated nitric acid was added to oxidize to phosphate any radio-phosphorus in the solution. (Radio-phosphorus and radio-chlorine were always present as a result of the action of neutrons on the chlorine originally present.) Phosphates were then removed by precipitation as $(NH_4)_3PO_4 \cdot 12MoO_3$ and manganese was recovered as $MnO(OH)_2$ by the action of sodium hydroxide and bromine water. A further purification of the $MnO(OH)_2$ was effected by dissolving it in an acidified solution of hydrogen peroxide and reprecipitating from concentrated nitric acid with potassium chlorate.

Results.—Measurements on the radioactivity of the two manganese samples showed that nearly all of the radio-manganese appeared in the first extract. Nevertheless, a very slight activity (0.7% of that in the first extract) appeared in the second extract, which was not to be expected from the extremely small distribution coefficient of manganese chloride between ether and 6 N hydrochloric acid (see below). It seems very probable, however, that traces of radio-silicon (half-life two and four-tenths hours) formed from the walls of the vessel may have entered the solution and been precipitated in part along with the manganese dioxide. Because of this uncertainty the conclusion to be drawn from this experiment is only qualitative. Thus, minute amounts of manganese chloride may be extracted from ether, at least qualitatively, in the same manner as manganese chloride in larger amounts.

It may be remarked, however, that the ether used to remove the ferric chloride from the first hydrochloric acid extract showed no detectable radio-manganese, a result to be expected if minute amounts behave in the same manner as larger amounts.

III. Distribution of $(NH_4)_2Co(SCN)_4$ between Water and Amyl Alcohol

Experimental Details.—Cobalt-free ammonium thiocyanate solution was prepared by shaking a 40% solution of the C. P. salt several times with doubly-distilled *s*-amyl alcohol. This procedure removed any cobalt which might be present, together with about half of the ammonium thiocyanate.

Cobalt-free iron was deposited in a thin film on a pure silver plate by electrolyzing (with a platinum anode and a silver cathode) a water solution of cobalt-free ferric chloride prepared as before. A scrupulously clean porous alundum cup prevented excessive diffusion of chlorine from the anode to the cathode. The film of iron so formed was bombarded in air with deuterons to form radio-cobalt with a half-life of eighteen hours, together with small amounts of radio-manganese, radio-iron, and long-lived radio-cobalt isotopes. The silver plate on which the iron was deposited also became strongly radioactive due to the formation of short-lived silver isotopes and due to the formation of a radio-cadmium isotope (half-life 7.2 ± 0.5 hrs.) heretofore observed only from the action of protons on silver. Part of the iron film was dissolved, after bombardment, with pure 6 *N* hydrochloric acid. The acid evidently reached the silver backing in places, for radio-cadmium, dissolved from the surface of the silver, was detected easily in all of the samples. To the solution of iron in hydrochloric acid, doubly-distilled (in Pyrex) 6 *N* nitric acid was added to oxidize ferrous iron, the solution was shaken with ether to remove the iron, evaporated to dryness, and taken up in ammonium thiocyanate solution prepared as described above. The distribution coefficient (between this solution and pure doubly-distilled *s*-amyl alcohol (b. p. 118.0 ± 0.5°) of the minute amounts of $(NH_4)_2Co(SCN)_4$ thus formed ($\sim 10^{-12}$ g.), was determined in substantially the same manner as that described above for gallium chloride. One difference lay in the fact that the two amyl alcohol extracts were finally shaken with dilute ammonium hydroxide solution which brought the radio-cobalt back into the aqueous layer. This was at once a convenience and a further test of the principle under consideration. In these extractions, of course, relatively large amounts of ammonium thiocyanate are transferred along with the ammonium cobaltothiocyanate.

Results.—The results so obtained are presented in Table II. Experiment 6 was identical with 5 except that ordinary pure iron, containing traces of cobalt, was used for the bombardment. Within the limits of the experimental error the results are the same, indicating again that very low concentrations of matter behave in partition processes like the same substances at ordinary concentrations.

Table II

Distribution Ratio of $(NH_4)_2Co(SCN)_4$ between *s*-Amyl Alcohol and Aqueous Ammonium Thiocyanate Solution

Expt.	Initial concn. of $CoCl_2$	Distribution ratio *K*
5	$\sim 10^{-12}$	10.9
6	$\sim 10^{-5}$	10.05

The samples obtained in experiment 5 were found to contain appreciable amounts of radio-cadmium (7.2 ± 0.5 hr.), and an approximate value for the distribution ratio of cadmium between *s*-amyl alcohol and ammonium thiocyanate solution was obtained ($K = 0.15$). Qualitative experiments with inactive cadmium salts in ordinary amounts showed a similar behavior.

The chemical identity of the seven and two-tenths-hour period here obtained was established by separating cadmium, manganese and cobalt from a new sample by adding carriers for the radio-elements and precipitating each in a conventional manner. The seven and two-tenths-hour period was found in the cadmium precipitate, and its radioactive properties were substantially the same as those reported by Ridenour, Delsasso, White and Sherr,[3] who produced this radioactive body by bombarding silver with protons.

IV. Distribution Ratios of Several Metallic Halides between Ether and Hydrochloric Acid

Since the hydrochloric acid used in the experiments listed in Table I had been shaken with ether several times, its quantitative composition was not accurately known. A series of experiments was performed in which the composition of the two phases could be easily and accurately reproduced. In these experiments the concentration of the substance whose distribution ratio was being measured was always small, but no effort was made to remove all traces of the element before the bombardment.

Experimental Details.—Hydrochloric acid of known concentration (standardized with anhydrous sodium carbonate) was shaken with an equal volume, at 20°, of dried ether. The heat of mixing was removed by cooling in a thermostat at 20°, and the two liquid phases were used at the compositions thus obtained. Experiments with gallium chloride were made in the manner already described except that traces of gallium originally present in the c. p. zinc chloride were not removed before bombardment. Measurements on ferric chloride were made in the presence of 0.01 *M* inactive iron. Experiment 14 with cobaltous chloride was made from a very active sample of long-lived radio-cobalt in which inactive cobalt was also present to the extent of about 10^{-7} mole per liter of solution. The ether and aqueous phases were evaporated and compared. Experiment 15 was carried out in the same manner with two and six-tenths-hour radio-manganese and the result checked by colorimetric experiments with inactive manganous chloride.

Results.—The results of these experiments are presented in Table III. The distribution ratio, *K*, for gallium chloride is seen to reach a maximum at about 5.5 *N* as originally reported by Swift.[4] His values do not agree very well with those in Table III, however, perhaps because his method of preparing the ether-saturated hydrochloric acid differed from that used in the present research. Experiments 12 and 13 were carried out in order to determine whether any marked

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[3] Ridenour, Delsasso, White and Sherr, *Phys. Rev.*, **53**, 770 (1938).

[4] Swift, This Journal, **46**, 2375 (1924).

TABLE III

DISTRIBUTION RATIOS OF SEVERAL METALLIC HALIDES BETWEEN ETHER AND HYDROCHLORIC ACID AT 20°

Expt.	Subst.	Half-life	[HCl], *N*	*K*
7	$GaCl_3$	83 hr.	6.50	10.6
8	$GaCl_3$	83 hr.	6.00	35.8
9	$GaCl_3$	83 hr.	5.50	53.8
10	$GaCl_3$	83 hr.	5.00	52.2
11	$GaCl_3$	83 hr.	3.97	4.9
12	$FeCl_3$	47 da.	6.00	31
13	$FeCl_3$	47 da.	5.00	23
14	$CoCl_2$	Long	5.5	$\sim 10^{-4}$
15	$MnCl_2$	2.6 hr.	6.0	$\sim 10^{-4}$

difference existed between the distribution ratios of ferric and gallium chlorides. Although experimental difficulties rendered the results from ferric chloride rather uncertain, there appears to be a marked difference between the results obtained for the two trichlorides. The somewhat anomalous behavior of ferric chloride in distribution processes noted by Dodson, Forney and Swift[5] was observed in these experiments, and was taken into account in calculating the distribution coefficients given in Table III. No elements other than iron were found to display anomalous behavior of this sort.

The completeness with which cobaltous chloride and manganous chloride may be held in the aqueous layer during an extraction is shown by the results of experiments 14 and 15. The values of *K* obtained in these two experiments may be regarded as upper limits.

Discussion.—It has been shown at ordinary concentrations that the activity coefficient of an ion in aqueous solution is determined by the ionic strength of the solution surrounding it and not by its own particular concentration. The results presented in Tables I and II may be considered as experimental evidence supporting this proposition at extremely low concentrations, since the ionic strength was essentially the same at the two concentrations studied. In the ether phase, also, the activity must have remained proportional to the concentration at the lowest concentrations attained, a result to be attributed, no doubt, to the presence of a relatively large amount of hydrochloric acid dissolved in the ether.

A result of considerable interest was obtained during one of the experiments with radio-cobalt and radio-cadmium. When a hydrochloric acid solution containing traces of radio-cobalt and radio-cadmium together with inactive iron in relatively enormous concentration was shaken with ether, the iron was readily and almost completely removed. The ether extract, however, showed no detectable radioactivity, indicating that the ether in removing 10^8 times as much iron as there was cobalt or cadmium in the solution showed no tendency to carry with it the other components of the solution. As a means of separating certain pairs of substances, extraction processes are evidently much superior to ordinary precipitation processes.

During the course of the experiments with radio-gallium a radioactive substance of half-life roughly seven and one-half hours was observed in addition to the well-known sixty-eight-minute and eighty-three-hour gallium isotopes. A description of the radioactive properties of the seven and one-half-hour body will be published elsewhere, but it is desired to note here that its chemical identity was established by showing that the distribution ratio of its chloride between ether and hydrochloric acid was always the same as that observed under the same conditions for the other radioactive isotopes of gallium present at the same time. This constitutes very strong evidence that the seven and one-half-hour period is due to an isotope of gallium rather than to some impurity present in the bombarded zinc.

The facts here presented indicate that in certain cases extraction processes may be used to advantage in the separation and identification of artificially produced radioactive elements. The advantages of such methods over the more conventional precipitation processes are: (1) no "carrying down" of unsuspected radioelements in unpredictable ways; (2) high concentration of the radioactive substance in the evaporated extract, thus eliminating self-absorption of the radiation and changes in the physical properties of the sample on standing; (3) chemical identification of the radioactive element by its distribution ratio, particularly if other known radioactive isotopes of the element are present. Extraction processes employing ammonium thiocyanate and amyl alcohol are of less value because they are less specific in their action.

We are greatly indebted to Professor E. O. Lawrence of the Department of Physics and to the staff of the Radiation Laboratory for the preparation of the radioactive substances used in this research.

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(5) Dodson, Forney and Swift, THIS JOURNAL, 58, 2573 (1936).

Summary

1. The distribution of minute quantities (*ca.* $10^{-12} - 10^{-15}$ g.) of soluble substances between liquid phases is shown in the cases studied to be quantitatively the same as that observed for the same substances in ordinary small concentrations.

2. Distribution ratios of several metallic halides between ether and hydrochloric acid are determined at low concentrations by the use of radioactive substances.

3. It is shown that the technique here employed may be of use in separating and identifying artificially prepared radioactive substances without the use of a non-radioactive carrier.

BERKELEY, CALIFORNIA RECEIVED JULY 19, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERISTY OF ILLINOIS]

Infrared Absorption Studies. VII. Complex Formation Due to Hydrogen Bonding

BY A. M. BUSWELL, W. H. RODEBUSH AND M. F. ROY

In an earlier paper[1] a considerable discussion was given of the conditions under which hydrogen bonding might occur. It was observed that for a hydrogen atom to be capable of forming a "bond" it must be active to a degree (*i. e.*, ionizable in the proper solvents). Furthermore, a generalization due to Venkateswaran[2] was noted. This generalization is that the shift of the fundamental absorption band when hydrogen forms a bond is the greater, and the band itself is the broader, the more active the hydrogen. In order to test the generalizations above it seemed to be desirable to examine compounds containing hydrogen that lay at either extreme of the range of activity. The two which seemed best suited for this purpose are chloroform and hydrogen chloride.

Ether Hydrochloride.—The existence of the ether–hydrogen chloride complex has been known for a long time and it was formerly characterized by organic chemists as an oxonium compound. More recently it has been recognized that it must be in the nature of a hydrogen bonded complex

$$R_2O \longleftarrow HCl$$

Of course by analogy with ammonium compounds, it might be supposed to be ionic in character. Undoubtedly a solution of hydrogen chloride in ether does show some conductance but the amount of ionization cannot be appreciable in a solvent of low dielectric constant for ions of small radius, and no typical salt-like crystal is formed as is the case with ammonium chloride.

Recently a number of spectroscopic studies have tended to confirm the foregoing conclusions. Walkenstein and Syrkin[3] have noted the absence of the Raman lines of hydrogen chloride in ether solutions. West and Edwards[4] have reported the absence of the harmonic at 1.7 μ for hydrogen chloride in ether. Similarly, West and Arthur[5] found no Raman lines for hydrogen chloride in ether solution.

Gordy and Martin[6] have observed the infrared spectrum of hydrogen chloride in ether, dioxane, and ethyl acetate and have found a broad intense band around 4 μ which they attribute to hydrogen bonding between the hydrogen chloride and the solvent.

In the investigation just mentioned the substance to which the hydrogen chloride bonds is used as the solvent. Since the solubility of hydrogen chloride is not large, this procedure has the obvious disadvantage of introducing an excess of solvent and hence a heavy absorption due to C–H in the region of the H–Cl absorption. It is necessary to work with thin layers of solution and as a result it is not possible to make definite observations upon the H–Cl vibration.

In our work we have avoided the above difficulty by using long cells containing a dilute solution of hydrogen chloride and ether in carbon tetrachloride. By changing the concentration of both hydrogen chloride and ether it is possible to produce and observe marked changes in the degree of association between the two substances.

Experimental

An 0.08 molal solution of ether in carbon tetrachloride was saturated with hydrogen chloride under a pressure slightly greater than atmospheric.

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[1] Article No. VI of this series, THIS JOURNAL, **60**, 2444 (1938).

[2] C. S. Venkateswaran, *Proc. Indian Acad.*, **7**, 13 (1938).

[3] M. Walkenstein and J. K. Syrkin, *Nature*, **139**, 288 (1937).

[4] W. West and R. T. Edwards, *J. Chem. Phys.*, **5**, 18 (1937).

[5] W. West and P. Arthur, *ibid.*, **5**, 10 (1937).

[6] W. Gordy and P. C. Martin, *ibid.*, **5**, 1075 (1937).

This solution was then diluted with carbon tetrachloride to the required concentrations and the ratio of the absorption of the solution to the absorption of a solution containing the same amount of ether but no hydrogen chloride was recorded. The hydrogen chloride concentration was determined for each solution by titration of a sample taken at the time the cell was filled. It was not possible in this procedure to maintain absolute constancy for the product of concentration times cell length. Molal absorption coefficients are plotted for the hydrogen chloride in Figs. 1 and 2.

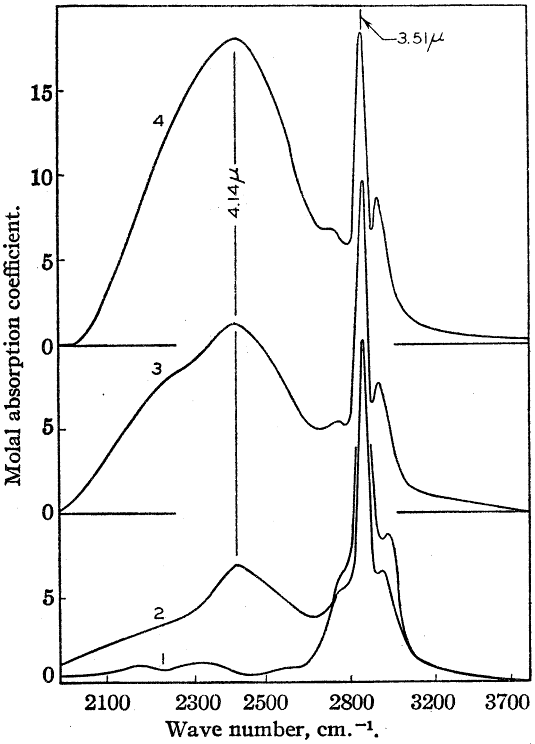

Fig. 1.—(1) 0.129 *M* HCl in CCl_4 *vs.* CCl_4 in 0.158-cm. cell; (2) 0.0264 *M* HCl in 0.02 *M* ether *vs.* 0.02 *M* ether in 0.640-cm. cell; (3) 0.0687 *M* HCl in 0.04 *M* ether *vs.* 0.04 *M* ether in 0.325-cm. cell; (4) 0.154 *M* HCl in 0.08 ether *vs.* 0.08 *M* ether in 0.158-cm. cell.

Discussion of Results

In all of the absorption curves (Fig. 1) for hydrogen chloride in carbon tetrachloride solutions of ether, the hydrogen chloride fundamental is quite evident at 3.51 μ. For the most concentrated solution of both hydrogen chloride and ether (Curve 4), a broad and intense band with a maximum at 4.14 μ is observed. As the concentrations of the hydrogen chloride and ether are decreased simultaneously (Curves 3 and 2), this band decreases in intensity and approaches the absorption for hydrogen chloride itself (Curve 1).

The inference is that hydrogen bonding between the hydrogen chloride and ether molecules causes a shift of the hydrogen chloride fundamental to 4.14 μ. As the concentrations are diminished the amount of H-bonding is decreased and the 4.14 μ band is correspondingly less intense.

The intensity of the hydrogen chloride fundamental decreases slightly as the concentrations increase, but this decrease is not enough to be given any particular significance.

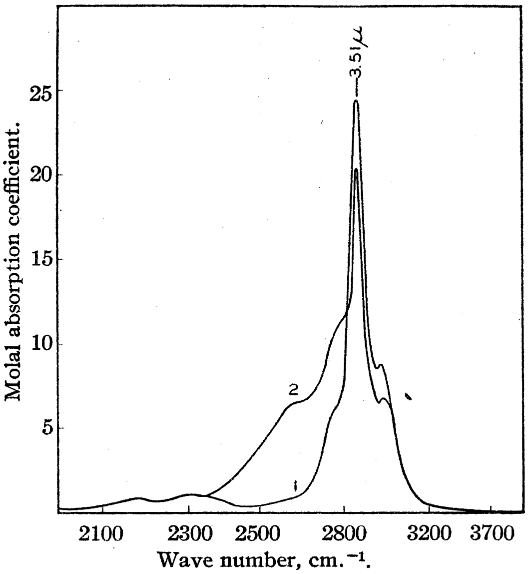

Fig. 2.—(1) 0.129 *M* HCl in CCl_4 *vs.* CCl_4 in 0.158-cm. cell; (2) 0.150 *M* HCl in 0.2 *M* anisole *vs.* 0.2 *M* anisole in 0.158-cm. cell.

The absorption of hydrogen chloride in the carbon tetrachloride solution of anisole is only slightly different from that for hydrogen chloride in carbon tetrachloride (Fig. 2), although the concentrations of both the hydrogen chloride and anisole are greater than the highest ones used in the case of ether. The absorption on the long wave side of the hydrogen chloride fundamental is somewhat increased but there is no intense absorption as there was even at the lower concentrations of ether.

It appears that there is a smaller tendency for the anisole to act as donor in the formation of hydrogen bonds than is the case with ether.

Hydrogen Bonding Involving Chloroform.—The tendency of chloroform to form complexes with a large number of substances such as ethers and ketones has been recognized by many investigators. Recently Huggins[7] has reviewed this evidence and explained it as due to hydrogen bonding. More recently Zellhoefer, Copley and Marvel[8] have studied exhaustively the tendency of chloroform to form complexes by the very simple method of solubility measurements and have adduced an enormous amount of evidence in favor of the activity of the hydrogen in chloroform. Since the hydrogen in chloroform is probably the least active of any hydrogen which is known to form bonds, it may be expected according to the rule of Venkateswaran that the shift in absorption would be so small as to be difficult of observation. Our first experiments showed that this is so, particularly with a molecule such as ether which has a strong C–H absorption. For that reason a considerable amount of our work was done with quinoline in which the absorption due to the aromatic C–H is less and is located at a somewhat different wave length than that for chloroform.

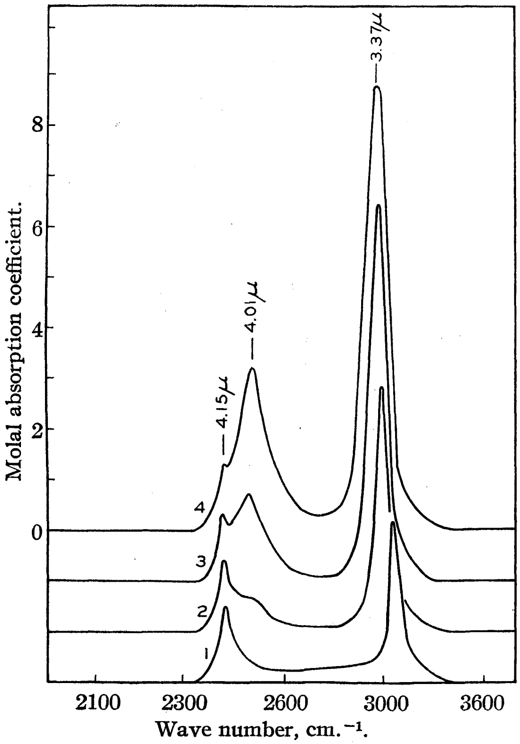

Fig. 3.—Quinoline–$CHCl_3$: (1) 4 *M* $CHCl_3$ in CCl_4 *vs.* CCl_4 in 0.0374-cm. cell; (2) 0.25 *M* $CHCl_3$–0.25 *M* quinoline *vs.* 0.25 *M* quinoline in 0.640-cm. cell; (3) 1 *M* $CHCl_3$–1 *M* quinoline *vs.* 1 *M* quinoline in 0.158-cm. cell; (4) 4 *M* $CHCl_3$–4 *M* quinoline *vs.* 4 *M* quinoline in 0.0374-cm. cell.

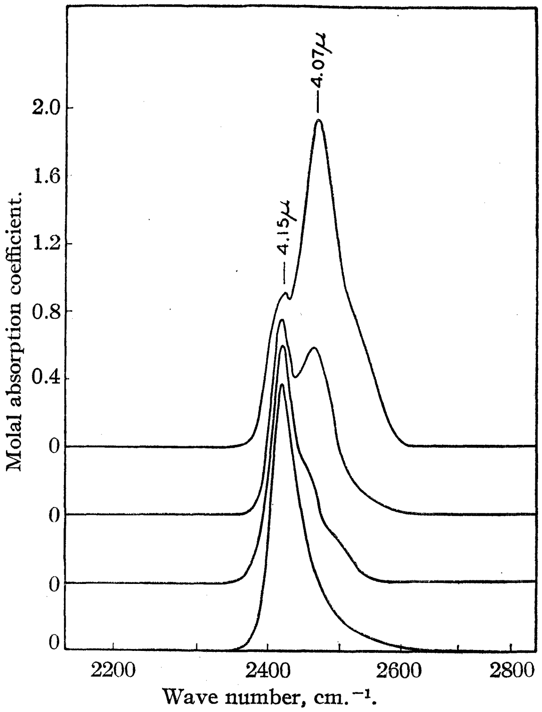

Fig. 4.—Acetone–$CHCl_3$: (1) 4 *M* $CHCl_3$ in CCl_4 *vs.* CCl_4 in 0.0374-cm. cell; (2) 0.25 *M* $CHCl_3$–0.25 *M* acetone *vs.* 0.25 *M* acetone in 0.640-cm. cell; (3) 1 *M* $CHCl_3$–1 *M* acetone *vs.* 1 *M* acetone in 0.158-cm. cell; (4) 4 *M* $CHCl_3$–4 *M* acetone *vs.* 4 *M* acetone in 0.0374-cm. cell.

Solutions containing various concentrations of chloroform and quinoline, chloroform and acetone, and chloroform and ether in carbon tetrachloride were studied. In Figs. 3, 4 and 5 the absorption due to chloroform only is plotted since the control cell in these experiments contained not the pure solvent but a solution containing the same concentration of the substance other than the chloroform of the pair that was being studied. In the solutions of chloroform and quinoline it was possible to observe the C–H absorption of the chloroform with precision. At low concentrations the absorption was of the same wave length and intensity as for solutions of chloroform alone in carbon tetrachloride. As the concentration was increased the absorption shifted toward longer wave lengths and increased in intensity. In a solution 4 molal with respect to chloroform and quinoline, the maximum absorption is at 3.37 μ as compared with 3.28 μ for chloroform alone and the height of the peak has increased nearly three-fold. This would appear to be conclusive evidence for the formation of a hydrogen bond between chloroform and quinoline. Upon inspection of Fig. 3,

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[7] M. L. Huggins, *J. Org. Chem.*, **1**, 407 (1936).

[8] G. F. Zellhoefer, M. J. Copley and C. S. Marvel, This Journal, **60**, 1337 (1938).

one's attention is attracted immediately to the absorption at 4.15 μ. This absorption increases with increasing concentration but is shifted to shorter wave lengths, which is contrary to any previous behavior noted. The positive identification of this relatively weak absorption is necessarily not easy. It is presumably an overtone or combination frequency and, since it is about the same for bromoform, one suspects it to be connected with the hydrogen.

Voge and Rosenthal[9] have assigned the value 1225 cm.$^{-1}$ as the frequency in wave numbers of the perpendicular vibration in chloroform which involves mainly the hydrogen atom; 2400 cm.$^{-1}$ or 4.15 μ would therefore be a reasonable value for the second harmonic. The fact that this frequency is affected by complex formation is confirmatory of the foregoing. It is easy from a rather crude mechanical picture of the hydrogen bond to argue that, while the stretching frequency should be lowered, the bending frequency should be increased, when a hydrogen bond is formed. However, these conclusions must be admittedly tentative until confirmed by further study.

In solutions of acetone and quinoline the same results confirmatory of complex formation are obtained but they are of much smaller magnitude. While the fundamental C–H frequency shows marked increase in height, the shift in wave length is barely observable. Similarly the behavior of the 4.15 μ absorption is less striking. In solutions of ether and chloroform it is impossible because of the strong absorption of the ether to observe the C–H fundamental but the harmonic at 4.15 μ shows quite clearly the same behavior as for chloroform and quinoline.

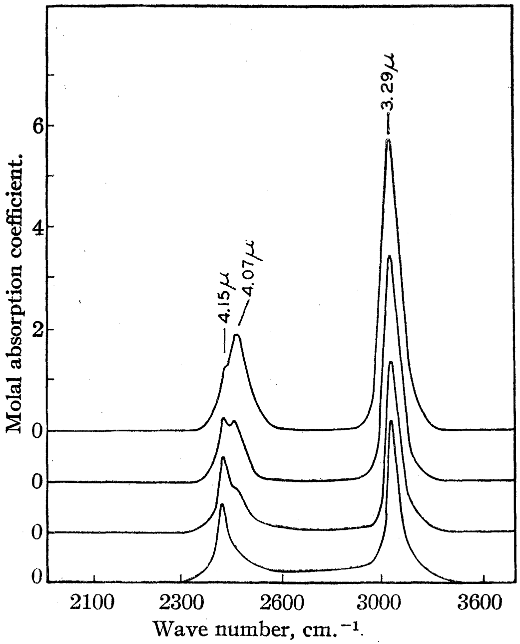

Fig. 5.—Ether–$CHCl_3$: (1) 4 *M* $CHCl_3$ in CCl_4 *vs.* CCl_4 in 0.0374-cm. cell; (2) 0.25 *M* $CHCl_3$–0.25 *M* ether *vs.* 0.25 *M* ether in 0.640-cm. cell; (3) 1 *M* $CHCl_3$–1 *M* ether *vs.* 1 *M* ether in 0.158-cm. cell; (4) 4 *M* $CHCl_3$–4 *M* ether *vs.* 4 *M* ether in 0.0374-cm. cell.

Summary

The tendency of hydrogen chloride and chloroform toward complex formation with ether and other substances through hydrogen bonding has been investigated. These two compounds stand at opposite extremes in the scale of activity of the hydrogen. The rule of Venkateswaran has been verified for the shift of the fundamental frequency of the hydrogen. An absorption band which shifts to shorter wave lengths upon bond formation has been observed in the case of chloroform and this absorption has been ascribed tentatively to the second harmonic perpendicular vibration of the hydrogen.

URBANA, ILLINOIS

RECEIVED JULY 20, 1938

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[9] H. H. Voge and J. E. Rosenthal, *J. Chem. Phys.*, **4**, 137 (1936).

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY OF THE UNIVERSITY OF CALIFORNIA]

Methyl Tetronate, Methyl α-Chlorotetronate, Methyl α-Bromotetronate and Methyl α-Iodotetronate

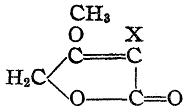
BY W. D. KUMLER

The tetronic acids are closely related structurally to ethyl acetoacetate and may be considered as derivatives of this compound. It is well known that when ethyl acetoacetate is treated with sodium and an alkyl halide the resulting substituted ethyl acetoacetate usually has the alkyl group attached to carbon. It was of interest to make some esters of the tetronic acids to see whether the alkyl group is attached to oxygen or to carbon. The first attempts at esterification of α-bromotetronic acid using dry hydrogen chloride and absolute alcohol failed,[1] and α-chlorotetronic acid resulted from the reaction. In a later experiment after passing hydrogen chloride through the solution for two weeks some evidence of esterification was obtained but the compound was not isolated in a pure state. Esterification by treating sodium α-bromotetronate with alkyl halides was not successful except in the case of *p*-nitrobenzyl bromide.[2] Diazomethane, however, reacted rapidly with all of the acids and the methyl esters that resulted could be isolated in a relatively pure state.

The carbon and hydrogen analysis in the case of methyl tetronate and the halogen analysis in the case of the other esters correspond to a lactone structure for the compounds and do not fit a hydroxycarboxylic acid ester structure. A methoxy estimation was carried out on the compounds to determine the position of the methyl group. If it is on the oxygen the percentage of methoxy found would be expected to be near the theoretical. If it is on the carbon the percentage found should be zero. The percentage of methoxy found shows that the compounds are oxygen esters.

	% Methoxy	
	Found	Calcd.
Methyl tetronate	25.6	27.2
Methyl α-chlorotetronate	19.6	20.9
Methyl α-bromotetronate	15.8	16.0
Methyl α-iodotetronate	12.6	12.9

The structure of these esters is then



where X is hydrogen, chlorine, bromine or iodine. This structure conforms to that found for the free acids and their salts.[2]

Experimental

The methoxy estimations were carried out using a semi-micro adaptation of the method of the British Pharmacopoeia, 1932. No empirical corrections were made for the incomplete precipitation of the alkyl iodide.[3]

The esters were prepared by suspending the corresponding acids in dry ether cooled to 0° and adding an excess of a solution of diazomethane in dry ether, also cooled to 0°. The excess diazomethane and ether was then evaporated on a steam-bath and the resulting ester crystallized from dioxane or methyl alcohol until a constant melting point was obtained.

Diazomethane was prepared from nitrosomethyl urea by Arndt's method.[4]

Methyl Tetronate.—M. p. 63°. *Anal.* Calcd. for $C_5H_6O_3$: H, 5.26; C, 52.6. Found: H, 4.96; C, 52.3.[5]

Methyl α-Chlorotetronate.—M. p. 66°. *Anal.* Calcd. for $C_5H_5O_3Cl$: Cl, 23.9. Found: Cl, 23.5.

Methyl α-Bromotetronate.—M. p. 116°. *Anal.* Calcd. for $C_5H_5O_3Br$: Br, 41.4. Found: Br, 41.1.

Methyl α-Iodotetronate.—M. p. 158°. *Anal.* Calcd. for $C_5H_5O_3I$: I, 52.9. Found: I, 52.6.

Summary

Methyl tetronate, methyl α-chlorotetronate, methyl α-bromotetronate and methyl α-iodotetronate have been made by the action of diazomethane on the corresponding acids. A methoxy estimation has been made on the compounds and this indicates that the methyl group is attached to oxygen and not to carbon. The structure of these esters is in accord with that previously found for the free acids and their salts.

SAN FRANCISCO, CALIF. RECEIVED AUGUST 16, 1938

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[1] Kumler, THIS JOURNAL, **60**, 857 (1938).

[2] Kumler, *ibid.*, **60**, 859 (1938).

[3] Niederl and Niederl, "Organic Quantitative Micro-Analysis,' John Wiley and Sons, Inc., New York, N. Y., 1938, pp. 192, 198.

[4] *Org. Syntheses*, **15**, 3 (1935).

[5] The author is indebted to Professor P. L. Kirk's laboratory of the University of California Medical School forcarrying out the micro-combustion on methyl tetronate.

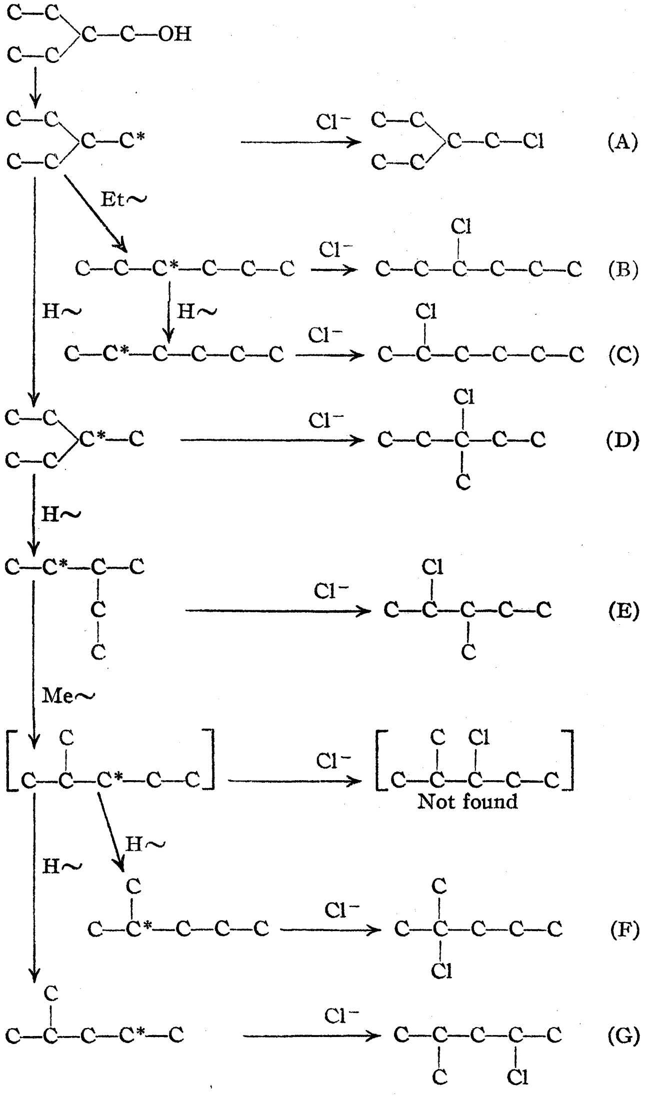
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Alkyl Chlorides Obtained from 2-Ethyl-1-butanol

BY FRANK C. WHITMORE AND F. A. KARNATZ

In connection with work in this Laboratory on the course of rearrangements,[1] it was decided to study the conversion of an alcohol of the type R_2CHCH_2OH to the corresponding chloride. While considerable work has been done on the rearrangement of hydrogen during the preparation of halides,[2] there are very few recorded cases of the rearrangement of the carbon skeleton during the replacement of hydroxyl by halogen.[3] Mainly rearranged halides were obtained from *t*-butyl- and *t*-butylmethyl-carbinols.[4] Wallis and Bowman[5] found no primary chloride in the product of the reaction of 2-methyl-2-phenyl-1-butanol with thionyl chloride. No instance of skeletal rearrangement during the preparation of halides from an aliphatic carbinol of the type R_2CHCH_2OH was found in the literature.

When 2-ethyl-1-butanol was treated with zinc chloride and hydrochloric acid,[6] a complex mixture of isomers was obtained in 70–80% yield. The presence of the following hexyl chlorides was established: (A) 2-ethyl-1-chlorobutane, (B) 3-chlorohexane, (C) 2-chlorohexane, (D) 3-methyl-3-chloropentane, (E) 3-methyl-2-chloropentane, (F) 2-methyl-2-chloropentane and (G) 4-methyl-2-chloropentane. The following mechanism based on the concepts current in this Laboratory[1] is given as a possible explanation of the formation of these products. The carbon with only 6 electrons is indicated as C*. The transitory existence is assumed for only one fragment for which the corresponding chloride was not found, namely, $(CH_3)_2CHC^*HCH_2CH_3$. There is strong evidence for its momentary presence in the finding of two chlorides, the structures of which can be derived from it by simple migration of hydrogen. The failure of the formation of a chloride $(CH_3)_2CHCHClCH_2CH_3$ agrees with results obtained by F. Johnston[7] of this Laboratory in which attempts to form chlorides of this type from the corresponding alcohol gave almost entirely the tertiary chloride analogous to (F).



It was necessary to determine whether these rearrangements took place chiefly during, rather than after, the replacement of hydroxyl by chlorine. This was accomplished by putting a

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(1) *Cf.* THIS JOURNAL, **54**, 3274 (1932).

(2) Brunel, *Ber.*, **44**, 1003 (1911); Michael and Zeidler, *Ann.*, **385**, 227 (1911); *ibid.*, **393**, 110 (1912); Shoesmith and Mackie, *J. Chem. Soc.*, 2336 (1928); Noller, THIS JOURNAL, **53**, 639 (1931).

(3) Demjanov, *J. Chem. Soc.*, **98**, 838 (1910); Kizhner, *J. Russ. Phys.-Chem. Soc.*, **40**, 994–1015; *ibid.*, **43**, 1157–1163; Favorskii, *ibid.*, **50**, 43–80 (1918).

(4) Whitmore and Rothrock, THIS JOURNAL, **54**, 3431 (1932); *ibid.*, **55**, 1106 (1933).

(5) Wallis and Bowman, *J. Org. Chem.*, **1**, 383 (1936).

(6) Compare Norris and Taylor, THIS JOURNAL, **46**, 753 (1924).

(7) Whitmore and Johnston, *ibid.*, **60**, 2265 (1938).

sample of pure 2-ethyl-1-chlorobutane through exactly the same treatment that gave the above mixture from the alcohol. While there was some isomerization of the chloride, over 70% of it was recovered unchanged.

No rearranged halides were obtained by treatment of 2-ethyl-1-butanol with thionyl chloride, 2-ethyl-1-chlorobutane of high purity being isolated in over 80% yield. This result is of interest in contrast to the work of Wallis and Bowman[5] and also to the behavior of neopentyl alcohol, which gives only a 4% yield of unrearranged chloride when treated with thionyl chloride and pyridine.[8]

Experimental

Purification of 2-Ethyl-1-butanol.—The 2-ethyl-1-butanol used in this research was kindly furnished by the Carbide and Carbon Chemicals Corporation. It was purified by two fractionations through an efficient column of the total condensation type,[9] 107 × 2.1 cm., packed with glass helices. A total of 4605 g. of pure carbinol, b. p. 145° (727 mm.) –146° (732 mm.), $n^{20}_{\rm D}$ 1.4220–1, d^{20}_4 0.8326, was obtained from 12,270 g. of the commercial material; yield 37.5%. This gave an α-naphthylurethan, m. p. 63.5–64.5°, which melted at 63–64.5° when mixed with the α-naphthylurethan, m. p. 63–64°, made from a known sample of 2-ethyl-1-butanol obtained by the hydrogenation of ethyl diethylacetate.[10]

Anal. Calcd. for $C_{17}H_{21}NO_2$: N, 5.17. Found: N, 5.22.

Treatment of 2-Ethyl-1-butanol with Thionyl Chloride.—The method of Darzens[11] was used. Addition of 167 g. (1.4 moles) of thionyl chloride to a solution of 102 g. (1 mole) of 2-ethyl-1-butanol in 79 g. (1 mole) of dry pyridine required two hours. The mixture was heated for three and one-half hours at 60–90°; sulfur dioxide was evolved. The crude product was washed with dilute hydrochloric acid, dried with anhydrous potassium carbonate and fractionated to give 99 g. of pure 2-ethyl-1-chlorobutane (82% yield), b. p. 88° (225 mm.), $n^{20}_{\rm D}$ 1.4230, d^{20}_4 0.8914. Conversion to the Grignard compound and treatment with oxygen gave 2-ethyl-1-butanol; α-naphthylurethan, m. p. and mixed m. p., 63–64°.

The only constants found[12] for 2-ethyl-1-chlorobutane are: b. p. 125–127°, $d^{23.5}_{23.5}$ 0.881. The compound was obtained in only 11% yield by the action of 45% hydrochloric acid in a sealed tube at 100°. Rothstein[13] treated 2-ethyl-1-butanol with thionyl chloride and pyridine but gave no data for the product.

Treatment of 2-Ethyl-1-butanol with Hydrochloric Acid and Zinc Chloride.—Many runs were made in order to obtain sufficient product for fractionation; a typical run by our technique is described. One mole, 102 g., of 2-ethyl-1-butanol was added to a solution of 1.25 moles, 171 g., of fused zinc chloride in 2 moles, 202 g., of concentrated hydrochloric acid in a 3-necked flask fitted with a reflux condenser, mercury-seal stirrer, and gas inlet tube leading to the bottom of the flask. The flask was heated in a bath to 80–85° for six and one-half hours. A slow stream of hydrogen chloride was passed into the mixture for the last four hours.

The dark halide layer was separated and washed with 15 cc. of water and 10 cc. of 10% sodium carbonate solution; the color faded markedly on washing. The product was dried with anhydrous sodium sulfate and anhydrous potassium carbonate, and was fractionated from fresh carbonate at 160 mm. pressure to give several fractions.

Fraction	Wt., g.	B. p. (160 mm.), °C.	$n^{20}_{\rm D}$
1	9.0	56–67.7	1.4155
2	16.3	67.7–68.5	1.4180
3	16.6	68.5–69.5	1.4190
4	10.0	69.5–69.6	1.4196
5	14.9	69.6–70.5	1.4198
6	7.4	70.5–71.6	1.4198
7	5.9	71.6–72.7	1.4198
8	7.0	72.7–74.0	1.4195
9	6.5	74.0–75.0	1.4195
10	6.2	75.0–76.5	1.4192
11	3.0	?	1.4198
12	3.0	Residue	
	105.8		

The yield of mixed hexyl chlorides, b. p. 67.7–76.5° (160 mm.), was 90.8 g., or 75%.

The fractions from five such runs were refractionated by parts three times at 160 mm. pressure. In the final distillation, referred to as Distillation B, 297 g. of chlorides was separated into 44 fractions.

Identification of 2-Methyl-2-chloropentane (F).—Fraction 2 from Distillation B, 5.3 g., b. p. 63.5–64.0° (160 mm.), $n^{20}_{\rm D}$ 1.4138, was converted to the Grignard reagent and this was treated with phenyl isocyanate in ether solution. The dimethyl-*n*-propylacetanilide was identified by m. p. and mixed m. p. 70.5–74°.

Anal. Calcd. for $C_{13}H_{19}NO$: N, 6.84. Found: N, 6.89.

The known sample was prepared in the same way from known 2-methyl-2-chloropentane, b. p. 64.5–64.7° (160 mm.), $n^{20}_{\rm D}$ 1.4126, obtained by the action of hydrochloric acid on the corresponding carbinol.

Similarly, fraction 4 from Distillation B, 4.8 g., b. p. 64.7–65.5° (160 mm.), $n^{20}_{\rm D}$ 1.4140, was converted to the Grignard reagent and this was treated with α-naphthyl isocyanate. The α-naphthalide of dimethyl-*n*-propylacetic acid was identified by m. p. and mixed m. p. 116–118°.

Anal. Calcd. for $C_{17}H_{21}NO$: N, 5.49. Found: N, 5.35.

Identification of 4-Methyl-2-chloropentane (G).—Fractions 9–14 from Distillation B, 35.9 g., b. p. 65.5–67.5° (160 mm.), $n^{20}_{\rm D}$ 1.4150–74, were converted to the Grignard reagent and this was treated with oxygen. The crude product remaining after distillation of the ether was heated with a few crystals of iodine[14] to dehydrate any tertiary

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[8] Whitmore and Karnatz, unpublished work.

[9] Whitmore and Lux, THIS JOURNAL, **54**, 3451 (1932); Wilson, Parker and Laughlin, *ibid.*, **55**, 2795 (1933).

[10] Kindly done by Prof. Homer Adkins of the University of Wisconsin.

[11] Darzens, *Compt. rend.*, **152**, 1314 (1911).

[12] Fourneau and Matti, *J. pharm. chim.*, [8] **14**, 513 (1931).

[13] Rothstein, *Bull. soc. chim.*, [5] **2**, 83 (1935).

[14] Hibbert, THIS JOURNAL, **37**, 1748 (1915).

carbinols. The residue was dried and was distilled from an 8-cc. distilling flask to obtain a fraction, weight 1.4 g., b. p. 115–128° (734 mm.), $n^{20}\mathrm{D}$ 1.4140. The α-naphthylurethan prepared from this material was found to melt at 94–95° after 2 crystallizations from ligroin and one from dilute alcohol. A mixture with the known α-naphthylurethan of 4-methyl-2-pentanol[15] of m. p. 93.5–94.5°[16] melted at 93.5–95°.

Another sample of crude carbinol, weight 1.68 g., b. p. 100–130° (735 mm.), was obtained in the same way from a similar cut of mixed chlorides, weight 65.0 g., b. p. 65.5–68.0° (160 mm.), $n^{20}\mathrm{D}$ 1.4158–80, from another distillation. This carbinol was oxidized to 4-methyl-2-pentanone with sulfuric acid and dichromate; semicarbazone, m. p. and mixed m. p. 127–131°. The known derivative was obtained from the ketone, b. p. 111–113° (738 mm.), $n^{20}\mathrm{D}$ 1.3967, prepared by the oxidation of synthetic 4-methyl-2-pentanol, b. p. 131° (738 mm.), $n^{20}\mathrm{D}$ 1.4111.

Identification of 3-Methyl-3-chloropentane (D).—A sample of chlorides from the fractionation before Distillation B, b. p. 69.5° (160 mm.), $n^{20}\mathrm{D}$ 1.4202, was converted to the Grignard reagent and this was treated with phenyl isocyanate. Purification gave crystals melting at 86.5–88.5°. A mixture with methyldiethylacetanilide of m. p. 87.5–89° similarly prepared from known 3-methyl-3-chloropentane[17] melted at 86.5–88.5°.

Anal. Calcd. for $C_{13}H_{19}NO$: N, 6.84. Found: N, 7.01.

Identification of 3-Methyl-2-chloropentane (E).—Fractions 29, 31 and 32 of mixed chlorides from Distillation B, wt. 22.9 g., b. p. 71.1–73.3° (160 mm.), $n^{20}\mathrm{D}$ 1.4198–201, were converted to the Grignard reagent and this was treated with oxygen. The crude carbinols were heated with a crystal of iodine[14] for two and one-half hours. The residue was dried and fractionated: (Distillation C).

Fraction	Wt., g.	B. p., °C.	Press., mm.	$n^{20}\mathrm{D}$
1	0.9	51–110	735	1.3900
2	1.2	128–132	735	1.4166
3	2.8	132–133	735	1.4188
4	1.4	?	Reduced	1.4190
5	1.3	Residue		

Yield of secondary hexanols was 5.4 g., or 28% of the theoretical. The α-naphthylurethan prepared from fraction 3 was found to melt at 72–72.5° after four crystallizations from ligroin and one from dilute alcohol. A mixture with a known sample of the α-naphthylurethan of 3-methyl-2-pentanol of m. p. 74.5–75.5°[18] melted at 72–75°. The known specimen was obtained from synthetic 3-methyl-2-pentanol, b. p. 132–132.5° (726 mm.), $n^{20}\mathrm{D}$ 1.4206.

A 1-cc. sample of fraction 3 of the above hexanols was oxidized to the ketones, which were fractionated and converted to 2,4-dinitrophenylhydrazones. A series of crystallizations of these from dilute alcohol gave first the impure derivative for hexanone-3 and then, from the mother liquor, the 2,4-dinitrophenylhydrazone of 3-methyl-2-pentanone, m. p. 67–71°. A mixture with a known sample, m. p. 70.5–72.5°,[19] prepared from a sample of ketone made by oxidation of the synthetic carbinol, melted at 69–72°.

By the same methods, fractions 33–36 of mixed chlorides from Distillation B, 23.9 g., b. p. 69.5–74.5° (160 mm.), $n^{20}\mathrm{D}$ 1.4188–94, were converted to the ketones. These were shaken with 15 cc. of a saturated solution of sodium bisulfite (to remove 2-hexanone, see below), and the addition compound was separated from uncombined ketones by dissolving it in water and extracting this solution with ether. The ether solution yielded a *m*-nitrobenzoylhydrazone melting at 143.5–144.5°. A mixture with a sample of m. p. 145–146° obtained from the known 3-methyl-2-pentanone melted at 144–145°.

Anal. Calcd. for $C_{13}H_{17}N_3O_3$: N, 15.99. Found: N, 15.97.

Identification of 3-Chlorohexane (B).—Fractions 37, 39, 41 and 42 of mixed chlorides from Distillation B, 24.8 g., b. p. 73.5–76.5° (160 mm.), $n^{20}\mathrm{D}$ 1.4187, were converted to the carbinols through the Grignard reagent. Fractionation gave (Distillation D): 1–2, 2.2 g., 34–123° (732 mm.), $n^{20}\mathrm{D}$ 1.370; 3–4, 3.5 g., 124–133.5°, 1.4144–1.4178; 5–6, 5.8 g., 133.5–141°, 1.4186; residue, 1.8 g.

Fractions 4 and 5 failed to give an α-naphthylurethan. The remaining portions of fractions 2, 3 and 4 from Distillation C (described under 3-methyl-2-chloropentane) and fractions 4, 5 and 6 above were combined and oxidized to the ketones. Fractionation gave at 730 mm. (Distillation E): 1, 1.2 g., 67–113°, 1.3978; 2, 1.3, 113–117°, 1.4010; 3, 1.7, 117–124°, 1.4030; 4, 1.0, 124–126°, 1.4080; residue, 1.1 g.

Fraction 2 gave the 2,4-dinitrophenylhydrazone of 3-hexanone, m. p. and mixed m. p., 146.5–148.5°.

Anal. Calcd. for $C_{12}H_{16}N_4O_4$: N, 20.00. Found: N, 19.89.

The known specimen was prepared from the ketone obtained by the oxidation of synthetic (Grignard) 3-hexanol, b. p. 133–134° at 740 mm.

All of the material of the proper boiling range obtained from Distillation B was consumed in unsuccessful attempts to isolate a second derivative for 3-chlorohexane. Hence, it was necessary to make 4 additional runs of 2-ethyl-1-butanol with hydrochloric acid and zinc chloride and to refractionate the hexyl chlorides by parts through column A. A sample of these chlorides, weight 60.1 g., b. p. 74–76° (160 mm.), $n^{20}\mathrm{D}$ 1.4190–97, was converted to carbinols through the Grignard reagent. These were dried and fractionated at 734 mm. pressure to give 5 fractions, 33.2 g., b. p. 131–145° (734 mm.), $n^{20}\mathrm{D}$ 1.4176–1.4210. The carbinols were oxidized to the ketones, washed with sodium bisulfite solution and fractionated. A fraction was obtained, 0.9 g., 110° (733 mm.), $n^{20}\mathrm{D}$ 1.4010, which gave the semicarbazone of 3-hexanone, m. p. and mixed m. p., 110.5–111.5°.

Identification of 2-Chlorohexane (C).—Fraction 4 of the ketones from Distillation E (described under 3-chlorohexane) gave the 2,4-dinitrophenylhydrazone of 2-hexanone, m. p. and mixed m. p., 106–107°.

The aqueous solution of the sodium bisulfite addition compound described under the identification of 3-methyl-2-

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(15) Kindly furnished by F. Johnston of this Laboratory.

(16) Levene and Walti, *J. Biol. Chem.*, **94**, 369 (1931) give m. p. 86–89°; Brooks, THIS JOURNAL, **56**, 1999 (1934), gives m. p. 87–88°.

(17) Kindly furnished by D. E. Badertscher of this Laboratory.

(18) Cottle and Powell, THIS JOURNAL, **58**, 2270 (1936), give 72°.

(19) Drake and Veitch, *ibid.*, **57**, 2624 (1935), give 71.2°.

chloropentane was made alkaline with sodium carbonate and the liberated ketone was distilled. The semicarbazone prepared from this melted at 122–123.5°. A mixture with the known semicarbazone of 2-hexanone of m. p. 124–125° melted at 122.5–124°.

Identification of 2-Ethyl-1-chlorobutane (A).—Fraction 7 of the hexanols from Distillation D (described under 3-chlorohexane) gave the α-naphthylurethan of 2-ethyl-1-butanol, m. p. and mixed m. p. 63–64°.

Fraction 43 of the mixed chlorides from Distillation B, 13.5 g., b. p. 76.5–77.5° (160 mm.), $n^{20}\text{D}$ 1.4198, was shaken with 50 cc. of normal aqueous silver nitrate solution for three hours at room temperature to remove secondary and tertiary halides. The organic material was distilled from the mixture, separated, washed with carbonate solution, dried and fractionated. Treatment of the Grignard reagent with phenyl isocyanate gave crystals melting at 80.5–81.5°. Mixture with a known sample of β-ethylvaleranilide of m. p. 83–84° melted at 80.5–82.5°. The known specimen was prepared in the same way from a sample of 2-ethyl-1-chlorobutane made by the action of thionyl chloride on the carbinol.

Anal. Calcd. for $C_{13}H_{19}NO$: N, 6.84. Found: N, 6.93.

The other fractions were studied without obtaining any evidence for the presence of chlorides other than the seven identified.

Treatment of 2-Ethyl-1-chlorobutane with Zinc Chloride in Hydrochloric Acid.—One mole, 120.5 g., of 2-ethyl-1-chlorobutane, $n^{20}\text{D}$ 1.4228–30, prepared by the action of thionyl chloride and pyridine on 2-ethyl-1-butanol, was stirred vigorously with a solution of 1.25 moles, 171 g., of fused zinc chloride in 2 moles, 202 g., of concentrated hydrochloric acid at 79–87° for seven hours. The halide layer was separated, washed with water and carbonate solution, dried and fractionated. The yield of chlorohexanes recovered was 108.6 g., or 90.0% of the starting material. The yield of unchanged 2-ethyl-1-chlorobutane was 86.1 g.; this is 71.4% of the starting material and 79.2% of the recovered halides. The remainder was rearranged hexyl chlorides.

Approximation of the Percentage of Individual Hexyl Chlorides Present.—Only a rough estimate, based on fractionation data, can be given. 3-Methyl-3-chloropentane (D), present in 35–40% yield, was the most abundant isomer. 2-Chlorohexane (C), 2-methyl-2-chloropentane (F) and 3-methyl-2-chloropentane (E) were present in 5–10%; the remaining isomers, 1–5% each. It is quite possible that other hexyl chlorides, present in smaller quantities, were not identified.

Summary

1. 2-Ethyl-1-chlorobutane is produced by the action of thionyl chloride and pyridine on 2-ethyl-1-butanol without any detectable rearrangement.

2. The action of zinc chloride in hydrochloric acid solution on 2-ethyl-1-butanol gives at least seven different chlorohexanes, namely, 3-methyl-3-chloropentane, 2-methyl-2-chloropentane, 3-methyl-2-chloropentane, 4-methyl-2-chloropentane, 3-chlorohexane, 2-chlorohexane, and 2-ethyl-1-chlorobutane.

3. At least the major part of the rearrangements occurred during the formation of the chlorides.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Preparation and Properties of 2- and 3-Chloropentanes

BY FRANK C. WHITMORE AND F. A. KARNATZ

Much work has been done on the secondary chlorides and bromides of *n*-pentane.[1] In the present study, it was found that both 2-pentanol and 3-pentanol gave mixtures of 2- and 3-chloropentanes even with as mild treatment as the action of hydrogen chloride gas at room temperature. The amount of rearrangement was considerably less with 2-pentanol.

In order to obtain pure samples of 2- and 3-chloropentanes for the determination of physical constants, it was necessary to use thionyl chloride in the presence of pyridine.[2] There is evidence[3] that this reaction gives least rearrangement. Samples of the two chlorides were obtained, the properties of which showed a maximum difference; namely, for 2-chloropentane, $n^{20}\text{D}$ 1.4069 and d^{20}_{4} 0.8695, and for 3-chloropentane, $n^{20}\text{D}$

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(1) Wagner and Saizew, *Ann.*, **179**, 321 (1875); Przewalski, *J. Russ. Phys.-Chem. Soc.*, **41**, 464–469 (1909); Clough and Johns, *Ind. Eng. Chem.*, **15**, 1032 (1923); Norris and Taylor, THIS JOURNAL, **46**, 753 (1924); Grignard and Ono, *Bull. soc. chim.*, [4] **39**, 1589 (1926); Norris and Reuter, THIS JOURNAL, **49**, 2630 (1927); Sherrill, Otto and Pickett, *ibid.*, **51**, 3027 (1929); Sherrill, Baldwin and Haas, *ibid.*, **51**, 3036 (1929); Ayres, *Ind. Eng. Chem.*, **21**, 899 (1929); Boord and Soday, THIS JOURNAL, **55**, 3296 (1933); Tabern and Volwiler, *ibid.*, **56**, 1139 (1934); Shonle, *ibid.*, **56**, 2490 (1934); Hass and Weber, *Ber.*, **67**, 974 (1934); Underwood and Gale, THIS JOURNAL, **56**, 2118 (1934); Lauer and Stodola, *ibid.*, **56**, 1215 (1934); Hass, McBee and Weber, *Ind. Eng. Chem.*, **27**, 1190 (1935); Hass and Weber, *Ind. Eng. Chem.*, *Anal. Ed.*, **7**, 231 (1935).

(2) (a) Darzens, *Compt. rend.*, **152**, 1314 (1911); (b) Clark and Streight, *Trans. Roy. Soc. Can.*, **23**, 77 (1929).

(3) McKenzie and Clough, *J. Chem. Soc.*, **103**, 687 (1913); Gilman and Harris, *Rec. trav. chim.*, **50**, 1052 (1931); Kirner, THIS JOURNAL, **50**, 1958 (1928); Ref. 2a; also, unpublished work in this Laboratory.

1.4104 and $d^{20}{}_4$ 0.8795. The boiling points, 96.8 and 97.8°, are too close together to be of any significance as criteria of purity.

The stability of the chlorides to heat was established by heating samples of them in sealed tubes to 100° for forty-eight hours without obtaining any significant change in refractive index. However, it was found that either chloride could be isomerized to an equilibrium mixture of the two by shaking it with $ZnCl_2$–HCl solution at room temperature for seventy-two hours. The composition of this mixture was about 80% 2-chloropentane.

The physical constants determined were

	2-Chloropentane	3-Chloropentane
B. p., Cottrell, 760 mm., °C.	96.84–96.88	97.76–97.82
Freezing points, °C.	−137–139	−105–106
Density, $d^{20}{}_4$	0.8695	0.8795
Refractive index, $n^{20}\text{D}$	1.4069	1.4104
Viscosities at 20°, centistoke	0.5672	0.5845

Experimental

Preparation of 3-Chloropentane.—A solution of 1 mole, 88 g., of 3-pentanol, b. p. 114.5–114.9° (730 mm.), $n^{20}\text{D}$ 1.4100, prepared from methyl formate and ethylmagnesium bromide, in 1.1 mole, 87 g., of dry pyridine, b. p. 113.3–114.5° (735 mm.), was treated with 1.3 moles, 154.8 g., of thionyl chloride (Eastman Kodak Co.), in the cold, over a period of fifty minutes. A heavy white precipitate formed. When addition was complete the ice-bath was removed, and after an hour the flask was warmed in a water-bath from 30 to 53° during two hours to drive off sulfur dioxide.

The reaction mixture, present as two brown layers, was poured on 200 g. of ice, and the layers were separated. The halide layer was washed with 10% sodium carbonate solution and dried. Fractionation at 731 mm. through a total condensation type column, 1.5 × 66 cm., packed with glass helices[4] gave a 46% yield of 3-chloropentane, b. p. 96°, $n^{20}\text{D}$ 1.4104, $d^{20}{}_4$ 0.8795. These values were checked in two similar runs.

Preparation of 2-Chloropentane.—The same procedure was used as for 3-pentanol. The 2-pentanol, 0.50 mole, b. p. 117.9–118.5° (739 mm.), $n^{20}\text{D}$ 1.4058, was prepared by the method of Sherrill, Baldwin and Haas.[1] The yield of 2-chloropentane, b. p. 95° (729 mm.), $n^{20}\text{D}$ 1.4068, was 28%. More non-volatile material was formed than with the 3-compounds.

Treatment of 3-Pentanol with Hydrogen Chloride.—The following is a description of a typical run. One mole, 88 g., of synthetic 3-pentanol, $n^{20}\text{D}$ 1.4100, b. p. 114.7–115.5° (734 mm.), and 10 g. of concentrated hydrochloric acid were saturated with hydrogen chloride at 0°; 25 g. was absorbed. After six weeks at room temperature, the solution was resaturated with hydrogen chloride at 0°; 17.5 g. was absorbed. After standing for an additional fourteen weeks, the layers were separated.

The colorless halide layer, washed with 10% sodium carbonate solution, dried first with sodium sulfate and then with potassium carbonate, was fractionated at 300 mm. to give an 84% yield of 2- and 3-chloropentanes, b. p. 69–69.3°, $n^{20}\text{D}$ 1.4092–1.4096. The constancy of the boiling point assured the absence of any compounds other than 2- and 3-chloropentanes. Judging from the refractive indices, the proportions were about 75% of the 3-chloro and 25% of the 2-chloro compounds.

A mixture of about this composition was obtained also in runs in which 0.01 mole of aluminum chloride, zinc chloride, or ferric chloride was added to the solution. The effect of these salts in this amount on the rate of the reaction was negligible.

Attempted Purification of 3-Chloropentane by Fractionation.—The best fractions from six runs of synthetic 3-pentanol with hydrogen chloride in sealed bottles, $n^{20}\text{D}$ above 1.4094, comprising 300 g., were combined and fractionated very carefully through column N[5] at atmospheric pressure. The time of the distillation was thirty-one and one-half hours. The refractive index of the product rose gradually as the fractionation proceeded but the highest value reached was 1.4100. This indicates that the isolation by distillation of *pure* 3-chloropentane from a mixture with 2-chloropentane is practically impossible.

Treatment of 3-Pentanol with $ZnCl_2$–HCl Solution.—An improved form[6] of the method of Lucas[7] was used. A solution of 2.2 moles, 300 g., of fused zinc chloride in 2.2 moles, 223 g., of concentrated hydrochloric acid was prepared in an ice-bath. This solution was put in a 500-cc. three-necked flask fitted with a stirrer, dropping funnel, and thermometer dipping into the solution. The flask was cooled in an ice–salt bath. One mole, 88 g., of synthetic 3-pentanol, $n^{20}\text{D}$ 1.4100, b. p. 114.3–114.7° (730 mm.), was added over a period of thirty minutes. After the mixture had been stirred for six hours, the dropping funnel was replaced with a gas inlet tube leading to the bottom of the flask, and a stream of hydrogen chloride was passed in with stirring for eight and one-half hours. The temperature of the mixture was kept below −1° throughout the reaction.

The halide layer was separated, washed with water and then with 10% sodium carbonate solution, and dried. Fractionation at 300 mm. gave an 81% yield of chloropentanes, b. p. 68.5–68.7° (300 mm.), $n^{20}\text{D}$ 1.4086–1.4093.

Treatment of 2-Pentanol with Hydrogen Chloride.—A sample of synthetic 2-pentanol, b. p. 117.3–118.3° (739 mm.), $n^{20}\text{D}$ 1.4056, was treated with hydrogen chloride at room temperature according to the procedure described for 3-pentanol. The product was fractionated at 738 mm. to give 8 fractions, b. p. 95–95.5°, $n^{20}\text{D}$ 1.4068–1.4071, $d^{20}{}_4$ 0.8696–0.8705. The yield of chloropentanes was 78.4%. The gradual changes in refractive index and density values show the presence of 3-chloropentane in 5–8% yield.

Identification of the Chlorides.—Samples of the chlorides were converted to the Grignard reagents and these

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[4] Wilson, Parker and Laughlin, THIS JOURNAL, **55**, 2795 (1933).

[5] Laughlin, Nash and Whitmore, *ibid.*, **56**, 1396 (1934).

[6] Developed by W. H. James of this Laboratory.

[7] Lucas, THIS JOURNAL, **51**, 248 (1929).

were treated with phenyl isocyanate. The derivative obtained from 3-chloropentane was identified as diethylacetanilide, m. p. and mixed m. p., 125–128°. The derivative obtained from 2-chloropentane was methyl-*n*-propylacetanilide, m. p. and mixed m. p. 94–96°.

Stability toward Heat.—Samples of the two chlorides were heated in sealed tubes at 100° for forty-eight hours. No change in refractive index was noted for either 2- or 3-chloropentane.

Isomerization of Chlorides with $ZnCl_2$–HCl Solution.—A sample of 0.2 mole, 21.3 g., of 2-chloropentane, $n^{20}D$ 1.4069, was shaken with a solution of 0.4 mole, 54.5 g., of fused zinc chloride in 0.4 mole, 40.5 g., of concentrated hydrochloric acid for twenty-four hours at room temperature (26–28°). The layers were separated, and the halide was washed with water, dried, and fractionated to give: nos. 1–3, 15.5 g., 95.5–96° (732 mm.), $n^{20}D$ 1.4076; no. 4, 1.5 g.; residue, 1.4089. Fractions 1–3 were combined and shaken with the same $ZnCl_2$–HCl solution for an additional forty-eight hours. The halide was separated, washed, dried, and distilled as before. The product had an index of 1.4076.

A sample of 0.2 mole, 21.3 g., of 3-chloropentane, $n^{20}D$ 1.40965, was treated according to the same procedure. At the end of the full seventy-two hours, the chlorides had an index of 1.4077.

Judging from the refractive index of the equilibrium mixture obtained from either isomer, its composition is roughly 80% 2-chloropentane.

Determination of Physical Constants.—Refractive indices were measured with a Valentine precision refractometer (Abbe type) calibrated by the Bureau of Standards. Densities were determined with a 4-cc. pycnometer, using a constant temperature bath held within ±0.03 of 20.00°.

The Cottrell boiling points were found using 20-cc. samples of the pure chlorides and a copper–copel thermocouple in the apparatus at the Petroleum Refining Laboratory of The Pennsylvania State College.[8] The 2-chloropentane, $n^{20}D$ 1.40690 and $d^{20}{}_4$ 0.8695, gave the following boiling points at 760 mm.:

Initial—96.84°	20% off—96.88°
5% off—96.84°	40% off—96.88°

The 3-chloropentane, $n^{20}D$ 1.41035 and $d^{20}{}_4$ 0.8795, gave these boiling points at 760 mm.:

Initial—97.76°	20% off—97.82°
5% off—97.76°	40% off—97.82°

The freezing points were determined by cooling samples of the pure chlorides with liquid air. Great difficulty was encountered due to persistent supercooling of the compounds. This trouble was about equally bad whether a simple outfit consisting of a jacketed test tube, wire loop stirrer, and chromel–copel thermocouple or a more refined apparatus[9] at the Petroleum Refining Laboratory was used. The best values are −105–106° for 3-chloropentane and −137–139° for 2-chloropentane.

The viscosities were measured at 20.00° in a microviscometer which used a 3-cc. sample and had a constant of 59040 sec./stoke.[10] Pure samples of the 2- and 3-chloropentanes were used having $n^{20}D$ 1.40690, $d^{20}{}_4$ 0.8695, and $n^{20}D$ 1.41035, $d^{20}{}_4$ 0.8795, respectively. The values obtained, 0.5672 and 0.5845 centistoke, respectively, were checked within 0.1%.

Summary

1. Pure samples of the 2- and 3-chloropentanes were made by the action of thionyl chloride and pyridine on the corresponding alcohols.

2. Various physical constants of these chlorides were determined.

3. The chlorides were found to be stable to heat, but were isomerized to an equilibrium mixture by long shaking with $ZnCl_2$–HCl solution at room temperature.

4. Mixtures of the chlorides were obtained in all cases of the treatment of the carbinols with hydrogen chloride.

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[8] Quiggle, Tongberg and Fenske, *Ind. Eng. Chem., Anal. Ed.*, 6, 466 (1934).

[9] To be described elsewhere.

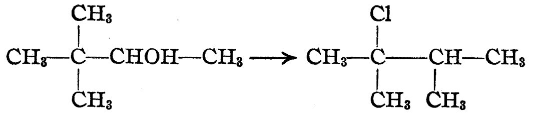
[10] Calibrated by R. Sobatzki of this Laboratory.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Pinacolyl Chloride from the Chlorination of Neohexane

BY FRANK C. WHITMORE, H. I. BERNSTEIN AND L. W. MIXON

Compounds of the type R_3CCHXR' were unknown prior to the present work. Several attempts have been made to prepare the simplest member of the series, pinacolyl chloride, from pinacolyl alcohol.[1] In each case, the product obtained was dimethylisopropylcarbinyl chloride.[2]



$$CH_3-\underset{CH_3}{\overset{CH_3}{C}}-CHOH-CH_3 \longrightarrow CH_3-\underset{CH_3}{\overset{Cl}{C}}-\underset{CH_3}{CH}-CH_3$$

Earlier workers therefore assumed pinacolyl chloride to be unstable, rearranging to give the tertiary chloride. In the present study, chlorination of neohexane, 2,2-dimethylbutane, gave 11% of the desired chloride, $(CH_3)_3CCHClCH_3$, which proved to be a stable secondary chloride. Refluxing and distillation at atmospheric pressure gave no change. With silver nitrate it behaved as a typical secondary alkyl chloride. It reacted with magnesium to give a Grignard reagent which was converted to a stable chloromercuri derivative. The relation of the preparation and properties of pinacolyl chloride to the rearrangement studies of this Laboratory is similar to that of neopentyl chloride.[3]

Neohexane was prepared from *t*-amyl chloride and methylmagnesium chloride. Chlorination gave, together with pinacolyl chloride, a good yield of *t*-amylcarbinyl chloride and some neopentylcarbinyl chloride.

Experimental

Preparation of Neohexane.—Methylmagnesium chloride was prepared from gaseous methyl chloride, 122 g. (5 moles) of magnesium and 1600 cc. of dry di-*n*-butyl ether. Addition of 610 cc. (5 moles) of *t*-amyl chloride in 1 liter of di-*n*-butyl ether was conducted at 50° for eight hours. Decomposition with ice and distillation of the ether layer gave impure hydrocarbon, b. p. 37–50°. Treatment with concd. sulfuric acid and refractionation produced pure neohexane in 36–39% yield, b. p. 49.5° (740 mm.), $n^{20}\mathrm{D}$ 1.3688.

Chlorination of Neohexane.—Chlorine was added to neohexane at salt–ice temperature until approximately half of the hydrocarbon had reacted. The excess hydrocarbon was removed by distillation. The yield of neohexyl chlorides was 67%. Higher chlorides appeared in only small amount.

Fractionation of Neohexyl Chlorides.—A 28-plate total condensation variable take-off column having a section of 262 × 1.2 cm. packed with glass helices was used. Fraction 1, 66.5 g., b. p. 109–110° (734 mm.), $n^{20}\mathrm{D}$ 1.4180, was pinacolyl chloride, identified by addition of oxygen to the Grignard compound[4] to give pinacolyl alcohol; phenylurethan, m. p. and mixed m. p. 78.5–79.5°. The constants for refractionated pinacolyl chloride are: b. p. (Cottrell) 109.9° (734 mm.), f. p. −0.9°, $n^{20}\mathrm{D}$ 1.4181, $d^{20}{}_4$ 0.8767. Fraction 2, 130.2 g., b. p. 113.5–115°, $n^{20}\mathrm{D}$ 1.4190, was largely *t*-amylcarbinyl chloride with a little neopentylcarbinyl chloride.

Preparation of Pinacolylmercuric Chloride.—The method of Marvel was used.[5] Recrystallization from dilute ethyl alcohol gave m. p. 88.5–90°. *Anal.*[6] Calcd. for $C_6H_{13}HgCl$: Hg, 62.5. Found: Hg, 63.3.

Summary

1. Neohexane was prepared in 36–39% yield from *t*-amyl chloride and methylmagnesium chloride.
2. Chlorination of neohexane gave 11% of pinacolyl chloride. *t*-Amylcarbinyl chloride and neopentylcarbinyl chloride were the chief products.
3. The preparation and stability of pinacolyl chloride accord with other work on molecular rearrangements.

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[1] Friedel and Silva, *Jahresber.*, 340 (1873); Couturier, *Ann. chim.*, [6] **26**, 433–501 (1892); Delacre, *Chem. Zentr.*, **77**, **II**, 498 (1906).

[2] Whitmore and Rothrock, THIS JOURNAL, **55**, 1106 (1933).

[3] *Ibid.*, **54**, 3460 (1932); **55**, 3403, 4161 (1933).

[4] *Cf.* Whitmore and Lux, *ibid.*, **54**, 3448 (1932).

[5] Marvel, Gauerke and Hill, *ibid.*, **47**, 3009 (1925).

[6] Whitmore and Sobatzki, *ibid.*, **55**, 1131 (1933).

[CONTRIBUTION OF THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Isomerization during the Preparation of *n*-Amyl Chloride

BY FRANK C. WHITMORE, F. A. KARNATZ AND A. H. POPKIN

Recent studies[1,2] have been made on the formation of isomeric chlorides by the action of zinc chloride and hydrochloric acid on methylneopentylcarbinol and on 2-ethyl-1-butanol. Formation of the equilibrium mixture of 2- and 3-chloropentane on treatment of either with zinc chloride and hydrochloric acid also has been reported.[3]

To determine whether isomerization could occur through the halide, *n*-amyl chloride prepared in 80% yields by the action of thionyl chloride on *n*-amyl alcohol in pyridine was treated with the same reagents. Only 3% of a mixture of 2- and 3-chloropentanes was isolated. The formation of more rearranged products during the replacement of hydroxyl by halogen than by similar treatment of the pure halide with zinc chloride and hydrochloric acid is significant.

The *n*-amyl chloride obtained from thionyl chloride was free from traces of isomerized chlorides, which is in agreement with previously recorded results.[4] The index of refraction $n^{20}\mathrm{D}$ 1.4128 was higher than the values of $n^{20}\mathrm{D}$ 1.41192[5] and 1.4120[6] in the literature. The *n*-amyl chloride recovered from the action of zinc chloride and hydrochloric acid on the pure *n*-amyl chloride had $n^{20}\mathrm{D}$ 1.4120. Moreover, the *n*-amyl chloride obtained from the treatment of *n*-amyl alcohol with zinc chloride and hydrochloric acid had a refractive index range of $n^{20}\mathrm{D}$ 1.4119–1.4121 which was raised to $n^{20}\mathrm{D}$ 1.4128 only after two refractionations through a 12-plate column.[7] It is apparent that the low refractive index values previously recorded for *n*-amyl chloride were due to traces of 2- and 3-chloropentanes.

The synthesis of *n*-amyl alcohol involved the preparation of a large quantity of *n*-butyl bromide by the action of sulfuric acid and hydrobromic acid on *n*-butyl alcohol. A careful investigation of the low boiling by-products gave no indication of the formation of rearranged products in this reaction.

Experimental

Action of Sulfuric Acid and Hydrobromic Acid on *n*-Butyl Alcohol.—*n*-Butyl bromide was prepared by the action of sulfuric acid and hydrobromic acid[8] on 12 moles of a very pure sample of *n*-butyl alcohol.[9] The product was fractionated at 731 mm. to give: fraction 1, 1.4 g., 93°, $n^{20}\mathrm{D}$ 1.4203; 2, 35.3, 96°, 1.4387; 3, 34.3, 98°, 1.4389; 4–5, 72.8, 99°, 1.4390; 6–15, 1270, 99–99.5° (734 mm.), 1.4390–1.4392.

To determine whether *s*-butyl bromide was present as rearranged product, fractions 1–5 were refractionated to give: 16, 7.7 g., 75–98° (734 mm.), $n^{20}\mathrm{D}$ 1.4352; 17, 10.7, 98°, 1.4389; 18–19, 113.8, 99.4–100.0°, 1.4392. Fraction 16 was then refractionated to give: 20, 0.56 g., $n^{20}\mathrm{D}$ 1.4102; 21, 0.9, 1.4366; 22, 0.4, 1.4385. The fractionation was conducted at a vapor velocity too low for significant temperature reading but the refractive index of fraction 20 indicates the depression in the indices to be due to a small amount of olefin with no indication of the presence of *s*-butyl bromide.

Preparation of *n*-Amyl Alcohol.—*n*-Butylmagnesium bromide was prepared by the addition of 685 g. (5 moles) of *n*-butyl bromide to 122 g. of magnesium in 1500 cc. of ether. The Grignard reagent was cooled to salt–ice temperature, a liter of ether added and formaldehyde, generated from paraformaldehyde at 175° and passed through a heated tube, was added until no further test for Grignard reagent was obtained. The complex was decomposed on ice and the product steam distilled. The resulting oil layer was washed with sodium bisulfite solution and dried over anhydrous potassium carbonate. Fractionation at 733 mm. gave: fractions 1–3, 19 g., 129–134°, $n^{20}\mathrm{D}$ 1.3972–1.4081; 4–22, 274 g., 136°, 1.4093; residue 11 g., yield 68%. A similar run was completed and all fractions of constant boiling point and constant refractive index were combined and refractionated at 100 mm. to give a forerun of two fractions, 15 g., 86°, $n^{20}\mathrm{D}$ 1.4080–1.4097; twenty-eight fractions, 87°, 1.4093, and weight 396 g. The constants for pure *n*-amyl alcohol were: 136.8° (734 mm.), 137.8° (760 mm.), using a Cottrell apparatus;[10] $n^{20}\mathrm{D}$, 1.40988 ± 0.00005;[11] freezing point, −78.24°, and d^{20}_4 0.8144.

Action of Zinc Chloride and Hydrochloric Acid on *n*-Amyl Alcohol.—A solution of 819 g. (6 moles) of fused zinc

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[1] Whitmore and James, unpublished work.

[2] Whitmore and Karnatz, THIS JOURNAL, **60**, 2533 (1938).

[3] This suggested the possibility of obtaining 2- and 3-chloropentane as by-products in the preparation of *n*-amyl chloride from the alcohol, zinc chloride and hydrochloric acid. Synthetic *n*-amyl alcohol was treated with zinc chloride and hydrochloric acid to give a 57% yield of *n*-amyl chloride. A 10% yield of a mixture of 2- and 3-chloropentanes was isolated from the low boiling products.

[4] McKenzie and Clough, *J. Chem. Soc.*, **103**, 687 (1913); Kirner, THIS JOURNAL, **50**, 1958 (1928); Gilman and Harris, *Rec. trav. chim.*, **50**, 1052 (1931).

[5] Karvonen, *Ann. Acad. Sci. Fenn.*, **A5**, No. 6, **124** (1914); *Chem. Abst.*, **14**, 2176 (1920).

[6] Rank, *J. Chem. Phys.*, **1**, 572–575 (1933).

[7] Whitmore and Lux, THIS JOURNAL, **54**, 3448 (1932); Wilson, Parker and Laughlin, *ibid.*, **55**, 2795 (1933).

[8] *Org. Syntheses*, **1**, 5 (1921).

[9] THIS JOURNAL, **54**, 3443 (1932).

[10] Quiggle, Tongberg and Fenske, *Ind. Eng. Chem., Anal. Ed.*, **6**, 466 (1934).

[11] Abbe type, Valentine refractometer checked by Bureau of Standards.

chloride in 606 g. of concentrated aqueous hydrochloric acid was heated for twelve hours at 113–128° with 264 g. (3 moles) of *n*-amyl alcohol. Stirring was conducted rapidly during reaction with vigorous refluxing. The amyl chloride layer was separated, washed with distilled water and a 10% solution of potassium carbonate. The chloride was then dried and fractionated at 736 mm. to give: 1, 2.0 g., 37–91°, $n^{20}\mathrm{D}$ 1.3894; 2, 19, 91–99°, 1.4092; 3, 22, 100–104°, 1.4112; 4, 22.2, 104–105°, 1.4117; 5–10, 105–106.5° (739 mm.), 183.1 g., 1.4119–1.4122. The 183.1 g. (57% yield) of fractions 5–10 was *n*-amyl chloride.

Fractions 2, 3 and 4 were refractionated at 733 mm. to give: 11, 1.2 g., 71–92.2°, $n^{20}\mathrm{D}$ 1.4032; 12, 9.8, 93.2°, 1.4082; 13, 13.2 g., $n^{20}\mathrm{D}$ 1.4092; 14, 11.5, 1.4112; 15, 7.4, 1.4122. Fractions 12, 13 and 14 were again refractionated at 735 mm. to give: 16, 1.5 g., 90–95°, $n^{20}\mathrm{D}$ 1.4071; 17, 11.2, 95°, 1.4084; 18, 11.7, 96°, 1.4092; 19, 2.8, 96–102°, 1.4110; 20, 4.1, $n^{20}\mathrm{D}$ 1.4120; residue, 1.5 g. Fraction 2 was converted to the Grignard reagent, treated with phenyl isocyanate and the complex decomposed with ice and hydrochloric acid. The ether layer, after many recrystallizations from ethyl alcohol, gave methyl-*n*-propylacetanilide, m. p. and mixed m. p. 95–96°, proving the presence of 2-chloropentane. Fractional crystallization of the crystals from the mother liquor yielded a product, m. p. 121–122.5°, which when mixed with known diethylacetanilide, m. p. 127–128°, gave a mixed m. p. of 122–125°. This indicated the presence of 3-chloropentane.

To verify the mixed melting point for diethylacetanilide, the following microscopic analysis was made.[12] The known diethylacetanilide, melting at 127–128°, crystallized in needles from ethyl alcohol (system probably triclinic), gave negative elongation and the following refractive indices (approximate, white light): η_α 1.516–1.519, η_β 1.535–1.540, η_γ 1.627–1.628; sign +, 2V = 32° and extinction angle 26°. The crystal analysis for the diethylacetanilide obtained from the rearranged 3-chloropentane, 121–122.5°, was identical with that of the known, above. Crystal analysis for methyl-*n*-propylacetanilide yielded: $\eta_\alpha > 1.520$, η_γ 1.625–1.630 for white light; sign +, negative elongation and parallel extinction.

Preparation of Pure *n*-Amyl Chloride.—*n*-Amyl chloride free from 2- and 3-chloropentanes was prepared by treating commercial (Sharples) *n*-amyl alcohol in pyridine with thionyl chloride.[13] A solution of 440 g. (5 moles) of fractionated commercial *n*-amyl alcohol, 136° (732 mm.), $n^{20}\mathrm{D}$ 1.4107–1.4109, in 435 g. (5.5 moles) of fractionated commercial pyridine, 113.0° (735 mm.), $n^{20}\mathrm{D}$ 1.5097, was treated with 772.5 g. (6.5 moles) of thionyl chloride at −10°. The reaction mixture was warmed to 104° during six hours and that temperature maintained for one and one-half hours. Sulfur dioxide was liberated at 73–104°. Three similar preparations of varying quantities of reactants failed to yield a sharp decomposition temperature for the alcohol–thionyl chloride complex. Decrease in the rate of thionyl chloride addition to one and three-fourths hours per mole and increase in length of heating period to five hours per mole did not improve the yield of chloride.

The crude chloride was separated in the usual way and fractionated to give at 741 mm.: fractions 1–3, 24.2 g., 106–106.5°, $n^{20}\mathrm{D}$ 1.4122–1.4123; 4–14, 394.7, 106.5°, 1.4126–1.4128; 15, 5.1, 106.5°, 1.4130; residue 56 g. The total halide formed, 424 g., was *n*-amyl chloride in 80% yield. The three additional preparations using thionyl chloride also gave *n*-amyl chloride, $n^{20}\mathrm{D}$ 1.4126–1.4128. The constants for refractionated *n*-amyl chloride were: b. p. 106° (725 mm.), $n^{20}\mathrm{D}$ 1.41280 ± 0.00005, $d^{20}{}_4$ 0.8828; *MR*, calcd., 30.15; obsd., 30.08.

Reaction of *n*-Amyl Chloride with Zinc Chloride and Hydrochloric Acid.—All fractions of *n*-amyl chloride having values of $n^{20}\mathrm{D}$ 1.4126–1.4128 were combined and refractionated through column A to give at 741 mm.: 1, 0.5 g., 91°, $n^{20}\mathrm{D}$ 1.4134; 2–3, 5.9, 96°, 1.4127; 4, 1.2, 102°, 1.4127; 5–19, 503.4, 106°, 1.4127; 20–25, 229.3, 106°, 1.4128. Into a two-necked two-liter round-bottomed flask was placed a solution of 819 g. (6 moles) of zinc chloride in 606 g. of concentrated aqueous hydrochloric acid. To this was added rapidly 319.5 g. (3 moles) of *n*-amyl chloride of fractions 7–11 and 13–17, above. The temperature of the bath was kept at 126–134° for twelve hours with vigorous stirring and rapid refluxing. The resulting chloride layer was separated, washed with distilled water, and a 10% solution of sodium carbonate. The chloride was dried and fractionated at 740 mm. to give: 1, 0.5 g., 32–50°, $n^{20}\mathrm{D}$ 1.3837; 2, 3.9, 50–96°, 1.4085; 3, 9.0, 96–103°, 1.4108; 4, 6.5, 103–105°, 1.4108; 5–6, 16.4, 105°, 1.4109; 7–11, 39.8, 105.2°, 1.4110–1.4114; 12–22, 194.9, 104.5–105.5° (732 mm.), 1.4118–1.4120; residue, 3.5 g.; 14 g. of olefin was collected in a dry ice–acetone trap.

Fractions 2–11 were combined and fractionated at 741 mm. to give: 23, 1.5 g., 56–90°, $n^{20}\mathrm{D}$ 1.4012; 24, 4.6, 1.4086; 25, 4.3, 101–103°, 1.4100; 26, 3.6, 104–105°, 1.4106; 27, 4.4, 105°, 1.4110; 28, 105–106°, 14.2, 1.4119. The remainder was *n*-amyl chloride. Based on fractions 24, 25 and part of 26, the yield of rearranged product is 3%. Fraction 24 was converted to the Grignard reagent, treated with phenyl isocyanate, and worked up in the usual manner. After many crystallizations from ethyl alcohol, methyl-*n*-propylacetanilide was obtained, m. p. and mixed m. p. 95–96°, proving the presence of 2-chloropentane. 3-Chloropentane was also probably present as an isomerization product.

Summary

1. The action of zinc chloride and hydrochloric acid on *n*-amyl alcohol produces *n*-amyl chloride in 57% yield and 10% of a mixture of 2- and 3-chloropentanes.

2. The action of zinc chloride and hydrochloric acid on *n*-amyl chloride yields 3% of a mixture of 2- and 3-chloropentanes.

3. The action of thionyl chloride on *n*-amyl alcohol in pyridine gives *n*-amyl chloride in 80% yield with no rearranged products.

4. A corrected refractive index for *n*-amyl chloride, free of traces of 2- and 3-chloropentanes, is recorded.

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[12] The microscopic analysis was completed by Dr. E. F. Williams of the Department of Minerology, The Pennsylvania State College.

[13] Darzens, *Compt. rend.*, 152, 1314 (1911).

5. The action of sulfuric acid and hydrobromic acid on *n*-butyl alcohol gives no rearranged bromide.

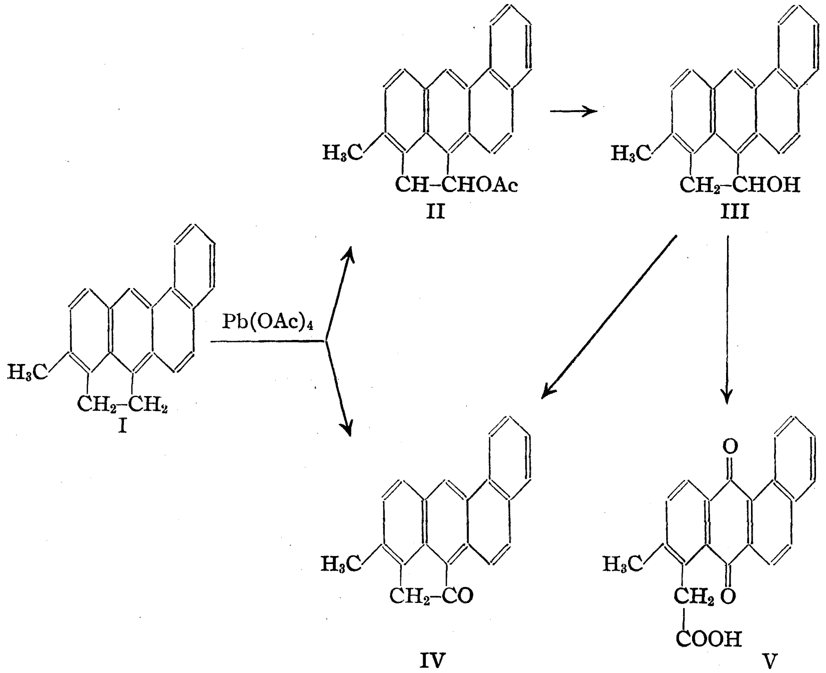
STATE COLLEGE, PENNA. RECEIVED JULY 20, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Oxidation of Methylcholanthrene and 3,4-Benzpyrene with Lead Tetraacetate; Further Derivatives of 3,4-Benzpyrene

BY LOUIS F. FIESER AND E. B. HERSHBERG[1]

In a recent paper[2] we reported that on treatment with lead tetraacetate 1,2-benzanthracene is converted into the 10-acetoxy derivative, 10-methyl-1,2-benzanthracene is attacked in the methyl group giving 10-acetoxymethyl-1,2-benzanthracene, and 1,2,5,6-dibenzanthracene is more resistant to oxidation by the reagent and under comparable conditions is largely recovered unchanged. This specific oxidation reaction provides a means of distinguishing between hydrocarbons of varying degrees of reactivity and of locating a reactive center in a hydrocarbon molecule whether this is in an aromatic nucleus or a side chain. Thus far nuclear oxidation by the reagent has been observed only in the case of the *meso*-acetoxylation of anthracene[3] and 1,2-benzanthracene,[2] and the known examples of the oxidation of an alkyl residue by lead tetraacetate all involve acetoxylation at an activated α-position in a side chain or side ring. The reaction with 10-methyl-1,2-benzanthracene[2] is one instance of the latter type of oxidation, and similar reactions have been observed with toluene,[4] acenaphthene,[5] and tetralin.[6]



On investigating methylcholanthrene and 3,4-benzpyrene, it was found that these powerfully carcinogenic hydrocarbons are highly susceptible to attack by lead tetraacetate. 3,4-Benzpyrene is oxidized rapidly at room temperature in acetic acid–benzene and converted in over 90% yield into a new monoacetoxy derivative. Methylcholanthrene is even more susceptible to attack and in the most satisfactory procedure, adopted because of the sensitivity of the reaction products, the oxidation was conducted under ice cooling. One reaction product, isolated only in small amounts when one equivalent of oxidizing agent was employed, is a rather sparingly soluble and high melting substance having the composition of a keto derivative of methylcholanthrene. The chief product was an acetoxy derivative, and on hydrolysis it gave a neutral alcohol. A relationship between the two substances was easily established, for the alcohol was found to yield the ketone on careful oxidation with sodium dichromate. Further oxidation with the same reagent gave a yellow anthraquinone (vat test) having an acidic group, and this proved to be identical with

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[1] Research Fellow on funds from the National Cancer Institute and the Eli Lilly Company.

[2] Fieser and Hershberg, THIS JOURNAL, **60**, 1893 (1938).

[3] K. H. Meyer, *Ann.*, **379**, 73 (1911).

[4] Dimroth and Schweizer, *Ber.*, **56**, 1375 (1923).

[5] Marquis, *Compt. rend.*, **182**, 1227 (1926).

[6] Criegee, *Ann.*, **481**, 263 (1930).

6-methyl-1,2-benzanthraquinone-5-acetic acid (V). Cook and Haslewood[7] obtained this acid by the oxidation of methylcholanthrene with sodium dichromate in boiling acetic acid and established the structure by decarboxylation to 5,6-dimethyl-1,2-benzanthraquinone. A comparison of our acid with a sample prepared in this way was made through the sharply melting methyl ester.[8] The alcohol and ketone therefore have the structures III and IV, the oxygen atom being located at the 15-position. Cook and Haslewood evidently had the ketone IV (m. p. 262–263°, corr.) in hand in an impure condition, for they observed that when the hydrocarbon is shaken with dichromate solution at room temperature it is changed into a substance of different crystalline form. They state that "This substance, m. p. 228–229° (dec.), probably an intermediate ketone, was not purified on account of its instability." On repeating the experiment, we found that by repeated crystallization a pure substance can be isolated and that it is identical with 15-keto-20-methylcholanthrene described above. The same ketone is therefore produced by both oxidizing agents. Whether or not the alcohol or its acetate is in each case a precursor of the ketone, the observed acetoxylation in the 15-position must be regarded as an important primary step revealing the site in the molecule most susceptible to oxidation. An oxidizing agent which introduces a hydroxyl group in a protected condition has obvious advantages for the study of primary changes.

15-Hydroxy- and 15-keto-methylcholanthrene are being tested for carcinogenic activity by Dr. M. J. Shear. The analogous alcohol, 10-hydroxymethyl-1,2-benzanthracene, has given a few subcutaneous tumors in mice[9] (slowly). Both the new alcohol, which has an asymmetric carbon atom, and the ketone present many possibilities for the preparation of additional derivatives of interest, and these are being investigated. As shown in Fig. 1, the absorption curve for 15-hydroxy-20-methylcholanthrene is very similar in form to that of the parent hydrocarbon except for a slight displacement of lower values of the extinction coefficient. The determinations, which were carried out in ether solution, using a Spekker photometer, were kindly made by Dr. George I. Lavin of the Rockefeller Institute.

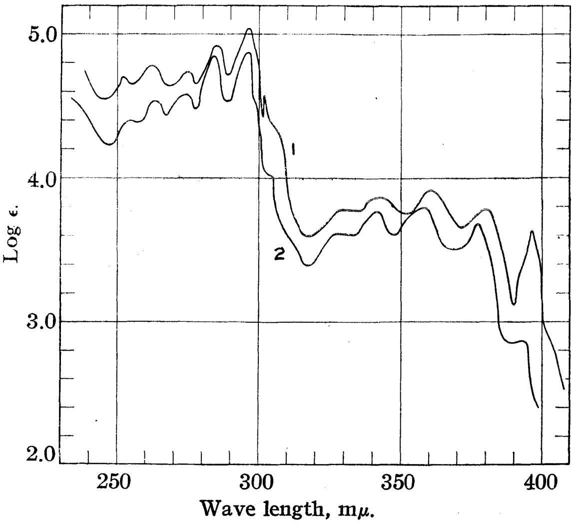

Fig. 1.—Curve 1, 20-methylcholanthrene (I); curve 2, 15-hydroxy-20-methylcholanthrene (III).

Observations concerning the structure and properties of the new acetoxy-3,4-benzpyrene will be reported in a later paper. Another substitution reaction studied is the condensation of the hydrocarbon with methylformanilide in the presence of phosphorus oxychloride in *o*-dichlorobenzene solution.[10] This gave in 90% yield a single, pure aldehyde, and on reduction by the Wolff–Kishner method the aldehyde yielded a methyl-3,4-benzpyrene different from any of the isomers hitherto known but identical with one of two isomers obtained synthetically from the recently described 2,1′-trimethylene-1,9-benzanthrone-10[11] (VI). It is known[12] that in the reaction of benzanthrone itself with various Grignard reagents addition may occur to the carbonyl group, giving a carbinol, and also to the 1,4-conjugated system formed by the carbonyl group and the adjacent nuclear double bond of the naphthalene nucleus. The primary product of 1,4-addition must be a dihydrobenzanthrone, but this evidently undergoes oxidation at some stage, probably in the course of working up the mixture, for the product isolated is a 4-aryl- or 4-alkyl-benzanthrone. We investigated the action of methyllithium on the trimethylenebenzanthrone VI, and from the resulting mixture isolated in 21% yield a pure, crystalline product having the composition of a methyl derivative of the trimethylenebenzanthrone. The analysis shows that the substance is

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[7] Cook and Haslewood, *J. Chem. Soc.*, 428 (1934).

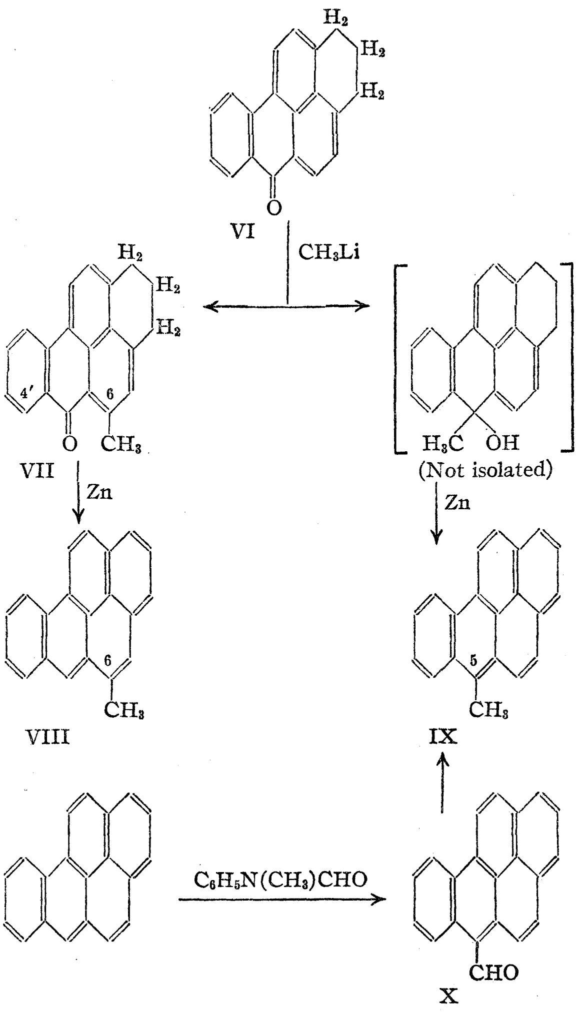
[8] Bachmann, *J. Org. Chem.*, **1**, 347 (1936).

[9] Shear, Proc. XVI Internat. Physiol. Congress, in press.

[10] Procedure of Vollmann, *et al.*, *Ann.*, **531**, 1 (1937); see also Ref. 15.

[11] Fieser and Hershberg, THIS JOURNAL, **60**, 1658 (1938).

[12] Charrier and Ghigi, *Gazz. chim. ital.*, **62**, 928 (1932); *Ber.*, **69**, 2211 (1936); Allen and Overbaugh, THIS JOURNAL, **57**, 740, 1322 (1935).



a product of addition to a conjugated system rather than to the carbonyl group, and in analogy with benzanthrone the probable structure is that of formula VII. It is perhaps conceivable that 1,4-addition occurs to the alternate conjugated system and that the methyl group is at the 4′-position, but this possibility is eliminated by the observation that the hydrocarbon obtained on zinc dust distillation is quite different from the known 4′-methyl-3,4-benzpyrene.[13] The new hydrocarbon therefore can be regarded with reasonable confidence as 6-methyl-3,4-benzpyrene (VIII). After careful removal of the crystalline product from the reaction with methyllithium, zinc dust distillation of the residual oil gave, after purification through the trinitrobenzene derivative, another methylbenzpyrene. This must have come from a carbinol, although in the small-scale experiment the intermediate was not isolated, and the position of the methyl group probably corresponds with that of the carbonyl group of the starting material. A certain assurance is provided by the fact that the final hydrocarbon differs from the 2′-,[11] 3′-,[11] 4′-[13] and 6-isomers, and the substance therefore is regarded as 5-methyl-3,4-benzpyrene (IX). That the same hydrocarbon was obtained from the aldehyde indicates, at least provisionally, that this has the structure X and that in the reaction with methylformanilide 3,4-benzpyrene is substituted at the 5-position. The compounds are being tested for carcinogenic properties by Dr. Shear.[14]

The smooth reaction of 3,4-benzpyrene with methylformanilide illustrates the susceptibility of the hydrocarbon to substitution but provides little distinction in reactivity between this hydrocarbon and pyrene,[10] anthracene,[15] and 1,2-benzanthracene,[15] which also give aldehydes in good yield under comparable conditions. From the present knowledge of the condensation one can say only that 3,4-benzpyrene is more reactive to the reagent than 1,2,5,6-dibenzanthracene, which gives no aldehyde even under forcing conditions,[15] and perhaps that it is also more reactive than 1,2-benzanthracene.[15] In the oxidation experiments with lead tetraacetate 3,4-benzpyrene and methylcholanthrene appear, from qualitative observations of the temperature at which reaction occurs and from the yields, to be distinctly more reactive than any of the hydrocarbons just mentioned or than 10-methyl-1,2-benzanthracene. Both the aldehyde reaction and the oxidation are substitutions, as is the recently reported diazo coupling.[16] The color reaction with benzenediazonium chloride provides a highly sensitive and selective means of recognizing hydrocarbons of particularly highly developed reactivity, and in this test 3,4-benzpyrene and methylcholanthrene stand out in sharp contrast to 1,2-benzanthracene, 10-methyl-1,2-benzanthracene, anthracene, pyrene and in fact to all other polynuclear hydrocarbons examined except those which, like methylcholanthrene, contain an aceanthrene nu-

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(13) Fieser and Fieser, THIS JOURNAL, **57**, 782 (1935).

(14) From 36 strain A mice given a subcutaneous injection of 10 mg. of crystalline 4′-methyl-3,4-benzpyrene,[13] Dr. Shear obtained 17 tumors, and the average induction time was 28 weeks. At the same dosage, 4′-methyl-1′,2′-dihydro-3,4-benzpyrene[13] gave 5 tumors in 27 strain A mice in an average induction time of 34 weeks. That Domagk, *Med. Chem.*, **3**, 274 (1936), found the compound inactive in a skin painting experiment may mean either that the hydrocarbon belongs to the type much more active to subcutaneous tissue than to the skin or that aromatization occurs in contact with one tissue but not the other.

(15) Fieser and Hartwell, THIS JOURNAL, **60**, 2555 (1938).

(16) Fieser and Campbell, *ibid.*, **60**, 1142 (1938).

cleus. At the time of observing the diazo coupling of methylcholanthrene, the obvious assumption in the absence of evidence was that substitution occurs in the nucleus, probably at the available meso position, but this assumption seems questionable in the light of information which has accumulated in the meantime. The corresponding meso position of 1,2,5,6-dibenzanthracene and of 10-methyl-1,2-benzanthracene is now known to be highly hindered and not readily amenable to substitution,[2,15] and there is little reason to suppose that coupling can occur at other nuclear positions. The lead tetraacetate reaction, however, discloses the fact that a methyl or methylene group attached to the 10-meso position of the 1,2-benzanthracene nucleus constitutes a highly reactive center, and the possibility that diazo coupling occurs at the methylene group of the cholanthrenes merits consideration. The greater reactivity of hydrocarbons having in this position the methylene group of a five-membered ring, as compared with the corresponding methyl compounds, is understandable on the basis of this hypothesis, and a ready explanation is at hand of the common property exhibited by all of the hydrocarbons derived from aceanthrene.

It was pointed out previously[16] that methylcholanthrene is rather sluggish, as compared to structurally related hydrocarbons, in the addition reaction with maleic anhydride[17] and in the catalyzed addition of hydrogen.[18] According to a personal communication from Dr. W. E. Bachmann, 3,4-benzypyrene, if able to add maleic anhydride at all, at least does so far less readily than anthracene and 1,2-benzanthracene. High reactivity, however, is displayed by both of these potent carcinogens in three substitutions of entirely different types. It is important to know how various hydrocarbons compare in the relative degree of susceptibility to substitution, and an approximate estimate can be made from present data on the assumption that all three of the observed reactions are manifestations of the same kind of reactivity. The aldehyde reaction is the least selective of the tests and shows little that is not recognized from other results. The oxidation experiments reveal the course of a typical substitution and indicate that 10-methyl-1,2-benzanthracene reacts in the same way as methylcholanthrene but does so somewhat less readily. The diazo coupling tests emphasize this difference in reactivity, for the pentacyclic hydrocarbon couples and the tetracyclic compound does not. From the results of oxidation it appears that in the highly selective coupling test a moderate difference in the degree of reactivity is considerably magnified. In view of the response of the 10-methyl compound to one reagent, its failure to respond to another reagent under certain restricted conditions can no longer be taken as an indication that it lacks appreciable susceptibility to substitution.

The special significance of these observations is that there are certain points of correspondence between the chemical reactivity of the hydrocarbons in substitutions and their carcinogenic activity. The order of chemical reactivity indicated by the above tests is: methylcholanthrene and 3,4-benzypyrene > 10-methyl-1,2-benzanthracene and 5,10-dimethyl-1,2-benzanthracene > 1,2,5,6-dibenzanthracene. The order of carcinogenic potency, as judged by all available criteria, is exactly the same.[19] The biological tests of simpler models of the methylcholanthrene molecule investigated in this Laboratory and of various other alkyl derivatives of 1,2-benzanthracene synthesized in London and at Harvard have brought out the importance, to the development of carcinogenic properties, of the presence of a methyl or methylene group attached to a meso carbon atom of the parent hydrocarbon, particularly at position 10; the course of the oxidation of methylcholanthrene shows that the side chain attached to the meso position 10 is the most reactive center in the molecule.[20] The superior biological potency of the cholanthrenes as compared with simpler model compounds is reflected in the distinctly higher chemical reactivity of the hydrocarbons containing the five-membered ring. Perhaps the most striking circumstance is that outstanding chemical reactivity of a special kind is encountered in the two compounds which surpass all other known hydrocarbons in the rapidity, as well as regularity, with which they induce tumors in various species and tissues of test animals. It is remarkable that substances of such distinctly different structural types as methylcholanthrene

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[17] Bachmann and Kloetzel, THIS JOURNAL, **60**, 481 (1938).

[18] Fieser and Hershberg, *ibid.*, **59**, 2502 (1937).

[19] For a review and analysis of the biological and chemical data on hydrocarbon carcinogenesis, see Fieser, *Am. J. Cancer*, **34**, 37 (1938).

[20] The reactivity manifested at this position is probably attributable to activation by the highly unsaturated center at the end of the quinonoid system of linkages, contrasting with the weaker activating influence on the alternate methylene group exerted by the terminal benzenoid ring.

and 3,4-benzypyrene both belong to the very small group of hydrocarbons capable of coupling rapidly with diazotized *p*-nitroaniline and that they show similar susceptibility to oxidation with lead tetraacetate, even though substitution occurs in one case in the nucleus and in the other in a side chain. That these unusual substances are also endowed to a high degree with the specific ability to initiate malignant growth in animal tissue may not be a mere coincidence. The relationships now observable suggest that the administered carcinogen may undergo some form of substitution reaction, possibly akin to a hydroxylation, and that this constitutes an important step in a complicated chain of events leading eventually to carcinogenesis.[21]

Experimental Part[22]

Oxidation of Methylcholanthrene.—A solution of 3.4 g. of lead tetraacetate in 100 cc. of glacial acetic acid was added dropwise in the course of one hour to a mechanically stirred solution of 2 g. of methylcholanthrene in 200 cc. of benzene, while cooling the reaction mixture with an ice-bath. The solution gradually turned deep orange during the period of the addition and when this had been completed the volume was reduced to about one-third the original by concentration at a pressure of 15–20 mm. and a temperature below 40°. Water was added and the precipitated solid was collected, washed with water, and dried in vacuum at 50°. The product was taken into acetone and after treatment with decolorizing carbon the solution was concentrated to a volume of about 100 cc. and allowed to stand overnight. The crystallizate amounted to 0.14 g. (7%) and consisted of crude **15-keto-20-methylcholanthrene (IV)**, m. p. 230–245°. Three crystallizations from acetone and one from glacial acetic acid gave yellow needles melting constantly at 262–263°. The substance is insoluble in alkali and does not give a vat test.

Anal. Calcd. for $C_{21}H_{14}O$: C, 89.34; H, 5.00. Found: C, 89.18; H, 4.89.

The acetone mother liquors remaining after the removal of the ketone were concentrated and twice treated with ligroin (60–70°) and evaporated. The acetone–ligroin solution then deposited 0.88 g. of **15-acetoxy-20-methylcholanthrene (II)**, m. p. 172–174°, dec., which when recrystallized afforded 0.78 g. of material, m. p. 177.5–178.5°, dec. From the mother liquors there was obtained 0.34 g. of acetate, m. p. 175–177°, dec., making a total yield of 46%. After three crystallizations from acetone–ligroin the acetate formed pale yellow needles melting constantly at 179.5–180.5°, with gas evolution.

Anal. Calcd. for $C_{23}H_{18}O_2$: C, 84.62; H, 5.59. Found: C, 84.50; H, 5.45.

On using two moles of lead tetraacetate the yield of ketone was increased slightly but the acetate was gummy and more difficult to purify.

15-Hydroxy-20-methylcholanthrene (III).—A suspension of 0.5 g. of acetoxymethylcholanthrene in 100 cc. of methanol containing 0.5 g. of potassium hydroxide was refluxed on the steam-bath. The solid dissolved rapidly and after about twenty minutes needles of the free alcohol began to form. After one hour the mixture was cooled and the solid collected, washed with dilute methanol, dilute acid, and water. Dried in vacuum, the solid weighed 0.31 g. (71%) and melted at 207–209° with decomposition (gas evolution). Two crystallizations from acetone–ligroin gave fluffy, very pale yellow needles, m. p. 209–211°, dec.

In another experiment 0.85 g. of the acetate gave 0.55 g. (74%) of alcohol which, after one crystallization from acetone–ligroin, melted at 221–222° without gas evolution. After a second crystallization, however, the material melted at 211–213° with gas evolution, and after a third crystallization the nearly colorless substance melted at 214–216°, dec. This variable behavior is probably due to a pronounced tendency to decompose under the influence of traces of catalyst.

Anal. Calcd. for $C_{21}H_{16}O$: C, 88.71; H, 5.67. Found (214–216° sample): C, 88.41; H, 5.77.

Conversion of the Alcohol into the Ketone.—A solution of 0.19 g. of 15-hydroxy-20-methylcholanthrene in 10 cc. of glacial acetic acid was treated with 90 mg. of anhydrous sodium dichromate and shaken at room temperature for fifteen minutes. The solution was diluted with water and the precipitated ketone was crystallized from acetone. There was obtained 85 mg. (43%) of 15-keto-20-methylcholanthrene in the form of yellow needles, m. p. 262.5–263°. This did not depress the melting point of the above sample.

Dichromate Oxidation of Methylcholanthrene to the Ketone.—A suspension of 0.5 g. of powdered methylcholanthrene and 0.98 g. of anhydrous sodium dichromate in 25 cc. of glacial acetic acid was shaken at room temperature for fifteen minutes and the solid was collected, extracted with warm dilute sodium carbonate solution, and crystallized from acetone. The purification is not easy, but after five crystallizations 70 mg. (13%) of satisfactory ketone was obtained melting at 261.5–262.5°. This gave no depression when mixed with the material obtained by oxidation with lead tetraacetate.

Proof of Structure.—A solution of 0.1 g. of 15-hydroxy-20-methylcholanthrene and 0.5 g. of anhydrous sodium dichromate in 10 cc. of glacial acetic acid was refluxed for ten minutes and water was added. On recrystallization of the precipitate from acetic acid **6-methylanthraquinone-5-acetic acid** was obtained as fluffy yellow needles, m. p. 292–295°, dec.; yield, 45 mg. (39%). The substance gives a vat test and is soluble in dilute sodium carbonate solution. The **methyl ester**, obtained by esterification with methanol and hydrogen chloride, melted initially at 220.5–221.5°, and on recrystallization from benzene–ligroin formed flat yellow needles, m. p. 221.5–222°. A sample prepared by oxidation of methylcholanthrene according to Cook and Haslewood[7] and esterified as above melted at the same temperature and there was no depression on mixing the samples. Bachmann[8] esterified the quinone-acid with diazomethane in xylene and reports the m. p. 213–214°, uncorr.

Oxidation of 3,4-Benzpyrene.—A solution of 4.5 g. of lead tetraacetate in 125 cc. of glacial acetic acid was added

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[21] For a further discussion of this hypothesis see Ref. 19.

[22] All melting points are corrected. Analyses by the Arlington Laboratories.

to a solution of 2.5 g. of 3,4-benzpyrene in 100 cc. of benzene, both solutions being at room temperature. After standing for one-half hour the benzene was removed by distillation and water was added to saturation. On cooling, 2.78 g. (94%) of greenish-yellow needles separated, m. p. 205.5–207.5°. Recrystallization from glacial acetic acid gave 2.5 g. (85%) of material of m. p. 208.5–209.5°, and repeated crystallization from glacial acetic acid and finally from benzene gave straw-yellow needles, m. p. 209.5–210°. The crystals from acetic acid hold this solvent tenaciously and satisfactory analytical results were obtained only after final crystallization from benzene.

Anal. Calcd. for $C_{22}H_{14}O_2$: C, 85.14; H, 4.55. Found: C, 85.33; H, 4.67.

Reaction of 2,1′-Trimethylene-1,9-benzanthrone-10 (VI) with Methyllithium.—A suspension of methyllithium was prepared from 0.5 g. of lithium and excess methyl chloride in ether and 4.85 g. of the benzanthrone VI was added. The ether was displaced by benzene, and after refluxing for fifteen hours the deep brownish-green solution was decomposed with dilute hydrochloric acid. The benzene layer was separated, washed, filtered and concentrated; it yielded two crops of crystalline product amounting to 1.06 g. (21%) and melting at 217–219°. This substance, regarded as **4-methyl-2,1′-trimethylene-1,9-benzanthrone-10 (VII)**, on further crystallization from benzene–ligroin formed golden-yellow needles, m. p. 220–220.5°.

Anal. Calcd. for $C_{21}H_{16}O$: C, 88.71; H, 5.67. Found: C, 88.67; H, 5.80.

6-Methyl-3,4-benzpyrene.—The ketone VII (0.65 g.) was mixed with 50 cc. of zinc dust and distilled at 250 mm. pressure. The oily product was redistilled at 0.5 mm. and crystallized from ether–alcohol, giving 0.27 g. (44%) of crude hydrocarbon, m. p. 154–156°. After filtering a solution of the material in benzene–ligroin through a tower of alumina, two crystallizations from benzene–ligroin gave light yellow needles, m. p. 171–171.5° (0.11 g.).

Anal. Calcd. for $C_{21}H_{14}$: C, 94.70; H, 5.30. Found: C, 94.47; H, 5.37.

The **picrate** formed silky bronze colored needles from benzene–ligroin and melted at 181.5–182.5°.

Anal. Calcd. for $C_{21}H_{14} \cdot C_6H_3O_7N_3$: N, 8.48. Found: N, 8.34.

The **trinitrobenzene derivative** crystallized as brilliant red needles from benzene-ligroin, m. p. 209–210°.

Anal. Calcd. for $C_{21}H_{14} \cdot C_6H_3O_6N_3$: N, 8.77. Found: N, 8.73.

5-Methyl-3,4-benzpyrene.—The liquors remaining from the methyllithium reaction after removal of the ketone VII were evaporated and the oily residue was distilled with zinc dust as above. On vacuum distillation of the product a yellow solid was obtained which when crystallized from benzene–ligroin melted at 130–155°. For purification this was converted into the trinitrobenzene derivative. After three crystallizations from benzene, which raised the melting point to 227–228°, this was decomposed by adsorption of the nitro component on alumina from benzene. After one crystallization from ligroin and two from ether–absolute alcohol, the hydrocarbon formed yellow plates, m. p. 215.7–216.2°; yield, 75 mg. (2%).

Anal. Calcd. for $C_{21}H_{14}$: C, 94.70; H, 5.30. Found: C, 94.89; H, 5.16.

The **picrate** formed purplish-black needles from benzene–ligroin, m. p. 207–208° (Found: N, 8.51), and the **trinitrobenzene derivative** formed short, brick-red needles from the same solvent mixture, m. p. 230–231° (Found: N, 8.58).

3,4-Benzpyrene-5-aldehyde.—A mixture of 1 g. of 3,4-benzpyrene, 1.1 g. of methylformanilide, 1.1 g. of phosphorus oxychloride, and 1 cc. of *o*-dichlorobenzene was warmed on the steam-bath for two hours; the solution became deep red and hydrogen chloride was evolved. The reaction mixture was poured into an aqueous solution of 5 g. of sodium acetate crystals and the solvent was removed with steam. The residual crystalline solid on crystallization from glacial acetic acid gave 1 g. (90%) of orange-yellow plates, m. p. 201–203°, and after two more crystallizations from benzene–ligroin the melting point was raised to 202.5–203.5°.

Anal. Calcd. for $C_{21}H_{12}O$: C, 90.00; H, 4.32. Found: C, 89.58; H, 4.39.

The **hydrazone** was prepared by adding 1 cc. of hydrazine hydrate in alcohol to a hot solution of 0.45 g. of the aldehyde in the minimum amount of dioxane. After warming for five minutes, more alcohol was added until the product began to crystallize. The hydrazone separated as fine yellow needles, m. p. 219.5–220.5°, dec. Since further crystallization from dioxane–alcohol resulted in decomposition, the original crystallizate, after thorough washing with alcohol, was analyzed.

Anal. Calcd. for $C_{21}H_{14}N_2$: N, 9.52. Found: N, 9.57.

For conversion to **5-methyl-3,4-benzpyrene,** 0.35 g. of the hydrazone was heated with a solution from 1 g. of sodium and 5 cc. of absolute alcohol for ten hours at 210–215°. The product was obtained directly as a solid; it was purified by passage of a benzene solution through a tower of alumina and crystallized from ether–absolute alcohol, giving 0.22 g. (70%) of yellow plates melting at 216.2–216.7° and giving no depression when mixed with the sample obtained from the methyllithium reaction product.

Summary

Methylcholanthrene and 3,4-benzpyrene are oxidized very readily by lead tetraacetate and seem to be more susceptible to attack by this reagent than other polynuclear hydrocarbons studied. 3,4-Benzpyrene gives a single monoacetoxy derivative in nearly quantitative yield, and methylcholanthrene is converted chiefly into the 15-acetoxy compound and in smaller part into 15-keto-20-methylcholanthrene.

On reaction with methylformanilide, 3,4-benzpyrene is converted in excellent yield into a single product which probably is the 5-aldehyde. This has been related to one of two new methyl-3,4-benzpyrenes obtained from products of the addition of methyllithium to a synthetic trimethylbenzanthrone and regarded as the 5- and 6-isomers.

The behavior of polynuclear hydrocarbons in the lead tetraacetate oxidation, aldehyde reaction, and diazo coupling test shows that the most powerfully carcinogenic hydrocarbons of the series possess special susceptibility to substitutions, and certain indications are discernible of a relationship between this specific type of chemical reactivity and carcinogenic activity.

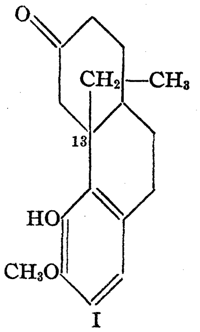
CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASS. RECEIVED AUGUST 4, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Synthesis of Phenanthrene and Hydrophenanthrene Derivatives. VIII. Substances Related to Degradation Products of Morphine

BY LOUIS F. FIESER AND H. L. HOLMES

In a previous paper[1] we described a diene synthesis by which it is possible to obtain hydrophenanthrene derivatives having a carboxyl group at a quaternary carbon atom corresponding to the 13-position of the morphine alkaloids. According to the Gulland–Robinson formula for morphine, these alkaloids contain an ethanamine chain joined at the hydrocarbon end to the 13-position of the hydrophenanthrene skeleton, but the exact position of attachment is the one remaining point of uncertainty concerning the structures. The new synthesis provides a possible method of obtaining compounds of known structure which, if the Gulland–Robinson formula is correct, may be obtainable from the alkaloids by degradation, and in the present work we have investigated the possibility of synthesizing suitable compounds.



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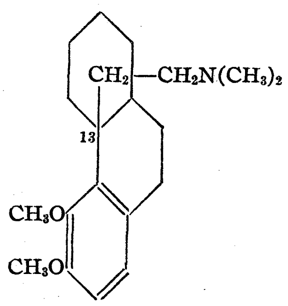

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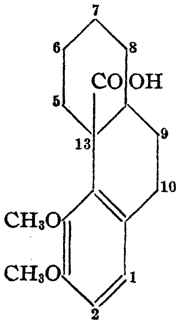

III

Degradative work on the alkaloids has not as yet provided many substances which seem within reach by the diene synthesis. A ketoethyloctahydromorphenol methyl ether of the probable structure I (Gulland–Robinson formulation) was obtained by Wieland and Kotake[2] and by Cahn[3] by various degradations, but Cahn encountered difficulties on attempting to reduce the carbonyl group and to methylate the compound. Speyer and Koulen[4] obtained as the methiodide a substance described as dihydrodesoxytetrahydro-α-methylmorphimethine and probably having the structure II, but an attempted Hofmann degradation to the corresponding vinyl compound apparently proceeded anomalously with demethylation at the 4-position and ring formation between the liberated hydroxyl and vinyl groups.[5] Our first objective was the synthesis of the acid III, which may be obtainable from these or other degradation products, and we also made some study of possible methods of lengthening the carbon side chain.

The synthesis of 3,4-dimethoxy-5,6,7,8,9,10,13,14-octahydrophenanthrene-13-carboxylic acid (III) was accomplished by application of the scheme of synthesis previously described. γ-(3,4-Dimethoxyphenyl)-butyric acid (IV) was prepared from veratrole by condensation with succinic anhydride and reduction, by the procedures already reported.[6,7] This acid undergoes cyclization very readily at the position para to one of the methoxyl groups,[8,9] and since it was

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[1] Fieser and Holmes, THIS JOURNAL, **58**, 2319 (1936).

[2] Wieland and Kotake, *Ann.*, **444**, 69 (1925).

[3] Cahn, *J. Chem. Soc.*, 702 (1930).

[4] Speyer and Koulen, *Ann.*, **438**, 34 (1924).

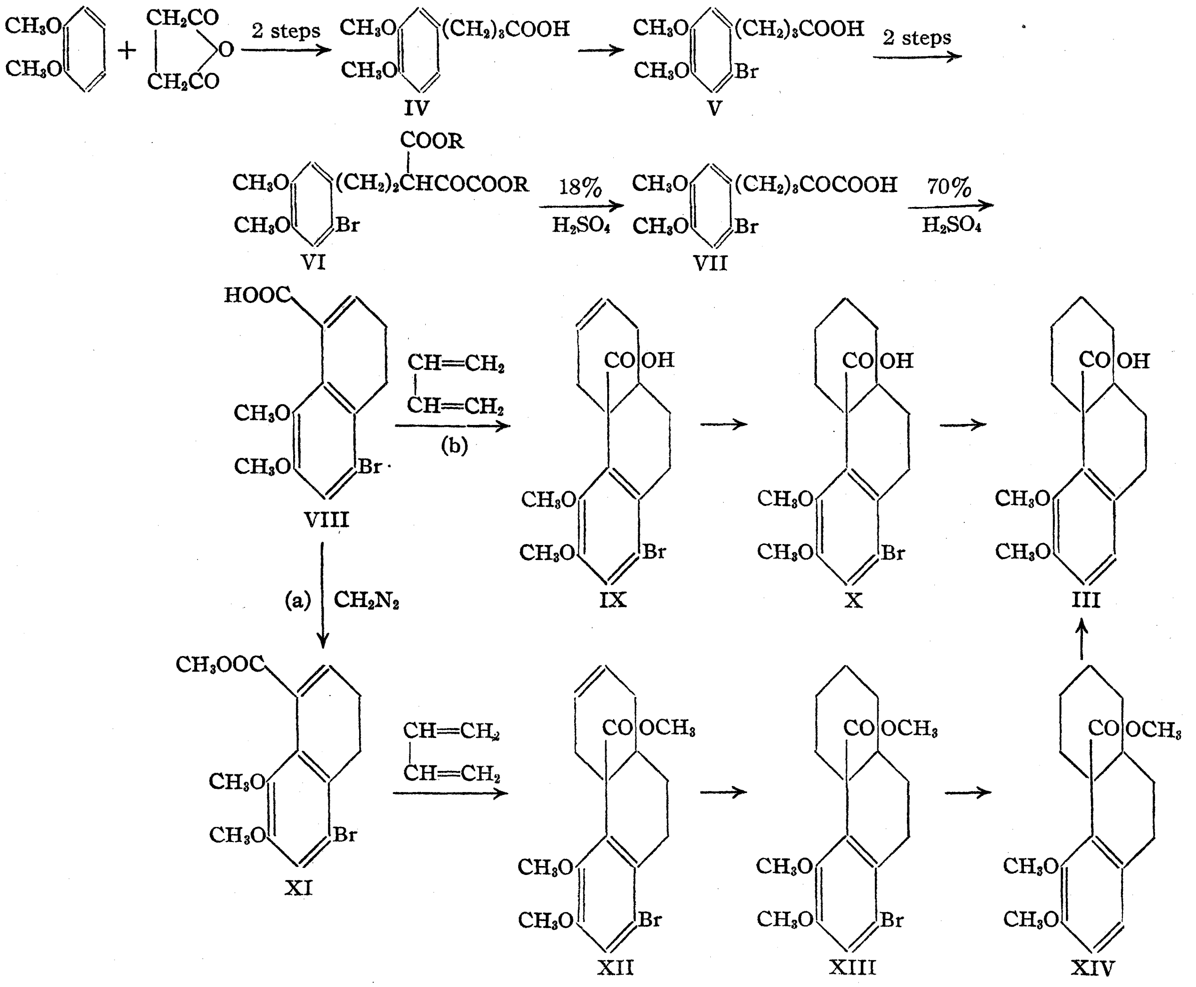
[5] Cahn, *J. Chem. Soc.*, 2562 (1926).

[6] Fieser and Hershberg, THIS JOURNAL, **58**, 2314 (1936).

[7] Martin, *ibid.*, **58**, 1438 (1936).

[8] Haworth, *J. Chem. Soc.*, 1485 (1932).

[9] Haworth, Mavin and Sheldrick, *ibid.*, 1423 (1934).



desired to effect cyclization of a derivative of the acid at the alternate position, the favored site of substitution was blocked by bromination. Haworth[9] described the bromo acid V briefly, but provided no rigid proof of the structure; this was supplied in the present work by permanganate oxidation to the known 2-bromo-4,5-dimethoxybenzoic acid, identical with a sample prepared from vanillin.[10] The ester of the bromo acid V was condensed with oxalic ester and the product (VI) hydrolyzed with dilute sulfuric acid to the α-keto acid VII. Cyclization with strong sulfuric acid gave in good over-all yield the dihydronaphthoic acid VIII desired for the diene addition reaction. It was observed incidentally that the α-keto acid VII is converted into a crystalline enol acetate on attempted cyclization with acetic anhydride–acid and zinc chloride catalyst.

Since in the examples previously investigated[1] the Diels–Alder reaction had been run only on the esters of α,β-unsaturated acids, our first trials were made with the ester XI (route a). Since attempted esterification of the acid VIII by the Fischer method was unsuccessful, the ester had to be made with the use of diazomethane. As anticipated from the previous observations,[1] the addition of butadiene to the bromo ester XI proceeded poorly, and the best conversion to the hexahydrophenanthrene derivative XII was about 9%, considerable starting material being recovered after heating at 230° for seven days. As in other cases, the reaction with 2,3-dimethylbutadiene proceeded much better (54% yield). The hexahydro ester XII was obtained in a pure crystalline condition and was easily hydrogenated in the presence of platinum catalyst to the octahydro ester XIII, but saponification of the highly hindered ester group could not be accomplished without disturbance of the bromine atom. The bromine was removed, if with difficulty, by hydrogenation of XIII in the presence of a large amount

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(10) Heap, Jones and Robinson, *J. Chem. Soc.*, 2021 (1927).

of palladium catalyst on barium sulfate with sodium acetate as acceptor for the hydrogen bromide. Saponification of the ester group was then accomplished with sodium ethylate at 180°, giving the desired acid III.

On repeating the whole synthesis with larger amounts, we investigated the possibility of using the free dihydronaphthoic acid VIII in the diene reaction in place of the ester, for an expensive reagent is required for the esterification and the subsequent saponification of the hindered ester group must be conducted in a sealed tube. The free acid can indeed be used, and after some exploration conditions were found permitting a better conversion than obtained with the ester. When heated with about two moles of butadiene in the presence of some benzene at 185–190° for one hundred hours, the acid was converted into the addition product IX in 18% yield, and over 50% of the starting material was recovered in a satisfactory condition. At higher temperatures there was some decarboxylation. The addition evidently proceeded in the same steric manner as before, for esterification of the addition product IX gave an ester identical with the product of the addition of butadiene to the bicyclic ester. Saturation of the double bond of IX and removal of the bromine with hydrogen and palladium catalyst gave the dimethoxyoctahydrophenanthrene-carboxylic acid III, identical with that obtained by the alternate method. The shorter route (b) clearly constitutes the better plan of synthesis, and the end-product can be obtained by this method in reasonable quantity if with a rather generous expenditure of time. The accumulation of a quantity of the diene addition product is a tedious process and the removal of bromine is slow and requires large amounts of catalyst.

It remains to be seen if an acid of the structure III can be obtained by the degradation of morphine, codeine, or thebaine, and if this can be done the stereochemical problem will require consideration. The acid has two asymmetric carbon atoms, but the addition apparently gives only one of the two possible *dl*-mixtures. The material obtained in several preparations by both methods (a) and (b) seemed entirely homogeneous, as did the various intermediates. Alder and Stein[11] have noted that at least in low temperature reactions dienes add to activated double bonds exclusively in the *cis* position but that at elevated temperatures *cis*-addition may be followed by rearrangement to the *trans*-configuration. Models (Stuart) of the two diastereomers of III do not indicate any great difference in the strain, and consequently in the energy content, of the two forms, and a rearrangement from the *cis*-configuration therefore seems improbable. The configuration of the alkaloid ring system at this part of the molecule is not known. A few preliminary attempts were made to effect a resolution, but without success. The trials were confined largely to the unsaturated bromo acid IX, using brucine and strychnine as the resolving agents. Should this become a crucial point in the correlation of synthetic and natural products, a solution of the problem might still be possible in case the resolution of the synthetic acid is found to present really serious difficulty. Sinomenine belongs to a stereochemical series opposite to that of the alkaloids of the morphine group and has been degraded to the optical antipode of dihydrothebainone, and a mixture of the acids from the dual degradation of thebaine and sinomenine should yield the synthetic acid or its diastereomer.

Another possibility would be to utilize the dimethoxyoctahydrophenanthrene-13-carboxylic acid III as the starting point for the synthesis of the degradation product II of Speyer and Koulen,[4] but difficulties are to be anticipated in attempting to convert the carboxyl group into an ethanamine chain because of the hindered nature of the functional group and the opportunity for rearrangement associated with the quaternary location. In the present work we have merely explored, with simpler compounds of the series, some of the possible starting points for a lengthening of the side chain. The experiments were made with the addition products of Δ^1-dihydro-α-naphthoic ester and its 6-methoxy derivative with butadiene and 2,3-dimethylbutadiene, and the following observations concerning ethyl 6,7-dimethyl-5,8,9,10,13,14-hexahydrophenanthrene-13-carboxylate (XV) are typical of the rest. The unsaturated hexahydro ester, m. p. 50°, gave a liquid octahydro compound (XVI) on hydrogenation, and on reduction with sodium and isoamyl alcohol it gave in good yield a crystalline carbinol, XVII (m. p. 74°). On hydrogenation this was converted into the corresponding octahydro carbinol, XVIII (m. p. 69°), which was obtained in a more easily purified condition by the Bouveault reduction of the saturated ester XVI. In these reductions

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[11] Alder and Stein, *Angew. Chem.*, **50**, 510 (1937).

with sodium and isoamyl alcohol a small amount of the ester invariably was saponified to the corresponding acid, but the yield of carbinol was good (about 70%), and nearly all of the substances were obtained in a crystalline condition. It is of interest that while ethyl abietate can be reduced to abietinol with sodium and ethyl alcohol,[12] the hydrophenanthrene-13-carboxylic esters are not attacked when ethyl alcohol is used.

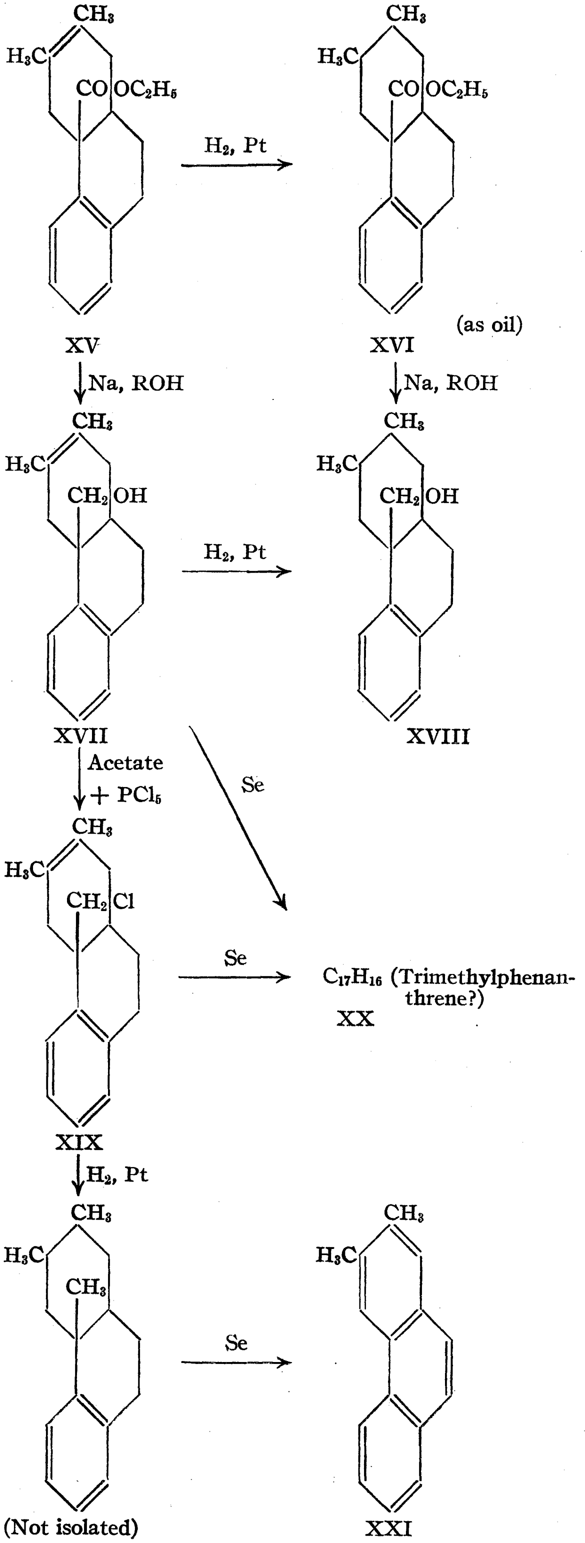
The use of mineral acids was avoided in seeking to transform the carbinols into the corresponding halides, and it was found that the hexahydro carbinol XVII can be converted by the action of phosphorus pentachloride on the liquid acetate into the chloride, XIX. Attempts to convert the chloride into the nitrile, however, were unsuccessful. A Rosenmund reduction of the chloride of one of the 13-carboxylic acids was also tried without success. Selenium dehydrogenation of either the unsaturated chloride (XIX) or the unsaturated carbinol (XVII) seemed to involve some form of rearrangement, for in each case there was obtained in good yield a nicely crystalline product, m. p. 149°, having the composition of a trimethylphenanthrene ($C_{17}H_{16}$). The normal dehydrogenation product, 2,3-dimethylphenanthrene (XXI), was obtained by hydrogenating the unsaturated chloride to the point of replacement of most of the halogen and treating the oily hydrocarbon with selenium. This observation indicates that there probably is no rearrangement of the skeletal structure in the formation of chloride.

Experimental Part[13]

Synthesis of 3,4-Dimethoxy-5,6,7,8,9,10,13,14-octahydrophenanthrene-13-carboxylic Acid (III)

γ-(2-Bromo-4,5-dimethxoyphenyl)-butyric Acid (V).—A solution of 387 g. of γ-(3,4-dimethoxyphenyl)-butyric acid[6,7] (b. p. 210° at 6 mm.) in 2400 cc. of glacial acetic acid was stirred mechanically in a cooling bath and treated with 122 cc. of bromine, added by drops while controlling the temperature to 4°. The bromination product soon began to separate as a pale yellow precipitate. The addition required twenty hours, and after stirring for two hours longer the crystalline bromo acid which had separated was collected and washed well with water. The product was colorless and weighed 469 g. (83%); m. p. 130–134.5°. A purified sample melted at 137.8–138.8° (Haworth,[8] 135–136°, uncorr.).

The ethyl ester, prepared by Fischer esterification, was suitable for use after distillation; b. p. 220–222° (17 mm.); yield from 50 g. of acid, 49.6 g. (91%). The ester crystallizes from ether in elongated, stout prisms, m. p. 49.5–50.5°.



For proof of structure a sample of the ester was refluxed with aqueous alkali and excess permanganate. The acidic product recovered from the filtrate was crystallized from alcohol, giving colorless needles, m. p. 184–185°.

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[12] Ruzicka and Meyer, *Helv. Chim. Acta*, **5**, 581 (1922).

[13] All melting points are corrected.

There was no depression on admixture with a sample of 2-bromo-4,5-dimethoxybenzoic acid prepared according to Heap, Jones, and Robinson,[10] m. p. 185–186° (compare 185°[14]).

Ethyl α-Oxalyl-γ-(2-bromo-4,5-dimethoxyphenyl)-butyrate (VI).—Forty grams of ethyl γ-(2-bromo-3,4-dimethoxyphenyl)-butyrate was condensed with 20 g. of ethyl oxalate in the usual manner, using sodium ethylate (2.78 g. of sodium). On decomposing the sodium derivative in ice-cold dilute sulfuric acid the condensation product crystallized in long, feathery needles; total yield, 52 g. (96%), m. p. 69–70°. Recrystallized from ether–petroleum ether, it melted at 74.7–75.3°.

Anal. Calcd. for $C_{18}H_{23}O_7Br$: C, 50.31; H, 5.37. Found: C, 50.11; H, 5.38.

α-Keto-δ-(2-bromo-3,4-dimethoxyphenyl)-valeric Acid (VII).—The oxalyl ester VI (42 g.) was refluxed with 18% sulfuric acid (500 cc.) for twenty hours, and on cooling the mixture the keto acid solidified in round nodules. The material was dissolved in sodium carbonate solution and, after clarification, precipitated. The solid weighed 29.1 g. (90%), m. p. 85–87°. Crystallized for analysis from dilute acetic acid the substance formed silky needles, m. p. 93–94°.

Anal. Calcd. for $C_{13}H_{15}O_5Br$: C, 47.15; H, 4.57; Br, 24.13. Found: C, 47.49; H, 4.96; Br, 24.09.

The ethyl ester boils at 225–227° (9 mm.). Both the acid and the ethyl ester give a brownish-black coloration with ferric chloride solution. The **enol acetate**[15] was obtained by refluxing 2 g. of the keto acid with 5 cc. of glacial acetic acid, 5 cc. of acetic anhydride, and 0.1 g. of zinc chloride for one hour, cautiously adding water, and allowing the solution to cool. The reaction product separated in a nearly pure condition (1.9 g.), m. p. 147–149°; on recrystallization from dilute acetic acid it formed slender needles, m. p. 148.4–149°. Saponification of the acetate gave the keto acid, m. p. 93–94°.

Anal. Calcd. for $C_{15}H_{17}O_6Br$: C, 48.27; H, 4.59; neut. equiv., 373. Found: C, 48.42; H, 4.83; neut. equiv., 369.

5-Bromo-7,8-dimethoxy-Δ'-dihydro-1-naphthoic Acid (VIII).—A total of 375 g. of the keto acid VII was cyclized in 65-g. batches, each batch being stirred vigorously with a mixture of 235 cc. of concentrated sulfuric acid and 135 cc. of water at 80° for one-half hour. The keto acid soon melted to a brown gum and the cyclization product then began to separate in a crystalline condition. The mixture was cooled, poured onto ice and water, and on vigorous stirring the product solidified completely in the form of pale buff-colored granules. After thorough washing, the acid was purified through the sodium salt, which crystallizes as flat white plates from a solution containing excess sodium carbonate (40 g. in 750 cc. of water for each 65-g. batch). An aqueous solution of the purified salt (25 g.) on acidification at 60° gave 17 g. (average) of acid, m. p. 168–171°. One crystallization from dilute alcohol raised the melting point to 171.5–172.5°, and the total yield of this material was 196 g. (55%). Further purification gave colorless plates, m. p. 172–173°.

Anal. Calcd. for $C_{13}H_{13}O_4Br$: C, 49.86; H, 4.19; Br, 25.52; neut. equiv., 313. Found: C, 49.92; H, 4.31; Br, 25.31; neut. equiv., 316.

The methyl ester (XI), prepared with diazomethane, distilled at 174–175° (2 mm.) and was obtained as a viscous oil in 97% yield. It slowly solidified on standing, and when purified by crystallization from hexane formed blades, m. p. 76–77°.

5-Bromo-7,8-dimethoxy-1,2,3,4-tetrahydro-1-naphthoic acid was obtained by hydrogenation of VIII in alcohol in the presence of Adams catalyst. It crystallized from dilute alcohol as long, flat needles, m. p. 147–148°.

Anal. Calcd. for $C_{13}H_{15}O_4Br$: C, 49.54; H, 4.84. Found: C, 49.48; H, 4.99.

7,8-Dimethoxy-1,2,3,4-tetrahydro-1-naphthoic Acid.—Hydrogenation of the above compound (0.9 g.) in absolute alcohol (40 cc.) was accomplished in the presence of palladium oxide catalyst (35 mg.) in about three hours. The recovered product (0.6 g.) was bromine free and crystallized from benzene–hexane as elongated prisms, m. p. 119.5–120°.

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.82. Found: C, 66.36; H, 6.66.

Methyl 1-Bromo-3,4-dimethoxy-6,7-dimethyl-5,8,9,10,-13,14-hexahydrophenanthrene-13-carboxylate.—The ester XI (14 g.) was heated with 2,3-dimethylbutadiene (5 g.) at 175–185° for thirty-one hours and the mixture on distillation gave a fraction boiling at 190–205° (2 mm.) and giving 9.6 g. (54%) of crystals from dilute alcohol. Further crystallization from alcohol gave plates, m. p. 154–155°. Some starting material was recovered from the fore-run.

Anal. Calcd. for $C_{20}H_{25}O_4Br$: C, 58.69; H, 6.16; Br, 19.52. Found: C, 58.91; H, 6.14; Br, 19.32.

This substance proved to be very resistant to hydrogenation under various conditions.

Methyl 1-Bromo-3,4-dimethoxy-5,8,9,10,13,14-hexahydrophenanthrene-13-carboxylate (XII).—In the most successful experiments 20 g. of the unsaturated ester XI was heated in a thick-walled Pyrex tube with 15 g. of butadiene at 220–230° for seven days. After several fractional distillations 9.2 g. of starting material was recovered and the bulk of the addition product was collected in an 8.6-g. fraction boiling at 185–196° (3 mm.). On crystallization of this from petroleum ether it gave in the first crop 3.2 g. more starting material, and the next crystallizate consisted of crude addition product (2.4 g.) m. p. 89–100°. Two further crystallizations raised the melting point to 101–103°, and the average yield, not allowing for recovery of considerable starting material, was 8–9%. The mother liquors contained about 3.4 g. of oil which failed to crystallize. The fully purified ester formed elongated prisms, m. p. 105–106°.

Anal. Calcd. for $C_{18}H_{21}O_4Br$: C, 56.70; H, 5.55; Br, 20.96. Found: C, 56.47; H, 5.67; Br, 21.02.

Methyl 1-Bromo-3,4-dimethoxy-5,6,7,8,9,10,13,14-octahydrophenanthrene-13-carboxylate (XIII).—The addition product XII (2.75 g.) in glacial acetic acid (50 cc.) with Adams catalyst (50 mg.) absorbed one mole of hydrogen in

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[14] Henry and Sharp, *J. Chem. Soc.*, 2286 (1930).

[15] The analogous enol acetate obtained by this method from α-keto-δ-phenylvaleric acid melted at 98.6–99.1° (Calcd.: C, 68.85; H, 6.03. Found: C, 68.68; H, 6.13); that from α-keto-δ-(4-methoxyphenyl)-valeric acid melted at 89–90° (Calcd.: C, 63.63; H, 6.10 Found: C, 64.03: H, 6.26).

fifteen minutes. The purified product crystallized from ether as fine needles, m. p. 112.5–113.5°.

Anal. Calcd. for $C_{18}H_{23}O_4Br$: C, 56.41; H, 6.06; Br, 20.85. Found: C, 56.45; H, 6.28; Br, 20.61.

Methyl 3,4-Dimethoxy-5,6,7,8,9,10,13,14-octahydrophenanthrene-13-carboxylate (XIV).—For removal of the bromine, 0.65 g. of XIII in 35 cc. of glacial acetic acid was shaken with hydrogen in the presence of 0.1 g. of fused sodium acetate and 2 g. of palladinized barium sulfate.[16] One mole of gas was absorbed in about seventeen hours. After concentration of the filtered solution in vacuum and dilution with water the product separated as a crystalline powder (0.49 g.), m. p. 135–142°. Four recrystallizations from dilute acetic acid raised the m. p. to 141.5–142.5° (previous softening), and crystallization from petroleum ether then gave glistening cubes, m. p. 142.8–143.2°. The substance gave no test for bromine.

Anal. Calcd. for $C_{18}H_{24}O_4$: C, 71.03; H, 7.94. Found: C, 70.85; H, 7.65.

In another experiment the unsaturated bromo ester XII (0.85 g.) was hydrogenated in acetic acid using the palladium catalyst (2 g.). Absorption of gas was rapid at first and then slower, and on working up the product after four hours there was obtained 0.65 g. (94%) of the saturated bromine-free ester, m. p. 142.5–143°.

3,4 - Dimethoxy - 5,6,7,8,9,10,13,14 - octahydrophenanthrene-13-carboxylic Acid (III). Method (a).—The ester XIV (0.2 g.) was heated in a sealed tube with a solution from 0.9 g. of sodium and 15 cc. of absolute alcohol at 175–180° for eighteen hours. The solidified product was taken up in water and the solution was shaken with dimethyl sulfate until neutral, cooled to 0°, and acidified. The acid which separated was taken into ether, extracted from the ether with sodium bicarbonate solution, and obtained on acidification as a cream colored solid; yield, 75 mg. (39%). Evaporation of the ethereal solution gave 0.1 g. of unchanged ester, m. p. 140–141°. The acid crystallized from dilute alcohol in the form of flat needles, m. p. 202.4–203.4°. It is readily soluble in dilute solutions of sodium bicarbonate and ammonia.

Anal. Calcd. for $C_{17}H_{22}O_4$: C, 70.33; H, 7.64; neut. equiv., 290. Found: C, 70.11; H, 7.39; neut. equiv., 286.

1 - Bromo - 3,4 - dimethoxy - 5,8,9,10,13,14 - hexahydrophenanthrene-13-carboxylic Acid (IX).—The best conditions found for effecting the reaction consisted in heating a mixture of 20 g. of 5-bromo-7,8-dimethoxy-Δ^1-dihydro-1-naphthoic acid, 8 g. of butadiene, and 15 cc. of dry benzene in a sealed tube at 185–190° for one hundred hours. The cooled mixture was diluted with 75 cc. of benzene and refluxed for two hours with a solution of 15 g. of sodium carbonate in 200 cc. of water. The pale yellow aqueous layer was separated from the benzene and polymer, decolorized with Norite, and acidified carefully. The precipitated acid was collected, dried, and crystallized from alcohol to separate the reaction product from the more soluble starting material. The crude addition product collected amounted to 4.3 g. (18%), m. p. 248–252°, dec. One recrystallization brought the m. p. to 256–258°, dec., and the purest sample formed small plates, m. p. 260–261° dec. Dilution of the mother liquors gave 11.1 g. of starting material, m. p. 163–164°.

Anal. Calcd. for $C_{17}H_{19}O_4Br$: C, 55.60; H, 5.21; neut. equiv., 367. Found: C, 55.65; H, 5.55; neut. equiv., 364.

Esterification with diazomethane gave a product which when crystallized from ether–petroleum ether melted at 105–106° and gave no depression when mixed with the ester XII prepared by method (a).

1 - Bromo - 3,4 - dimethoxy - 5,6,7,8,9,10,13,14 - octahydrophenanthrene-13-carboxylic Acid (X).—The unsaturated acid IX (1 g.) in glacial acetic acid (65 cc.) with Adams catalyst (30 mg.) absorbed one mole of hydrogen in twenty minutes, and the product, recrystallized from alcohol, formed glistening plates, m. p. 233–234°; yield, 0.7 g. (70%).

Anal. Calcd. for $C_{17}H_{21}O_4Br$: C, 55.28; H, 5.73. Found: C, 54.65; H, 5.93.

Esterification with diazomethane and crystallization from ether gave an ester melting at 112.5–113.5° and identical with the sample of XIII described above.

3,4 - Dimethoxy - 5,6,7,8,9,10,13,14 - octahydrophenanthrene-13-carboxylic Acid (III). Method (b).—The saturated bromo acid X (0.35 g.) in glacial acetic acid (25 cc.) with palladinized barium sulfate (1 g.) and fused sodium acetate (0.1 g.) in two trials absorbed somewhat less than the theoretical amount of hydrogen in twelve to eighteen hours, when the reaction stopped. Three crystallizations from aqueous alcohol gave 0.2 g. (57%) of bromine-free acid melting constantly at 202–203°. This did not depress the melting point of the sample described above, and the ester formed cubes, m. p. 142.5–143.5°, identical with the other sample of XIV.

Concerning Other Diene Addition Products

In preparing a larger quantity of **ethyl hexahydrophenanthrene-13-carboxylate**[1] 90 g. of the unsaturated ester was heated with 30 g. of butadiene at 170–180° for thirty-six hours, giving 26.2 g. (23%) of purified product, b. p. 197–198° (14 mm.), 214–215° (31 mm.). The corresponding acid on hydrogenation in glacial acetic acid solution gave **octahydrophenanthrene-13-carboxylic acid** in 85% yield as small needles from dilute alcohol, m. p. 144–145°.

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.22; H, 7.88; neut. equiv., 230. Found: C, 78.59; H, 8.20; neut. equiv., 233.

Ethyl octahydrophenanthrene-13-carboxylate, prepared by hydrogenation of the hexahydride, was obtained as a viscous liquid, b. p. 180–181° (16 mm.).

The yield of **ethyl 6,7-dimethylhexahydrophenanthrene-13-carboxylate**[1] was increased considerably by heating 50 g. of the unsaturated ester with 30 g. of the diene at 170–180° for thirty-six hours; yield, 52.5 g. (74%); b. p. 197–198° (14 mm.). Similarly, **ethyl 3-methoxyhexahydrophenanthrene-13-carboxylate**,[1] b. p. 212–215° (17 mm.), was obtained in 31% yield from 30 g. of ester and 15 g. of butadiene at 150–160° for sixty-three hours. 3-Methoxyhexahydrophenanthrene-13-carboxylic acid[1] (1 g.) on dehydrogenation with selenium (2 g.) at 300–320° for twenty-four hours gave 3-methoxyphenanthrene, m. p. 58.5–59.5°; picrate, m. p. 123–124°.

3-Methoxyoctahydrophenanthrene-13-carboxylic acid, prepared from the hexahydride[1] with Adams catalyst in

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[16] Schmidt, *Ber.*, **52**, 409 (1919).

TABLE I

CARBINOLS FROM THE HYDROPHENANTHRENE-13-CARBOXYLIC ESTERS

Substituents	Yield, %	Crystal form	M. p., °C.	B. p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Derivatives of 13-Hydroxymethyl-5,8,9,10,13,14-hexahydrophenanthrene								
6,7-Dimethyl	72	Needles	73–74	Acetate: 176–177 (5 mm.)	84.21	84.41	9.15	9.45
3-Methoxy	43	Prisms	122.4–122.8		77.87	77.86	8.26	8.30
3-Methoxy-6,7-dimethyl	77	Small prisms	66–67		79.35	79.31	8.89	8.72
Derivatives of 13-Hydroxymethyl-5,6,7,8,9,10,13,14-octahydrophenanthrene								
None	77	Fine needles	48.8–49.5	Acetate: 136–138 (3 mm.)	83.28	83.55	9.32	9.47
6,7-Dimethyl	73	Small needles	68–69	203–205 (15 mm.) Acetate: 210–212 (15 mm.)	83.56	83.57	9.90	10.23
3-Methoxy-6,7-dimethyl	70	Micro crystals	76.7–77.9		78.76	79.15	9.55	9.80

acetic acid, formed thin plates from dilute acetic acid, m. p. 174.5–175.5°.

Anal. Calcd. for $C_{16}H_{20}O_2$: C, 73.82; H, 7.75; neut. equiv., 260. Found: C, 74.05; H, 7.90; neut. equiv., 260.

Ethyl 3-methoxy-6,7-dimethylhexahydrophenanthrene-13-carboxylate, prepared from 15 g. of unsaturated ester and 10.6 g. of 2,3-dimethylbutadiene at 120–160° for forty-eight hours and isolated in the usual way, was obtained as a viscous oil, b. p. 197–199° (5 mm.); yield, 17.3 g. (85%). The ester slowly crystallized and when purified from petroleum ether formed crusts of microcrystals, m. p. 67–68°.

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.74; H, 8.52.

Saponification of the above ester with sodium ethylate at 170° for seventeen hours gave in 72% yield **3-methoxy-6,7-dimethylhexahydrophenanthrene-13-carboxylic acid,** which forms glistening, slender needles from dilute alcohol and melts at 164–165°.

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74; neut. equiv., 286. Found: C, 75.90; H, 7.83; neut. equiv., 290.

The chloride of this acid was a liquid, b. p. 215° (15 mm.). Dehydrogenation of the acid (1 g.) with selenium as above gave **3-methoxy-6,7-dimethylphenanthrene,** which crystallized in plates, m. p. 119–120° (0.1 g.), from dilute alcohol. The picrate formed reddish-orange needles from alcohol; m. p. 160–162°.

Anal. Calcd. for $C_{17}H_{16}O$: C, 86.41; H, 6.83. Found: C, 86.22; H, 6.71.

Hydrogenation of the unsaturated acid gave **3-methoxy-6,7-dimethyloctahydrophenanthrene-13-carboxylic acid** as long blades, m. p. 204–206°, from dilute alcohol.

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39; neut. equiv., 288. Found: C, 75.05; H, 8.65; neut. equiv., 288.

Carbinols from the Hydrophenanthrene-13-carboxylic Esters

The following procedure for the preparation of **13-hydroxymethyl-5,6,7,8,9,10,13,14-octahydrophenanthrene** illustrates the general method of conducting the Bouveault reduction of the esters. A solution of 11 g. of ethyl octahydrophenanthrene-13-carboxylate in 250 cc. of isoamyl alcohol was stirred mechanically and kept at 90–95° in a water-bath and 9 g. of sodium was added in small pieces. After the sodium had all reacted the solution was cooled, treated with 8–9 cc. of water added by drops, and stirred for one-half hour at 90–95°. The solvent was then removed by steam distillation, the brown oil extracted with ether, and the washed solution was dried, clarified with Norite, and evaporated. The residual oil was dissolved in petroleum ether (20–40°), and seed was obtained by cooling a portion for several hours in a carbon dioxide bath. The carbinol then crystallized from the main solution on seeding at room temperature, and it was obtained in rosets of fine, feathery needles (colorless). The alkaline layer from the reduction gave an oily product on acidification (1.2 g.), and on purification from dilute alcohol this formed needles, m. p. 144–145°, identical with the sample of octahydrophenanthrene-13-carboxylic acid described above.

The other reductions were conducted in the same manner and the yields, properties, and analyses of the carbinols are recorded in the table. The neutral reaction products usually were not distilled; crystals were obtained by cooling a petroleum ether solution with solid carbon dioxide. The same solvent was used for recrystallization. The presence of the hydroxyl group was shown in representative cases by Zerewitinoff determination (0.88 mole gas) and by the preparation of the acetates, using hydrogen chloride-free acetyl chloride (80% yield). The 6,7-dimethyloctahydro derivative was prepared both by the Bouveault reduction and by hydrogenating the hexahydride in acetic acid in the presence of Adams catalyst; the reaction product in the latter case was not as easily purified as before, but a satisfactory sample was obtained (m. p. 68–69°) giving no depression with the other material. The acidic by-product of the Bouveault reduction, **6,7-dimethyloctahydrophenanthrene-13-carboxylic acid,** has not been described before. It formed long needles from alcohol and crystallized from benzene–hexane in flat prisms, m. p. 189–191°, with some previous softening.

Anal. Calcd. for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58; neut. equiv., 258. Found: C, 79.19; H, 8.95; neut. equiv., 256.

5,6-Dimethyl-13-chloromethylhexahydrophenanthrene (XIX).—The carbinol XVII (4 g.) was converted into the acetate by heating for two hours with one equivalent of purified acetyl chloride and the mixture was poured onto ice and extracted with ether. After washing with bicarbonate solution and water, the solvent was removed and the acetate distilled, b. p. 176–177° (5 mm.); yield, 4.1 g. The viscous oil, which showed no sign of crystallizing, was allowed to stand in dry benzene (10 cc.) with phosphorus pentachloride (12 g.) for two hours, the solution turning brownish-yellow. After refluxing for one-half hour, the mixture was decomposed with ice and water and the product extracted with ether, washed with bicarbonate, dried, and distilled. After several distillations of the yellow oil a fraction was obtained boiling at 196–198° (3 mm.); yield, 2.5 g. (65%).

Anal. Calcd. for $C_{17}H_{21}Cl$: C, 78.30; H, 8.13; Cl, 13.59. Found: C, 77.87; H, 7.76; Cl, 13.19.

In an attempt to prepare the nitrile, 13 g. of the chloride was heated with 2 g. of potassium cyanide in 30 cc. of alcohol at 160–180° for twenty-four hours; repeated distillation gave a fraction boiling at 210–220° (2 mm.) and containing nitrogen (1.8 g.) but this did not solidify and gave only a small amount of oily acidic material on alkaline hydrolysis.

The unsaturated chloride (1.3 g.) absorbed hydrogen fairly rapidly in glacial acetic acid solution in the presence of Adams catalyst, and considerable hydrogen chloride was found to have been produced. The oily reaction product appeared to be a mixture; on dehydrogenation with selenium it gave a solid (0.5 g.), m. p. 59–63°, giving a picrate, m. p. 145–146°. The hydrocarbon recovered from the picrate and crystallized from alcohol formed fluorescent plates, m. p. 77.5–78°. Mixed with **2,3-dimethylphenanthrene** and its picrate, the samples showed no depression.

Dehydrogenation of the unsaturated chloride or carbinol with selenium gave a much less soluble hydrocarbon which after purification by crystallization from alcohol and from hexane formed small scales, m. p. 148–149°. The substance gives a red coloration in alcohol or benzene with picric acid, but no picrate could be isolated. The yield from the carbinol was 66% and from the chloride 35%.

Anal. Calcd. for $C_{17}H_{16}$: C, 92.69; H, 7.32. Found: C, 92.66; H, 7.31.

Summary

As a step toward a proof of the location of the ethanamine chain in the morphine alkaloids, 3,4-dimethoxy-5,6,7,8,9,10,13,14-octahydrophenanthrene-13-carboxylic acid has been synthesized for comparison with a possible degradation product of the alkaloids. The synthesis involves a diene addition to a brominated Δ^1-dihydro-α-naphthoic acid or ester obtained synthetically, the bromine being required to control the direction of cyclization and being removed in the end stages of the synthesis.

In a preliminary study of a possible lengthening of the carbon chain at C_{13}, a number of esters of substituted hexa- and octahydrophenanthrene-13-carboxylic acids have been reduced to the corresponding carbinols.

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Meso Aldehydes of Anthracene and 1,2-Benzanthracene

BY LOUIS F. FIESER AND JONATHAN L. HARTWELL[1]

Substitution reactions of polynuclear aromatic hydrocarbons have gained special interest with the observation that the most actively carcinogenic compounds of the hydrocarbon series show a high degree of susceptibility to diazo coupling[2] and to oxidation with lead tetraacetate.[3,4] Another substitution which it seemed of interest to investigate is the reaction with methylformanilide, which Vollmann, Becker, Corell and Streeck[5] recently applied with success for the conversion of pyrene into pyrene-3-aldehyde.

$$ArH + C_6H_5N(CH_3)CHO \xrightarrow{POCl_3} ArCHO + C_6H_5NHCH_3$$

Previous applications of the reaction were concerned chiefly with ortho–para substitutions of phenol ethers and amines, but the above observation shows that a sufficiently reactive hydrocarbon is capable of entering into the condensation. According to a brief report in the patent literature,[6] anthracene also reacts with methylformanilide. The present investigation of other applications of the reaction was undertaken with the idea that information might be obtained on the relative reactivities of carcinogenic hydrocarbons and in the hope of obtaining derivatives of carcinogens having the reactive aldehydic group.

By modifying slightly the procedure of Vollmann, *et al.*,[5] it was found possible to obtain the known 9-anthraldehyde in 92% yield after heating the reaction mixture for two hours on the steam-bath. 1,2-Benzanthracene reacts less readily, for under the same conditions about half of the hydrocarbon was recovered unchanged and

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(1) Research Fellow of the National Cancer Institute.

(2) Fieser and Campbell, THIS JOURNAL, **60**, 1142 (1938).

(3) Fieser and Hershberg, *ibid.*, **60**, 1893 (1938).

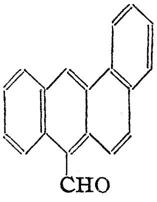
(4) Fieser and Hershberg, *ibid.*, **60**, 2542 (1938).

(5) Vollmann, Becker, Corell and Streeck, *Ann.*, **531**, 1 (1937).

(6) I. G. Farbenindustrie A.-G., English Patent 311,208 (1928).

about half converted into an aldehyde. With 1,2,5,6-dibenzanthracene no aldehyde could be isolated even under forcing conditions; after heating the reaction mixture for twenty-four hours in a sealed tube at 155°, for example, 72% of the starting material was recovered. This is a further example of the marked hindrance at both *meso* positions of the hydrocarbon,[3] and the observation shows clearly that the reaction with methylformanilide can be applied only to specific hydrocarbons at specific nuclear positions. The order of susceptibility of the three hydrocarbons to this substituting agent is: anthracene > 1,2-benzanthracene > 1,2,5,6-dibenzanthracene.

For proof of structure the new aldehyde of the 1,2-benzanthracene series was converted through the hydrazone to the corresponding hydrocarbon, which was found to be identical with 10-methyl-1,2-benzanthracene.[7] The substance, therefore, is 1,2-benzanthracene-10-aldehyde (I), the position of substitution being the same as in nitration[3] and in acetoxylation with lead tetraacetate.[3] The hydrocarbon was obtained from the aldehyde in 84% yield, and the yield of aldehyde, based on the 1,2-benzanthracene consumed, was 64%. The 10-methyl compound, which is a valuable agent for the rapid production of experimental sarcomas, thus can be obtained in a simple three-step process from a commercially available starting material in 54% yield.


I

The new aldehyde, which may be of use in the preparation of interesting conjugated compounds, is being tested for carcinogenic activity by Dr. M. J. Shear. 10-Cyano-1,2-benzanthracene, prepared in good yield by dehydration of the oxime, is of interest in connection with the observations reported by Newman.[8] The aldehyde was also converted into the corresponding 10-α-hydroxyethyl compound by reaction with methylmagnesium iodide.

Preliminary to the preparation of these and other compounds derived from the aldehyde, a few trials were made with 9-anthraldehyde. This yielded 9-methyl-, 9-cyano- and 9-α-hydroxyethylanthracene by the above methods, and it was converted also into 9-anthralmalonic acid. This acid is yellow but yields on crystallization under certain conditions an orange substance which probably is a monohydrate; it was also observed that the acid is unusually resistant to decarboxylation. Methyl-9-anthranylcarbinol when heated with potassium bisulfate yielded a colored tar from which anthracene was isolated. Application of the Tschugaeff reaction gave anthracene and 9-ethylanthracene. Bergmann and Bergmann[9] similarly obtained 9-ethylphenanthrene in certain experiments in investigating the Tschugaeff dehydration of the isomeric methylphenanthrylcarbinol. When heated with phosphorus pentoxide in benzene solution, methyl-9-anthranylcarbinol is converted into a high melting product having the composition of an ether: $[C_{14}H_9CH(CH_3)—]_2O$. It yields anthraquinone on oxidation.

Experimental Part[10]

9-Anthraldehyde.—The procedure of Vollmann, *et al.*,[5] for effecting the condensation of methylformanilide with pyrene was found satisfactory for anthracene, but their method of isolating the reaction product was not well adapted to the present case and a more generally applicable method was developed.

One hundred and thirty-five grams of phosphorus oxychloride was added slowly with external cooling to a mixture of 135 g. of methylformanilide, prepared according to Morgan and Grist,[11] and 100 cc. of dry technical *o*-dichlorobenzene, keeping the mixture at about room temperature, and 89.1 g. of anthracene (colorless, m. p. 215–216.4°) was added. The mixture was stirred mechanically and heated on the steam-bath under protection from moisture, applying heat cautiously at first. As the temperature rose the hydrocarbon gradually dissolved, the solution became deep red and hydrogen chloride was evolved. After the first vigorous reaction was over, heating on the steam-bath with stirring was continued for two hours and the viscous mass was transferred to a large flask, mixed with 1 liter of water containing 480 g. of crystalline sodium acetate and steam distilled. The *o*-dichlorobenzene distils rapidly and products other than the aldehyde are largely retained in the aqueous acetate solution. The undissolved residue consisted of a dark oil which on cooling solidified to a mass of yellow crystals. Collected, washed and crystallized from acetic acid, the aldehyde formed long, deep yellow needles, m. p. 98.4–99.4°, total yield, 94.9 g. (92%). Hinkel, Ayling and Beynon[12] give the m. p. 104–105°.

9-Methylanthracene.—The aldehyde was converted in the hydrazone by adding 2.8 g. of hydrazine hydrate in on

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[7] Fieser and Newman, THIS JOURNAL, **58**, 2376 (1936).

[8] Newman, *ibid.*, **60**, 1368 (1938).

[9] Bergmann and Bergmann, *ibid.*, **59**, 1447 (1937).

[10] All melting points are corrected. Analyses by the Arlington Laboratories.

[11] Morgan and Grist, *J. Chem. Soc.*, **113**, 690 (1918).

[12] Hinkel, Ayling and Beynon, *ibid.*, 344 (1936).

portion to a solution of 11 g. of aldehyde in 250 cc. of alcohol at 70°. After heating at the boiling point for five minutes, 10 cc. of water was added. A large crop of yellow needles, m. p. 108–110°, separated on cooling and a further amount was obtained by dilution of the mother liquor; total yield, 9.9 g. (89%). The hydrazone seems to be subject to slight hydrolysis when dissolved for recrystallization in aqueous alcohol (separation of amorphous orange material); the best sample formed orange-yellow needles, m. p. 118–119.5°, but was not analytically pure.

A mixture of 4.4 g. of the hydrazone and a solution from 0.77 g. of sodium and 25 cc. of absolute ethyl alcohol was shaken in a sealed tube until uniform and heated at 200–205° for twenty-one hours. The cooled mixture was poured into water, neutralized with acetic acid, extracted with ether and the dried solution evaporated. Crystallization of the residue from methanol gave 1.5 g. of the known 9-methylanthracene, m. p. 76.3–77.8° (lit.,[13] 79–80°, 81.5°); picrate, m. p. 133–135° (lit.,[13] 137°, dec.).

9-Cyanoanthracene.—The **oxime** was prepared from 15 g. of 9-anthraldehyde in 300 cc. of alcohol by the addition at 75° of a solution of 5.5 g. of hydroxylamine hydrochloride in 50 cc. of water, neutralized with sodium carbonate. Heated on the steam-bath for ten minutes, diluted with water until cloudy and cooled, the solution deposited 15 g. (93%) of yellow needles in two crops. For purification the substance was precipitated from a filtered solution in hot alkali and crystallized from alcohol, giving long yellow needles, m. p. 165–165.5° (Hinkel, Ayling and Beynon,[12] 186–187°). *Anal.* Calcd. for $C_{15}H_{11}ON$: C, 81.42; H, 4.98. Found: C, 81.72; H, 5.08. A solution of 2 g. of the oxime in 10 cc. of acetic anhydride was refluxed for fifteen minutes, and on cooling the mixture went solid with lemon-yellow needles. Washed with acetic acid and petroleum ether, the product melted at 175.5–177.5°; yield, 1.8 g. (98%). Two crystallizations from glacial acetic acid (strong blue fluorescence) raised the m. p. to 177.5–179°. Karrer and Zeller[14] give the m. p. 170–172°.

Anal. Calcd. for $C_{15}H_9N$: C, 88.61; H, 4.46. Found: C, 88.36; H, 4.54.

9-Anthraldoxime Acetate.—Since our sample of the oxime melted considerably lower than reported,[12] this further derivative was prepared for analysis. Acetyl chloride (6 cc.) was added to the oxime (2 g.) in dry ether (50 cc.), and after five minutes 10% sodium carbonate was added by drops until there was no longer a reaction; from the washed and dried ether layer there was obtained a total of 1.65 g. (70%) of crystalline product. The substance forms long lemon-yellow needles from ether, m. p. 131.5–132°.

Anal. Calcd. for $C_{17}H_{13}O_2N$: C, 77.56; H, 4.98. Found: C, 77.29; H, 4.96.

Condensation of 9-Anthraldehyde with Malonic Acid.—A mixture of 10.3 g. of the aldehyde, 6 g. of malonic acid and 0.5 cc. of pyridine was heated on the steam-bath for six hours, and the cooled mixture was extracted with sodium carbonate solution, which left a residue containing unchanged aldehyde. Acidification of the carbonate extract gave a voluminous, deep yellow precipitate (4.1 g.). Crystallization of the crude product from acetic acid–petroleum ether or from methanol–petroleum ether gave chiefly bright yellow needles of **9-anthralmalonic acid,** melting indefinitely at 240–246°, dec.

Anal. Calcd. for $C_{18}H_{12}O_4$: C, 73.97; H, 4.14; neut. equiv., 146. Found: C, 73.86; H, 4.18; neut. equiv., 138.

The dimethyl ester, prepared with diazomethane and crystallized from ether–petroleum ether, formed large transparent yellow prisms, m. p. 134.5–135.5° (87% yield).

Anal. Calcd. for $C_{20}H_{16}O_4$: C, 75.00; H, 5.04. Found: C, 74.97; H, 4.98.

The malonic acid is quite resistant to decarboxylation. Pyrolysis at 250° for five minutes gave a tar, and little change other than hydration (see below) occurred on refluxing the acid with an acetic–hydrochloric acid mixture. After heating in quinoline with copper bronze or basic copper carbonate at temperatures up to 245° (one hour), 22–27% of the starting material was recovered unchanged.

When the crude, deep yellow condensation product was crystallized from a mixture of methanol, ordinary ether and petroleum ether, large orange prisms were obtained, along with some yellow needles, from which they were easily separated. When heated in a capillary tube the orange material turned yellow at about 80° and showed the m. p. 246°, dec. Even at room temperature the orange prisms soon became coated yellow on the surface, and an analysis of partially transformed material is significant only in showing that the carbon and hydrogen values are lower than for the yellow material (Found: C, 71.00; H, 4.37). The neutralization equivalent determined on a fresh sample (162) is close to that required for a monohydrate (155). The orange hydrate gives the yellow needles of the anhydrous acid on crystallization from acetic acid–petroleum ether. The orange prisms on treatment with diazomethane give yellow prisms, m. p. 134.5–135.5°, identical with the dimethyl ester described above.

Methyl-9-anthranylcarbinol.—This was prepared by adding 30 g. of the aldehyde in 300 cc. of benzene to the Grignard reagent from 21.5 g. of methyl iodide and 4.05 g. of magnesium in 400 cc. of ether and refluxing for one-half hour. After adding ammonium chloride solution and working up the product there was obtained in all 29.6 g. (92%) of satisfactory material. Crystallization from ether–petroleum ether gave glistening, colorless needles having a blue fluorescence in daylight and a blue-violet fluorescence in ultraviolet light; m. p. 125–126.5°.

Anal. Calcd. for $C_{16}H_{14}O$: C, 86.46; H, 6.81. Found: C, 86.62; H, 6.62.

The only crystalline product obtained on heating the carbinol with potassium bisulfate was anthracene, and sulfuric acid of various strengths gave only colored tars. In a trial of the Tschugaeff reaction 2.5 g. of the carbinol was treated in xylene with 0.35 g. of sodium, and after refluxing for two days the dark liquid was cooled and treated with 3 cc. of carbon bisulfide, followed by 3 cc. of methyl iodide. After refluxing for about one hour the mixture turned yellow and sodium chloride precipitated. The filtered solution was then evaporated and the product distilled at 23 mm. From the distillate there was obtained a crystalline product, m. p. 215.5–217°, identified as anthracene, and a trinitrobenzene derivative, m. p. 122.5–123.5°,

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[13] Krollpfeiffer and Branshied, *Ber.*, **56**, 1617 (1923); Sieglitz and Marx, *ibid.*, **56**, 1619 (1923).

[14] Karrer and Zeller, *Helv. Chim. Acta*, **2**, 485 (1919).

found to be that of **9-ethylanthracene.** A sample of this hydrocarbon was prepared from anthrone and ethylmagnesium bromide according to Sieglitz and Marx[13] in 89% yield, m. p. 56–58°. **9-Ethylanthracene–trinitrobenzene** from this source crystallized from ether–benzene in the form of bright red needles, m. p. 125.3–125.6° (no depression with the above product).

Anal. Calcd. for $C_{16}H_{14}\cdot C_6H_3O_6N_3$: C, 63.00; H, 4.09. Found: C, 62.71; H, 4.15.

In another attempted dehydration the carbinol (14.5 g.) was refluxed in benzene (250 cc.) with excess phosphorus pentoxide for about one hour, the solution was decanted, and the residue was treated with benzene and water and extracted thoroughly with benzene. The washed and dried benzene solution was concentrated somewhat and passed through a tower of activated alumina. Material collecting in blue and deep yellow zones at the top was discarded while that adsorbed in light yellow and colorless (fluorescent) zones was washed into the filtrate with fresh benzene. The solution was filtered through a fresh tower and concentrated, giving in three crops 8.7 g. (35%) of nearly colorless needles. After further purification by repeated crystallization from benzene–ligroin the substance formed glistening, colorless needles having a blue fluorescence in ultraviolet light and melting at 247.5–248°, with some previous softening.

Anal. Calcd. for $C_{32}H_{26}O$: C, 90.11; H, 6.15. Found: C, 89.67; H, 6.30.

This substance, which evidently is an ether, yielded anthraquinone (mixed m. p.) on oxidation with chromic acid in acetic acid solution. No other crystalline product was obtained as such or as the trinitrobenzene derivative from the oily material from the mother liquor.

1,2-Benzanthracene-10-aldehyde.—The 1,2-benzanthracene employed was prepared as described by Bachmann.[15] The yellow color was removed by two treatments with lead tetraacetate[3] but the method of chromatographic adsorption of the chrysogen on activated alumina from benzene solution seemed more satisfactory for large-scale operation. Colorless material, m. p. 160.5–161°, was obtained in this way with little loss.

Phosphorus oxychloride (24.8 g.) was added at a temperature controlled to 25° to 24.8 g. of methylformanilide and 18.5 cc. of *o*-dichlorobenzene; 21 g. of 1,2-benzanthracene was introduced and the mixture heated on the steam-bath with occasional shaking until the hydrocarbon had dissolved (twenty minutes). After a total of two hours the mixture was processed as above and the solidified residue from the steam distillation crystallized from glacial acetic acid (slow cooling). Yellowish plates of the hydrocarbon and yellow prisms of the aldehyde were deposited together. A separation was accomplished most conveniently as follows. The mixture of crystals was collected, washed, dried, moistened with a little alcohol and shaken thoroughly with about 100 cc. of water. The prisms settle rapidly, leaving the plates suspended, and by decanting the suspension and repeating the flotation several times a fairly clean separation can be effected. The two crude products were dried and crystallized from glacial acetic acid (decolorizing carbon), giving in all 8.3 g. of slightly yellow hydrocarbon, the bulk of which melted at 156–159° (no depression with starting material), and 8.1 g. of aldehyde (64%, based on material consumed), m. p. 147–148°. The aldehyde on further purification formed yellow, prismatic needles, m. p. 147.5–148°.

Anal. Calcd. for $C_{19}H_{12}O$: C, 89.03; H, 4.72. Found: C, 89.00; H, 4.98.

The hydrazone was prepared by adding 1 g. of hydrazine hydrate to a solution of 2.6 g. of the aldehyde in 350 cc. of boiling alcohol and heating the mixture just below the boiling point for fifteen minutes. On cooling, the product separated almost completely in the first crop as yellow needles, m. p. 187.5–188°; yield, 2.2 g. (84%). Recrystallization from absolute alcohol did not alter the m. p.

Anal. Calcd. for $C_{19}H_{14}N_2$: C, 84.42; H, 5.22. Found: C, 84.38; H, 5.38.

10-Methyl-1,2-benzanthracene.—The hydrazone (1.9 g.) was heated in a sealed tube with the reagent from 0.27 g. of sodium and 9 cc. of absolute alcohol for ten hours at 205–210°. After dilution with water and acidification of the mixture, the nearly colorless solid when collected and dried was found to melt at 136.5–139°; yield 1.7 g. (quantitative). One crystallization from acetic acid gave faintly yellow, glistening flat needles, m. p. 139.5–140.5°, which did not depress the m. p. of a synthetic sample,[7] m. p. 140.2–140.8°.

1,2-Benzanthracene-10-aldoxime.—A mixture of 2 g. of the aldehyde, 250 cc. of alcohol, 3.13 g. of sodium acetate crystals and 0.93 g. of hydroxylamine hydrochloride was heated just below boiling for fifteen minutes, and the solution was filtered and cooled. The product which separated (1.7 g.) on recrystallization from absolute alcohol formed crusts of light yellow needles melting at 203.5–204.5°, and remelting at 231–232.5°, dec.

Anal. Calcd. for $C_{19}H_{13}ON$: C, 84.11; H, 4.83. Found: C, 83.82; H, 4.90.

10-Cyano-1,2-benzanthracene.—After refluxing the oxime (1.35 g.) with acetic anhydride for fifteen minutes, the solution set to a thick paste of yellow crystals of the nitrile on cooling; m. p. 188–189.5°, yield, 1.25 g. (99%). Recrystallized from glacial acetic acid, it formed light yellow blades, m. p. 188.5–189.5°.

Anal. Calcd. for $C_{19}H_{11}N$: C, 90.09; H, 4.38. Found: C, 90.47; H, 4.40.

Methyl-10-benzanthranylcarbinol.—Prepared as above from 1,2-benzanthracene-10-aldehyde and methylmagnesium iodide, this carbinol was obtained in a satisfactory crystalline condition from ether–petroleum ether in 56% yield. Recrystallized from methanol it formed nearly colorless prisms, m. p. 148–150°.

Anal. Calcd. for $C_{20}H_{16}O$: C, 90.27; H, 5.92. Found: C, 90.55; H, 5.51.

Summary

Methylformanilide in the presence of a condensing agent reacts less readily with 1,2-benzanthracene than with anthracene, and does not react with 1,2,5,6-dibenzanthracene even under considerably more drastic conditions. The prod-

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[15] Bachmann, *J. Org. Chem.*, **1**, 349 (1936).

uct from 1,2-benzanthracene is the 10-aldehyde, and this on Wolff–Kishner reduction affords the carcinogenic 10-methyl compound. The 10-nitrile and 10-α-hydroxyethyl derivatives have also been prepared and various reactions of 9-anthraldehyde investigated.

CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASS. RECEIVED AUGUST 18, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

The Preparation of α- and β-Gentiobiose Octaacetates

BY DELBERT DANIEL REYNOLDS AND WILLIAM LLOYD EVANS[1]

Recent investigations in this Laboratory gave rise to a need for considerable quantities of β-gentiobiose octaacetate. The five most important methods for its preparation are as follows: (1) isolation from gentian root,[2] (2) the action of emulsin on glucose to form gentiobiose, which is then connected to β-gentiobiose octaacetate,[3,4] (3) the catalytic hydrogenolysis of amygdalin followed by acetylation,[5] (4) separation from the commercial mother liquors ("Hydrol") obtained in the manufacture of glucose[6] and (5) the condensation of acetobromoglucose with β-*d*-glucose-1,2,3,4-tetraacetate by means of the Königs–Knorr reaction.[7]

The inferior quality of most gentian root renders the first method undesirable. The second method proved objectionable for two reasons, namely, (1) from ten to twelve weeks are required to complete the synthesis, and (2) emulsin is not readily available. The third method has not been tried in this Laboratory because of the relatively high cost of amygdalin. Since the percentage of gentiobiose in "Hydrol" varies greatly, this method leaves much to be desired.

A yield of 23.4% of the theoretical value has been reported for the fifth method.[7] This low yield may be attributed to numerous possible side reactions. The most probable of these is the reaction of acetobromoglucose with water in the presence of silver oxide to form β-*d*-glucose-2,3,4,6-tetraacetate, silver bromide and water. The water formed in this reaction may react with more acetobromoglucose, thus setting up a series of changes which would continually use up the acetobromo compound. Moreover, the β-*d*-glucose-2,3,4,6-tetraacetate may react with acetobromoglucose in the presence of silver oxide to form a trehalose octaacetate and more water. Accordingly, the yield of the β-gentiobiose octaacetate would be greatly lowered.

It was the purpose of this work to make the latter method a practical one for the preparation of β-gentiobiose octaacetate by reducing these side reactions to a minimum. This may be accomplished only if the reaction is carried out under anhydrous conditions. Such conditions are realized by (1) ensuring complete absence of water at the beginning of the reaction and (2) removal of the water from the reaction mixture as rapidly as it is formed, thus keeping the concentration of water in the reaction mixture relatively small at any given time. A preliminary stirring of the tetraacetate, silver oxide and chloroform with a large excess of Drierite assures complete absence of water when the reaction is begun. The addition of a chloroform solution of acetobromoglucose over a considerable period of time, as opposed to adding it in one large portion, permits only a small amount of water to be formed at any given time. The water formed during the reaction may be removed by employing an effective internal desiccant. Studies in this Laboratory[8] have shown that anhydrous calcium sulfate (Drierite) is an excellent substance for this purpose. Other investigators[9] have used powdered calcium chloride in similar reactions. By proceeding with the foregoing facts in mind, β-gentiobiose octaacetate has been obtained in yields as high as 82% of the theoretical value.

After β-gentiobiose octaacetate had been obtained in good yields, it seemed reasonable to believe that α-gentiobiose octaacetate might be prepared by the same method even though α-*d*-glucose-1,2,3,4-tetraacetate could be obtained

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(1) Presented at the Milwaukee Meeting of the American Chemical Society, September 8, 1938.

(2) E. Bourquelot and H. Herissey, *Compt. rend.*, **132**, 571 (1901); *Bull. Soc. chim.*, [3] **29**, 363 (1903).

(3) E. Bourquelot, H. Herissey and J. Coirre, *Compt. rend.*, **157**, 732 (1913).

(4) J. F. Leete, Ph.D. Dissertation, The University of Greifswald, Greifswald, 1929.

(5) M. Bergmann and W. Freudenberg, *Ber.*, **62**, 2783 (1929).

(6) H. Berlin, THIS JOURNAL, **48**, 2627 (1926).

(7) B. Helferich and W. Klein, *Ann.*, **450**, 219 (1926).

(8) L. C. Kreider and W. L. Evans, THIS JOURNAL, **58**, 797 (1936).

(9) B. Helferich, E. Bohm and S. Winkler, *Ber.*, **63**, 990 (1930).

only as a sirup. Since the preparation of 6-trityl-*β-d*-glucose-1,2,3,4-tetraacetate is always accompanied by the formation of the *α*-isomer, the sirupy *α-d*-glucose-1,2,3,4-tetraacetate may be prepared advantageously from this source. This affords a new and convenient method for the synthesis of *α*-gentiobiose octaacetate. Thus the over-all yield of gentiobiose octaacetate is greatly increased.

Experimental Part

Purification of Chloroform.—U. S. P. chloroform (500 cc.) was shaken with 12% sulfuric acid for one hour on a mechanical shaker. The chloroform layer was separated, neutralized by a saturated solution of sodium bicarbonate and washed well with water. It was then shaken for an hour with calcium chloride (100 g.), filtered and distilled. After drying for a short time over phosphorus pentoxide, the chloroform was redistilled and stored over Drierite.

Silver Oxide.—The silver oxide was prepared according to the method of Helferich and Klein.[7]

Trityl Chloride.—The trityl chloride was prepared after the method of Gomberg[10] in a modified apparatus and under such conditions that the pure compound was obtained. A mixture of anhydrous aluminum chloride (150 g.) and dry thiophene-free benzene (500 cc.) was placed in a two-liter wide-mouthed bottle equipped with a mercury-sealed stirrer, a dropping funnel and a side tube leading to a beaker of water. Stirring was begun and a mixture of dry carbon tetrachloride (100 cc.) and dry benzene (70 cc.) was added through the dropping funnel. The solution was stirred for an additional hour and then refluxed in a round-bottomed flask until hydrogen chloride was no longer evolved. It was then cooled and poured into a three-liter separatory funnel containing 350 g. of ice and 300 cc. of concentrated hydrochloric acid. The benzene layer was separated immediately and the water portion extracted with benzene. The combined benzene portions were washed with 1:1 hydrochloric acid solution and then dried over calcium chloride. The benzene solution was decolorized by heating it with Carboraffin. The benzene was removed completely under reduced pressure by heating on a water-bath. The residue was refluxed for twenty minutes with acetyl chloride (200 cc.) and allowed to cool. The trityl chloride crystallized at once in a very pure state: m. p. 112–113° (corr.); yield 230 g. (80%).

6-Trityl-*β-d*-glucose-1,2,3,4-tetraacetate.—6-Trityl-*β-d*-glucose-1,2,3,4-tetraacetate and the corresponding *α*-isomer have been prepared from both trityl chloride and trityl bromide. Experiments in which equivalent quantities of the trityl halide compounds were used gave approximately the same percentage yield of the 6-trityl-*d*-glucose-1,2,3,4-tetraacetates. Since trityl bromide is obtained quantitatively in the detritylation process, its re-use reduces both the cost and time of subsequent preparations.

The trityl chloride method as used by Helferich[11] was modified such that the time of preparation was shortened considerably.

A mixture of anhydrous glucose (120 g.), trityl chloride (193.2 g.) and anhydrous pyridine (500 cc.) was shaken mechanically at room temperature. Solution was effected within five hours. Acetic anhydride (360 cc.) was added in one portion without cooling. After standing for about twelve hours the reaction mixture was poured into ten liters of ice water and stirred vigorously for three hours with a mechanical stirrer. The water was renewed once in the meantime. The white granular precipitate was filtered, washed and air dried. It was then mixed with U. S. P. ether (500 cc.) and filtered. This treatment removed most of the 6-trityl-*α-d*-glucose-1,2,3,4-tetraacetate. The insoluble portion was taken up in hot 95% ethanol. Upon cooling, the 6-trityl-*β-d*-glucose-1,2,3,4-tetraacetate crystallized in fine needles usually of sufficient purity for subsequent use. Recrystallization yielded the pure compound: yield 175 g.; m. p. 166–166.5° (corr.).

The trityl bromide method was carried out as follows: 50 g. of trityl bromide (m. p. 130°) obtained by detritylation of the 6-trityl-*d*-glucose-1,2,3,4-tetraacetate was digested in U. S. P. ether (150 cc.) at room temperature for fifteen minutes to remove most of the impurities. It was then filtered and dried. Thirty-eight grams of trityl bromide was recovered which melted at 151–152° (corr.) with slight softening at 147°.

Thirty-seven grams of trityl bromide thus obtained was shaken for eleven hours at room temperature with anhydrous glucose (20 g.) in dry pyridine (200 cc.). Acetic anhydride (60 cc.) was then added and the reaction mixture allowed to stand for twelve hours, after which it was poured into four liters of ice water and stirred vigorously for about five hours. The water was changed twice during this time. The precipitate was filtered, washed and air dried. It was then dissolved in hot 95% ethanol (800 cc.). The crude product (20.6 g.) after one recrystallization from ethanol (400 cc.) melted at 166–166.5° (corr.); yield 19.7 g.

***β-d*-Glucose-1,2,3,4-tetraacetate.**—*β-d*-Glucose-1,2,3,4-tetraacetate was prepared according to the method of Helferich and Klein[7] except for the method of crystallization. The chloroform solution was concentrated to a very thick sirup. Anhydrous ether was added and the sirup rubbed with a glass rod. The tetraacetate separated immediately as small white crystals. This was further purified by dissolving it in the least possible amount of chloroform and adding anhydrous ether until crystallization began, the crystallization being complete in a very short time.

***β*-Gentiobiose Octaacetate.**—Thirty-five grams (1 mol.) of *β-d*-glucose-1,2,3,4-tetraacetate, silver oxide (25 g.), Drierite (100 g.) preheated at 240° for two hours, and dry, alcohol-free chloroform (100 cc.) were placed in a 500-cc. three-necked round-bottomed flask equipped with a mercury-sealed mechanical stirrer, a calcium chloride drying tube and a dropping funnel. The flask was wrapped in black paper. The contents of the flask were stirred for about one hour to ensure the complete absence of water. After the manner of Helferich, Bohm and Winkler[9] 5 g. of iodine was then added to the reaction mixture. Acetobromoglucose (41.3 g., *i. e.*, 1 mol.) was dissolved in dry, alcohol-free chloroform (150 cc.) and then added through the dropping funnel to the reaction mixture over a course of about one hour. The stirring was then continued for an additional twenty-four hours. The reaction mixture was filtered through a layer of "Filter-Cel" and the residue

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(10) M. Gomberg, *Ber.*, **33**, 3144 (1900).

(11) B. Helferich, L. Moog and A. Junger, *ibid.*, **58**, 877 (1925).

washed well with U. S. P. chloroform. The filtrate was concentrated under reduced pressure and the white crystalline residue taken up in two liters of hot absolute ethanol. Upon cooling, the *β*-gentiobiose octaacetate separated as very pure white crystalline needles: m. p. 195–196° (corr.); yield 50.5 g., 74.1%.

α-*d*-**Glucose-1,2,3,4-tetraacetate.**—*α*-*d*-Glucose-1,2,3,4-tetraacetate was prepared in a manner similar to that of *β*-*d*-glucose-1,2,3,4-tetraacetate with the following exceptions. The chloroform extract of the tetraacetate was shaken with an ice-cold, saturated solution of sodium bicarbonate in order to remove all acetic acid. It was then washed with ice water, dried over anhydrous sodium sulfate, filtered and concentrated to a thick sirup. The concentrate was taken up in a small amount of methanol and the triphenylcarbinol allowed to separate out. After filtering, the methanol was removed under reduced pressure and the resulting sirup repeatedly taken up in chloroform, and reconcentrated. The sirup thus obtained was dissolved in dry ether and shaken with calcium chloride in order to remove any water or methanol still present. The sirup remaining after the removal of the ether under reduced pressure was used for the preparation of *α*-gentiobiose octaacetate.

α-**Gentiobiose Octaacetate.**—Thirty-eight grams of the *α*-*d*-glucose-1,2,3,4-tetraacetate sirup, silver oxide (15 g.), preheated "Drierite" (75 g.), iodine (5 g.), acetobromoglucose (20 g.) and dry, alcohol-free chloroform (300 cc.) were used in this preparation. The reaction was carried out according to the method described for *β*-gentiobiose octaacetate. The sirup obtained by concentrating the chloroform solution of the reaction products was taken up in absolute ethanol (250 cc.) and rubbed with a glass rod. Crystallization began after a few minutes. A yield of 50.9% (16.8 g.) of *α*-gentiobiose octaacetate was obtained. After two recrystallizations the product melted at 191–192° (corr.) and $[\alpha]^{29.5}_{D}$ +51.6° (*c*, 4.29; *l*, 2; $CHCl_3$) C. S. Hudson and J. M. Johnson[12] reported a m. p. 188–189° (corr.) and $[\alpha]^{30}_{D}$ +52.4° for the product obtained by the action of acetic anhydride and zinc chloride on *β*-gentiobiose octaacetate.

Acknowledgment.—The authors wish to acknowledge the assistance given by William G. Dauben and Harold D. McDowell during the progress of this work.

Summary

1. An improved Königs–Knorr synthesis has increased the yield of *β*-gentiobiose octaacetate from 23.4 to 75–80% of the theoretical.

2. A 50% yield of *α*-gentiobiose octaacetate has been obtained by condensing acetobromoglucose with *α*-*d*-glucose-1,2,3,4-tetraacetate. So far as the authors are aware, this is the first time that a 6-linked *α*-octaacetate has been prepared by this method.

3. The complete synthesis of *α*- and *β*-gentiobiose octaacetates by this method may be completed in approximately one week.

4. Trityl bromide, a side product, has been introduced as a tritylating agent, thus decreasing both the time and cost of preparing the gentiobiose octaacetates.

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[12] C. S. Hudson and J. M. Johnson, This Journal, 39, 1272 (1917).

COLUMBUS, OHIO RECEIVED SEPTEMBER 3, 1938

NOTES

The Activity Coefficient of Perchloric Acid, and a Correction to the Value of the Argentous–Argentic Oxidation Potential in Perchloric Acid

By Don DeVault

The calculation of activity coefficients by Pearce and Nelson[1] from their measurements of the vapor pressure of perchloric acid solutions is apparently incorrect. Rosenfeld[2] has completely recalculated their data, obtaining results varying from 7.0% higher at 0.6 molal to 85.4% lower at 12 molal. Professor Redlich[3] has checked his values.

Professor William C. Bray and I have also recalculated the data. The method which Pearce and Nelson report using gave us activity coefficients about 5% lower than those of Redlich and Rosenfeld. Although we examined a number of possibilities, we could not find the source of disagreement with Pearce and Nelson.

Our values of the activity coefficients agree with those of Redlich and Rosenfeld if we substitute, as did they, activity coefficients of hydrochloric acid for those of perchloric acid at 0.6 molal and lower concentration. This procedure receives justification from the electromotive force measurements of Popoff, Riddich, Wirth and Ough,[4]

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[1] Pearce and Nelson, This Journal, 55, 3075 (1933).

[2] Landolt–Börnstein, "Physikalisch-chemische Tabellen," Erg. B. III, 2144 (1936).

[3] Private communication to Professor Bray. See also Redlich, Rosenfeld and Stricks, This Journal, 58, 375 (1936).

[4] Popoff, Riddich, Wirth and Ough, *ibid.*, 53, 1195 (1931).

which show that $\gamma_{HClO_4} = \gamma_{HCl}$ up to 0.4 molal. The difference between the activity coefficients in dilute solution calculated from vapor pressure data directly and calculated from the more extensive hydrochloric acid data indirectly are probably due in the main to experimental error in the former measurements, for the assumption of errors of 0.001–0.006 mm. in the vapor pressure of water above the perchloric acid solutions in the points discarded would bring the calculations into agreement. We choose, therefore, the Landolt–Börnstein values as the most probable ones until more experimental work is done.

The Pearce and Nelson activity coefficient values were used to calculate the potentials of the hydrogen half-cells in perchloric acid and also of the perchloric–nitric acid liquid junctions in a series of researches by Professor A. A. Noyes and collaborators[5–9] on the oxidation potentials of strong oxidizing agents. The corrected activity coefficients lead to values of the argentous–argentic potential in 4 *m* perchloric acid[8] of **1.970** v. at 0.2° and **1.987** v. at 25.0°, changes of −12 and −13 mv., respectively. The corrections to the values in mixed nitric–perchloric acid solutions[8] have the small effect of changing the slope of the line in Fig. 2 (representing an average number of nitrates per silver atom in the argentic nitrate complex) from 1.6 to 1.5.

The hydrogen half-cell and the liquid junction potential corrections are of opposite sign and nearly cancel each other in the measurements of the argentous–argentic potential in nitric acid,[5,8] the cerous–ceric,[6] the thallous–thallic,[7] and the cobaltous–cobaltic[9] potentials in nitric acid. Dr. C. S. Garner[10] has corrected these potentials taking into account the newer Landolt–Börnstein values for the activity coefficient of nitric acid also. The over-all corrections range from −1.3 to +0.6 mv. and are probably negligible in view of the uncertainties in the liquid junction potentials. No other arguments or conclusions in these papers are affected by these changes.

I wish to acknowledge with gratitude the help and advice of Professor Bray, Dr. C. D. Coryell and Dr. C. S. Garner in preparing this note.

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(5) Noyes and Kossiakoff, THIS JOURNAL, **57**, 1238 (1935).

(6) Noyes and Garner, *ibid.*, **58**, 1265 (1936).

(7) Noyes and Garner, *ibid.*, **58**, 1268 (1936).

(8) Noyes, DeVault, Coryell and Deahl, *ibid.*, **59**, 1326 (1937).

(9) Noyes and Deahl, *ibid.*, **59**, 1337 (1937).

(10) Garner, Thesis, Calif. Inst. of Tech., 1938.

The Physical Constants of *cis*-Pentene-2

BY MARY L. SHERRILL AND ELIZABETH H. LAUNSPACH

In a recent article[1] the synthesis of *cis*-pentene-2 by the semi-reduction of pentyne-2 was reported. The designation of this pentene-2 as the *cis* form was based on the method of preparation and the assignment of structure was confirmed by its ultraviolet absorption in the Schumann region.[2] Because the quantity of the pentene-2 was insufficient for column fractionation, it was thought that there might be traces of pentyne present which would have the most marked effect on the boiling point and the density. The work has been repeated and the pentene-2 fractionated twice through a Fenske column (Column A). This column was 35 × 1.5 cm., with 1-turn 4-mm. glass helices. The reflux ratio for the two fractionations of the pentyne-2 was 1:20. The index of refraction was identical with that of the earlier preparation but the boiling point and the density were appreciably lower. The physical constants remained unchanged by the second fractionation and it is believed that the values so obtained constitute the most reliable data for the pure *cis*-pentene-2. Absorption spectrum measurements on this product gave no evidence of the presence of any of the *trans* isomer. These results therefore confirm the assignment of the *cis* structure to the higher boiling pentene-2, as is the case for the higher boiling isomer of butene-2.

The pentyne-2 was prepared in satisfactory yield from 2,3-dibromopentane by the action of alcoholic potassium hydroxide. This reaction takes place in two stages: the first being the formation of the pentyne-2 together with a mixture of 2-bromopentene-2 and 3-bromopentene-2. In the second stage of the reaction with more concentrated potassium hydroxide and prolonged heating at a higher temperature, these bromopentenes are converted into pentyne-2. In some cases appreciable amounts of pentyne-1 were also obtained; by further treatment with alcoholic potash this was transformed into pentyne-2. It is of interest to note that the 2,3-dibromopentane was prepared from pentene-2 which was a mixture of 25% of the *cis* and 75% of the *trans* isomer. In the course of fourteen different preparations of pentyne-2 there was always a 25% yield of pentyne-2 in the first stage of the reaction.

Half mole portions of a constant boiling frac-

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(1) Sherrill and Matlack, THIS JOURNAL, **59**, 2134 (1937).

(2) Carr and Stücklen, *ibid.*, **59**, 2138 (1937).

tion of pentyne-2 (b. p. 55.9 ± 0.05° at 760 mm., n^{20}_D 1.4040, d^{20}_4 0.7115) were hydrogenated in an alcohol–water solution in the presence of colloidal palladium. Slightly less than the theoretical quantity of hydrogen was used. The pentene with alcohol distilled from the mixture through a Vigreux column at 34–36°. The hydrocarbon (78.5% yield) freed from alcohol had a refractive index n^{20}_D 1.3824. One fractionation through Fenske column A gave (1) 5% boiling at 36.8–37.0° and (2) 90% boiling at 37.0 ± 0.05°; the refractive indices of these fractions were, respectively, n^{20}_D 1.3824 and 1.3822, that of the residue was n^{20}_D 1.3840. In a second fractionation of (2) the entire distillate (98%) boiled constantly at 37.0 ± 0.05°, had a refractive index n^{20}_D 1.3822 and a density d^{20}_4 0.6562. The refractive index of the residue was n^{20}_D 1.3826.

THE CHEMICAL LABORATORY OF
MOUNT HOLYOKE COLLEGE
SOUTH HADLEY, MASS.
RECEIVED AUGUST 1, 1938

The Specific Heat of "Lucite" (Methyl Methacrylate Polymer)

BY FRANK T. GUCKER, JR., AND WILLIAM L. FORD

We have found the polymerized methyl methacrylate plastic now made by the du Pont Company under the trade name of "Lucite" a useful insulating material in our calorimetric work. Many of its physical properties have been tabulated.[1] For our purposes, the specific heat was important and, since we could not find it listed, we determined it as follows.

Fifteen disks each 3 mm. thick were cut from a Lucite rod, $^3/_8$ inch (9 mm.) in diameter. A small hole was drilled in the center of each. The disks were then threaded on pieces of fine copper wire and suspended from the thermel tubes in one calorimeter of the apparatus developed in this Laboratory[2] for measuring heat capacities of aqueous solutions. The disks were spaced apart to allow free circulation of water, with which the calorimeter was filled to the standard height. The resistance ratio required to balance this calorimeter against the tare was then measured in the usual way, with an accuracy of about 0.01%. The heat capacity of the Lucite was calculated from this ratio and the known heat capacities of the water, the calorimeter and the copper wire. Since the heat capacity of the 3 g. of Lucite was only about 0.3% of that of the whole system, the uncertainty in its value is about 3%. The results of two independent experiments actually agreed somewhat better than that, yielding 0.342 and 0.344, and we may take as the probable value of the specific heat 0.343 (±0.005) cal. deg.^{-1} g.^{-1}.

Although its specific heat is larger than that of Pyrex glass, its density is only half as great, and the heat capacity *per unit volume* is only 82% of that of glass. This factor, in combination with a thermal conductance less than half that of glass, equal transparency, great mechanical strength and easy machining, makes Lucite a useful substitute for glass as an insulating material in calorimetric work.

CHEMICAL LABORATORY
NORTHWESTERN UNIVERSITY
EVANSTON, ILLINOIS
RECEIVED JULY 5, 1938

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[1] "Methacrylate Resins," *Ind. Eng. Chem.*, **28**, 1160 (1936).

[2] Gucker, Ayres and Rubin, THIS JOURNAL, **58**, 2118 (1936).

The Methylation of Sugars

BY B. CLIFFORD HENDRICKS AND ROBERT E. RUNDLE

The importance of fully methylated sugars as reference compounds in carbohydrate chemistry has led to many attempts to find more satisfactory methods for their synthesis. Irvine and Purdie[1,2] used methyl iodide and silver oxide in their preparation. A more generally used method[3] is that of Haworth in which dimethyl sulfate and sodium hydroxide are the reagents used. More recently West and Holden[4] have modified the method of Haworth by using carbon tetrachloride as a solvent, a more concentrated alkali and a different method of hexoside hydrolysis to obtain the free methylated sugar.

The authors found that the concentrated alkali, used by West and Holden for the last step in the methylation, produced sugar decomposition. Their first steps, however, were satisfactory for partial methylation.

Muskat[5] has shown that methylation may be accomplished by using free alkali metal and methyl iodide on a hexoside in liquid ammonia. He used potassium which is expensive and prepared only small amounts of the sugars. If sodium metal is substituted for the potassium the cost is reduced but for larger quantities of reactants the insolubility of the tetrasodium salts

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[1] Irvine and Purdie, *J. Chem. Soc.*, **83**, 1021 (1903).

[2] Irvine and Purdie, *ibid.*, **85**, 1052 (1904).

[3] Haworth, *ibid.*, **107**, 11 (1915).

[4] West and Holden, THIS JOURNAL, **56**, 930 (1934).

[5] Muskat, *ibid.*, **56**, 695 (1934).

of the hexosides makes it difficult to methylate more than one or two carbons of the sugar. For that reason the procedure here reported uses liquid ammonia only for completing methylation started by the West and Holden process.

Experimental

Forty grams of hexoside with 25 ml. of water was put into a flask equipped with a heavy stirrer, separatory or dropping funnel and attached to a condenser. This mixture was then warmed to 50° by a water-bath. A mixture of 108 ml. of dimethyl sulfate in 150 ml. of carbon tetrachloride was then added and the resulting mixture vigorously stirred. A solution of 92 g. of sodium hydroxide in 130 ml. of water was introduced into the flask by means of the separatory funnel at the rate of one drop in two seconds. This rate was increased in such manner that heat resulting barely raised the reaction mixture to the boiling point of the carbon tetrachloride. After the first half of the alkali solution was used the remainder was added more rapidly and the stirring continued for thirty minutes after the last addition.

The contents of the flask were then treated as directed by West and Holden[4] except the partially methylated sirup was dried thoroughly in preparation for the ammonia methylation. To accomplish this it was dissolved in ethyl ether, this solution dried by calcium chloride and after filtering the ether evaporated under reduced pressure.

The liquid ammonia methylation was done in two unsilvered Dewar flasks of about 750 ml. capacity. Flask number one equipped with separatory funnel, an outlet tube and protected from moisture by some desiccant such as calcium oxide was to contain the sirup. The other flask was connected to the first by a glass tube which extended to the bottom of the second. This second flask also had an outlet tube closed by a clamp by means of which liquid ammonia could be forced into flask one by closing the clamp.

Into the first flask 500 ml. of liquid ammonia was passed direct from the tank. A piece of metallic sodium was added to dry the ammonia, after which the sirup was added. The 150 ml. of liquid in the second Dewar received the shavings of metallic sodium (3–4 g.). The sodium salt of the methylated hexoside was then prepared by forcing small portions of the sodium–ammonia solution into the first flask, containing the sirup, as described above. As the hexoside reacts with the sodium the blue color of the solution clears. Successive additions of the sodium were continued until the blue color persisted for an hour after the last addition. At that point 12 ml. of methyl iodide was added dropwise through the separatory funnel. Less of the iodide was used if less than the prepared amount of sodium–ammonia solution had been previously consumed. The liquid ammonia was then permitted to vaporize off and the residue neutralized by 2 *N* hydrochloric acid. After neutralization 400 ml. more of 2 *N* hydrochloric acid was added and the mixture steam hydrolyzed.[4] The product of this hydrolysis was isolated and crystallized as described by West and Holden.

The authors successfully prepared the following tetramethylhexoses by this combination method.

Tetramethyl- M. p., °C.			α-*d*-Glucose 92.5–93.5	α-*d*-Mannose 49–50	α-*d*-Galactose 70.5–71.5
Specific rotation	Init.	$[\alpha]^{0}\mathrm{D}$	+104.0	+11.5	+146.0
		$[\alpha]^{25}\mathrm{D}$	+104.0	+ 6.3	+150.5
	Final	$[\alpha]^{0}\mathrm{D}$	+ 80.4	+ 2.5	+112.1
		$[\alpha]^{25}\mathrm{D}$	+ 84.8	− 0.2	+119.9

The yield for the tetramethyl α-*d*-glucose was 20–25 g.: for the other two somewhat less. Those two sugars were rather difficult to crystallize[6] though the quantity of sirup in each case was as great as for the glucose.

In this combination method of methylation the amounts of methylating agents used were but slightly more than the theoretical, making the cost comparatively small. The time required was more than for the procedure of West and Holden but much less than that by Haworth's method. The quantities of sugars processed were larger than those used by Muskat.

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[6] Accomplished by aid of seed crystals generously furnished by Dr. M. L. Wolfrom of The Ohio State University.

AVERY LABORATORY
UNIVERSITY OF NEBRASKA
LINCOLN, NEBRASKA

RECEIVED JULY 29, 1938

The Ineffectiveness of β-Aminopyridine in Blacktongue

BY F. M. STRONG, R. J. MADDEN AND C. A. ELVEHJEM

Subbarow, Dann, and Meilman[1] recently reported that β-aminopyridine was highly active in the treatment of blacktongue in dogs. Our attempts to demonstrate the activity of this compound have given uniformly negative results.

The compound was prepared by a Hoffman degradation of nicotinamide according to Pollak,[2] and after being purified by distillation (b. p. 132–134° at 20 mm.) and crystallization from Skelly solve "B," formed glittering, colorless plates, m. p. 61–63°. *Anal.* Calcd. for $C_5H_6N_2$: C, 63.82; H, 6.43. Found: C, 63.80; H, 6.35.

The picrate was prepared in dilute alcohol solution, and after being crystallized from alcohol melted at 200–201°. The chloroaurate precipitated instantly on mixing aqueous solutions of the reactants and was crystallized from 1–1 hydrochloric acid as red-brown needles, m. p. 237–239° (dec.). *Anal.* Calcd. for $C_5H_6N_2 \cdot HAuCl_4$: Au, 45.4. Found: Au, 44.8, 44.8.

The dihydrochloride which was obtained from the free base and concentrated hydrochloric acid was recrystallized twice from concentrated hydrochloric acid and then from absolute alcohol. Colorless, granular crystals of m. p. 170–173°

[1] Subbarow, Dann and Meilman, THIS JOURNAL, **60**, 1510 (1938).

[2] Pollak, *Monatsh.*, **16**, 54 (1895).

were obtained. *Anal.* Calcd. for $C_5H_8N_2Cl_2$: Cl, 42.47. Found: Cl, 42.34, 42.54. Mixed with a sample of β-aminopyridine dihydrochloride kindly sent to us by Dr. Y. Subbarow, the melting point was 173–175°. There thus seems to be no question but that the compound assayed in each laboratory was actually β-aminopyridine.

The following results were obtained when the compound was administered to dogs suffering from blacktongue. The method of producing blacktongue has been described.[3]

1. On 6/13 a 6800-g. dog showing slight symptoms of blacktongue was given 23 mg. of β-aminopyridine orally, and on the next day a further oral dose of 23 mg. was given. During the next two days the symptoms became progressively worse, and the weight dropped 100 g. On 6/15 two 30-mg. doses of nicotinic acid were fed. Two days later the symptoms were much improved and the dog weighed 7200 g. On 6/22 the weight was 8000 g. and the dog was completely cured.

2. On 6/21, 100 mg. of β-aminopyridine was given orally to a 5400-g. dog suffering from severe blacktongue. Two days later the symptoms were slightly worse, and the weight had dropped to 4900 g. One hundred mg. of nicotinic acid was then fed. Four days later the dog weighed 5500 g. and was completely cured.

3. An aqueous solution of β-aminopyridine dihydrochloride containing 6.67 mg. per cc. was adjusted to *p*H 4.4 with sodium hydroxide. A dog which had been kept on the blacktongue-producing diet until its weight had dropped from 5600 g. to 4800 g., but in which symptoms of blacktongue had not yet appeared, was given daily doses of 20, 20, 20, 20, 15 and 15 mg., respectively, of the dihydrochloride by subcutaneous injection of the above solution. During this six-day period (7/7–13) the weight remained at 5000 g., and no symptoms of blacktongue appeared. On each of the four succeeding days (7/13–16) 15 mg. of nicotinic acid were administered by subcutaneous injection. After four days of this treatment the animal's weight had increased to 5600 g., and three days later (7/19) to 6200 g.

4. A 4250-g. dog suffering from rather severe blacktongue was given three 20-mg. doses of β-aminopyridine dihydrochloride on three successive days. Administration was by subcutaneous injection of the above described solution, which had been readjusted to *p*H 1.8 (approximately the *p*H of a solution of 6.67 mg. of the pure dihydrochloride in 1 cc. distilled water). Since the dog weighed only 3800 g. and was much worse on the third day, the dose for the fourth day was increased to 40 mg. On the fifth day of the assay the dog weighed 3400 g., and was in such bad condition that death ensued, despite the injection of 30 mg. of nicotinic acid.

5. A 10-kg. dog was given 100 mg. of β-aminopyridine dihydrochloride daily for three days (7/29–31). The substance was injected subcutaneously in the form of a solution containing 12.3 mg. per cc., *p*H 1.25. The β-aminopyridine used in this case was obtained from Dr. T. Spies, University of Cincinnati. The symptoms of blacktongue which were slight at first had become worse at the end of the third day, and the weight had dropped to 9600 g. The dog was allowed to remain untreated for two more days and the weight dropped to 9100 g., while the symptoms became very severe. One hundred mg. nicotinic acid was then injected (8/2) and after two days the dog weighed 9600 g. and showed definite improvement. On 8/5 50 mg. of nicotinic acid was injected and on 8/8 the weight was 10,100, and the animal was completely cured.

6. A 9200-g. dog was given 100 mg. of β-aminopyridine dihydrochloride daily for three days (8/19–21). The substance was injected subcutaneously in the form of a solution containing 12.3 mg. per cc., *p*H 1.25. The β-aminopyridine dihydrochloride used in this case was obtained from Dr. Y. Subbarow, Harvard University. The symptoms of blacktongue which were slight at first remained unchanged but the weight dropped to 8900 g. The dog was allowed to remain untreated for one more day and the weight dropped to 8400, while the symptoms remained the same. One hundred mg. of nicotinic acid was then injected (8/23) and after two days the dog weighed 9200 g. and the symptoms of blacktongue were markedly improved. On 8/25 100 mg. of nicotinic acid was injected and on 8/29 the animal weighed 10,400 g. and was completely cured.

In this connection it has been found in this Laboratory (unpublished data) that β-aminopyridine cannot replace nicotinic acid as a growth essential for *Staph. aureus.*

It is evident from these results that β-aminopyridine as tested in our laboratory has no activity as compared to nicotinic acid in the treatment of blacktongue.

DEPARTMENT OF BIOCHEMISTRY
COLLEGE OF AGRICULTURE
UNIVERSITY OF WISCONSIN
MADISON, WISCONSIN
RECEIVED SEPTEMBER 12, 1938

The Inactivity of β-Aminopyridine in Blacktongue

BY Y. SUBBAROW AND W. J. DANN

Dr. Elvehjem has informed us privately of his findings as reported in the preceding communication and as a result we have re-examined the question of the activity of β-aminopyridine in blacktongue. We have been unable to repeat our earlier observation that small doses of this substance will cure blacktongue, or to account for the cures then obtained. It is, however, clear that our earlier conclusion is incorrect and that β-aminopyridine is not a blacktongue preventive factor.

MEDICAL SCHOOL
HARVARD UNIVERSITY
BOSTON, MASS.

DUKE UNIVERSITY
MEDICAL SCHOOL
DURHAM, N. C.
RECEIVED SEPTEMBER 16, 1938

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[3] Woolley, Strong, Madden and Elvehjem, *J. Biol. Chem.*, **124**, 715 (1938).

COMMUNICATIONS TO THE EDITOR

THE QUANTUM YIELD OF CHLOROACETIC ACID HYDROLYSIS

Sir:

Following the report by Rudberg [*Z. Physik*, **24,** 247 (1924)] of a quantum yield of unity for the hydrolysis of monochloroacetic acid in aqueous solution at 2537 Å., this reaction has been employed in a number of cases as an actinometer.

A deviation in the results obtained with the uranyl oxalate and chloroacetic acid actinometers at 2537 Å. has led us to reinvestigate both reactions. A solution 0.01 *M* in uranyl sulfate and 0.05 *M* in oxalic acid gave an average quantum yield of 0.60, in agreement with the value reported by W. G. Leighton and Forbes for this wave length [THIS JOURNAL, **52,** 3139 (1930)]. For a solution 0.5 *M* in monochloroacetic acid, at 25° and an incident intensity of 2×10^{12} to 1×10^{13} quanta/mm.^{2} sec., we find a quantum yield of 0.3 to 0.4 at 2537 Å. This result has been checked on two independent experimental set-ups, using different thermopiles and standard lamps as well as different samples of chloroacetic acid. Amount of hydrolysis was determined in both cases by potentiometric titration of the chloride ion. The results show some variability the source of which has not been located. There seems little doubt, however, but that under our conditions the quantum yield at 2537 Å. is much below unity, and we wish to call this to the attention of any who may be using or considering the use of this reaction as an actinometer.

DEPARTMENTS OF CHEMISTRY
POMONA COLLEGE AND
STANFORD UNIVERSITY
CALIFORNIA

W. G. LEIGHTON
R. N. SMITH
P. A. LEIGHTON

RECEIVED SEPTEMBER 19, 1938

LOCATION OF OXYGEN IN CERTAIN STEROIDS

Sir:

In certain compounds of a steroid nature which occur in the adrenal gland there is an atom of oxygen which is exceedingly inert whether in the form of a ketone or of a hydroxyl group [Mason, Hoehn, McKenzie and Kendall, *J. Biol. Chem.*, **120,** 719 (1937)]. Consideration of the possible locations for such an oxygen atom led to the conclusion that it must occupy position 11 or 12 of the steroid nucleus [Kendall, Mason, Hoehn and McKenzie, *Proc. Staff Meet. Mayo Clinic*, **12,** 136, 270 (1937); Steiger and Reichstein, *Helv. Chim. Acta*, **20,** 817 (1937)]. Steiger and Reichstein [*Helv. Chim. Acta*, **21,** 828 (1938)] have recently compared the acid (our acid 1) obtained by oxidation of corticosterone (our compound B) with the 3,11-diketo-Δ^4-*etio*-cholenic acid prepared by degradation of digoxigenin and have found it to be different. They consider that this result casts doubt on position 11 as the location of the oxygen atom in question although it is not conclusive in view of the possible isomerism of the steroid skeleton. We have made a similar comparison with 3,12-diketo-Δ^4-*etio*-cholenic acid and have found that the acid derived from corticosterone differs widely in its properties. This result eliminates the possibility that the oxygen atom in question occupies position 12 of a normal steroid nucleus. The close similarity of the behavior of this oxygen atom with that of the oxygen atom of sarmentogenin which has been assigned to C-11 argues for an identity of position. Degradation of sarmentogenin, which is known to differ from digoxigenin only in the configuration of 1 asymmetric center, probably C-9, should yield a definite answer to this problem.

The degradation of desoxycholic acid to 3,12-diketo-*etio*-cholanic acid has been described [Hoehn and Mason, THIS JOURNAL, **60,** 1493 (1938)]. Bromination in acetic acid solution gave 4-bromo-3,12-diketo-*etio*-cholanic acid, m. p. 197–198° (dec.); $[\alpha]^{25}{}_{5461}$ + 109 ± 2°. (Calcd. for $C_{20}H_{27}O_4Br$: C, 58.52; H, 6.64; Br, 19.42. Found: C, 58.40; H, 6.65; Br, 19.19.) This bromo acid lost hydrogen bromide when refluxed with pyridine to yield 3,12-diketo-Δ^4-*etio*-cholenic acid, m. p. 205–207°; $[\alpha]^{25}{}_{5461}$ +240 ± 5°. (Calcd. for $C_{20}H_{26}O_4$: C, 72.68, H, 7.93. Found: C, 72.35; H, 8.24.) Our acid 1 melts at 267–269°; $[\alpha]^{25}{}_{5461}$ +291°. Use of the methyl esters gave better yields and the final product was more readily purified. The ester of the bromo acid melts at 200–201°; $[\alpha]^{25}{}_{5461}$ +170 ± 3°. (Calcd. for $C_{21}H_{29}O_4Br$: Br, 18.79. Found: Br, 18.94.)

Methyl 3,12-diketo-Δ^4-*etio*-cholenate melts at 235–237°; $[\alpha]^{25}_{5461}$ $+242 \pm 2°$. (Calcd. for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19. Found: C, 73.25; H, 8.36.) The methyl ester of acid 1 melts at 178–179°; $[\alpha]^{25}_{5461}$ $+289 \pm 7°$.

DEPARTMENT OF BIOCHEMISTRY
THE MAYO FOUNDATION
ROCHESTER, MINNESOTA

H. L. MASON
W. M. HOEHN

RECEIVED SEPTEMBER 16, 1938

NEW BOOKS

An Introduction to Microchemical Methods for Senior Students of Chemistry. By CECIL L. WILSON, M.Sc., Ph.D., Senior Assistant in Chemistry, The Queen's University of Belfast. Chemical Publishing Company of New York, Inc., 148 Lafayette Street, New York, N. Y., 1938. 196 pp. 93 figs. 12.5 × 19 cm. Price, $3.00.

The book is written for the use of senior students in introductory courses on microchemistry. The author will acquaint the students "with the large field covered by microchemistry," but he has no intention of making the students capable "of undertaking advanced work utilizing microchemical methods." The scope of the proposed course is wide as may be derived from the following list of chapters: the compound microscope and its use (35 pp.), crystallization (6 pp.), observation of transition points and Liesegang rings (7 pp.), the polarizing microscope (16 pp.), classification of crystals (9 pp.), crystal tests (6 pp.), spot tests (8 pp.), inorganic qualitative analysis (29 pp.), inorganic gravimetric analysis (16 pp.), inorganic volumetric analysis (4 pp.), the tintometer (3 pp.), the colorimeter (6 pp.), the nephelometer (3 pp.), organic operations (12 pp.), residue- and Kjeldahl determinations (3 pp.), photomicrography (6 pp.), and the spectrograph (10 pp.). It is obvious that the number of suggested experiments must be small in every chapter.

The reviewer is of the opinion that the book would have gained in value if various rather unimportant discussions had been suppressed in favor of a more detailed description of the procedures. Nearly the whole page 169 is devoted to a discussion of the reasons for not including the more important determinations of quantitative organic elementary analysis, but a list of apparatus is missing, and the concentrations of the inorganic solutions listed in the appendix are not indicated.

The introduction contains the statement "...this was the acknowledged motive which first led Pregl to develop his invaluable work on organic microanalysis. Almost at the same time Emich was laying similar foundations in the inorganic branch, his work being at least in part inspired by the spectacular success attained by Pregl."

It may be permitted to recall the facts that Emich started his microchemical investigations before 1900, that Pregl did not enter the field before 1909 and acknowledged in his book that Emich had laid the groundwork, and finally that Pregl's "spectacular success"—obviously the Nobel Prize awarded in 1923—came far too late to have any influence on Emich's numerous contributions to the development of microchemistry.

A. A. BENEDETTI-PICHLER

Katalyse und Determinismus. Ein Beitrag zur Philosophie der Chemie. (Catalysis and Determinism. A Treatise on the Philosophy of Chemistry.) By ALWIN MITTASCH. Verlag von Julius Springer, Linkstrasse 22–24, Berlin W 9, Germany, 1938. ix + 203 pp. 10 figs. 14.5 × 22 cm. Price, RM. 9.60.

This work consists of a discussion of general philosophical problems, especially those in the philosophy of science, *e. g.*, causality, determinism, organicism and teleology. The author takes account particularly of the bearing of what is now known about catalysis as a basis for his considerations. His standpoint is that of a physical chemist who has read widely and carefully in the literature of philosophy and who probably attaches more importance to philosophical speculation than do most chemists.

L. J. HENDERSON

Die Theorie der Komplexität und der Allotropie. (The Theory of Complexity and Allotropy.) By DR. A. SMITS, Professor and Director of the Laboratory of General and Inorganic Chemistry of the University of Amsterdam. Verlag Chemie, G. m. b. H., Corneliusstrasse 3, Berlin W 35, Germany, 1938. xii + 372 pp. 153 figs. 15.5 × 22 cm. Price, RM. 19.50.

The author states that he has set himself the task of setting forth the new material which has accumulated in the sixteen years since the appearance of his book on "The Theory of Allotropy," and of discussing it from the standpoint of the theory of complexity of phases. He has wished to include some of the topics treated in the earlier book, but for reasons of space has omitted some of the chapters, more particularly that chapter dealing in detail with the systems phosphorus and cyanogen.

The early chapters of the book set forth clearly the author's theory of phase complexity and his concept of pseudocomponents, with plentiful diagrams showing the relationship of the unary system at equilibrium to the pseudobinary or pseudoternary systems obtainable when the approach to internal equilibrium can be inhibited. Here, as also in later chapters, it is shown that recent theoretical work has postulated an increasing number of finer differences in atomic or molecular structure which are in accord with the author's theory of a very general occurrence of complexity within a single phase.

The sixth chapter discusses two of the conditions which favor the detection of phase complexity, intensive drying and low temperatures. The discussion of intensive drying omits the consideration of Baker's well-known experiments, which were treated *in extenso* in the earlier book, but gives the author's results on the heat of condensation of benzene vapor, which are in accord with Baker's in showing that intensive drying gives definite evidence that benzene is complex. The separation of ortho and para hydrogen at low temperatures is viewed as a notable example of complexity in a substance as supposedly simple as hydrogen gas.

The later chapters contain discussions, many of them in extended form, of the occurrence of complexity in the cases of acetaldehyde, the ammonium halides, sulfur trioxide, etc. The use of the Raman effect in the study of the various modifications of sulfur trioxide is given in detail.

It hardly needs to be said that Smits' latest book contains a fuller exposition of the data and theory of phase complexity than exists elsewhere, since the theory and much of the data are Smits' own contribution to chemical science. Those who have given little thought to the subject will be surprised at the frequency with which complexity in a phase has been shown to exist, and may well bear the facts in mind when baffling and supposedly inexplicable experimental results turn up. Those who are more familiar with the subject will profit by reading Smits' book, though they may find it occasionally somewhat repetitious. The printing and diagrams are good; page references occasionally are wrong. The "gesenkter Auslandspreis" is RM. 19.50.

ARTHUR E. HILL

BOOKS RECEIVED

August 15, 1938–September 15, 1938

J. G. CROWTHER. "About Petroleum." Oxford University Press, 114 Fifth Ave., New York, N. Y. 181 pp. $2.25.

F. W. GODDARD AND E. J. F. JAMES. "The Elements of Physical Chemistry." Longmans, Green and Co., 114 Fifth Ave., New York, N. Y. 251 pp. $1.80.

J. B. S. HALDANE. "The Chemistry of the Individual. Being the 38th Robert Boyle Lecture." Oxford University Press, 114 Fifth Ave., New York, N. Y. 17 pp. $0.40.

ARTHUR E. HAAS AND IRA M. FREEMAN. "Elementary Survey of Physics." E. P. Dutton and Co., 286–302 Fourth Ave., New York, N. Y. 203 pp. $1.90.

BENJAMIN HARROW. "Biochemistry for Medical, Dental and College Students." W. B. Saunders Company, West Washington Square, Philadelphia, Pa. 383 pp. $3.75.

FELIX HAUROWITZ. 'Fortschritte der Biochemie. III Teil (1931–1938)." Verlag von Theodor Steinkopff, Residenzstrasse 32, Dresden-Blasewitz, Germany. 167 pp. RM. 9; bound, RM. 9.75.

DOROTHY JORDAN LLOYD AND AGNES SHORE. "Chemistry of the Proteins." P. Blakiston's Son and Co., 1012 Walnut St., Philadelphia, Pa. 532 pp. $5.50.

A. MATAGRIN. "Manuel du Savonnier." Gauthier-Villars, Éditeur, 55 Quai des Grands-Augustins, Paris 6^e, France. 268 pp. Fr. 30.

GILBERT T. MORGAN AND DAVID DOIG PRATT. "British Chemical Industry. Its Rise and Development." Longmans, Green and Co., 114 Fifth Ave., New York, N. Y. 387 pp. $6.25.

ALFRED O'RAHILLY. "Electromagnetics. A Discussion of Fundamentals." Longmans, Green and Co., 114 Fifth Ave., New York, N. Y. 884 pp. $12.50.

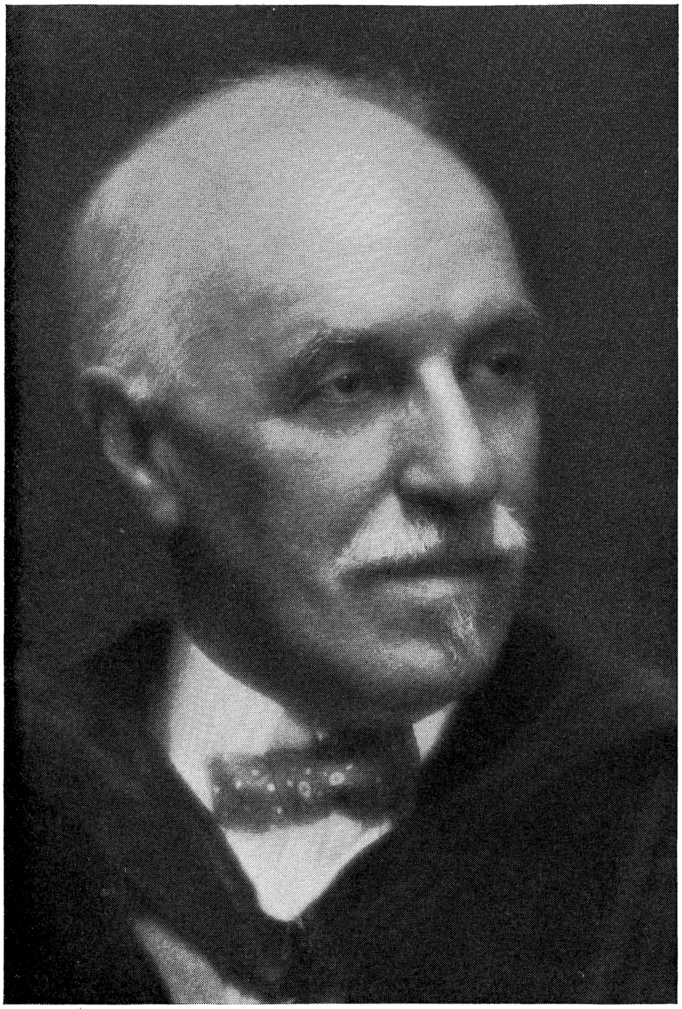
JULIUS SCHÜLEIN. "Die Bierhefe als Heil-, Nähr- und Futtermittel." Second edition. Verlag von Theodor Steinkopff, Residenzstrasse 32, Dresden-Blasewitz, Germany. 262 pp. RM. 11; bound, RM. 12.

BYRON A. SOULE. "Library Guide for the Chemist." McGraw-Hill Book Co., Inc., 330 West 42d St., New York, N. Y. 302 pp. $2.75.

CECIL L. WILSON. "An Introduction to Microchemical Methods." Chemical Publishing Company of New York, Inc., 148 Lafayette St., New York, N. Y. 196 pp. $3.00.

"Copper Mining in North America." Bulletin 405, Bureau of Mines, U. S. Department of the Interior. Superintendent of Documents, Government Printing Office, Washington, D. C. 300 pp. $0.40.

"Minerals Yearbook, 1938." Bureau of Mines, U. S. Department of the Interior. Superintendent of Documents, Government Printing Office, Washington, D. C. 1339 pp. $2.00.



Julius Stieglitz
(1867–1937)

JULIUS STIEGLITZ

May 26, 1867–January 10, 1937

Julius Stieglitz, as also his identical twin, Leopold, was born in Hoboken, New Jersey, May 26, 1867. His father, Edward Stieglitz, was a native of Thuringia, Germany; his mother, Hedwig (Werner) Stieglitz, of New York.

The father came to America in 1849 when he was fifteen years of age and settled in New York City where he was in a short time established as a successful importer of woolen goods and after due time became a man of considerable wealth.

Other children of the woolen merchant and his wife were Alfred, older by three years than the twins, as they were always referred to in childhood, and three sisters, Agnes, Flora, and Selma.

The father is remembered as an austere and stern man, but always very fair toward his children. Neither father nor mother had had much formal schooling but, with a keen interest in literature, music, and art, they gradually acquired that self-made education that led, as is often the case, to a high degree of culture.

Julius' father early determined to give his sons the best possible education and all the advantages he had lacked in his youth. With this incentive, when the twins were four years old, the family moved across the Hudson to New York City where a home was established at No. 14 East 60th Street.

The schooling of the twins began at the Charlier Institute in New York. Here instruction was largely in the French language. German was much spoken in the family circle. Later the twins were sent to the city schools where their English was developed. There by hard work, they soon led their class and maintained this standard until 1881 when the work of the primary schools was completed.

The family treasures a story at which they still laugh; in an old fashioned spelling match of those days for the schools of the city, Julius had come through the contest with flying colors until only himself and one other contestant were left, when he was tripped on the word, "Israelite."

In 1873 the father took Alfred, the oldest son, on a vacation trip which included a visit to Lake George, New York. He was so pleased with the splendid scenery of the place and the very good fishing he found there that he decided to make this the site for his summer residence. The following year he brought the family to the Fort Henry Hotel on the lake. Some years later the beautiful estate, "Oak Lawn," was acquired which became the beloved center of family life. Here the entire Stieglitz family gathered, together with a host of friends: musicians, artists, actors, and other brilliant and talented people drawn together by kindred interests. The dinner table, at which rarely less than eighteen were present, was presided over by the mother, a typical matriarch full of gentle kindness, wit, and unlimited hospitality. The entire family was a large clan which kept in touch with each other for fifty years.

At the age of fourteen, having finished the elementary school, the twins were ready for high school. The father, thinking always of the greatest good for his sons, knowing of the superior advantages of German schools at that time and convinced of the broadening influence of travel and life abroad, interrupted his business and took his entire family to Germany.

The twins were placed in the famous Real Gymnasium at Karlsruhe.

Here all was new; they were far from home for the first time. The going was hard at first, the language caused uncertainty for a while; but, at the end of six months, most of the difficulties cleared up and before long, as in New York, they were at the top of their classes. They maintained this position throughout their five years at the Real Gymnasium.

During the Karlsruhe period they found a home with Professor Trautlein who was director in the Karlsruhe Gymnasium (not the Real Gymnasium). This turned out to be a most happy and genial connection. The family and their friends were given to philosophical discussions. These greatly interested and stimulated the twins.

Aside from their studies, there were other interests and diversions in the life at Karlsruhe. The study of music which had been taken up earlier was now continued. Julius studied the cello under Lindner, first cellist at Beyreuth and a noted teacher; Leopold studied the violin. These lessons pleased the twins much since they had real talent for music.

Social dancing and skating to music offered further entertainment in winters. Bicycling in the Black Forest and hiking in Switzerland were their favorite summer pastimes.

At the age of eighteen, Julius fell in love with a girl who was, later, to become his wife. Nothing was more natural than that Leopold should enjoy the same good fortune with the sister, with like ultimate result. The young ladies were Anna Maria and Elizabeth Stieffel, daughters of a German Lutheran family.

The writer, from personal knowledge, can vouch for the beauty, wit, charm, and vivacity of Mrs. Julius Stieglitz, whom he came to know well in later years.

These early engagements were most fortunate for the twins. If the seven years that were to elapse before marriage seemed long to Julius, the wait had its compensations. He devoted himself assiduously and with undivided attention to his studies in order to hasten the day when he should be able to claim his beloved Anna.

During all these years of study the twins remained in Europe. Their father often advised them but left the decision of their careers to their own free choice. It is true that his advice was strongly against their entering business. He wrote that his inquiries led him to think that the most promising professions in the future would be in engineering, medicine, and chemistry. This advice the three sons took seriously. By 1886, when the course at Karlsruhe was finished, the older brother, Alfred (see "Who's Who"), had already begun his studies in engineering.

Leopold chose medicine as his life work and doubtless Julius would have preferred this profession also but for one consideration that, as the years passed by, had become more and more apparent.

As far back as memory extended he and his brother had been to every one, "The Twins." They were so much alike in appearance as to defy identification except by their most intimate friends. Their mentalities were equal; their tastes and dispositions were identical; what one did, the other did also. In school they were always in the same class, where they were equally proficient.

They began to realize that if they were ever to make for themselves separate and independent careers they must choose different professions and each must go his own way. Therefore when Leopold chose to follow medicine and went to Heidelberg, Julius decided to take up chemistry and for this purpose entered the University of Berlin.

Julius began his studies at Berlin in 1886; his professors were Tiemann, Hofmann, and Rammelsberg in chemistry and Helmholtz in physics.

His thesis, under Tiemann's direction, entitled, "Ueber die Kondensation der Säureamide und analoger Körper durch Abspaltung von Ammoniak oder dessen Derivaten," was completed in 1889 and led to the granting of the Ph.D. degree. Later Stieglitz went from Berlin to Göttingen for a short time to work with Victor Meyer. In 1889 he returned to New York. He was now 22 years old and had lived in Germany the previous eight years.

In 1890 Dr. Stieglitz spent a few months at Clark University as a scholar. He was attracted there by John U. Nef, a brilliant young organic chemist and a Harvard graduate who gained his doctorate at Munich with Adolph von Baeyer.

Later in 1890, Stieglitz found a position with Parke, Davis and Company, manufacturers of pharmaceuticals in Detroit, where his work was chiefly in toxicology. His duties centered about the examination of bodies of persons suspected of having been poisoned. His findings, reported to the coroner, often formed when positive the basis of indictments for murder. Since life or death was dependent upon the accuracy of his analyses, the responsibility of his duties weighed heavily upon him and the lugubrious work was painfully distasteful. After two years he resigned and decided to return to academic life as much better suited to his tastes.

He thought he saw his opportunity at the newly revived University of Chicago which was to open October 1, 1892, with William R. Harper as president. Hitherto colleges had started as academies and had grown painfully and slowly. Now it was proposed, with the backing of John D. Rockefeller, to launch a true university. A faculty of outstanding strength had been chosen by Harper, whose ability to judge men was phenomenal.

Nef was called from Clark University to head the department of chemistry. Michelson was in physics, Chamberlin in geology, Donaldson in neurology, Moore in mathematics, Coulter in botany, Whitman in zoology, Loeb in physiology, and Hale in astronomy. What wonder that young Stieglitz should wish to join such a remarkable group of scientists! His letter to Nef applying for an assistantship in chemistry brought the reply that none was available but that if he wished he could come as docent without salary, but with the privilege of giving lectures from which part of the students' registration fees were allowed him in lieu of salary. This opportunity Stieglitz promptly accepted, thanks to the financial help from his father which allowed him to do so.

The work in chemistry at Chicago was started in temporary quarters over a store at 55th Street and Ellis Avenue. A year and three months later, January 1, 1894, Kent Chemical Laboratory, a stately and commodious Gothic structure in Bedford stone was dedicated. In June, 1895, when the writer began his work under Dr. Stieglitz, not more than one third of the building was in use for chemistry. At the start the faculty embraced John U. Nef as professor; Henry N. Stokes and Edward A. Schneider, assistant professors; Massuri Ikuta, assistant; Felix Lengfeld, Julius Stieglitz, docents; later Alexander Smith succeeded Stokes when the latter went to the United States Geological Survey.

The new university under the guidance of the magnetic president Harper developed in a way that even the latter could scarcely have expected although his hopes knew no bounds. And with the rapid, unprecedented growth of the university, the advancement of the youthful docent kept equal pace. The progress of Dr. Stieglitz is marked by the following steps:

1892–93	Docent
1893–94	Assistant
1894–97	Instructor
1897–02	Assistant professor
1902–05	Associate professor
1905–33	Professor
1912–24	Director of University Laboratories
1915–33	Chairman of the Chemistry Department
1933–37	Professor Emeritus

The chairmanship of the department followed the death of Professor Nef.

During this time the home life of Dr. Stieglitz had developed very happily. In 1891 came the long-hoped-for marriage to Fräulein Stieffel, who had remained in Germany up to this time. The ceremony was celebrated at Oak Lawn, Lake George, New York. Julius was now twenty-four years of age. Three children soon arrived, the first died at birth, the others were Hedwig and Edward.

One of the strongest traits possessed by Dr. Stieglitz was his love for children. His solicitous care led to such precautions that the family became known in university circles as the "sterilized Stieglitzes."

I shall never forget an incident that illustrates the point. It happened at a departmental picnic on the shores of Lake Michigan. One of the ladies had washed a lot of fine strawberries, brought by Mrs. Stieglitz, in water dipped from the lake and mentioned the fact to Mrs. Stieglitz. At this that good lady threw up her hands and sighed, "Ach! Du lieber Gott. I had carefully washed them in *distilled* water at home; now the poor children must get along without strawberries." To this the children, now both doctors of medicine, added, "and we kids caught everything that went the rounds!"

The home was at 6026 Kenwood Avenue where the family lived in simple but comfortable style. With advancing rank and prosperity, emphasis was placed on health and education rather than on elegance and entertainment. This continued to be the home of Dr. Stieglitz and family for the rest of his life, thirty-five years.

With his family life so well settled, Stieglitz was now in a position to devote his energies to his academic work. At first this was two-fold: teaching and research. Later he began to take an active part in university affairs, in which he soon became one of the leaders. As his fame spread his advice was sought by numerous organizations beyond the campus.

The activities of Dr. Stieglitz after joining the university can best be treated under four headings: Teaching, Research, Academic Committees, and Extra-mural Activities.

It was as a teacher that Stieglitz was engaged by the university and it was to this task that he gave his sincere attention first. His work was along two distinct lines: Qualitative and Quantitative analyses, and lectures to graduate students on special topics in organic chemistry. These early lecture courses were on Carbohydrates, Complex Nitrogen Derivatives, and Terpenes. Each course consisted of two lectures a week for a "quarter." The lectures were most carefully prepared in written form, then memorized, and finally given without a trace of notes. They were highly prized and well attended by graduate students and were models of conciseness and accuracy. Not a surplus word was used; when the bell signaled the end of the hour, the last word of the argument had usually been given. The lecture was a finished whole and might well have been printed as delivered. Each time they were offered they were revised so as to include the latest published work on the subject. In later years other courses were offered.

As an illustration of the meticulous care used in the preparation of each lecture, one of his assistants recalls having been sent to Dr. Stieglitz' desk to search for a certain paper. In going through the desk the assistant dug up no less than eight different versions of the same lecture all written out in an effort to arrive at an ideal form for delivery.

Almost from the beginning of his work at the university, analytical chemistry was in Stieglitz' charge. By 1895 he was giving lectures on the fundamental principles on which qualitative analysis is based. At every lecture the long table was filled with apparatus used to illustrate the fundamental principles of his subject. The uniform success of these demonstrations and the clarity and simplicity of his arguments aroused great enthusiasm and attracted many advanced students, other than the undergraduates for which they were given. Through these lectures Dr. Stieglitz exercised great influence over the student body, not only those who went on with chemistry, but others who eventually specialized in other fields. These found his point of view an unforgettable inspiration.

In 1911 the two volume work entitled "Qualitative Chemical Analysis" appeared. Its scope is indicated by the sub-title, "With special consideration of the laws of equilibrium and of modern theories of solution." The introductory sentences of the preface clearly state the reason for their publication, "In venturing to add another book on Qualitative Chemical Analysis to the long list of publications on this subject the author has been moved chiefly by the often expressed wish of students and friends to have his lectures on qualitative analysis rendered available for reference and for a wider circle of instruction." Volume I embodies these lectures in the form to which they have been developed in the course of the last sixteen years. The treatment follows the lines first suggested by Ostwald's pioneering work, "Wissenschaftliche Grundlagen der analytischen Chemie." These volumes are too well known to warrant further description of their contents. Mr. Dana H. Ferrin, Vice-President of the Appleton–Century Company, writes "There have been twenty-two printings (of this work) and I estimate that over two hundred universities and colleges in the United States have used these volumes as their class texts." A most illuminating comment comes from Professor Stanley Wilson, Yenching University, Peiping, China, "I think perhaps that those of you who have been so close to him (Julius Stieglitz) all these years may not realize the full measure of his influence as a teacher." Referring to an article in which the writer speaks of Stieglitz' book as revolutionizing the teaching of qualitative analysis in the United States, Wilson wrote: "The text had a far wider influence than this statement would indicate. In my judgment it is practically the only text produced during the past thirty years which has had a really world wide influence upon the teaching of this branch of the subject. When I came to China twenty years ago I found it was employed in nearly all colleges and universities here. In 1923 I visited a considerable number of outstanding educational institutions in Burma and India. Here again I found the text was known everywhere and widely employed. I was quite surprised at the situation in India as the science staffs of these institutions were either British or British trained."

During a period of approximately twenty-five years Dr. Stieglitz carried on correspondence courses in qualitative analysis and in organic chemistry. It seems evident he enjoyed this contact with students.

The incentive which had led Stieglitz to go to Chicago as a docent without salary was that here he hoped to find not only opportunity for research but, what was more important, adequate facilities, and the encouragement and stimulation of colleagues with similar tastes. He keenly appreciated the belief that research must accompany effective teaching and this for him meant investigation of the problems of pure chemistry.

In all his research Stieglitz was most meticulous and thorough. Of his own work, he was always critical; he dealt with opposing views with candor tempered with moderation and justice. No contrary evidence was deemed too trivial to consider. If experimental work was lacking or inadequate he withheld judgment until he or his students could supply it. No point was too small or too difficult to be thoroughly investigated.

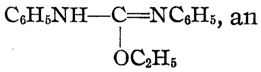
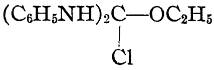
The research papers bearing his name number sixty-six; numerous other addresses, reviews, etc., bring the total to one hundred and thirty. These are supplemented by the theses mostly published in whole or in part, of one hundred and eighteen doctors who took their degrees with him. If we add to this number those whose work was interrupted before having attained the doctorate and those who came to work with him after having obtained their degrees elsewhere, the total would not be far from two hundred.

We may classify his work, which was in pure organic chemistry, into a first period of the early nineties followed by a group of five subjects carried on more or less simultaneously throughout his life. These were: molecular rearrangements, catalysis, indicators and theory of color production, stereoisomerism, and the electron theory in organic chemistry. These groups are so related and were so naturally developed one from another that they form a rather closely knitted whole.

The first eight papers covering the work of 1892 to 1895 resulted from a joint undertaking with Dr. Felix Lengfeld (1863–1938). Lengfeld, older by four years than Stieglitz, had gone from the University of California to Johns Hopkins where he made his doctorate in 1888. After two years at the Universities of Zürich, Liège, Munich, and two more in academic work, he, like Stieglitz threw his fortune in with the new and promising university.

The earlier work of Lengfeld and Stieglitz began with the study of the behavior of bromoamides toward sodium methylate. A specific case is that of the reaction between *p*-nitrobenzbromoamide and a solution of $NaOCH_3$ in $HOCH_3$. The product was a urethan, $NO_2C_6H_4NHCO$-OCH_3, formed as a result of a typical rearrangement.

Lengfeld and Stieglitz saw in the urethans, so easily obtained, intermediate products which might lead, through the corresponding isocyanates, to unsymmetrical ureas by the action of ammonia or amines. Hofmann had found that urethans give isocyanates when treated with phosphorus pentoxide. Lengfeld and Stieglitz tried phosphorus pentachloride which they hoped would react at lower temperatures. In this hope they were right; but the reaction went in a different way. The first product of the reaction was unstable and decomposed giving chlorobromoformanilide and ethyl chloride. They concluded that these products had been formed from an unstable intermediate body, $RNHCCl_2OC_2H_5$, and this they considered as the salt of a carbon base. Numerous stable salts of this class, soluble in water and forming double platinum chlorides, were made. In all such salts it appeared that the halogen was attached to carbon. Even nitrates having the NO_3 attached to carbon were obtained.

In the following paper carbodiphenylimide $C_6H_5N{=}C{=}NC_6H_5$ was found to react with alcohol at 200° to form  $C_6H_5NH{-}\underset{OC_2H_5}{\underset{|}{C}}{=}NC_6H_5$, an isourea. The same compound was obtained at temperatures below zero by means of sodium ethylate. The isourea easily forms with dry hydrogen chloride a salt,  $(C_6H_5NH)_2\underset{Cl}{\underset{|}{C}}{-}OC_2H_5$, which decomposes when warmed (60–80°) giving diphenyl urea and ethyl chloride.

Later, Dains, working with Stieglitz, made other isourea ethers and converted them into ureas by these reactions.

Two short papers on thiamines by Lengfeld and Stieglitz report the last joint work of the authors.

There was in these earlier studies some foreshadowing of Stieglitz' later work, particularly that on molecular rearrangements to which he devoted so much time and energy throughout his productive years.

Molecular rearrangements[1] are generally known by the names of their discoverers as the Lossen, Hofmann, Beckmann, or Curtius rearrangements. Porter[1] calls those involving triphenylmethane derivatives Stieglitz rearrangements. In that which follows an attempt will be made to give a brief account of the nature of the problem and Stieglitz' contribution to the subject.

By way of introduction it may be noted that the well-known Hofmann method of converting acid amides into amines affords one of the simplest examples of rearrangements. The bromoamide RCONHBr first formed by the action of a hypobromite on an amide gives with excess alkali first an isocyanate, RNCO, which is hydrolyzed by more alkali to form an amine, RNH_2, and a carbonate.

Similarly, all the rearrangements considered by Stieglitz exhibit the same striking singularity; the radical R originally bound to carbon becomes in the product attached to nitrogen. In these reactions the ordinary laws of substitution no longer hold.

Stieglitz' interest in this subject came about from a deep appreciation of its bearing on the fundamentals of organic chemistry. In an address before the National Academy of Science, December, 1914, he pointed out the importance of rearrangements in the following words: "In most chemical actions taking place at moderate temperatures a change affecting an atom or group of atoms in a molecule leaves the remaining atoms in undisturbed relation one to another. This stability of grouping of atoms led, especially, in the domain of organic chemistry, to the theory of the structure of molecules and underlies our methods for determining structure. Occasionally, however, the study of the products of a reaction shows that a profound rearrangement of the grouping of the atoms in the reacting molecule has taken place. Molecular rearrangements of this kind are of special importance for the reason that their study should shed some light on the forces holding atoms in place in molecular structures."

At the time the lines here quoted were written, Stieglitz' researches on the subject were in their nineteenth year. All rearrangements so far studied seemed to find an explanation under one simple and unique hypothesis, in which it was assumed that a hypothetical body having univalent nitrogen is an intermediate product in each case.

By Stieglitz' hypothesis, the primary action of alkali on benzoic bromoamide is the removal of hydrogen bromide, leaving C_6H_5CO-N. The great reactivity of the assumed univalent nitrogen then causes the observed rearrangement. The product, phenyl isocyanate, C_6H_5NCO, finally hydrolyzes in aqueous alkali solution giving aniline and a carbonate as end-products. Stieglitz tested this view in a wide variety of cases. Only those bodies which can lose constituents and form a hypothetical intermediate containing univalent nitrogen are capable of rearrangement. Similar rearrangements occur when each of the following classes of compounds is treated with the appropriate reagent.

I	Acid bromoamides	RCONHBr
II	Acyloximido acid salts	RC(NOAcyl)ONa
III	Ketoximes	$R_2C(NOH)$
IV	Oximido acid esters	RC(NOH)(OR)
V	Oximido acids	RCO—NOH
VI	Amide oximes	$RC(NOH)NH_2$
VII	Acid azides	$RCN(N_2)$
VIII	Benzylazides	$RCH_2N(N_2)$

One of the strongest points in Stieglitz' theory is that in all cases the reagent that must be used to bring about the rearrangement is one which will combine with the constituents to be removed. In the case of azides since only nitrogen is lost no reagent is needed; heat alone is sufficient to cause the typical reaction.

Stieglitz' original explanation of the Beckmann rearrangement based as it was on the earlier prevailing views of valence could not be more than an approach to the ultimate solution; this he himself realized.

During the following decade the electron theory as proposed by J. J. Thomson had thrown a new light on the whole subject of valence. A number of chemists had begun to apply Thomson's suggestions to organic as well as inorganic problems. In his National Academy address in December in 1914, Stieglitz expresses his theory of rearrangements in terms of the newer views. In a chloroamine the chlorine is the radical of hypochlorous

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(1) C. W. Porter, "Molecular Rearrangements," Chemical Catalog Co., New York, 1928 and A. H. Blatt, "The Beckmann Rearrangement," *Chemical Reviews*, **12**, 215 (1933), give extended accounts of the subject. Later critical reviews are to be found in the chapters by Hurd and by Wallis in Henry Gilman's "Organic Chemistry," John Wiley and Sons, New York, 1938.

acid. It is an atom of chlorine that has lost an electron, and is therefore electro-positive. In ordinary chlorides the atom of chlorine has gained an electron, becoming the familiar negative chlorine ion.

He illustrated his newer views by means of a reaction studied by Stieglitz and Leech. Triphenylmethyl chloroamine, $(C_6H_5)_3CNHCl$, when treated with sodium hydroxide gives phenylimidobenzophenone, $(C_6H_5)_2CNC_6H_5$, by loss of hydrochloric acid.

The hypothetical intermediate, $(C_6H_5)_3C\text{-}N$, with univalent nitrogen owes its activity to the loss of two electrons required to convert the positive chlorine, Cl^+, into negative chlorine, Cl^-. The intermediate then undergoes rearrangement. Stieglitz then generalizes as follows: "Finally there is a whole group of rearrangements analogous to that of the chloroamines. In each instance one can plainly recognize as the common characteristic of all rearranging compounds that the labile component in the original molecule is an unstable electro-positive radical or atom, which tends to go over into its stable negative form. In every instance, this tendency is found satisfied in the action, and as this involves the absorption of two electrons from neighboring atoms in the original molecule, one must conclude that in all these cases the tendency mentioned and its satisfaction bring about the rearrangement."

With Miss Vosburg and Mrs. Morgan, Stieglitz found, as he expected, that $(C_6H_5)_3CNCH_3Cl$ which contains the very stable NCH_3 group could not be made to rearrange. On the other hand, when the closely analogous hydroxylamine derivative $(C_6H_5)_3CNCH_3OH$ was treated with phosphorus pentachloride, Stieglitz with Leech and with Stagner proved that a normal rearrangement occurs, as shown by the identification of benzophenone and methylaniline after hydrolysis of the products of the reaction. Stieglitz now recognized that this exception to the result expected by his hypothesis established for the first time that substances which could not form simple univalent nitrogen derivatives may rearrange and that Beckmann's postulate of the direct exchange of radicals should be considered.

However, he concluded: "The first result is that the positive group of the hydroxyl amines and of the oximes undoubtedly becomes a negative group in the course of the reaction; it still would be the unstable radical in the original molecule and the satisfaction of its tendency to become negative would still be the prevailing influence in the rearrangement."

The work of Stieglitz on rearrangements represents an enormous effort. He took up a little known subject, developed it in many details, showed its extent and its limitations, and proposed theories for its explanation. The importance of his work had been recognized by his contemporaries as of outstanding significance.

The second of the four major topics of research, catalysis, had its inception soon after Stieglitz began his work at Chicago. It continued to occupy his attention for more than thirty years, although little of significance was added to his views on this subject after 1917. His war time activities together with already heavy academic interests left but little time for this subject.

In a paper in 1893 Lengfeld and Stieglitz discussed briefly the salts of imido esters and concluded with the statement, "The main importance of the subject is in its application to esterification and saponification by halogen acids." They follow this with graphic equations showing the formation of salt-like chlorides of esters as intermediates in their saponification.

The subject was taken up again experimentally by Stieglitz and McCracken in 1899.

In 1904 Stieglitz discussed his theory of catalysis in an address before the International Congress of Arts and Sciences at the St. Louis Exposition. His more mature views, based on further extensive experimental work with Derby, Schlesinger, and others, were set forth in numerous papers in 1908 to 1913.

According to classical theory, catalytic action can only be studied in reactions that conform to three fundamental principles: (1) Acceleration is proportional to the concentration of the catalytic agent. (2) The catalytic agent acts simply by its presence and does not form a compound with any of the components of the reaction. (3) The condition of equilibrium in a reversible reaction is not measurably changed by the catalytic agent. Stieglitz proposed to set aside these principles and consider the fact of acceleration as the true criterion for catalysis. He returned to the hypothesis that, in the catalysis of esters, the acid forms a salt with the ester, which acts as a weak base. He further supposed that the speed of the ensuing catalysis depends on the concentration of the salt so formed and proposed to subject the question to a quantitative examination from the standpoint of the laws of equilibrium and reaction velocity.

Since simple esters, although they are theoretically weak bases, are far too weak to allow direct measurement of their affinity constants, Stieglitz turned to the imido esters as bases whose ionization constants could be measured. The imido esters proved to be much weaker bases than ammonia, but somewhat stronger than aniline.

The imido esters react catalytically at measurable speeds with acids forming ammonia (or its salts) and simple acid esters. As a result of extensive studies with Derby, McCracken, and Schlesinger, Stieglitz concluded that the positive ion of the imido ester salt is the active substance and that the accelerating action of the acid is due to the formation of larger reacting masses of the active ion from the scarcely ionized, weak base.

To arrive at this result other possibilities such as the activity of the free base or of the total imido ester were taken into account by mathematical methods and shown not to be valid. But the so-called "Salt effect" was noted here, just as in catalysis of acid esters, sugar inversion, etc., and its effect, which is proportional to the hydrogen ion concentration, was deducted in reaching the conclusion that it is the positive ion of the imido ester salt that reacts with water.

In the work with McCracken nine imido esters were studied and a further interesting relationship was noted. The affinity constants of the imido esters as measured by Stieglitz and Derby were not only much smaller than that of ammonia but in general the smaller the constant the faster the decomposition with water took place.

Although the action of water on an imido ester when catalyzed by an alkali yields an alcohol and a nitrile instead of ammonia and an acid ester, as when an acid is a catalyst, Stieglitz showed that the speed of reaction is in accord with his theory. In this case it is the negative ion formed by the imido ester and alkali whose active mass determines the speed of catalysis.

Stieglitz now concluded that the three tenets of the classical theory of catalytic action are practically true only for limiting cases where the proportion of salt formed is negligible. None of the three is absolutely true under any conditions. When the amount of salt formation becomes measurable they need not hold even approximately. It was therefore concluded that acceleration due to an increase in the active mass of a reacting component is the only fundamental fact common to all catalytic reactions.

At the time of his first papers on catalysis, 1904–1907, his brilliant attempt to use the imido esters as a basis of a quantitative analysis of the true factors of hydrogen and hydroxyl ion catalysis made a great impression. However, the work was done before the newer applications of thermodynamics to the study of solutions. In these he did not participate.

The incentive for the papers on indicators seems to have been found when Stieglitz reviewed H. C. Jones' book, "Physical Chemistry," in 1902. In the chapter on indicators color change was explained by Jones according to one part of Ostwald's theory. This, it will be recalled, assumed that phenolphthalein, for example, is a very weak acid which is therefore un-ionized as long as the solution remains even faintly acid. But at the point where a minute excess of alkali prevails, the indicator is converted into its ionized salt. According to Ostwald, the change of color is explained by assuming that the un-ionized phenolphthalein is colorless whereas its negative ion is red.

This very simple explanation seemed so convincing that it was pretty generally accepted, especially as so many other physico-chemical facts had found their elucidation in the magic theory of ionization. Textbooks of physical chemistry all presented the view of Ostwald without reference to other possible explanations.

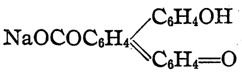
Stieglitz, whose familiarity with analytical as well as organic chemistry enabled him to see clearly the inadequacy of the theory of Ostwald respecting change of color, presented briefly in this review the contrary evidence from the standpoint of the organic chemist. A year later he elaborated these views into a critical paper on the theory of indicators.

After readily endorsing Ostwald's views of the cause of sensitivity as being due to the weak acidic or weak basic character of an indicator, he called attention to the fact that ten years earlier Bernthsen had given an explanation of the color change that greatly appealed to organic chemists. According to this view the change of color is due to a change of constitution of the indicator brought about by the excess of alkali or acid, the subsequent ionization being merely incidental.

The free (colorless) phenolphthalein is pictured as a lactone, without a chromophoric group

I $\underbracket{\mathrm{OCOC_6H_4C}}\mathrm{(C_6H_4OH)_2}$

while the red salt has the chromophoric form

II 

$$\mathrm{NaOCOC_6H_4}\left\langle\begin{matrix}\mathrm{C_6H_4OH}\\ \mathrm{C_6H_4{=}O}\end{matrix}\right.$$

The solid (and therefore un-ionized) silver salt, is also intensely colored. It undoubtedly has a quinoid form like II. This view is further supported by the work of Nietzki and Bruckhardt, who made colorless esters having lactoid forms corresponding to I and colored (un-ionizable) esters of quinoid form II.

Stieglitz pointed out similar relations for the para rosaniline dyes which contain the chromophoric quinoid grouping, whereas the free base is a colorless carbinol. When dyes in general are converted by reduction into leuco forms, the change of color is concomitant with similar changes of structure.

The work of Hantzsch is cited as showing that the change of colorless organic compounds (pseudo acids) into deeply colored salts is always accompanied by a change in the structure of the molecule as illustrated by the case of nitrolic acid. The regeneration of the free (colorless) form of the pseudo acid often takes place quite slowly.

Stieglitz points out that to be useful as an indicator the reversible color change must be a rapid one.

The behavior of indicators like litmus or methyl orange, which show one color in acid solution and another in alkaline, is explained quite simply by the same theory.

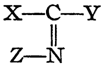
The great merit of Stieglitz' work on indicators lies in the fact that he, more than any other, was instrumental in showing the insufficiency of Ostwald's ionization theory, and in leading chemists to the acceptance of the sounder view based on facts and theories of organic chemistry.

The work on indicators led Stieglitz to propose in an address before the National Academy of Science and the Franklin Institute a highly suggestive theory of color production.

Even if the seat of color in dyes is ascribed to certain rather definite arrangements of atoms in the molecule, there still remains to be explained why such an arrangement causes the light absorption that produces the complementary color in the compound, and why if such atomic groupings are absent the compound is colorless.

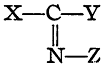
Stieglitz showed that all dyes which easily can be reduced to colorless leuco compounds are oxidizing agents. The leuco bodies are reducing agents which readily are reconverted again into dyes. Stieglitz believed it is the vibration of these mobile but restrained electrons of the dyes that causes the light absorption which results in color.

In his researches on the stereoisomerism of nitrogen compounds, Stieglitz worked with a number of assistants and students, including, Earle, Hale, Eckstein, Hilpert, Peterson, Raiford, and others. In the course of this work a new class of nitrogen stereoisomers was sought for and found. A dozen years earlier Hantzsch and Werner had suggested that the isomerism of the benzil oximes of Victor Meyer was to be likened to that in the case of derivatives of ethylene. Accordingly, we would have the two forms:



$$\begin{matrix}\mathrm{X{-}C{-}Y}\\ \Vert\\ \mathrm{Z{-}N}\end{matrix}$$

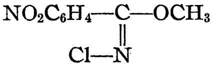
and



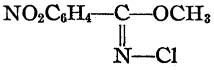
$$\begin{matrix}\mathrm{X{-}C{-}Y}\\ \Vert\\ \mathrm{N{-}Z}\end{matrix}$$

cis and *trans* forms containing doubly bound carbon and nitrogen.

Hitherto all efforts to produce unquestioned nitrogen stereoisomers among bodies other than oximes and hydrazones, where Z is an atom or a simple radical, had been in vain. Stieglitz and Earle had sought such bodies in connection with studies on the rearrangement of halogen amides like $\mathrm{RC({=}NCl)OCH_3}$. This search was at last rewarded when they succeeded in making two methyl chloroimido-*m*-nitrobenzoates



$$\begin{matrix}\mathrm{NO_2C_6H_4{-}C{-}OCH_3}\\ \Vert\\ \mathrm{Cl{-}N}\end{matrix}$$



$$\begin{matrix}\mathrm{NO_2C_6H_4{-}C{-}OCH_3}\\ \Vert\\ \mathrm{N{-}Cl}\end{matrix}$$

A little later Stieglitz and Hale made the analogous pair of ethyl esters. Hilpert made three and Peterson made several others. It was shown conclusively that each of a given pair of substances has identical composition, molecular weight, and structural arrangement, excepting of course in the orientation of the nitrogen–chlorine groups. Each isomer maintains its identity under physical conditions, such as solution, melting, and even volatilization in vacuum.

The only means found to convert the isomers, each into an equilibrium mixture of the two, was the action of chlorine gas on the fused substance. Although the stereoisomers have different solubilities and melting points, their complete individuality was established. Like acid chloroamides these bodies react with hydrochloric acid to form salts of imido esters and free chlorine.

This record of achievement in research marks Stieglitz as one of the strong men of his time. In addition to splendid teaching and high class research, he carried on other activities of great importance both to his university and to the nation.

It was no part of Stieglitz' philosophy that teaching, research, and the writing of textbooks should constitute all of one's duties as professor. His horizon had a much wider scope and not many years had passed before he took an active part in faculty matters. His thorough investigation of the questions involved, his logical and forceful method of presentation of their significance, and his fairness to both sides soon were recognized.

He became a key man whose advice on university affairs was eagerly sought; his was the guiding influence in many committees. I will mention only two instances of the many where his services were of great value; and, in later years, there was scarcely an important question about which he was not consulted.

Of his many memorable achievements, one was that concerned with the conflict between science and the classics. In the early nineties Chicago in common with most other colleges still adhered to a rigid requirement in the classics as a prerequisite for the bachelor's degree even for science students. This inheritance from medieval times was becoming very irksome to the students in Physical and Biological sciences. The preceding twenty years had witnessed amazing and unprecedented developments in Natural Philosophy which had now become a group of experimental sciences with seemingly unlimited possibilities. To be required to thumb through musty tomes of Latin and Greek when so much of greater interest and practical value was at hand seemed, to science students, a sacrilegious waste of time. The battle for the removal of this restriction waxed long and hard; Stieglitz was the leader for the cohorts of science.

In the department of Chemistry at Chicago, Stieglitz' students commemorated the ultimate triumph of the science group by presenting him with a parchment scroll expressing their gratitude for his untiring efforts in their behalf; the names of many who have since risen to prominence are appended.

For one without special training in the subject, Stieglitz was outstanding among his colleagues for having a remarkable knowledge of medicine. This interest arose in early life and doubtless would have led him into that profession but for reasons already mentioned. Perhaps, also, the facts that Mrs. Stieglitz was afflicted with asthma for long years, and that their first child had died at birth and the other two passed through numerous contagious ailments had much to do with the strengthening of this interest.

It seems natural then that in 1901 when President Harper in his desire for a medical school at Chicago began to strive for a union with Rush Medical College as a means to this end, Stieglitz should find a place on the committee of which the late Dr. H. H. Donaldson was chairman.

With only $50,000 in sight, Harper proposed to begin in a modest way by transferring to the university campus the work of the two preclinical years. After a memorable conference of President Harper with the combined committee of the two institutions, in which ways and means were thoroughly discussed, Stieglitz asked Dr. Ingals, treasurer of Rush, the critical question he long had had in mind; that was, whether the tuition fees of the transferred students would revert to the university. When Ingals replied in the affirmative, Stieglitz saw at once that with this additional income the union so greatly desired by the University could be safely made with the $50,000 available. Harper was equally quick to grasp the situation and, in his characteristic fashion, changed the subject immediately and quickly brought the conference to a close. On the way out he said privately to Stieglitz, "Mr. Stieglitz, let me have your budget by next Saturday morning."

Stieglitz had already worked out the details, but to avoid any serious blunders he and Dr. Donaldson made a hurried visit to four leading eastern medical schools prospectuses of which they had studied. They returned convinced that with the laboratories and staffs at the University, together with the modest sum the President had mentioned as being in sight, they could offer facilities equal or superior to those of the schools they had visited.

The union of Rush and the University was soon consummated and proved successful from the start. The hitherto nearly empty Hull laboratories were filled with medical students. The departments of anatomy, physiology, pathology, physiological chemistry, and bacteriology became realities instead of mere names, and suddenly took on new life.

The union with Rush was looked upon by Stieglitz as a vital transfusion of blood into all science departments. He was justly proud of the part he had played in helping to lay the foundation of a great medical institution now a part of the University.

After the premedical courses had been brought to the university the deanship for the new division was offered to Dr. Stieglitz by President Harper. The former with characteristic farsightedness begged to decline the honor and pointed out to the President that he considered it a better policy to put a Rush medical professor in the deanship.

Stieglitz' close association with physicians and surgeons during the period of negotiations with Rush Medical College led to lifelong friendships with many leading medical men. This was the beginning of his affiliation with the American Medical Association that lasted officially two decades, but actually existed throughout his lifetime. In 1905, he became vice-chairman of the powerful Council of Pharmacy and Chemistry, a responsibility he held until 1924. A record for the year 1920 shows Stieglitz' name on five of the fourteen committees of the Council.

Dr. Leech, present secretary of the Council, commenting on Stieglitz' services to the American Medical Society says: "It is proof of his fine judgment and parliamentary ability to note that the rules are essentially the same today as thirty-two years ago. He took great interest in seeing that every safeguard was put in the rules for impartiality of decisions.

"In his capacity as vice-chairman of the Council, Stieglitz exerted a powerful influence on its action during the nineteen years of his tenure of office."

The summer of 1914 marked the beginning of the most critical period for chemistry in America. The British blockade that quickly followed the beginning of the World War shut off importation from Germany and thus soon produced a dearth of the previously imported fine chemicals so necessary for medicine and industry. The situation threatened speedy disaster. In the decade that followed Stieglitz played a conspicuous part among the army of loyal chemists whose efforts proved so successful in this emergency.

On January 1, 1917, Dr. Stieglitz became president of the American Chemical Society. The war was now in the middle of its third year. Three and a half months later America joined the cause of the Allies. As never before, war had developed into a conflict of chemists. Few officers of our society faced graver tasks than did Stieglitz and none deserves greater credit than he for his unselfish services in aiding in the stupendous developments that finally brought relief to medicine and industry and chemical independence to America. His notable success was due not only to his sound and extensive knowledge of organic chemistry, to his love of the science and art of medicine, to his deep interest in synthetic drugs, as evinced by his long service on the Council of Pharmacy and Chemistry of the American Medical Association; but, in no small measure, to his subsequent election or appointment to leading positions in organizations where his opportunities for acquiring information about existing conditions were unexcelled.

On February, 1917, he was appointed Chairman of the Committee on Synthetic Drugs of the National Research Council which committee was the scientific adviser of the Government, and which had been organized in the foregoing year under the authority of the National Academy of Sciences. He also held a semi-official position as adviser to the Federal Trade Commission.

In 1918, he became president of the Chicago Institute of Medicine, an organization having for its object the promotion of medicine through scientific research. At the same time he accepted an appointment in the United States Public Health Service as Special Expert in Arsenicals.

The Chemical Foundation was incorporated in February, 1918; the following month Mr. Francis Garvin became its president and Dr. Stieglitz its Chemical Adviser. In 1920 he was chosen Consultant for Chemical Warfare Service by General Amos A. Fries. During this period he also maintained his position as Director of the Department of Chemistry at the University of Chicago.

Thus his facilities for acquiring accurate information regarding the chemical situation in America were unexcelled, and his prestige assured him a sympathetic hearing among those in authority whenever his advice was offered.

For months the lamentably insufficient supply of synthetic drugs had been an acute problem. Such drugs were formerly imported from Germany almost exclusively. Their number had been much greater than necessary. Many of them had been introduced merely for commercial reasons. Through his various medical connections Stieglitz was able to ascertain that most of these could be dispensed with if but a very small number of the most reliable ones were made available. Only four or five were indispensable and for several reasons it seemed desirable to give these substances new, American names. Arsphenamine was the name coined by Stieglitz for the drug called Salvarsan by the Germans. It is the "606" of Ehrlich and is the recognized cure of syphilis, a disease with which ten million Americans were said to be afflicted.

Barbital (formerly called Veronal) was the most widely used and reliable hypnotic. Procaine (formerly called Novacaine) was the most useful of all local anesthetics. Lack of it necessitated the so-called "Bulgarian operations," those made without anesthesia. Cincophen (Atophan) was the most efficient drug in the treatment of gout and rheumatism. Phenobarbital (luminal) a sedative and hypnotic, was a specific drug for the prevention of the seizures of epilepsy. Physicians and hospitals were literally begging for this drug for two years before it was made in America.

As a member of the Committee on Synthetic Drugs, it was the duty of Stieglitz to see that the public received supplies of these indispensable drugs as quickly as possible. To this end he either induced or encouraged certain reliable pharmaceutical manufacturers to take up their production. He gave them chemical advice and aided them in obtaining the supplies of auxiliary chemicals that were required, as, for example, hydrosulfite, needed to make arsphenamine and bromine, used in the synthesis of procaine.

As Adviser to the Federal Trade Commission, his trying duty was to decide to which manufacturers licenses were to be issued, for the production of each drug.

When, in 1918, it became known to the Federal Health Service that some domestic supplies of arsphenamine were causing serious trouble in the treatment of army cases, Stieglitz, as Special Expert in arsenicals, rendered much valuable service.

Speaking of the Public Health Service, Dr. George W. McCoy, chief of its Hygienic Laboratory, says, "We were urgently in need of the very best advice available anywhere with respect to the standardization as to quality and safety of the preparation of the arsphenamine group. Professor Stieglitz gave unstintedly of his time and effort. It was always a source of great comfort to know that we were proceeding in accordance with the advice and suggestions of Professor Stieglitz."

In his capacity as Professor of Chemistry of the University, Stieglitz and his students conducted important researches on arsphenamine in the course of which it appeared to his satisfaction that the specifications given in the patent were not sufficient to guide a trained chemist to the preparation of a safe product. The additional steps which he employed were highly necessary. His investigations on Phenobarbital, so long in demand by physicians, led to work by Stieglitz and Mary M. Rising that resulted in the finding of improved methods for its preparation through substitution of methyl esters, which are solids easily purified by recrystallization, for the liquid ethyl esters used originally.

It was Stieglitz more than any other chemist who stressed the close genetic relationship between the three great classes of organic substances: dyes, war chemicals, and medicinals. To these, of course, may be added photographic chemicals. In all his efforts to keep this connection to the forefront he clearly saw that an ultimate solution could only be reached through the establishment in this country of a great dye industry. The dye "intermediates" are just those chemicals which form the starting material for explosives, war gases, synthetic drugs, and photographic chemicals. For economic reasons all must go together. The works and equipment for the manufacture of one class of products serves with little modification for all. It was through his connection with the Chemical Foundation that his greatest efforts on this subject were made. In the record of the trial of this organization, Stieglitz' achievements are recorded in much detail.

It will be remembered that this was the celebrated case in which the Government tried to set aside as illegal the purchase of over four thousand German patents covering dyes and related substances and their subsequent license to American firms. The Chemical Foundation had acquired title to the patents through their purchase for $250,000 from the Alien Property Custodian.

The trial occurred in Wilmington, Delaware, in December, 1923, before the Honorable Hugh M. Morris, United States District Judge. In the course of the trial Stieglitz gave valuable testimony in support of the contention of the defendant (C. F.) that a complete domestic dye industry is the logical and only practical defense against a recurrence of the perilous situation in which the country was placed at the outbreak of the World War.

He showed clearly to the satisfaction of the court how and why an adequate supply of dye intermediates would provide those chemicals indispensable for the manufacture, not only of the dyes themselves but also of explosives, war gases, medicinals, photographic, and other fine chemicals. The climax of Stieglitz' testimony, at least for the non-technical audience, was reached when by permission of the court he illustrated his point by an actual demonstration in which he showed that a given intermediate might serve for the preparation of a dye, a medicinal, or a war gas. He placed a few drops of aniline in each of three test-tubes: in the first he produced the dye, mauve, by oxidation of the crude aniline with a drop or two of ferric chloride. In the second tube he converted the aniline into the popular sedative, acetanilide ("aspirin"), by the action of acetyl chloride. To the aniline in the third tube he added alcoholic potash and a drop of chloroform. The nauseating phenyl isocyanate formed was convincing as a war gas.

Referring to Stieglitz' testimony in this suit, Dr. Charles L. Parsons writes: "I remember how completely he confounded the opposition who thought they were going to make a point by asking him as to the fees he drew from the Chemical Foundation by quietly stating that he never went into court except in the public interest and consequently never accepted any fee therefor. The statement was extremely affective in the outcome of the trial, which was won by the Chemical Foundation."

Dr. Stieglitz was editor of and contributor to the well known book, "Chemistry and Medicine," a most interesting and informing document. This contribution of forty-three leading scientists was sponsored by the Chemical Foundation and widely distributed, gratis, by Mr. Garvan as a memorial to his daughter, Patricia, who died in childhood.

His services as Adviser to the Chemical Foundation are thus described in a letter by Mr. William Buffum, treasurer and general manager of the organization, "His council was often sought and freely given. He was always very coöperative in assisting us to solve our general and specific problems. It can undoubtedly be said that Dr. Stieglitz was the foremost exponent for American chemotherapeutic research. He was one of Mr. Garvan's and my closest friends." As concrete evidence of his friendship and admiration, Mr. Garvan created the Stieglitz Foundation which was put at the disposal of Dr. Stieglitz for research on problems in the field of Chemistry as applied to medicine.

In accord with university regulations Stieglitz' retirement took place in September, 1933, at the age of sixty-five. This change in official status did not prevent his retention of his rooms at Jones Chemical Laboratory, the splendid new home of the department given by George Herbert Jones, where, as emeritus professor, he continued to give advice on departmental matters whenever requested to do so. His students were so loath to give him up that they raised a special fund which permitted him to continue his lectures and direct research.

Although he had numerous attractive opportunities he had steadfastly refused to act as a consulting chemist for industry during his professorship. It was only after his retirement that he made his first and only connection of this kind, a "half-time" position on the staff of Universal Oil Products Company. Here he was associated with the able organic chemists Egloff, Ipatieff, and others.

Many additional honors came to Professor Stieglitz. Several honor societies elected him to membership: the National Academy of Sciences, the American Philosophical Society, and the American Academy of Arts and Sciences. The Society of Sigma Xi elected him national president in 1917. In 1920 he was the presiding officer of the Chicago Chapter of the same society. He was a member of the Société Chimique de France, the Washington Academy of Sciences, and the American Association for the Advancement of Science, of which he was vice-president in 1916.

For the years 1912–1919 he was an associate editor of THIS JOURNAL.

Stieglitz was a charter member of the Chaos Club, an informal group whose personnel is chosen from eminent scientists in and about Chicago.

In 1909 Clark University conferred upon him the honorary Doctor of Science degree and in 1916 he received the honorary degree of Doctor of Chemistry from the University of Pittsburgh. In 1923 he was the recipient of the Willard Gibbs medal.

Many institutions honored him with special lectureships. He was Lecturer at the Exposition of Arts and Sciences at St. Louis in 1904; he held the Hitchcock Lectureship at the University of California in 1909 and later in 1915. Stanford University honored him with a lectureship in 1921 and he also held the Dohme lectureship at The Johns Hopkins University in 1924, the Fenton lectureship at the University of Buffalo in 1933, and in 1936 he delivered the Edgar F. Smith Memorial Lecture at the University of Pennsylvania.

He was a trustee for International Critical Tables, as representative of the American Chemical Society, and contributed materially to its ultimate successful publication. He was a member of the International Commission for the Annual Tables of Constants 1915–1921. For approximately a quarter of a century, he was a member of the advisory council of the Sprague Institute in Chicago.

The bust of Dr. Stieglitz that has occupied a pedestal in the entrance hall of Jones Chemical Laboratory, along with those of Dr. Nef and Dr. Alexander Smith, was the gift of his admiring students and other friends. It stands as a lasting memorial of the esteem in which he was held by those who knew him best.

The personal life of Professor Stieglitz has been sketched up to the time he joined the University of Chicago. In the years that followed he and Mrs. Stieglitz with their two children continued a happy and uneventful home life. Both children passed through the University and Rush Medical College, and subsequently established homes for themselves. Both are actively engaged in the practice of Medicine. The elder, Hedwig, is the wife of Dr. Hugh Kuhn (M.D.) of Hammond, Indiana. The younger, Edward J., in addition to his practice is also Associate Clinical Professor at Rush Medical College.

After having been afflicted with asthma for many years, Mrs. Anna Stieglitz died on December 25, 1932.

Following his great loss, Dr. Stieglitz tried to live alone in the old home. His friends were delighted when he married his former student and colleague, Dr. Mary Meda Rising, August 30, 1934.

Dr. Rising is the daugher of Roland S. and Meda (Menardi) Rising who now reside in Hollywood, California. Mr. Rising is a retired banker; Mary Rising was born in Ainsworth, Nebraska, in 1889. After graduation from Mt. Holyoke College in 1912, where she was a student under Professor Emma P. Carr, she went to the University of Chicago for graduate work in chemistry. There she received her doctorate degree in 1922 and from that time to the date of her marriage Dr. Rising was a member of the Department of Chemistry where she was Associate Professor at the time of her marriage. She then gave up her professorship to become Research Associate.

A few years prior to her marriage, Dr. Rising had adopted a baby daughter, Kate. It is not strange that after the marriage, little Kate was soon so firmly established in the affection of Dr. Stieglitz that he too adopted her. Professor Stieglitz often spoke feelingly of his fondness for children. A typical remark was "Babies, I love them. If I could, I would like to have them in the house all the time!" With his three grand-children, two sons of Mrs. Kuhn and the daughter of Edward, his desires seem to have been realized. The home, thus newly established, provided those things which for him were so necessary for life and productive work.

In spite of a most strenuous and time-consuming schedule, Stieglitz found some time for diversions. In his younger days, tennis and billiards were favorites. Later their place was substituted by golf. Stieglitz never played bridge; once when the subject was brought up, Stieglitz remarked, "I hate cards, that is, except poker; that's not cards but a play of human nature."

A hobby in which he attained results of high artistic merits was photography. This was the field in which his elder brother, Alfred, had reached world-wide distinction. Much time was spent at this diversion and many splendid prints attest his skill.

Dr. Stieglitz' love for music inspired him to maintain his practice on the cello throughout his life. He was very fond of opera, which he patronized as often as time and finances permitted; his favorite was Tristan and Isolde. Of composers, Mozart, Beethoven, Bach, Schubert, and Wagner interested him most. In later years he found great pleasure in the radio, which brought to him both opera and symphony.

Up to the time of his last illness, Stieglitz had enjoyed consistent good health; on but very few occasions were his regular duties interrupted by illness.

In the summer of 1936 he suffered a heart attack which caused Mrs. Stieglitz to be summoned home from California. From this illness he recovered quickly. The following Thanksgiving Day he had a more severe attack. This was followed by pneumonia, from which he rallied after some weeks. The end came suddenly on January 10, 1937, due to coronary thrombosis.

This account would be incomplete without further comment on the remarkable character of the man whose career was thus brought to a close.

To the countless thousands who knew him only by his published works Julius Stieglitz was a chemist of high attainments. To the smaller favored number whose acquaintance was more intimate, his friends, colleagues, and students, he was a unique and highly gifted personality.

His life work formed an exceptionally consistent whole in full accord with his oft-expressed formula of a complete academic career. His activities were apportioned with rare idealism between teaching, research, university administration, and public service. To have made a success in one or two of these lines of endeavor would have assured him a lasting remembrance. His pre-eminence in all four is a symbol of his versatility and stamps him as one of the outstanding men of his time.

Although Dr. Stieglitz' solicitous care for the welfare of his family was at all times uppermost in his mind, his personal interests were always subordinated in favor of the attainment of his ideals. As an example of this it is related on excellent authority that he once refused a position as chemist in a major industry at $50,000 a year.

It was a rare trait of Stieglitz' character that in the accomplishment of a desired end he did not merely lend his support to the movement. It was his custom to work out in complete detail a plan by which the project could be carried out. Thanks to his prodigious and accurate memory he could take a conflicting mass of details, sift them, discard the irrelevant, and weave the sound arguments into a convincing whole. His erstwhile opponents were wont to give way with the remark, "What's the use; Stieglitz is too logical."

Perhaps it was in his relations with his students that his memory is most highly cherished. His popularity as a teacher is attested by the significant fact that in all the University, the number of students who made their doctorate with him was greater than with any other professor. Among this number, 118, are many men and women who have achieved a national reputation. Among those whose life's work is complete and who were most widely known are Dr. Otto Folin, Professor of Biological Chemistry, Harvard Medical School, and Dr. Edwin E. Slosson, author of "Creative Chemistry" and founder of Science News Service. Numerous others occupy high places in the field of pure and applied Chemistry.

The problems he set for his research students were always well thought out in advance, never too difficult or impossible. In the laboratory his attitude was dignified and formal, but quiet and kindly, never seemingly hurried, but never wasting time or words, never neglecting students but always keeping before them the highest ideals. A typical remark, "I think the compound can exist, Mr. X. In a week you should have at least ten grams of it," was taken by the student as an order that he exerted himself to the utmost to fulfill, although its accomplishment won only the equally mild, but greatly valued, approval, "Very good, Mr. X."

Excepting during the earliest years at Chicago, Dr. Stieglitz rarely carried out his researches with his own hands. Nevertheless he was always critical of apparatus and technique. Often when he was forced to disapprove, his criticism was couched in so humorous a vein as only to spur the man to greater efforts toward improvement. A beginner at research had set up a piece of apparatus that differed greatly from that described in the reference given. On seeing it Dr. Stieglitz remarked, "That is not the apparatus used by ......, Mr. Y." When the student excused the fault as due to his scanty knowledge of German, Dr. Stieglitz left without a word;

a minute later he returned, placed on the desk the volume in question, opened to the page showing a figure of the apparatus, saying, "The picture is not in German, Mr. Y."

On another occasion when a student in qualitative analysis explained that he was evaporating a solution of ammonia to concentrate it, Stieglitz' only comment was, "Go right ahead, Mr. Z."

To his students Dr. Stieglitz always lent his helpful sympathy when other resources failed. He was ever ready and willing to listen to their problems and was most happy when he was able to work out a satisfactory solution of their difficulties. With students, as with others, he had a great reputation for fair dealing. In many cases the advice was more personal, extending as his daugher (Dr. Hedwig Stieglitz Kuhn, M.D.) humorously avers, "To every subject from the proper selection of the bride's silver to the choice of an obstetrician."

Always overworked, with his time sorely crowded, it is not strange that those who came to his room unannounced to speak on trivial matters often mistook a brusque dismissal for surliness. This was only apparent and not intended. Until late in life he had no secretary who could protect him from thoughtless intrusions.

On his part Dr. Stieglitz was always considerate of the time of others. For years the writer's laboratory was directly across the hall from his. He very rarely came informally to discuss matters, instead it was his custom to place handwritten notes in my box.

The esteem in which Dr. Stieglitz was held by his contemporaries is amply attested by the many positions of honor and responsibility to which he was called. Little can now be added to his fame by the laudation of his biographer. To employ a favorite maxim of Dr. Stieglitz: "Let the work show its worth by itself." The work of Julius Stieglitz is his memorial; a fitting testimony to a splendid career. In this work he realized his highest ideal: a life devoted to the advancement of science and the promotion of human welfare.

HERBERT N. MCCOY

PUBLICATIONS OF JULIUS STIEGLITZ

"Ueber die Kondensation der Säueramide und analoger Körper durch Abspaltung von Ammoniak oder dessen Derivaten" (Inaugural Dissertation zur Erlangung der Doctor-würde von der philosophischen Facultät der Friedrich-Wilhelms Universität zu Berlin, am 14 December, 1889), A. W. Schade's Buchdruckerei (L. Schade), Berlin, 1889.

"Ueber das Verhalten der Amidoxime gegen Diazobenzolverbindungen," *Ber.*, **22**, 3148–3160 (1889).

"On Benzoquinonecarboxylic Acids," *Am. Chem. J.*, **13**, 38–42 (1891).

Felix Lengfeld and, "Derivatives of Nitrogen Halogen Compounds. I," *ibid.*, **15**, 215–222 (1893).

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

The Separation of Primary Active Amyl Alcohol from Fusel Oil by Distillation

BY FRANK C. WHITMORE AND J. HARRIS OLEWINE

Fusel oil, regardless of its origin, generally consists of primary active amyl alcohol $CH_3CH_2CH(CH_3)CH_2OH$, and isoamyl alcohol $(CH_3)_2CHCH_2CH_2OH$. These two alcohols, boiling at 128° and 130.5°, respectively, had never before been separated effectively by distillation alone.

Klages and Sautter[1] obtained active amyl alcohol in 42–61% purity by distillation of fusel oil from beet sugar molasses. Votocek and Vesely[2] isolated the active alcohol in only 46% purity by the distillation of fusel oil obtained from molasses. Since the completion of the present study (1936), Brauns has reported such a successful separation.[3] In this paper, the fractionation of fusel oil to give primary active amyl alcohol of approximately 95% purity, is described. The separation necessitated the use of very efficient columns.[4,5]

Experimental

The fusel oil used was a refined product[6] obtained in the fermentation of cane molasses, $\alpha^{33}\text{D}$ −0.69°. Prior to fractionation, it was dried at 0° for forty-eight hours with anhydrous sodium sulfate.

Preliminary Fractionation.—In a series of trial fractionations, two packed columns of metal construction were used. One column was 27 feet (7.9 meters) long and 3 inches (7.6 cm.) in diameter with a capacity of 13 gallons (49 liters), the other column was 52 feet (15.4 meters) long and $^3/_4$ inch (1.9 cm.) in diameter with a capacity of 1.5 gallons (5.7 liters). The construction and operation of these columns already has been described in detail.[4] In one preliminary fractionation, 40 liters of the refined fusel oil was first distilled in the 27-foot (7.9-m.) column and the best intermediate fractions therefrom were then twice redistilled in the 52-foot (15.4-m.) column. Approximately 0.6 liter of primary active amyl alcohol was obtained, b. p. 128° (760 mm.), $n^{20}\text{D}$ 1.4111, having an average observed rotation of $\alpha^{33}\text{D}$ −4.27° in a 1-dm. tube. The maximum rotation included in this average value was −4.34°, specific rotation $[\alpha]^{33}\text{D}$ −5.32°. Based on −5.9° as the specific rotation of pure primary active amyl alcohol, the alcohol thus obtained was approximately 90% pure.

Isolation of Primary Active Amyl Alcohol.—The design and efficiency of the distillation equipment used in this fractionation had been described previously.[5] The column was of nickel construction with a height of packed section of 38 feet (11.4 meters) and having a distilling capacity of 12 liters. When tested with *n*-heptane and methylcyclohexane and operating at a velocity of 3.4 liters per hour at the top of the tower, the column had the equivalent of 101 theoretical plates.

Four fractionations were made using a total of 35.2 liters of fusel oil. The following describes a typical run. A charge of 10 liters of fusel oil was refluxed for twelve hours to bring the column to equilibrium, after which the distillate was collected at a rate of approx. 70 cc. per hour during a period of continuous operation for eight and one-half days. This rate enabled an average reflux ratio of 30:1 to be maintained and to give at 760 mm.: Fractions 1–13, 1310 cc., b. p. (Cottrell) 107.8–117.4°, $n^{20}\text{D}$ 1.3835–1.4000; 14–17, 450 cc., 119.6–128.7°, 1.4025–1.4102, obsd. rotation (1-dm. tube) $\alpha^{27}\text{D}$ −0.72 to −3.81°; 18–42, 3300 cc., 129.3–130.8°, 1.4101–1.4069, −3.49 to 0.00°; 43–62, 3973 cc., 130.8–131°, 1.4069; residue, 725 cc.

The cuts of the four fractionations having the highest concentration of active alcohol were combined (8209 cc.) and refractionated through the nickel column during seven days to give: Fractions 1–7, 625 cc., b. p. 125.1–127.9° (760 mm.), $n^{20}\text{D}$ 1.4003–1.4110, $\alpha^{28}\text{D}$ −0.41 to −4.90; 8–22, 1310 cc., 127.7–128.5°, 1.4110, −4.91 to −4.93°,

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[1] Klages and Sautter, *Ber.*, **37**, 649 (1904).

[2] Votocek and Vesely, *ibid.*, **47**, 1515 (1914).

[3] Brauns, *J. Research Nat. Bur. Standards*, **18**, 315–31 (1937).

[4] Fenske, Quiggle and Tongberg, *Ind. Eng. Chem.*, **24**, 408 (1932).

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[6] Obtained from the U. S. Industrial Chemical Company, Baltimore, Maryland.

d^{28}_4 0.8169–0.8137; 23–34, 1465 cc., 128.5–129.8°, 1.4110–1.4103, −4.92 to −4.12°, 0.8137-0.8130; 35–44, 1210 cc., 129.7–131.0°, 1.4097–1.4070, −3.55 to −0.70°, 0.8130.

Fractions 8–34 are primary active amyl alcohol of high rotatory power. The maximum observed rotation for the best fraction was $\alpha^{28}\text{D}$ −4.93°; specific rotation $[\alpha]^{28}\text{D}$ −6.04°. The constants (average) of the primary active amyl alcohol are: b. p. 128–129° (760 mm.), $n^{20}\text{D}$ 1.4109, d^{20}_4 0.8189, $d^{27.5}_4$ (calcd.) 0.813, $\alpha^{27.5}\text{D}$ −4.77°, $[\alpha]^{27.5}\text{D}$ −5.86° (1-dm. tube). The rotation of an aliquot sample was kindly checked by Levene,[7] who reports $\alpha^{25}_{5875.6}$ −9.186 ± 0.003° (2-dm. tube), and Wallis,[8] who reports $\alpha^{24.5}_{5893}$ −4.52° (1-dm. tube).

Summary

Primary active amyl alcohol having a high optical purity can be separated from fusel oil by a laboratory distillation process. The physical constants are reported.

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[7] Dr. P. A. Levene, Rockefeller Institute of Medical Research, New York City, private communication.

[8] Dr. E. S. Wallis, Princeton University.

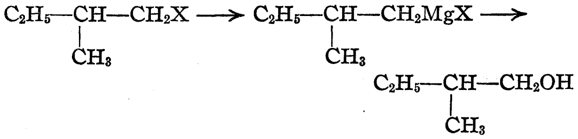
STATE COLLEGE, PENNA. RECEIVED JULY 11, 1938

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

The Primary Active Amyl Halides

BY FRANK C. WHITMORE AND J. HARRIS OLEWINE

The separation of approximately 95% pure primary active amyl alcohol by fractionation of fusel oil has been described in the preceding paper.[1] Disagreement concerning the optical purity of the halides prepared from this alcohol exists in the literature.[2] In the present work, the preparation and properties of the active halides are reported. The chief objective of the study was the determination of the amount of racemization on conversion to the Grignard reagent and then to the alcohol.



$$\underset{\substack{|\\ CH_3}}{C_2H_5\text{—}CH\text{—}CH_2X} \longrightarrow \underset{\substack{|\\ CH_3}}{C_2H_5\text{—}CH\text{—}CH_2MgX} \longrightarrow \underset{\substack{|\\ CH_3}}{C_2H_5\text{—}CH\text{—}CH_2OH}$$

The action of thionyl chloride on primary active amyl alcohol in pyridine gave the corresponding chloride in 77% yield, specific rotation $[\alpha]^{28.5}\text{D}$ +1.66°. Treatment of the alcohol with phosphorus tribromide produced the active halide in 29% yield, $[\alpha]^{29}\text{D}$ +3.75°. These values agree closely with those of Brauns[2] but are lower than those of Marckwald.[3] The iodide, $[\alpha]^{28}\text{D}$ +4.84°, was prepared in 17.5% yield by conversion of the alcohol to the benzoate and treatment with magnesium iodide. The low value for the rotation indicated racemization.

Conversion of the chloride and bromide to the Grignard reagents, and treatment with oxygen regenerated the active amyl alcohol with a total racemization not greater than 10% for the four reactions. Similar treatment of the iodide gave no active amyl alcohol. This reaction will be investigated further.

Experimental

Preparation of Primary Active Amyl Chloride.—The method of Clark and Streight[4] was used in a series of one mole preparations. Addition of 2 moles of thionyl chloride to a solution of one mole of primary active amyl alcohol in one mole of dry pyridine gave the crude chloride. Purification in the usual fashion and fractionation with an efficient column, 75 × 2 cm.,[5] packed with 4-mm. single-turn glass helices,[6] gave a 77% yield of primary active amyl chloride, b. p. (Cottrell) 50.5–51° (140 mm.), $n^{20}\text{D}$ 1.4125, d^{20}_4 0.8852, $[\alpha]^{28.5}\text{D}$ +1.66°.

Preparation of Primary Active Amyl Bromide.—The method of Jones[2] was used. The crude product from the addition of 0.37 mole of phosphorus tribromide to one mole of primary active amyl alcohol at 5–15° was purified and fractionated to give a 29% yield of active amyl bromide, b. p. 69.6° (140 mm.), $n^{20}\text{D}$ 1.4450, d^{20}_4 1.2239, $[\alpha]^{29}\text{D}$ +3.75°.

Preparation of Primary Active Amyl Iodide.—The halide was prepared by the action of magnesium iodide on active amyl benzoate.[7] Treatment of 1.5 moles of primary active amyl alcohol with 2 moles of benzoyl chloride gave an 80% yield of the benzoate, b. p. (Cottrell) 140.2° (20 mm.), $n^{20}\text{D}$ 1.4948, d^{20}_4 0.9913, $\alpha^{28}\text{D}$ +6.09° (1-dm. tube). Magnesium iodide was prepared from magnesium and iodine in dry ether. Refluxing of a solution of 1.5 moles of

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[2] Le Bel, *Bull. soc. chim.*, **25**, 546 (1876); Marckwald, *Ber.*, **37**, 1046 (1904); Klages and Sautter, *ibid.*, **37**, 649 (1904); Neuberg and Federer, *ibid.*, **38**, 1248 (1905); Jones, *J. Chem. Soc.*, **87**, 138 (1905); Hardin and Sikorsky, *J. chim. phys.*, **6**, 179–211 (1908); McKenzie and Clough, *J. Chem. Soc.*, **103**, 690 (1913); Brauns, *J. Research Nat. Bur. Standards*, **18**, 315–31 (1937).

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[5] Whitmore and Lux, THIS JOURNAL, **54**, 3451 (1932).

[6] Wilson, Parker and Laughlin, *ibid.*, **55**, 2795 (1933).

[7] Zal'kind, *J. Russ. Phys.-Chem. Soc.*, **46**, 692 (1914); Gomberg and Bachmann, THIS JOURNAL, **50**, 2762 (1928).

	Average values for original primary active amyl alcohol to make the		Average values for regenerated primary active amyl alcohol obtained from the	
	Chloride	Bromide	Chloride	Bromide
B. p., °C. (20 mm.)	50.1	50.1	50.1	50.1
$n^{20}D$	1.4109	1.4109	1.4109	1.4109
$d^{20}{}_4$	0.81876	0.81846	0.81842	0.81829
d_4	$0.813^{27.5}$	$0.813^{27.5}$	0.796^{26}	0.795^{27}
αD	$-4.8^{27.5}$	$-4.8^{27.5}$	-4.28^{26}	-4.48^{27}
$[\alpha]D$	$-5.9^{27.5}$	$-5.9^{27.5}$	-5.38^{26}	-5.63^{27}

magnesium iodide and one mole of the ester in 500 cc. of ether for two weeks gave 126.5 g. of crude iodide and much resin formation. Fractionation of the crude product gave 17.5% of primary active amyl iodide, b. p. (Cottrell) 47.1° (20 mm.), $n^{20}D$ 1.4969, $d^{20}{}_4$ 1.5227, $[\alpha]^{28}D$ +4.84°.

Regeneration of Primary Active Amyl Alcohol from the Corresponding Chloride and Bromide.—The primary active amyl chloride and bromide were converted into the Grignard compounds in 83 and 76% yields, respectively. Treatment of the Grignard compounds with oxygen at 0° and decomposition of the complex with water regenerated the primary active amyl alcohol. A comparison of the constants for the regenerated alcohol with those of the original alcohol is given.

A similar attempt to regenerate the active alcohol from primary active amyl iodide failed.

Summary

1. The preparation and physical constants of the primary active amyl chloride, bromide and iodide are reported.

2. Primary active amyl alcohol can be regenerated from the corresponding chloride or bromide by conversion to the Grignard compound and treatment with oxygen. The iodide cannot be used for the conversion.

3. The total racemization in the steps alcohol → bromide or chloride → Grignard reagent → alcohol is not over 10%.

STATE COLLEGE, PENNA. RECEIVED JULY 11, 1938

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

The Nonanes. 2-Methyloctane, 3-Ethylheptane, 2,3-Dimethylheptane and 2,2,4,4-Tetramethylpentane[1]

BY FRANK C. WHITMORE AND HARRIET A. SOUTHGATE

The present work was undertaken because of the interest in this Laboratory in petroleum hydrocarbons, in rearrangements in the aliphatic series, in the limitations of typical aliphatic reactions and in the relation of structure to physical properties of aliphatic compounds.

Theoretically, thirty-five structurally isomeric nonanes are possible. Twelve were known when the present work was started, namely, *n*-nonane, the three monomethyloctanes, 2,4-, 2,5-, 2,6- and 3,3-dimethylheptanes, 4-ethylheptane, 2,3,5- and 2,2,5-trimethylhexanes, and 3,3-diethylpentane. The scattered and incomplete data on the physical properties of these eleven nonanes indicate that regularities exist similar to those found in the hexanes, heptanes and octanes.

Three new nonanes, 3-ethylheptane, 2,3-dimethylheptane and the most highly branched nonane, 2,2,4,4-tetramethylpentane, have been synthesized in the present study. Since the data on 2-methyloctane are meager,[2] this compound also was prepared.

The 2,2,4,4-tetramethylpentane was obtained in poor yield from 2,2,4-trimethyl-4-bromopentane or the corresponding chloride with dimethylzinc. The main course of the latter reaction involved the removal of halogen acid to form the known diisobutylenes. This agrees with results obtained by S. N. Wrenn of this Laboratory on the action of a variety of alkaline agents with these halides. The other three nonanes were obtained by dehydration of the tertiary alcohols, 2-methyl-2-octanol, 3-ethyl-3-heptanol, and 2,3-dimethyl-3-heptanol by Hibbert's[3] iodine method and hydrogenating the olefin mixtures at high pressure using a nickel catalyst supported on alumina.

The reactions involved in these syntheses are not ones which are accompanied by rearrange-

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[1] Original manuscript received April 23, 1934.

[2] Späth, *Monatsh.*, **34**, 1965 (1913); Richards and Shipley, THIS JOURNAL, **41**, 2002 (1919); Dobjranski and Chessin, *Chem. Zentr.*, **101**, I, 2662 (1930).

[3] Hibbert, THIS JOURNAL, **37**, 1748 (1915).

ments. The physical constants recorded for the four nonanes indicate a high degree of purity. It is interesting that the most highly branched nonane boils lower than *n*-octane.

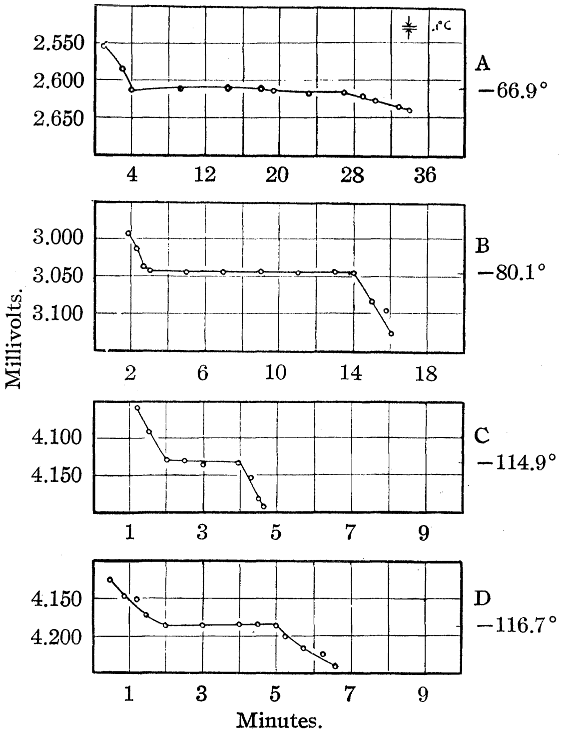

Fig. 1.—A. Freezing curve of 2,2,4,4,-tetramethylpentane: cooling medium, carbon dioxide + acetone; B, C, D. Freezing curves of 2-methyloctane, 3-methylheptane, and 2,3-dimethylheptane: cooling medium, liquid air.

Experimental

Dimethylhexylcarbinol.—Methyl hexyl ketone, b. p. 169.9–171.5° (735 mm.), n^{20}D 1.4150, was prepared in 26–32% yield by dehydrogenation with a copper catalyst of capryl alcohol supplied by the Röhm and Haas Company of Philadelphia. It was treated in 2-mole lots with methylmagnesium chloride solution in the usual way. The product was fractionated under reduced pressure through a 43 × 1.4 cm. column of the usual type used in this Laboratory. The dimethylhexylcarbinol, b. p. 82–85° (20 mm.), n^{20}D 1.427, was obtained in 85% yield.

Methylisopropyl-*n*-butylcarbinol.—Methyl isopropyl ketone, b. p. 93–95° (732 mm.), prepared from *t*-amyl alcohol[4] supplied by the Sharples Solvents Corporation of Philadelphia was treated in 3-mole lots with *n*-butylmagnesium bromide as usual. The methylisopropyl-*n*-butylcarbinol, b. p. 75–78° (16 mm.), n^{20}D 1.4355, was obtained in 65% yield.

Diethyl-*n*-butylcarbinol.—Diethylcarbinol, b. p. 113–118° (732 mm.), was oxidized by chromic acid mixture to diethyl ketone, b. p. 102–105°, in 65% yield. Diethyl ketone in a 4-mole lot was treated as usual with *n*-butylmagnesium bromide. The yield of diethyl-*n*-butylcarbinol, b. p. 95–97° (36 mm.), was 67%.

Dehydration of the Carbinols.—This was done by refluxing with a trace of iodine. The olefins were dried with anhydrous copper sulfate, refluxed over sodium and fractionated. Dehydration of 260 g. of 2-methyl-2-octanol gave 165 g. of olefins, b. p. 144.5–146° (722 mm.), n^{20}D 1.4223; 360 g. of 3-ethyl-3-heptanol gave 242 g. of olefins b. p. 137.5° (734 mm.), 1.4261; 319 g. of 2,3-dimethyl-3-heptanol gave 181 g., b. p. 135–140° (735 mm.), 1.4237–1.4252. Hydrogenation using a nickel catalyst on activated alumina and hydrogen under pressure gave the corresponding hydrocarbons in 98–100% yield.

2,2,4,4-Tetramethylpentane.—Dimethylzinc was prepared in 82–100% yields in lots up to 4 moles.[5] 2,2,4-Trimethyl-4-bromopentane, b. p. 75° (36 mm.), n^{20}D 1.455, was prepared by saturating a diisobutylene fraction of n^{20}D 1.4085 with dry hydrogen bromide at 15°.[6] Removal of excess hydrogen bromide was found to be essential. This was done by cooling the mixture and applying reduced pressure and by passing carbon dioxide through the mixture. The corresponding chloride has been obtained by heating diisobutylene with fuming hydrochloric acid in sealed tubes at 105°[7] and by simply saturating diisobutylene with hydrogen chloride at 15°. The 2,2,4-trimethyl-4-chloropentane, b. p. 53° (29 mm.), n^{20}D 1.431 was obtained in 75% yield.

Dimethylzinc was treated in an atmosphere of carbon dioxide with 2,2,4-trimethyl-4-chloropentane or the corresponding bromide. The chloro compound gave better results. During ten hours 408 g. (2.8 moles) of the chloride was added to a stirred solution of 147 g. (1.55 moles titrated) of dimethylzinc in 150 cc. of dry tetralin in a 3-necked flask provided with a dropping funnel, condenser, and mercury-seal stirrer. The temperature was maintained at 40°. Precipitation started almost immediately and rendered stirring difficult. After standing overnight the mixture was acidified with hydrochloric acid. The organic layer was washed with sodium bicarbonate solution and dried with 10 g. of calcium chloride. Fractionation through the 43 × 1.4 cm. column yielded mainly diisobutylenes formed by the removal of hydrochloric acid from the chloride, a small amount of higher polyisobutylenes and a yield of 18% (average of many runs) of the crude 2,2,4,4-tetramethylpentane, b. p. 120–125° (730 mm.), n^{20}D 1.408.

Purification of the Nonanes.—Each of the four nonanes was shaken with successive one-tenth volume portions of concentrated sulfuric acid until a fresh portion showed no color. All acid was removed by washing with sodium bicarbonate solution and then with water. After drying over calcium chloride the product was fractionated.

Measurement of Physical Properties.—A Valentine No. 451 refractometer was used for determining the refractive indices. The temperature was controlled to 0.1°.

Boiling points were measured with a Cottrell type boiling point apparatus. The temperature was read by means of a copper–copel thermocouple checked against a

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(4) Whitmore, Evers and Rothrock, *Org. Syntheses*, **13**, 68 (1933).

(5) Lachman, *Am. Chem. J.*, **19**, 410 (1897); Noller, THIS JOURNAL, **51**, 494 (1929); Renshaw, *ibid.*, **42**, 1472 (1920).

(6) Tongberg, *et al.*, *ibid.* **54**, 3706 (1932).

(7) Butlerow, *Ann.*, **189**, 44 (1877); Kondakow, *J. prakt. Chem.*, [2] **54**, 449 (1897).

TABLE I

SUMMARY OF PHYSICAL PROPERTIES

Nonane	F. p., °C.	B. p. (760 mm.) °C.	B. p. °C.	B. p. Mm.	$n^{20}{}_D$	$d^{20}{}_4$	Viscosity 37.8°	Viscosity 100°
							poises × 10	
2-Methyloctane	−80.1	142.80	141.65	727.5	1.40285	0.7107	5.25	2.79
2,3-Dimethylheptane	(−116.7) glass	140.65 initial	139.05 initial	728.0	1.40850	.7235	5.21	3.30
3-Ethylheptane	glass (−114.9)	143.10	142.10	738.5	1.40900	.7260	4.90	2.61
2,2,4,4-Tetramethylpentane	−66.9 to −67.1	122.30	121.30	738.5	1.40695	.7185	6.80	3.39

Bureau of Standards couple and also checked at the boiling points of *n*-hexane, *n*-heptane, water, 2,2,4-trimethylpentane, naphthalene and toluene. Boiling points recorded represent the boiling point when 50% of the sample had been removed.

The freezing points were determined with samples of about 20 cc. of the nonane placed in a glass-jacketed test-tube which was lowered into a Dewar flask containing a mixture of carbon dioxide snow and acetone or liquid air. The sample was stirred vigorously and the temperature determined every twenty to thirty seconds by means of a chromel–copel thermocouple[8] and a Leeds Northrup Portable, Double Range Potentiometer. The cooling curves are given in Fig. 1.

Densities and viscosities were determined by W. A. Herbst of this Laboratory.

Summary

2-Methyloctane and three new nonanes, 2,3-dimethylheptane, 3-ethyloctane and 2,2,4,4-tetramethylpentane have been prepared.

Boiling point, index of refraction, density, freezing curves and viscosity have been determined for the four nonanes.

STATE COLLEGE, PENNA. RECEIVED AUGUST 15, 1938

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[8] Tongberg, Pickens, Fenske and Whitmore, THIS JOURNAL, **54**, 3706 (1932).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

A New Synthesis of Tertiary Hydrocarbons

BY FRANK C. WHITMORE AND H. PHILIP OREM

The general method of preparation of saturated aliphatic hydrocarbons involves the hydrogenation of an olefin formed by dehydration of the corresponding alcohol or by removal of halogen acid from the alkyl halide.[1] Other methods, such as the hydrolysis of the Grignard reagent and the reduction of the halide with "nascent" hydrogen[2] have been used.

Levene[3] prepared hexadecane from cetyl iodide by adding zinc dust to the iodide and passing in dry hydrogen chloride with heating for several hours. In the present study, a modification of this method has been applied to tertiary iodides. Five tertiary aliphatic hydrocarbons have been prepared from their corresponding tertiary alcohols by the modified method. This offers a new and simple method of preparing branched-chain hydrocarbons from tertiary alcohols.

Experimental

Preparation of the Alcohols.—Four of the alcohols were prepared from Grignard reagent and ketone; the other from Grignard reagent and acid chloride.

Preparation and Purification of the Hydrocarbons.—The hydrocarbons were prepared by treating the tertiary alcohols with dry hydrogen iodide[4] until one and one-half times the theoretical quantity of hydrogen iodide had been added. Then zinc dust (Baker C. P. 95%) was added in small quantities until reaction ceased. The mixture was then stirred and dry hydrogen chloride was passed in with the addition of more zinc until four times the theoretical quantity was added. The flask was heated to 70–80° with stirring and the addition of hydrogen chloride for approximately ten hours for each half mole of alcohol used. Water was then added slowly to give equal volumes of water and reaction product in the flask. The hydrocarbon was steam distilled and separated from the water layer.

The hydrocarbon was purified by washing with 70% (by weight) sulfuric acid until only a pale yellow color remained, then with 85% sulfuric acid, and finally with concentrated sulfuric acid until little color appeared upon adding fresh acid. The product was then washed once

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[1] Edgar, Calingaert and Marker, THIS JOURNAL, **51**, 1483 (1929); Calingaert and Soroos, *ibid.*, **58**, 635 (1936).

[2] Clarke, *ibid.*, **30**, 1147 (1908); **31**, 589 (1909).

[3] Levene and West, *J. Biol. Chem.*, **20**, 523 (1915).

[4] Kastle and Bullock, THIS JOURNAL, **18**, 109 (1896).

Carbinols	n^{20}_D	d^{20}_4	Reaction		Yield, %
2-Methylhexanol-2	1.4186	0.8146	BuMgBr	Me_2CO[a]	80
2-Methyloctanol-2	1.4280	.8210	MeMgCl	Me-*n*-hexyl ketone	74
3-Ethylheptanol-3	1.4360	.8429	EtMgBr	*n*-Valeryl chloride[b]	66
3-Methylnonanol-3	1.4358	.8311	EtMgBr	Me-*n*-hexyl ketone	76
4-Methyldecanol-4	1.4375	.8296	PrMgBr	Me-*n*-hexyl ketone	56

[a] Acetone was purified by fractional distillation from solid potassium permanganate and freshly prepared calcium oxide.

[b] *n*-Valeryl chloride (b. p. 126° (730 mm.); n^{20}_D 1.4200) was prepared from the acid by treatment with thionyl chloride in 84% yield. The valeric acid (b. p. 86° (18 mm.), n^{20}_D 1.4080) was prepared in 81% yield by treating *n*-butylmagnesium bromide with carbon dioxide. The flask containing the Grignard reagent was cooled to 0°, solid lumps of carbon dioxide were dropped into the solution and the material allowed to stand overnight. Secondary and tertiary alcohols may be formed if the addition of carbon dioxide gas is slow. Gilman, *Rec. trav. chim.*, **49**, 1172 (1930).

PROPERTIES OF THE HYDROCARBONS

Hydrocarbons	B. p. °C.	Mm.	B. p. °C.[a]	Mm.	n^{20}_4	n^{20}_D	F. p., °C.	Yield, %
2-Methylhexane	89.1	735	90.3	760	0.6794	1.3851	−120.3	23.7
2-Methyloctane	141.6	736	142.8	760	.7132	1.4030	[b]	48.8
3-Ethylheptane	141.9	736	143.1	760	.7272	1.4090	[b]	38.3
3-Methylnonane	166.3	732	167.6	760	.7319	1.4123	−90.0	30.1
4-Methyldecane	186.8	739	188.1	760	.7422	1.4177	−92.9	27.8

[a] The boiling points were taken at 760 mm. with a Cottrell b. p. apparatus and a barostat.

[b] Refer to Frank C. Whitmore and H. A. Southgate, THIS JOURNAL, **60**, 2571 (1938).

with water, twice with 25% sodium hydroxide solution, and dried over sodium. It was carefully fractionated[5] from sodium–potassium alloy, washed with concentrated sulfuric acid, water, 25% sodium hydroxide, dried over sodium, and refractionated from sodium–potassium alloy to give a constant index material that gave no halide test with copper wire and no olefin test with bromine in carbon tetrachloride.

Summary

A new synthesis of tertiary hydrocarbons has been described, and applied to five aliphatic hydro carbons.

STATE COLLEGE, PENNA. RECEIVED AUGUST 16, 1938

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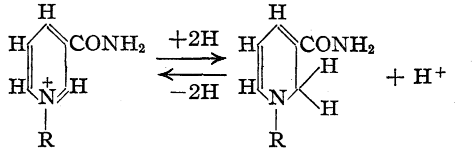
[5] Whitmore and Lux, THIS JOURNAL, **54**, 3451 (1932).

[CONTRIBUTION FROM THE BIOLOGICAL INSTITUTE OF THE CARLSBERG FOUNDATION, COPENHAGEN]

Hydrogenation of Vitamin B_1 and Other Quaternary Thiazoles[1]

BY FRITZ LIPMANN AND GERTY PERLMANN

Dehydrogenation of various substrates in the cell is effected by quaternary pyridine compounds—nicotinic acid derivatives[2,3]—acting as hydrogen-transporting systems between the respective substrates and other hydrogen carriers.[2,4] The catalytic action of these pyridinium compounds is due to alternate hydrogenation and dehydrogenation at the double bond adjoining the quaternary nitrogen.



(1)

The action of vitamin B_1 (which hereafter in this paper will be referred to as "thiamin") as codehydrase for pyruvic acid dehydrogenation was made highly probable by the work of Peters and co-workers[5] with avitaminotic tissues (see also Lipmann[6]). Using the pyruvic acid dehydrogenase of *Bacterium Delbrückii*, the codehydrase function of thiamin—as thiamin pyrophosphate, Lohmann's cocarboxylase[7]—could be shown definitely.[8]

The presence of a quaternary thiazole in thiamin,[9] the well-known similarity between thiazoles and pyridines together with the codehydrase function of thiamin suggested a similar mode of action for the pyridine and thiazole codehydrases.

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[1] This investigation was supported by a grant from the Ella Sachs Plotz Foundation.

[2] (a) O. Warburg and W. Christian, *Biochem. Z.*, **287**, 291 (1936); (b) O. Warburg, *Ergebnisse Enzymforschung.*, **7**, 210 (1938).

[3] P. Karrer, G. Schwarzenbach, F. Benz and U. Solmsson, *Helv. Chim. Acta*, **19**, 811 (1936).

[4] H. v. Euler, *Ergebnisse Physiol.*, **38**, 1 (1936).

[5] R. A. Peters, *Biochem. J.*, **31**, 2240 (1937).

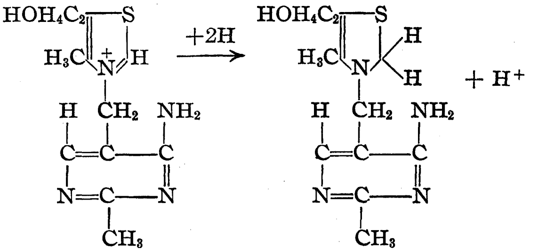
[6] F. Lipmann, *Skand. Arch. Physiol.*, **76**, 255 (1937).

[7] K. Lohmann and P. Schuster, *Biochem. Z.*, **294**, 188 (1937).

[8] F. Lipmann, *Enzymologia*, **4**, 65 (1937).

[9] R. R. Williams and A. E. Ruehle, THIS JOURNAL, **57**, 1856 (1935).

In a previous short communication[10] the dehydrogenation of thiamin with sodium hyposulfite ($Na_2S_2O_4$) was described. The reaction was followed by the use of Warburg's manometric method,[11,12] which measures bicarbonate decomposition due to oxidation of neutral hyposulfite to acid sulfite ($Na_2S_2O_4 + R + 2NaHCO_3 = 2Na_2SO_3 + H_2R + 2CO_2$). It was found that for each mole of thiamin approximately 3 moles of bicarbonate was decomposed. In accordance with the findings of Warburg[2b] and Karrer[3] with the quaternary pyridines (equation 1), the appearance of one extra equivalent of acid was interpreted as being due to the change from strong to weak basicity on reduction. This led to the conclusion that the hydrogenation of thiamin takes place at the double bond adjoining the quaternary nitrogen in the thiazole part of the molecule


(2)

This interpretation is supported by the recent findings of Erlenmeyer[13] that thiazole-5-carboxylic ester methiodide is hydrogenated with hyposulfite in exactly the same manner as the corresponding pyridine compound, both yielding one extra equivalent of acid on reduction.

The results mentioned above made it desirable to study the hydrogenation of thiamin and other quaternary thiazoles more in detail.

Throughout the work, the hydrogenation with hyposulfite was measured by the manometric method of Warburg.[11,12] Hydrogenation with platinum black and hydrogen was measured in Warburg manometers. The platinum black was prepared according to the directions of Willstätter and Waldschmidt-Leitz.[14]

For all the experiments carried out with thiamin, the synthetic product of the I. G. Farbenindustrie was used, for a large gift of which we are greatly indebted to the staff of the I. G. Farbenindustrie.

The Hydrogenation of the "Cleavage Products."—To exclude the possibility that hydrogenation takes place upon the pyrimidine part, the split products obtained by the sulfite cleavage of Williams[15] were tried separately. As shown by Williams, thiamin is split into pyrimidine-sulfonic acid and thiazole by the action of acid sulfite

$$C_{12}H_{16}N_4OS + H_2SO_3 \longrightarrow C_6H_9N_3SO_3 + C_6H_9NOS$$

Thereby the quaternary thiazole is converted into a tertiary. The methiodide of the thiazole part was prepared according to Buchman, Williams and Keresztesy.[16]

Hydrogenation with Hyposulfite.—The results of the manometric measurements are assembled in Table I.

TABLE I

HYDROGENATION OF THE "CLEAVAGE PRODUCTS" WITH HYPOSULFITE: MANOMETRIC MEASUREMENTS

No.	Substance	Moles CO_2	Atoms hydrogen	Extra acid
1	Pyrimidine sulfonic acid	0	0	..
2	Thiazole part (tertiary)	0	0	..
3	Thiazole part (quaternary)	3.1	2	1.1
4	Thiamin	2.75	2	0.75

It appears from the table that none of the split products (Nos. 1 and 2) reacts with hyposulfite but that the thiazole methiodide (No. 3) reacts in the same manner as thiamin (No. 4), but more slowly (see last column and Fig. 1). In both

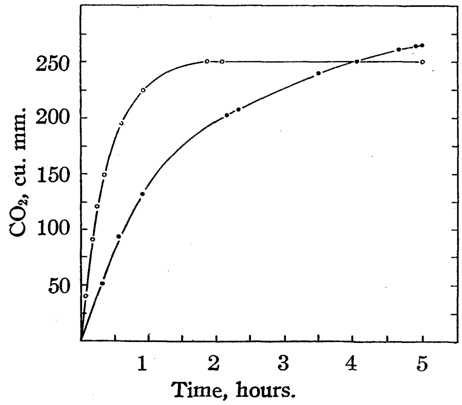


Fig. 1.—Manometric experiment with 0.405 × 10^{-2} millimole of thiamin (upper curve) and 0.383 × 10^{-2} millimole of 4-methyl-5-hydroxyethylthiazole methiodide (lower curve); temperature 30°.

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[10] F. Lipmann, *Nature*, **138**, 1097 (1936).

[11] O. Warburg, W. Christian and A. Griese, *Biochem. Z.*, **282** 157 (1935).

[12] E. Haas, *ibid.*, **285**, 368 (1936).

[13] H. Erlenmeyer, A. Epprecht and H. von Meyenburg, *Helv. Chim. Acta*, **20**, 514 (1937).

[14] R. Willstätter and E. Waldschmidt-Leitz, *Ber.*, **54**, 113 (1921).

[15] R. R. Williams, R. E. Waterman, J. C. Keresztesy and E. R. Buchman, THIS JOURNAL, **57**, 536 (1935).

[16] E. R. Buchman, R. R. Williams and J. C. Keresztesy, *ibid.*, **57**, 1849 (1935).

cases nearly one equivalent of extra acid appears on reduction. Since the pyrimidine part does not and the thiazole part, when quaternary, does, react as the whole, evidence is thus obtained that the hydrogenation of thiamin with hyposulfite takes place in the thiazole part of the molecule.

Hydrogenation with Platinum Black–Hydrogen.—Though only the hydrogenation with hyposulfite can be taken as significant as a model reaction, reduction with Pt–H_2 was also measured for comparison. The results are assembled in Table II. As mentioned in the first publication,[9] thiamin absorbs nearly one mole of hydrogen (Nos. 7 and 8). The reactivity of the pyrimidine part depends on *p*H (or buffer system). In borate at *p*H 10.5 a very sluggish absorption takes place (No. 1). In phosphate at *p*H 8 approximately two moles of hydrogen were taken up at a medium rate. The thiazole part (tertiary) absorbs virtually no hydrogen (No. 3). The quaternary thiazole absorbs a total of two moles. The absorption curve shows a break after one mole is taken up (No. 4 a and b). Besides, two other quaternary thiazoles were tried: 4-methyl-5-carboxylic ester thiazole methiodide and 4-methylthiazole methiodide, both prepared according to Clarke and Gurin.[17] The ester thiazole, like thiamin, takes up approximately one mole at a rapid rate, the methylthiazole takes approximately two moles; the first at a rapid, the second at a slower, rate.

TABLE II

HYDROGENATION OF THE "CLEAVAGE PRODUCTS" AND QUATERNARY THIAZOLES WITH PLATINUM BLACK AND HYDROGEN

No.		Substance	*p*H	Moles H_2	Time, hours
1		Pyrimidine sulfonic acid	10.5	0.12	4
2		Pyrimidine sulfonic acid	8	1.88	20
3		Thiazole part tertiary	10.5	0.1	4
4	a	Thiazole part quaternary	8	1.0	1.5
	b			1.97	20
5		Thiamin	8	0.92	4
6		Thiamin	10.5	1.07	8
7		4-Methyl-5-carboxylic ester thiazole methiodide	8	1.2	18
8		4-Methylthiazole methiodide	8	1.8	18

The reactivity of the second double bond in quaternary thiazoles depends apparently to a large extent on the nature of the substituents. When reacting, it always went more slowly than the first. It is to be noted that the pyrimidine-sulfonic acid is hydrogenated with Pt–H_2. That the one mole of hydrogen taken up by the thiamin goes to the same place as on hydrogenation with hyposulfite seems quite probable, since it was found that with Pt–H_2 also one mole of acid appears on reduction (by titration of a larger sample before and after reduction, in Na_2HPO_4 with thymolphthalein as indicator).

The Colored Intermediate Hydrogenation Product.—It was observed that a transient yellowish-green color appears on addition of hyposulfite to neutral thiamin solutions.[18] Experiments with various thiazoles (see next paragraph) have shown that the greenish colored intermediate appears generally on hydrogenation of quaternary thiazoles with hyposulfite. In the special cases, the intensity of the color depends on the rate of reaction. With the fast-reacting ester thiazole (Table III, No. 3) a bright color appears in very dilute solution; with a slow reacting substance as 4-methyl-5-ethoxythiazole methiodide only concentrated solutions give a coloration. To compare the described phenomenon with the corresponding one found by Karrer and Benz[19] and Adler, Hellström and von Euler[20] with quaternary pyridines and cozymase, nicotinic acid amide ethiodide[21] was prepared. The course of events is exactly the same with the two classes of compounds. With the pyridines the color is more orange.

On reduction of thiamin with zinc and normal hydrochloric acid, a very similar transient color appears. After the disappearence of the color vigorous hydrogen sulfide formation sets in, indicating that here hydrogenation is followed by profound degradation.

The most obvious explanation for the transient coloration, proposed already for the pyridines,[19] is that hydrogenation occurs in two steps.[22] The half reduced colored compound, of a semiquinone type, is decolorized by further reduction. As the two-step oxidation or reduction is very common with the oxido–reduction catalysts of the cell (flavin, pyocyanine, pyridine coferments, etc.), it seems of importance that it occurs also with thiamin.

The Hydrogenation of Various Quaternary Thiazoles with Hyposulfite.—We have studied the reaction with 4-methyl-5-carboxylic acid

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(17) H. T. Clarke and S. Gurin, THIS JOURNAL, **57**, 1876 (1935).

(18) F. Lipmann, *Nature*, **140**, 849 (1937).

(19) P. Karrer and F. Benz, *Helv. Chim. Acta*, **19**, 1028 (1936).

(20) E. Adler, H. Hellström and H. v. Euler, *Z. physiol. Chem.*, **242**, 225 (1936).

(21) P. Karrer and F. J. Stare, *Helv. Chim. Acta*, **20**, 418 (1937).

(22) L. Michaelis, *Chem. Rev.*, **16**, 243 (1935).

ethyl ester methiodide, a compound similar to that studied by Erlenmeyer.[13] From the ester the corresponding acid amide was prepared, following a procedure used by Karrer[3] to prepare nicotinic acid amide. The similarity of constitution of the two acid amides made the study of this thiazole interesting. Benzothiazole methiodide was prepared according to Möhlau and Krohn.[23] This substance has been studied by Mills and co-workers.[24] Their work, to be discussed later, made the inclusion of it desirable.

In Table III all our manometric experiments with quaternary thiazoles are summarized. For comparison the nicotinic acid amide ethiodide is included. In all the cases approximately one mole of extra acid appears in addition to the two moles originating from the transfer of two hydrogens. The rate of reaction (see last column) is greatest for derivatives of the acid, nearly approaching that of the pyridine compound. It is intermediate with thiamin and slowest with the methiodide of the cleavage product.

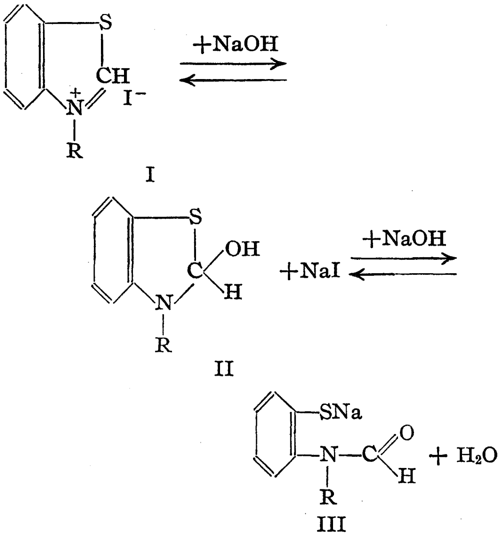
TABLE III

HYDROGENATION OF QUATERNARY THIAZOLES WITH HYPOSULFITE: MANOMETRIC MEASUREMENTS

No.	Substance	Moles CO_2	Atoms H	Extra acid	50% Reduction time, min.
1	Nicotinic acid amide ethiodide	3.1	2	1.1	1.5
2	Thiamin	2.8	2	0.8	15
3	4-Methyl-5-ethoxy thiazole methiodide	3.1	2	1.1	57
4	4-Methyl-5-carboxylic acid ethyl ester thiazole methiodide	2.9	2	0.9	3
5	4-Methyl-5-carboxylic acid amide thiazole methiodide	2.88	2	0.88	5

The behavior of benzothiazole methiodide was somewhat different. Mills and co-workers have described the reduction of this compound with zinc and hydrochloric acid. The α-dihydrobenzothiazole, a water-insoluble substance of characteristic odor, was isolated in good yield. They described also the reversion of the dihydrothiazole to thiazole methiodide by oxidation with iodine in alcoholic solution.

When benzothiazole methiodide, freshly dissolved in bicarbonate, is treated at once with hyposulfite, we found that the bright greenish color of the intermediate appeared, the solution became cloudy and a characteristic odor, the same as on reduction with Zn–HCl, developed. The experiment showed that benzothiazole methiodide is reduced by hyposulfite in the same manner as other quaternary thiazoles. Therefore, it was surprising to find that the manometric experiment did not show any reaction, when carried out in the usual manner—that is to dissolve the thiazole in bicarbonate, equilibrate the vessel in the thermostat and to tip the hyposulfite into the solution. The explanation is found in the fact that benzothiazole methiodide reacts rapidly with bicarbonate. In about fifteen minutes at 30° two moles of bicarbonate was decomposed. It is known from the work of Mills and of Williams that by the action of strong alkali the pseudobase is formed first and then the thiazole ring is opened in the following manner



(3)

Mills called attention to the strong acidity of the thiophenol derived from benzothiazole. It must be an appreciably stronger acid than carbonic acid. Therefore in bicarbonate at the end of the reaction practically only molecule III is present in the solution. Molecule I, which reacts with hyposulfite, has disappeared.

The amide reacts similarly, but only incompletely. The equilibrium can be driven back in the direction of molecule I by saturation with carbon dioxide. Therefore the manometric experiment with the amide was carried out with carbon dioxide in the gas phase. The other thiazoles did not decompose bicarbonate.

The Question of Reversibility. Discussion

At an early stage of this investigation, attempts were made to isolate the hydrogenated thiamin,

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[23] R. Möhlau and C. W. Krohn, *Ber.*, **21**, 59 (1888).

[24] W. H. Mills, L. M. Clark and J. A. Aeschlimann, *J. Chem. Soc.*, **123**, 2353 (1923).

but met with great difficulties, which it has not been possible to overcome up to now. On extraction of the more or less alkaline solutions with chloroform or ether, the greater part of the products of reaction remained always in the water phase. The brownish oily residue from chloroform or ether was obviously inhomogeneous. Furthermore, it was not possible to reoxidize the product of reduction to thiochrom with ferricyanide and alkali. Only a comparatively feeble blue fluorescence appeared. Therefore it was not surprising to find that the biological activity was lost after hydrogenation.

A similar behavior was found with the ester thiazole and the acid amide thiazole methiodides. The latter substance required attention because the work of Karrer[25] showed that the acid amide group has a stabilizing effect on the equally unstable dihydropyridines. The only thiazole which yielded with hyposulfite a stable hydrogenated product, was benzothiazole. The identity of this product with benzodihydrothiazole obtained on reduction with Zn–HCl by Mills and co-workers, though still to be established, can scarcely be doubted. With this compound the reversibility of dehydrogenation had been shown before. As our experience makes it quite probable that the primary process of reduction is the same in all cases, it might be concluded that, primarily a reversible hydrogenation product, the 2-dihydrothiazole is always formed which subsequently undergoes irreversible rearrangements.

If the codehydrase action of thiamin or, better, thiamin pyrophosphate should—as was suggested in the beginning of this paper—be due to a reversible hydrogenation of the thiazole, the hydrogenated thiamin must be stabilized in the enzyme (codehydrase–protein compound). This could possibly be effected by the combination with the specific protein. It has been described elsewhere[8] and has been confirmed recently[26] that in pyruvic acid dehydrogenase the codehydrase is strongly bound to the protein and most probably does not dissociate in the cell. Thus the thiamin enzyme differs from the pyridine enzymes, in which the pyridine–protein dissociates easily.

We wish to thank Dr. Albert Fischer, Director of this Laboratory, for the kind support he has given to the above work. We also wish to express our gratitude to Dr. Stig Veibel for his help in obtaining materials for the preparation of some of the compounds used.

Experimental

4-Methyl-5-carboxylic Acid Amide Thiazole Methiodide.—One and one-half ml. of 4-methyl-5-carboxylic ester thiazole[17] was dissolved in 3 ml. of methanol and saturated with ammonia at −18°. The mixture was heated in a bomb tube for twelve hours to 150°. On cooling crystals separated from the methanolic solution. The methanol and ammonia were distilled off. From the brownish, mostly crystalline residue, the amide was extracted by boiling three times with benzene. The substance crystallized from the benzene in only slightly discolored crystals, yield 0.75 g. *Anal.* Calcd. for $C_5H_6N_2OS$: N, 19.67. Found: N (Dumas), 18.81. Without further purification the product was treated with methyl iodide. It was dissolved in 2 ml. of absolute alcohol mixed with 7 ml. of methyl iodide and boiled gently on the reflux condenser for twelve hours. After removal of the methyl iodide, the methiodide was crystallized twice from absolute alcohol.

Anal. Calcd. for $C_6H_9N_2OSI$: N, 9.84. Found: N (Dumas), 9.73.

4-Methyl-5-carboxylic Acid Ethyl Ester Thiazole Methiodide.—The ester was mixed with an excess of methyl iodide and warmed in a sealed tube to 40° for twenty-four hours. A brown oil separated on the surface. After removal of the methyl iodide, the solid, partly crystalline residue was dissolved in absolute alcohol. On careful addition of ether, the methiodide crystallized in large light yellow needles, m. p. 140°.

Summary

The dehydrogenation of vitamin B_1 (thiamin) and other quaternary thiazoles is studied in connection with the codehydrase function of thiamin.

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(25) P. Karrer, F. W. Kahnt, R. Epstein, W. Jaffe and T. Ishii, *Helv. Chim. Acta,* **21**, 223 (1938).

(26) Unpublished experiments.

[CONTRIBUTION NO. 135 FROM THE DEPARTMENT OF BIOLOGY AND PUBLIC HEALTH, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Quantitative Measurement of the Ultraviolet Activation of Sterols. I. Ergosterol

BY ROBERT S. HARRIS, JOHN W. M. BUNKER AND L. MALCOLM MOSHER

Ten years ago Kon, Daniels and Steenbock[1] reported that the ergs of radiant energy necessary to form from ergosterol an amount of vitamin D sufficient to demonstrate a deposition of calcium in the bones of rachitic rats was constant (700–1000 ergs) for mercury lines 2560, 2652, 2804 and 2937 Å.

Another paper, that by Marshall and Knudson,[2] reported that the rate of production of vitamin D is directly proportional to the number of light quanta absorbed by ergosterol and is independent of the wave length. They also stated that one quantum produced an average of 0.3 molecule of vitamin D.

A more recent publication[3] has reported that one International Unit of vitamin D was synthesized from ergosterol by 900 ergs of ultraviolet energy and that lines 249, 254, 265, 275, 280, 297 and 303 mμ were equally effective on a quantum basis. These results have created confusion, since they indicate that the photochemical conversion of ergosterol into vitamin D by various frequencies is dependent upon (1) the ergs of radiant energy irrespective of wave length (in the active region), (2) the quanta of energy irrespective of wave length and (3) equal ergs and equal quanta for the various wave lengths. Since ergs and quanta do not have a constant relation as wave lengths are varied, there is some obvious discrepancy.

The study which is being reported at this time was undertaken to determine more accurately the antirachitic effectiveness of the various lines in the mercury arc spectrum, and to determine the efficiency of the photochemical reaction in which ergosterol is converted into its antirachitically active isomer vitamin D (vitamin D_2 or calciferol). In this study 600 rachitic rats were used with a double quartz monochromator in a study of the active ultraviolet lines.

Procedure.—In this study we used the five active lines[4] of the mercury arc spectrum. The quantum–erg relationship of these lines is as follows.

Å.	Ergs/quantum
3025	6.50×10^{-12}
2967	6.62×10^{-12}
2804	7.01×10^{-12}
2652	7.41×10^{-12}
2537	7.74×10^{-12}

Irradiation Procedure.—In all experiments a cylindrical quartz vessel (27 mm. diameter, 152 mm. long) with flat ends was filled to capacity (approximately 80 cc.) with a 0.1% solution of ergosterol (du Pont) in C. P. anhydrous ethyl ether. This cell was mounted against the exit slit of a Bausch and Lomb quartz monochromator[4] (type no. 33-86-05) with prisms 8 × 8 cm. in such a way that the incident energy entered the front face of the vessel and passed into the ergosterol solution along the axis of the vessel.

By the use of photographic paper and malachite green leucocyanide reagent,[5] it was shown with all wave lengths studied that the energy was all absorbed in passing through the ergosterol solution.

These experiments were designed to compare the relative ability, on a quantum basis, of the different lines to activate ergosterol. Exposure times were calculated so that in a given experiment the ergosterol solution was exposed to the same number of quanta. Because of variations in the energy emission of the mercury arc the exposure times were different for each line. The emission from this lamp was measured from time to time during the course of the investigation.

To ensure the greatest accuracy the time was varied until an exposure would produce an amount of vitamin which, when fed to eight standard rachitic rats (Steenbock diet 2965), would produce a Steenbock unit of healing. Concurrent assays were run with USP Reference Oil so that in all cases a conversion into USP or International Units was possible.

The amount of energy entering the quartz cell was determined with the thermopile–galvanometer (type HS, Leeds and Northrup), using a Bureau of Standards K-4 lamp as a reference. The vertical six-inch (15 cm.) Uviarc was housed in a white transite box with an open window. The lamp was placed in the principal optical axis of the monochromator, at a distance of 13 cm. from its front face. The lamp was operated at 170–174 v. and 4.0–4.5 amp. The voltage was controlled by a photoelectrically operated voltage regulator (Stockbarger, to be published).

Following exposure the ergosterol solution was run into 20.0 g. of pure olive oil, three rinsings with anhydrous ether were added to the oil. The ether was removed from the oil under carbon dioxide by vacuum and the oil solution of irradiated ergosterol then thoroughly incorporated into 360 g. of Steenbock diet 2965. The mixture was divided into eight portions of 45 g. each and fed to eight

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(1) Kon, Daniels and Steenbock, THIS JOURNAL, **50**, 2573 (1928).

(2) Marshall and Knudson, *ibid.*, **52**, 2304 (1930).

(3) Haman and Steenbock, *Ind. Eng. Chem., Anal. Ed.*, **8**, 291 (1936).

(4) Bunker and Harris, *N. E. J. Med.*, **216**, 165 (1937).

(5) L. Harris and J. Kaminsky, THIS JOURNAL, **57**, 1154 (1935).

rachitic rats. Additional 2965 diet was placed in the cages of the animals when this special mixture had been consumed. The animals were killed at the end of ten days, their leg bones X-rayed and line tested so that the degree of healing could be calibrated. In all cases, Wistar strain albino rats were placed in individual cages and given the rachitogenic diet when twenty-eight days old. They were fed the irradiated ergosterol supplement after twenty to twenty-four days on the diet.

Results

Early in the research it was found that the efficiency of our irradiation procedure was better than that reported by Marshall and Knudson,[2] for 11.6 × 10^{13} quanta in our hands produced more than one USP unit of vitamin D. In six successive stages the irradiation time was decreased until it was established that 7.5 × 10^{13} quanta produced a unit of rachitic healing.

Space does not permit a presentation of the data in full. A total of sixteen complete experiments has been run with each active mercury line, the last ten of which are summarized in Table I.

Table I

Quantum Efficiency of Activation of Ergosterol in Ether

Number of Runs	Number of Animals	Lambda in Å.	Energy received in Ergs/sec.	Energy received in Quanta	Average healing
10	77	2537	81.1	7.5 × 10^{13}	2.26
10	77	2652	86.2	7.5 × 10^{13}	2.39
10	78	2804	48.5	7.5 × 10^{13}	2.58
10	78	2967	60.3	7.5 × 10^{13}	2.20
10	78	3025	120.9	7.5 × 10^{13}	2.46
10	74	USP Reference Oil			2.33

Discussion

The arithmetical values of healing displayed in Table I show a variation between 2.20 and 2.58 for the averages of recorded response to administration of ergosterol activated by monochromatic ultraviolet of various wave lengths. The interpretation of these mathematical differences is complicated by the fact that there is no evidence that the scale of healing (1+ to 4+) represents corresponding linear variations in physiological response. The intent of the experimental work was to produce a degree of healing as nearly identical as possible with that induced by measured dosages of USP Reference Oil in the neighborhood of 2.0. Individual animal variations in response are compensated to some degree by employing groups of at least eight animals for each feeding level.

The mathematical symbols used to represent observational data in the bioassay for vitamin D are in general recognized to be approximations rather than precise values. Differences in such values, to be significant, must be greater than those which can be computed mathematically as significant upon a purely statistical basis. This defect in the assay procedure is universal and is not peculiar to the experiments reported herein. We believe that the results herein reported comprise a minimum of probable error for such work.

Considering the results for the several wave lengths on the basis of the averages for eighty animals and comparing them with the value 2.33 which is the average for control animals fed USP Reference Oil concurrently, we are of the opinion that no significant differences have been demonstrated in the quantum efficiency of the several active wave lengths of ultraviolet in the photochemical activation of ergosterol.

Upon examining the original data from another point of view, namely, by groups of eight animals, and having regard for the slight changes in severity of experimental rickets, one is impressed with a tendency for more effective activation by the mercury line 2804, and whether or not it be coincidence that this line is one that shows maximum absorption by ergosterol or whether it be an indication of correlation between absorption and activatability only further work, with probably greater refinements than are now known to us, can definitely demonstrate.

Conclusion

1. The photochemical activation of ergosterol in ether by monochromatic ultraviolet light of 2537, 2652, 2804, 2967 or 3025 Å. is substantially uniform per quantum of energy applied.

Cambridge, Mass.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, GREENSBORO COLLEGE]

Aqueous Solubilities of Some Isomeric Heptanols

BY P. M. GINNINGS AND MARY HAUSER

Aqueous solubilities of the pentanols[1] and some hexanols[2] have been determined in previous investigations. This is a similar investigation of nine heptanols that seemed of greatest interest. These nine include the seven tertiary and the two secondary isomers of most compact structure. Apparently the solubility of only one heptanol has been determined precisely. Butler[3] using an interferometric method found a value of 0.180 weight per cent. at 25° for normal heptanol.

The results of our determinations, which are given in the table, seem to be in accord with the theory outlined in previous investigations. As in the lower alcohols, the seven tertiary isomers are more soluble than the two secondary isomers of most compact structure, and increase of temperature is always accompanied by a decrease in solubility. Six of the seven tertiary heptanols can be considered as being derived from the six secondary hexanols by addition of a methyl group to the alpha carbon atom. It is noteworthy that the *relative* solubilities of the resulting six heptanols remain in the same order as in the hexanols. In the case of compound no. 1, the measurement of the solubility at the usual temperatures of the others was prevented by separation of the solid phase of the crystalline hydrate of the alcohol. However, determination of the solubility of the next alcohol (no. 2) at 40° also supplied a definite basis for comparison with the rest of the isomers. The importance of the compact molecule is easily noticed by a comparison of the solubilities of compounds nos. 1 and 2, where the former has a much more compact molecule than the latter. In the case of the two secondary isomers (nos. 8 and 9), the asymmetrical molecule containing the tertiary butyl group seems to dominate slightly the symmetrical molecule of no. 9.

TABLE I

No.	d^{25}_4 of pure alc. and b. p., °C. (760 mm.)	Temp., °C.	Wt. % alc.		d_4 of liquid phase	
					Alc. rich	Water rich
	2,3,3-Trimethylbutanol-2					
1	0.8380	40	2.20	94.72	0.8352	0.9902
	130.3–130.8					
	3-Ethylpentanol-3					
2	0.8402	20	1.91	94.25	.8541	.9964
	143.1–	25	1.68	94.24	.8502	.9957
	143.2	30	1.50	94.21	.8457	.9945
		40	1.26	94.31	.8366	.9921
	2,3-Dimethylpentanol-3					
3	0.8365	20	1.87	94.11	.8513	.9965
	139.6–	25	1.64	94.12	.8470	.9961
	139.8	30	1.43	94.12	.8430	.9945
	2,3-Dimethylpentanol-2					
4	0.8307	20	1.69	93.69	.8477	.9964
	138.5–	25	1.54	93.69	.8441	.9955
	139.5	30	1.40	93.71	.8404	.9943
	2,4-Dimethylpentanol-2					
5	0.8100	20	1.50	93.49	.8279	.9962
	132.5–	25	1.34	93.48	.8240	.9954
	133.5	30	1.22	93.49	.8199	.9943
	3-Methylhexanol-3					
6	0.8202	20	1.35	94.77	.8348	.9965
	142.7–	25	1.19	94.75	.8312	.9958
	142.9	30	1.07	94.73	.8272	.9946
	2-Methylhexanol-2					
7	0.8093	20	1.08	93.77	.8268	.9967
	143.0–	25	0.97	93.65	.8233	.9958
	143.2	30	.87	93.56	.8199	.9946
	2,2-Dimethylpentanol-3					
8	0.8224	20	.88	97.00	.8329	.9971
	134.7–	25	.82	96.94	.8289	.9962
	135.1	30	.79	96.88	.8253	.9950
	2,4-Dimethylpentanol-3					
9	0.8254	20	.78	96.79	.8351	.9974
	138.4–	25	.70	96.68	.8315	.9965
	138.9	30	.67	96.56	.8271	.9955

Experimental

All compounds were prepared by some modification of the Grignard reaction with the usual procedure and purified by careful fractionation through a 1-meter column with a reflux ratio of about 10:1. Usually calcium oxide was also used in the distillation. The following specific reagents were used: no. 1 from *t*-butylmagnesium chloride and acetone; no. 2 from ethylmagnesium bromide and ethyl propionate; no. 3 from ethylmagnesium bromide and *i*-propyl methyl ketone; no. 4 from *s*-butylmagnesium bromide and acetone; no. 5 from *i*-butylmagnesium bromide and acetone; no. 6 from *n*-propylmagnesium bromide and methyl ethyl ketone; no. 7 from *n*-butylmagnesium bromide and acetone; no. 8 from *t*-butylmagnesium chloride and propionaldehyde; no. 9 from *i*-propylmagnesium chloride and *i*-butyraldehyde.

The procedure used for the measurement of the solubilities was essentially identical with that used in the work on

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(1) Ginnings and Baum, THIS JOURNAL, **59**, 1111 (1937).

(2) Ginnings and Webb, *ibid.*, **60**, 1388 (1938).

(3) Butler, Thomson and Maclennan, *J. Chem. Soc.*, 674 (1933).

pentanols and hexanols. If details are desired, reference should be made to the article on pentanols. The results seem reliable to better than 0.1 weight per cent. and the authors feel that the validity of the results will approach this limit.

Summary

Aqueous solubilities of eight isomeric heptanols have been determined for 20, 25 and 30° and one for 40°. The seven tertiary isomers are more soluble than the two most compact secondary isomers. Maximum solubility is obtained by having the hydroxyl group as close as possible to the center of a compact tertiary molecule. Solubility of the isomers decreases as the temperature increases from 20 to 30°.

GREENSBORO, N. C. RECEIVED JUNE 27, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Densities of Aqueous Solutions of Urea at 25 and 30° and the Apparent Molal Volume of Urea[1]

BY FRANK T. GUCKER, JR., FRED W. GAGE AND CHARLES E. MOSER

Introduction

In 1929 Masson[2] showed that the apparent molal volume of an electrolyte is a linear function of the square root of the concentration, while that of a weak electrolyte or a non-electrolyte is a linear function of a higher power of the concentration. The relationship for electrolytes has been confirmed by numerous investigators. In reviewing this and other properties of electrolytic solutions, one of us[3] pointed out that the data of Perman and Urry[4] for the apparent molal volumes and compressibilities of sucrose and of urea also might be represented as linear functions of the square root of the concentration. Redlich and Klinger[5] subsequently proved from more accurate density data that the change of the apparent molal volume of sucrose was much more nearly linear with the first power than with the square root of the concentration. We then found that the data of Perman and Urry could be represented equally well by either plot, within the limit of 0.1% to which their data were tabulated. The present work was undertaken to determine the apparent molal volumes of urea in aqueous solutions with high enough precision to determine whether it was also a linear function of the concentration—like sucrose.

Experimental Methods.—In order to attain an accuracy of a few parts per million (p. p. m.) the densities were measured differentially, using three pycnometers of about 60-ml. capacity. Two of them were filled with solution and the third with water. After all three had come to equilibrium in a thermostat and the volumes were adjusted in the capillaries, the pycnometers containing solution were weighed successively against the water-filled tare. Such a differential arrangement minimizes errors due to changes in the temperature of the thermostat, and also decreases the errors due to adsorption of moisture on the surface of the pycnometers and the correction required in reducing the weights to the vacuum standard.

In adjusting the pycnometers, they were placed in a thermostat holding 36 liters of water. The bottom and sides of the thermostat were protected by a 5-cm. layer of magnesia insulation and the top was covered with a wooden lid, in the center of which was a glass panel, through which the capillaries of the pycnometers were read.

The thermostat was equipped with an adequate stirrer and heated by means of three coils of bare nichrome wire connected to the lighting circuit through a thyratron relay. During the first series of measurements (made by F. W. G.) the relay was actuated by a large ether-filled regulator with mercury contact, which kept the temperature constant to ±0.002° under most conditions and to ±0.005° at all times. The temperature throughout the bath was found to be uniform to 0.001°. These temperatures were measured with a calibrated Beckmann thermometer. During the second series of measurements (made by C. E. M.) the regulator consisted of a pair of 100-ohm nickel resistance thermometers, connected in opposite arms of a Wheatstone bridge, equipped with a sensitive galvanometer. The light from the galvanometer mirror actuated a photoelectric cell which controlled the relay. This system gave more rapid response and kept the temperature constant to ±0.0004°, as measured by a platinum resistance thermometer. This regulator has the added advantage of great flexibility and instant response at any desired temperature.

The pycnometers were constructed of Pyrex glass, which has the advantage of chemical inertness but the disadvantage of changing volume appreciably with time. The body of each pycnometer was made from 2-cm. tubing bent into a U which was 6 cm. in total width and about 13 cm. high.

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[1] Part of this paper was presented before the Symposium on "The Electrochemistry of Solutions" held by the Division of Physical and Analytical Chemistry at the Kansas City meeting of The American Chemical Society, April, 1936.

[2] Masson, *Phil. Mag.*, [7] **8**, 218 (1929).

[3] Gucker, *Chem. Rev.*, **13**, 111 (1933).

[4] Perman and Urry, *Proc. Roy. Soc.* (London), **A126**, 44 (1929).

[5] Redlich and Klinger, *Sitzb. Akad. Wiss. Wien*, Abt. IIb, **143**, 489 (1934); *Monatsh.*, **65**, 137 (1934).

Heavy capillary tubes of 0.4–mm. bore, sealed to the tops of the U, extended vertically for 2 cm. and then were bent at right angles. Each horizontal section was 6 cm. in length and its end was covered with a ground glass cap to minimize evaporation. The end of one was drawn down to a bore of about 0.1 mm., while the central portion of the other was graduated with 20 clearly-etched lines about 1 mm. apart. This allowed a latitude of about 0.002 ml. in setting the pycnometer. If a single mark were used, the volume would have to be set to 0.00006 ml. in order to give a sensitivity of 1 p. p. m.

Before the graduated capillaries were sealed into place, each was tested by measuring the length of a short mercury thread in different positions. When it was found to be uniform,[6] it was calibrated by measuring the length of a mercury thread which nearly filled the graduated section and then weighing the mercury. The volume per graduation was 0.00012 ml. in pycnometers 1 and 3, and 0.00013 ml. in number 2. An error of 0.5 mm. in reading the capillary therefore would only make an error of 1 p. p. m.

The volume of each pycnometer was determined by filling it with distilled water to some point on the graduated capillary and weighing the water it contained. The volume from the constricted end to the *first* mark on the graduated arm was then found by subtracting the volume of water in the graduated arm. The pycnometers were standardized at 25° and then at 30° in the summer of 1936. Two standardizations were carried out at each temperature, agreeing on the average to 12 p. p. m. No regular change in volume was observed during the few weeks in which the work was done. However, when the second series of measurements were made, starting in December, 1937, a decrease of 0.114% was found in the volume of pycnometer 2 and a decrease of 0.115% in 1 and 3. This evidently was due to the contracting of the pycnometers on aging, although they were annealed when they were made.

The weights used in this investigation were standardized to 0.01 mg. by the well-known method of Richards[7] as modified by Weatherill to employ transposition. They were checked from time to time and found consistent to a few hundredths of a milligram. The weighings in the first series of experiments were made on a good analytical balance of the required sensitivity. Those in the second series were made on a semi-micro balance with a notched beam graduated in hundredths of a milligram and with magnetic damping which decreased the time required to determine the balance point. In the second series, all weighings were made by transposition, to eliminate the effect of a difference of about 0.01% in the length of the balance arms.

Throughout this work, all weighings were reduced to the vacuum standard. The density of the brass weights was taken as 8.4, the figure given by the manufacturer. Calculations showed that an error of 10% in this value would not affect the results by 1 p. p. m. The density of 2.25 for Pyrex, given in the "International Critical Tables,"[8] was used in calculating the vacuum corrections for the pycnometers in the first series of experiments. Later, direct weighings in air and in water gave the value 2.234 which was used in the second series. The density of solid urea was taken as 1.335[9] at 20°. At the end of this work we found the value 1.329 at 25° as described in a later paragraph. Both these differences are negligible in calculating vacuum corrections. The atmospheric pressure was read on a mercurial barometer, corrected for temperature and the local value of the gravitational acceleration. The relative humidity was read on a hair hygrometer. The density of the air was calculated from these values, the room temperature and corresponding aqueous tension, by the formula given in the "International Critical Tables."[10]

Materials and Solutions.—The urea used in this work was prepared by crystallizing the commercial C. P. product twice from water, draining the crystals centrifugally and drying the product *in vacuo* at 50–60°, as described in a previous paper.[11] After use in the pycnometers, the solution was evaporated at 50° until crystallization began, then poured into an equal volume of redistilled ethanol held in an ice-bath at 0°. The urea precipitated in this way was collected on a sintered glass crucible and dried as before. Since urea is fairly soluble in 50% alcohol the filtrate was evaporated further and a second batch of crystals was reclaimed.

The water used in this work was redistilled from alkaline permanganate and had a specific conductance of about 1.5×10^{-6} mhos. It was always deaerated immediately before use by means of a water aspirator.

The solutions were made up determinate from the dry urea and this water. The urea was weighed into a 500-ml. flask to which the desired amount of water was added. After the solution was mixed thoroughly and brought up to room temperature, it was weighed and the amount of water found by difference. The solutions more concentrated than 4 molar required special treatment to prevent the appearance of small air bubbles which coalesced very slowly in the viscous medium. It was necessary to apply the full suction of the water aspirator, or the partial suction of a Hyvac pump, and to shake the flask at intervals for about a half hour in order to deaerate the solution completely. The final weighing was not made until this process was complete.

The pycnometers were cleaned with sulfuric acid and dichromate solution, rinsed with distilled water and dried with a current of filtered air. One of the capillary tubes was then connected, by means of a piece of gum-rubber tubing, to a glass tube extending through a rubber stopper into the suction flask containing the solution. The solution was forced into the pycnometer by air pressure from a rubber aspirator bulb connected to the side-arm of the flask. In some of the most concentrated solutions, a small amount of insoluble matter was removed by connecting a platinum sponge filter to the end of the glass tube through which the solution was forced.

After the pycnometers had come to equilibrium in the water-bath, the liquid menisci were adjusted as usual with a thin V-shaped piece of filter paper. When the meniscus remained stationary for five minutes, its position was read

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[6] These fine, uniform tubes were supplied to us by the Corning Glass Works, through the courtesy of Dr. Ralph K. Day.

[7] T. W. Richards, THIS JOURNAL, **22**, 144 (1900); Weatherill, *ibid.*, **52**, 1938 (1930).

[8] "I. C. T.," Vol. II, p. 93.

[9] "I. C. T.," Vol. I, p. 177.

[10] "I. C. T.," Vol. I, p. 71.

[11] Gucker and Ayres, THIS JOURNAL, **59**, 2152 (1937).

TABLE I[a]

DENSITIES OF AQUEOUS SOLUTIONS OF UREA AT 30° AND CORRESPONDING APPARENT AND PARTIAL MOLAL VOLUMES

Expt.	c	d	Δd (in p. p. m.)	ΦV_2 (obsd.)	ΦV_2 (calcd.)	$\bar{V}_2$ (calcd.)	$\bar{V}_1$ (calcd.)
	0.00000	0.995673			44.546	44.546	18.0945
6a	.08056	.996976	39	44.1	44.55	44.56	18.0945
b		.996926	−11	44.7			
10a	.15060	.998069	33	44.34	44.56	44.58	18.0945
b		.998017	−19	44.69			
3	.19976	.998785	−21	44.67	44.57	44.59	18.0944
4a	.39455	1.001898	45	44.47	44.59	44.63	18.0941
b		1.001842	−11	44.61			
8a	.49616	1.003471	32	44.53	44.60	44.65	18.0940
b		1.003407	−32	44.66			
7a	.66822	1.006159	40	44.56	44.62	44.69	18.0936
b		1.006104	−15	44.64			
9a	.82859	1.008651	39	44.59	44.64	44.72	18.0931
b		1.008596	−16	44.65			
1a	1.15522	1.013644	−27	44.695	44.672	44.791	18.0919
b		1.013631	−40	44.706			
2a	1.92868	1.025517	−43	44.778	44.756	44.948	18.0872
b		1.025506	−54	44.784			
5	2.95029	1.041061	− 5	44.868	44.867	45.145	18.0774
11a	4.39481	1.062650	46	45.013	45.024	45.406	18.0566
b		1.062601	− 3	45.024			

[a] In this table and the next, c is the concentration of solute in moles per liter; d, the density of the solution in g. per ml.; and Δd, the observed density minus that calculated from the equation. The density of pure water is taken from the "I. C. T.," Vol. III, p. 25.

and recorded. All three pycnometers were then removed from the water-bath, rinsed with distilled water, wiped with a lintless towel and hung in the balance room. After a period of thirty or forty-five minutes, the weighings were made.

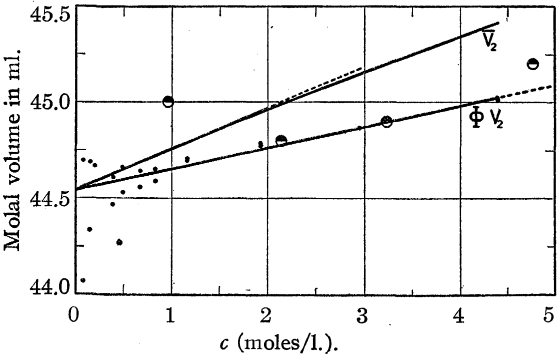

Fig. 1.—Apparent and partial molal volumes of urea at 30°: ●, this investigation; ⊖, Perman and Urry.

Experimental Results.—We originally planned a series of experiments over the whole concentration range at 25°. After the first six of these were made (by F. W. G.), hot weather necessitated a change to 30°. The series at 25° was completed later (by C. E. M.). The experimental results, numbered chronologically, are collected in Tables I and II, which include all the experiments except those affected by some known error. Duplicate experiments were always made, but in seven cases minor accidents prevented the completion of one of the pair. From the densities, the apparent molal volumes were calculated by the equation

$$\Phi V_2 = \frac{1000}{c}\left(\frac{d_1 - d}{d_1}\right) + \frac{M_2}{d_1} \qquad (1)$$

where c is the concentration in moles per liter, d_1 and d the densities of water and of solution, and M_2 the molecular weight of urea (60.058). A plot of the apparent molal volume at 30° (Fig. 1) showed that within experimental error it is a linear function of c up to the highest concentration studied. The best straight line representing the experimental values was found by the method of least squares, weighting each point according to its probable accuracy, measured by $(d - d_1)$. It was found to be

$$\Phi V_2 = 44.546 + 0.1087c$$

Substituting this value in equation (1) gives for the density the equation

$$d = 0.995673 + 0.015705c - 1.082 \times 10^{-4} c^2$$

Values calculated from this equation were compared with the experimental results and the differences, as shown in Table I, average ±29 p. p. m.

TABLE II

DENSITIES OF AQUEOUS SOLUTIONS OF UREA AT 25° AND CORRESPONDING APPARENT AND PARTIAL MOLAL VOLUMES

Expt.	c	d	Δd (in p. p. m.)	ΦV_2 (obsd.)	ΦV_2 (calcd.)	$\bar{V}_2$ (calcd.)	$\bar{V}_1$ (calcd.)
	0.00000	0.997074			44.218	44.218	18.0691
4a	.11394	.998896	5	44.20	44.23	44.25	18.0691
b		.998888	− 3	44.26			
2	.15077	.999475	− 4	44.26	44.24	44.26	18.0690
7a	.35215	1.002682	2	44.26	44.27	44.32	18.0688
b		1.002683	3	44.26			
1a	.41500	1.003676	− 1	44.28	44.28	44.34	18.0687
b		1.003674	− 3	44.28			
3	.62386	1.006983	0	44.30	44.30	44.38	18.0681
5a	1.00812	1.013039	6	44.351	44.356	44.486	18.0666
b		1.013038	5	44.352			
8a	1.36866	1.018667	− 9	44.411	44.405	44.576	18.0646
b		1.018670	− 6	44.409			
6a	1.88532	1.026703	2	44.472	44.473	44.698	18.0607
b		1.026694	− 7	44.477			
13a	2.42107	1.034945	− 9	44.546	44.542	44.817	18.0556
b		1.034936	−18	44.550			
12a	3.33355	1.048842	− 9	44.659	44.656	45.004	18.0445
b		1.048833	−18	44.662			
10a	3.98193	1.058615	4	44.734	44.734	45.123	18.0350
b		1.058608	− 3	44.735			
9	5.05362	1.074560	17	44.856	44.859	45.302	18.0168
11a	5.92297	1.087291	− 7	44.958	44.956	45.428	18.0002
b		1.087287	−11	44.958			
14	7.28543	1.106989	−17	45.103	45.100	45.597	17.9717
15a	8.20269	1.120038	−60	45.199	45.191	45.690	17.9516
b		1.120039	−59	45.199			
16a	9.52555	1.138980	220	45.293	45.315	45.801	17.9220
b	9.52469	1.138878	130	45.302	45.315	45.801	17.9220
17a	9.53161	1.138911	67	45.310	45.316	45.802	17.9219
b		1.138909	65	45.310			

The partial molal volumes of solvent ($\bar{V}_1$) and solute ($\bar{V}_2$) are defined as

$$\bar{V}_1 = \left(\frac{\partial V}{\partial n_1}\right)_{n_2,\,T} \text{ etc.}$$

where V is the volume occupied by n_1 moles of solvent and n_2 of solute. These values were calculated from the apparent molal volume of the solute by the equations[12]

$$\bar{V}_1 = \frac{1000\,\bar{V}_1^\circ}{1000 + c^2\dfrac{\partial \Phi V_2}{\partial c}} \qquad (2)$$

$$\bar{V}_2 = \Phi V_2 + \left[\frac{1000 - c\Phi V_2}{1000 + c^2\dfrac{\partial \Phi V_2}{\partial c}}\right] c\,\frac{\partial \Phi V_2}{\partial c} \qquad (3)$$

These values are also collected in Table I and $\bar{V}_2$ is plotted in Fig. 1. It starts with twice the slope of the ΦV_2 curve and is practically linear to 1 molar, above which it increases somewhat less rapidly, as shown.

In Table II are given the results of the more complete series at 25°, which extends nearly to the saturated solution. Here also the apparent molal volume of urea may be represented as a linear function of c to a concentration of 3 molar by the equation

$$\Phi V_2 = 44.224 + 0.1319c$$

which was fitted to these data by the method of least squares. The corresponding equation for the density

$$d = 0.997074 + 0.015964c - 1.315 \times 10^{-4}c^2$$

reproduces the experimental values with an average deviation of ±5 p. p. m.

In more concentrated solutions, the increase is less rapid, as shown in Fig. 2. The whole series

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[12] The first is analogous to that derived by Gibson, *J. Phys. Chem.*, **38**, 320 (1934), and listed as equation (6). The second was derived by Geffcken, *Z. physik. Chem.*, **A155**, 1 (1931), and used by Gucker, *J. Phys. Chem.*, **38**, 311 (1934).

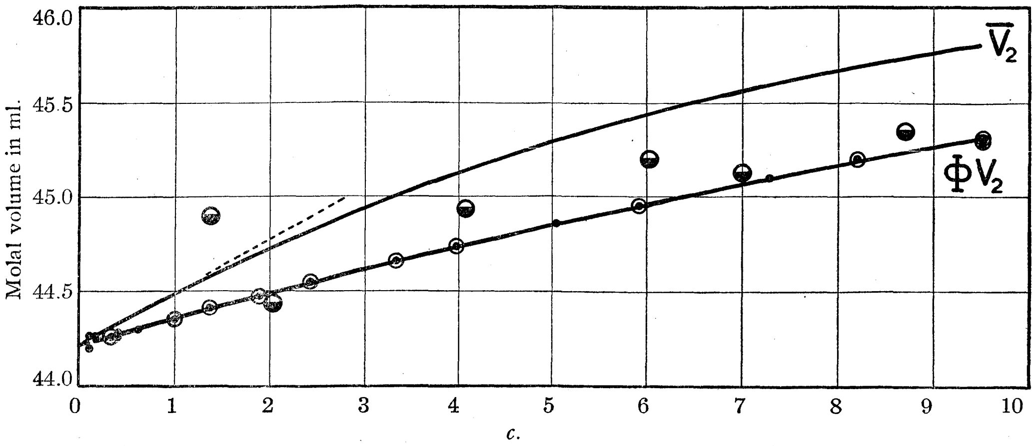

Fig. 2.—Apparent and partial molal volumes of urea at 25°: ● and ○, our data; ◒, Dunstan and Mussell.

lies along a smooth curve which is represented very satisfactorily by the second order equation

$$\Phi V_2 = 44.218 + 0.13999c - 0.002601c^2$$

The corresponding expression for the density is

$$d = 0.997074 + 0.0159686c - 1.3958 \times 10^{-4}c^2 + 2.593 \times 10^{-6}c^3$$

The experimental results agree with the values calculated from this equation with an average deviation of only ±7 p. p. m. up to 7 molar and ±26 p. p. m. over the whole range. The values of $\overline{V}_1$ and $\overline{V}_2$ were calculated as before and are included in Table II.

One other interesting experimental value was the density of solid urea, from which its molal volume in the solid state could be calculated. The value of 1.335 for the density at 20° which is tabulated in the "International Critical Tables"[9] apparently was determined by Mez.[13] It is frequently quoted in the literature. We were surprised to find, however, that another volume of the same Tables[14] listed, among "values reliable to four decimals or values over a temperature range," the figures of 1.3190 and 1.3617 determined by Dewar[15] at 17 and −188°, respectively. Assuming linear expansion, this would give the value 1.3184 at 20°, which is 1.2% lower than the value of Mez. Further search also disclosed the values of 1.333 and 1.323 found by Schröder[16] by the displacement of benzene and olive oil, respectively. No statement of the temperature was found, but it was probably 18 or 20°. Because of the diversity of these results, we measured the density at 25° in a specific gravity bottle with a ground plug. As the displacing liquid we used *n*-heptane, in which urea was found to be insoluble. The urea was powdered and dried as before and the liquid level was adjusted in the same thermostat. Five experiments were made. One of these was discarded because, for an unknown reason, the weight of the bottle increased upon standing on the balance pan. The other results were 1.3308, 1.3286, 1.3284 and 1.3279. We therefore took as a reliable average of our results the value 1.329 g./ml. at 25°. Correcting the other values to 25° we find that our results are half-way between those of Schröder and Mez, and about 1% higher than those of Dewar, as the following comparison shows:

Dewar (corr.)	1.317
Schröder (corr.)	1.327
This investigation	1.329
Mez (corr.)	1.334

Discussion

These measurements show conclusively that the apparent molal volume of urea is a linear function of the first power of the volume concentration from 0.1 to about 3 molar. This is demonstrated in Fig. 3, where the results for 25° are plotted against c along the upper line and against $c^{1/2}$ in the lower curve. The same conclusion follows from the results at 30°, although the experimental uncertainty is somewhat greater. Our results at 25° show a maximum difference from those of Dunstan and Mussell[17] of −0.6% and an average of −0.2%. Since their results are only given to 0.1%, this agreement is quite satisfactory. Our results at 30° agree with those of Perman and

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[13] Mez, *Z. Krist.*, **35**, 247, quoted in Beilstein, "Handbuch" 4th Edition, Vol. III, p. 45.

[14] "I. C. T.," Vol. III, p. 45.

[15] Dewar, *Chem. News*, **91**, 216 (1905).

[16] Schröder, *Ber.*, **12**, 562 (1879).

[17] Dunstan and Mussell, *J. Chem. Soc.*, **97**, 1935 (1910).

Urry[4] within the accuracy of 0.1% with which they were tabulated. Four of their values, covering the range of our results, are plotted in Fig. 1, and six of the eight data of Dunstan and Mussell in Fig. 2. One of the others fell above and the second below the range of our figure. The large scattering emphasizes the difficulty of determining the true function of the concentration from them. Taking our value of the density of the solid, we find that its molal volume is 45.19 ml. at 25°. This differs very little from the volume in solution. In fact, it is the same as the apparent molal volume in a 6.5 molar solution or the partial molal volume in a 3.5 molar solution. Urea therefore is very nearly a perfect solute and does not cause the large electrostriction typical of electrolytes and of polar non-electrolytes,[18] nor does its apparent molal volume change so much with concentration. The increase from 0 to 1 molar solution is only about 4% of that of a typical 1-1 electrolyte.

Since the apparent molal compressibility[19] is the pressure derivative of the apparent molal volume

$$\Phi K_2 = -\left(\frac{\partial \Phi V_2}{\partial P}\right)_T$$

we would expect it to be the same function of the concentration as the apparent molal volume. A review of the literature did not disclose enough accurate data to prove this point, but we may reasonably assume that accurate compressibility measurements would show that the apparent molal compressibility of urea is also a linear function of c rather than $c^{1/2}$ as we first thought.[3]

In the case of electrolytes, the apparent molal heat capacity was found to parallel the volume properties.[3] The same is true of sucrose,[20] but the case of urea is different, since the apparent molal heat capacity[11] does not change in a simple manner with either c or $c^{1/2}$.

Added in Proof.—Recently we have found an article by Skarre, Demidenko and Brodskiĭ,[21] on the densities and apparent molal volumes of urea at 25° from 0.003 to 1.3 molar. They employed the differential flask method which Washburn[22] and his collaborators used to determine the density of heavy water, and consider their results accurate to 1 p. p. m. Their ten results from 0.003 to 0.09 molar differ on the average by only ±1.3 p. p. m. from the densities calculated from our equation, using the 1936 value of the molecular weight (60.047) which they apparently employed. Their results at the four higher concentrations show increasingly negative deviations of 16, 26, 66 and 102 p. p. m. for which we have no explanation.

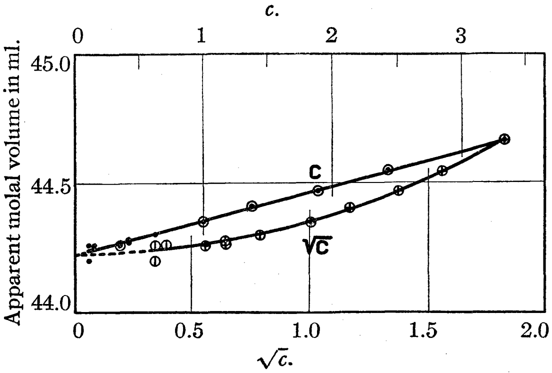

Fig. 3.—Comparison of abscissas for urea at 25°.

They plotted their results against $c^{1/2}$ and found a nearly linear relationship from 1.3 down to 0.05 molar. At greater dilution, their results fell *below* the line, and they hesitated to extrapolate to infinite dilution. However, their values of the apparent molal volume, tabulated to 0.001 ml., are accurate only to 0.1 ml. at 0.1 molar and 1 ml. at 0.004 molar. The average deviation in density is only 1 p. p. m., which seems to us to be within their probable experimental error. Their range of concentrations was not great enough to allow a satisfactory comparison of the $c^{1/2}$ and c plot, although they state that unpublished work by Dikowa in their laboratory indicates an upward concavity in the $c^{1/2}$ plot such as we have found.

Acknowledgments.—It is a pleasure to acknowledge our indebtedness to Dr. Ralph K. Day of the Corning Glass Works for supplying us with the capillary tubing used in our pycnometers; to Paul Kleppisch who, working on an N. Y. A. grant, purified the urea for these measurements; and to Nicholas Boukidis, also an N. Y. A. assistant, who helped in the construction of the thermostat.

Summary

Using a differential pycnometer method, we have measured the densities of aqueous solutions of urea from 0.1 to 4 molar at 30° and from 0.1 to 9.5 molar at 25°.

The apparent molal volume of urea is a linear

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(18) Cohn, McMeekin, Edsall and Blanchard, THIS JOURNAL, **56**, 784 (1934).

(19) Gucker, *ibid.*, **55**, 2709 (1933), see also reference (3).

(20) Gucker and Ayres, *ibid.*, **59**, 447 (1937).

(21) Skarre, Demidenko and Brodskiĭ, *J. Phys. Chem.* (U. S. S. R.), **9**, 152 (1937); *Acta Physicochim., U. R. S. S.*, **6**, 297 (1937).

(22) Washburn, Smith and Frandsen, *Bur. Standards J. Research*, **11**, 457 (1933); **12**, 306 (1934).

function of the volume concentration, *c*, over the whole range at 30° and up to 3 molar at 25°. Urea therefore behaves like sucrose and not like typical electrolytes, the apparent molal volumes of which increase linearly with $c^{1/2}$. The experimental results and the partial molal volumes of urea and water are tabulated. Equations giving the apparent molal volume and density as functions of concentration are also included.

The density of solid urea is found to be 1.329 g./ml. at 25° and its molal volume 45.19 ml.

EVANSTON, ILLINOIS RECEIVED AUGUST 1, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

Kinetics of Neutralization of Pseudo Acids in H_2O and D_2O

BY SAMUEL H. MARON[1] AND VICTOR K. LA MER

In this paper are reported kinetic measurements by a conductance method on the neutralization at 0 and 5° of nitromethane, nitroethane, and nitroisopropane by hydroxyl and deuteroxyl ions.

The familiar protolytic processes of ionization and neutralization of acids are in most cases not amenable to kinetic study for they proceed, if not instantaneously, at least with velocities too high to measure. In the class of substances designated as pseudo acids, however, ionization and neutralization proceed at a much slower rate, and in certain cases can be followed kinetically.

This difference in rates of protolytic transfer has been employed by Hantzsch[2] to define a pseudo acid as a substance whose salt formation is a function of time, as against the acid whose neutralization is essentially instantaneous. He states, further, that "if the salt formation is a function of the time, then it is evidence that the molecule undergoes a change in the salt formation process; it is also evidence for the fact that the undissociated substance and its ions are constitutionally different."

As a class, the primary and secondary nitroparaffins have long been recognized as pseudo acids. Ley and Hantzsch[3] have postulated that the primary and rate determining step in the neutralization of a nitroparaffin by a base is the isomerization of the nitro to the aci form, with subsequent rapid neutralization of the latter, *i. e.*

$$RCH_2NO_2 + B \xrightarrow[k_1]{} RCH{=}NOOH + B \xrightarrow[k_2]{} RCH{=}NOO^- + BH^+ \quad (1)$$

and $k_1 << k_2$. In this mechanism the sequence of transformations is nitroparaffin → undissociated aci acid → aci ion. However, Pedersen[4] has shown that this view is inconsistent with present ideas of acid–base catalysis as outlined by Brönsted.[5] The isomerization of a nitroparaffin must be considered a prototropic process, and as such it cannot take place spontaneously, but must involve the intermediary of an acid or basic catalyst. In conformity with this view he actually found the isomerization of nitromethane to the aci form to be a reaction subject to general base catalysis.[4] He consequently postulated as the mechanism of neutralization

$$RCH_2NO_2 + B \xrightarrow[k']{} RCH^-{\cdot}NO_2 + BH^+ \xrightarrow[k']{} RCH{=}NO_2^- + BH^+ \quad (2)$$

i. e., the nitro form donates a proton to the base, and the residue is converted rapidly by an electron shift to the ion. Thus $k_1' << k_2'$, and is rate determining. The aci ion may associate under the proper conditions, to form the aci acid. In this scheme the sequence is nitroparaffin → aci ion → aci acid.

Pedersen's formulation of the mechanism of isomerization of the nitroparaffins has been accepted by Junell,[6] Wynne-Jones,[7] and Reitz,[8] and will be employed to explain the results of this paper.

Following Hantzsch and Veit's[9] orienting semiquantitative conductivity measurements, Junell[6] studied in H_2O at 0° the neutralization by sodium hydroxide of nitromethane, nitroethane, nitropropane, and nitroisopropane by a modification of

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[1] Present address: Department of Chemical Engineering, Case School of Applied Science, Cleveland, Ohio.

[2] Hantzsch, *Ber.*, **32**, 575–600 (1899).

[3] Ley and Hantzsch, *ibid.*, **39**, 3149 (1906).

[4] Pedersen, *Det. Kgl. Vidensk. Selskab., Math.-fys. Medd.*, **12**, 1–16 (1932) (in English).

[5] Brönsted, *Chem. Rev.*, **5**, 231 (1928).

[6] Junell, (a) *Arkiv Kemi*, **11B**, No. 34 (1934); (b) *Svensk Kem. Tid.*, **46**, 125–136 (1934); (c) Dissertation, Uppsala, 1935.

[7] Wynne-Jones, *J. Chem. Phys.*, **2**, 381–385 (1934).

[8] Reitz, *Z. physik. Chem.*, **A176**, 363–387 (1936).

[9] Hantzsch and Veit, *Ber.*, **32**, 607–627 (1899).

the bromination method. Wynne-Jones, on the other hand, employing a conductance method, studied the neutralization of nitroethane by Ba$(OH)_2$ and $Ba(OD)_2$ at 0° in both light and heavy water.

A reinvestigation of the problem by the conductance method has been undertaken in order: (a) to confirm, refine, and extend Wynne-Jones' measurements, which in heavy water were restricted to a single experiment employing a very small volume of solvent; (b) to ascertain whether the bromination method gives a true measure of the rate of isomerization; (c) to determine the effect of substitution of alkyl groups in the molecule on prototropic rates in light and heavy water; (d) and to determine the rates of proton and deuteron transfer, and their temperature coefficients.

Experimental

Of the two methods available for following the rates of neutralization of nitroparaffins, conductance is more direct, avoids analytical determinations, and is free of the assumptions of the bromination method. The conductance method depends on the fact that as neutralization proceeds in an equivalent mixture of nitroparaffin and hydroxide, the highly mobile hydroxyl ions are removed, to be replaced by the considerably slower anions of the aci acid formed. Consequently the resistance of the solution increases with time from an initial value, R_0, to a final limiting value R_∞, due to the salt of the aci acid. The concentrations and velocity constants can be calculated in terms of the measured resistances.

Apparatus.—The bridge employed for measuring resistances was composed of a 1000-cycle microphone hummer, tuned Brown headphones, two variable, 10,000-ohm standard resistance boxes, and an L & N Student Type slide wire. This form of slide wire was preferred to the more accurate Kohlrausch type because balancing and reading could be accomplished with greater speed—an important consideration with the very fast reactions studied.

Four cells differing in size and shape of both cell and electrodes were employed. One was of the Henry type, one of the Freas type, while two were of special design. The latter had a total capacity of 20–25 ml., but required only 2–3 ml. of liquid to cover the electrodes. In these cells measurements could be made with small or large quantities of material; dilutions or additions of reagent could be made with ease. All the runs in D_2O were made in these special cells.

The electrodes were in all cases platinized. No catalytic effect due to the electrodes was observed.

One thermostat consisted of a 12-liter Dewar vessel of large opening, and filled with distilled water and crushed ice. Once charged, and with only occasional manual stirring, the temperature could be kept constant for twenty-four hours. For the experiments at 5° a large capacity water thermostat was operated in conjunction with a refrigerating unit, and regulated to ±0.005°.

Chemicals.—The nitromethane and nitroethane were Eastman products, and were purified by repeated fractional distillation. For nitromethane only the fraction boiling at 100.0° at 741.5 mm. was retained, while for nitroethane the fraction boiling at 112.5–113.0° at 739.3 mm. was used.

Nitroisopropane was prepared from purified isopropyl iodide and freshly prepared silver nitrite according to the directions of Kohler.[10] The fraction boiling between 119–120° was collected. Since the product was found to contain nitrous acid, it was treated with urea, dried with calcium sulfate and calcium chloride, and distilled twice under vacuum. The final product was a very mobile, colorless liquid, with a characteristic odor.

The distilled H_2O had a specific conductance of about 1×10^{-6} mhos. The D_2O, obtained from Hydro Norsk, was purified by molecular distillation under high vacuum twice from alkaline permanganate, and once without any addition. After use the D_2O was freed from organic matter by heating to 60–70° with alkaline permanganate and then distilling several times molecularly *in vacuo*. Water of satisfactory purity could be obtained in this manner without difficulty. Density measurements were made with a 10-ml. pycnometer.

The $Ba(OH)_2$ solution was prepared by dissolving C. P. $Ba(OH)_2 \cdot 8H_2O$, peroxide free, in distilled water. Carbonate was removed by filtration in a closed system through a sintered glass funnel. The $Ba(OD)_2$ was prepared in the same manner by dissolving anhydrous C. P. $Ba(OH)_2$, peroxide free, in D_2O, and removing the carbonate by filtration through a micro, all-glass funnel.

The H_2SO_4 was prepared by diluting concentrated C. P. acid with distilled water. The D_2SO_4 was prepared from thrice recrystallized pyrosulfuric acid and D_2O. The recrystallization was accomplished by melting the solid, and allowing part to crystallize.

Both acid and alkali were standardized by titration and on several occasions also gravimetrically as barium sulfate. The $Ba(OH)_2$ and $Ba(OD)_2$ were approximately 0.17 *N*, the acid solutions 0.3 *N*.

Procedure.—Since it is difficult to weigh into a cell 1–4 mg. of a volatile liquid with the desired accuracy, stock solutions, 0.04–0.06 *N* in nitroparaffin, were prepared in both light and heavy water. No decomposition in these solutions could be detected after several weeks at 0°.

A definite quantity of solution of the nitroparaffin in H_2O (or D_2O) was pipetted into a cell, water added in quantity sufficient to give the desired initial concentration, and the cell placed in the thermostat. The total volumes ranged from 2.4 to 7 cc. for the D_2O and from 5 to 18 cc. for H_2O. To initiate reaction an equivalent quantity of Ba$(OH)_2$ [or $Ba(OD)_2$], precooled to the same temperature, was delivered into the cell with a hypodermic syringe; a stop watch was started simultaneously.

Since the reactions are very rapid, and the quantity of reagent to be added in each case was small, 0.15–1.60 cc., it was especially important to deliver the reagent rapidly, with accuracy, and at the same time produce thorough mixing. A set of hypodermic syringes, ranging in capacity from 0.25–2.00 cc., was found to be highly satisfactory

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(10) Kohler, THIS JOURNAL, 38, 898 (1916).

after calibration.[11] When provided with rustless steel or platinum needles these syringes deliver their charge in one to three seconds with a force sufficient to stir the contents of the cell thoroughly. This stirring was supplemented in the initial stages of a run by manual shaking of the cell to eliminate any possibility of concentration differences in the solution.

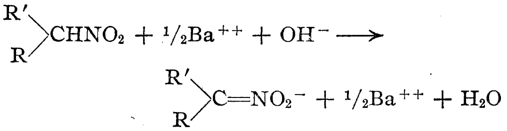
Resistance readings were taken within ten to thirty seconds after the addition of hydroxide. For nitromethane and for nitroethane at 5°, readings were taken at ten-second intervals for the first few minutes, and less frequently thereafter; for nitroisopropane, and for nitroethane at 0°, readings were made at fifteen-second intervals or less frequently, as the occasion demanded. In practically all cases the reaction was followed considerably past the point of half neutralization.

In many of the runs after completion of neutralization the nitroparaffin was regenerated from its barium salt by the addition of an equivalent quantity of sulfuric acid which precipitated the barium and liberated the aci acid. The isomerization of the aci acid to the nitro form is also a time reaction, subject to general acid catalysis.[6b,c] The kinetics of this reaction will be reported in another paper.

Once the nitro form of the pseudo acid had been regenerated, barium hydroxide in equivalent quantity was again added, and the whole sequence of measurements repeated. Thus the reproducibility of the rate and the reversibility of the isomerization process could be established.

Results of Measurements

The neutralization of a primary or secondary nitroparaffin by $Ba(OH)_2$ proceeds according to the equation



$$\begin{matrix}R'\\R\end{matrix}\!\!>\!CHNO_2 + {}^1/_2Ba^{++} + OH^- \longrightarrow \begin{matrix}R'\\R\end{matrix}\!\!>\!C{=}NO_2^- + {}^1/_2Ba^{++} + H_2O \quad (3)$$

where R and R′ are either a hydrogen atom or an alkyl group. The rate of reaction follows the equations

$$dx/dt = k_2\left(\begin{matrix}R'\\R\end{matrix}\!\!>\!CHNO_2\right)(OH^-) \qquad (4a)$$

$$= k_2\,(a - x)^2 \qquad (4b)$$

In terms of resistances it can be shown that Eq. (4b) on integration takes the form

$$k_2 = \frac{1}{at}\left[\frac{R - R_0}{R_\infty - R}\right]\frac{R_\infty}{R_0} \qquad (5)$$

where a is the initial concentration of nitroparaffin (and hydroxyl ion), R_0 the initial resistance, R_∞ the final, and R the resistance at time t.[12]

R and R_∞ in (5) can be measured directly, but R_0 must be obtained by extrapolation of the R values to zero time. For rapid reactions, like those of nitromethane and nitroethane, where the resistance increases rapidly with time in the initial stages, it is practically impossible to make such an extrapolation with any certainty or accuracy. Equation (5) can be rearranged to

$$t(R_\infty - R) = \left[\frac{R_\infty}{ak_2R_0}\right]R - \frac{R_\infty}{ak_2} \qquad (6)$$

Since for any one experiment the variables are only t and R, a plot of $t(R_\infty - R)$ *vs.* R should be a straight line with slope given by

$$\text{slope} = R_\infty/ak_2R_0 \qquad (7)$$

and y-intercept, b

$$b = -R_\infty/ak_2 \qquad (8)$$

From the latter k_2 follows as

$$k_2 = -R_\infty/ab \qquad (9)$$

This method of evaluating k_2 was found to be satisfactory, and eliminated the uncertainty in the determination of R_0.

In Fig. 1 are shown plots of $t(R_\infty - R)$ *vs.* R for nitroethane and nitroisopropane in H_2O and in D_2O. The linear character of the plot furnishes evidence of the fidelity with which equation (6), and hence equation (4), reproduces the data in a given experiment.

The results obtained with nitromethane, nitroethane, and nitroisopropane in both light and heavy water are summarized in Tables I, II and III. The A runs refer to the first neutralization of the nitroparaffin; the B runs are those made with nitroparaffin which had been neutralized, reconverted to the nitro form, and again neutralized. Because of its high rate, the neutralization of nitromethane was measured only at 0° in light water. Nitroethane has been studied at both 0 and 5° in light water and at 5° in heavy water. Only once were we fortunate in maintaining supercooling to obtain a measurement at 0° in heavy water; in five subsequent attempts the supercooled D_2O solutions froze and made rate measure-

TABLE I

THE NEUTRALIZATION OF NITROMETHANE IN H_2O AT 0°

Run	Concn., equiv. l.	k_2
43-A	0.00693	235.1
41-A	.00489	240.1
40-A	.00451	237.2
44-A	.00306	238.1
44-B	.00298	(254.2)
		237.6 ± 1.5 ± 0.63%

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[11] The syringes, manufactured by Becton, Dickinson & Co., Rutherford, N. J., were of the Tuberculin or Precision type. The 0.25-cc., the 0.50-cc., and the 1.00-cc. syringes were subdivided into 0.01 cc., and could be estimated further to 0.001, 0.002, and 0.003 cc., respectively. The 2.00-cc. syringe was subdivided into 0.05 cc. and could be read easily to 0.01 cc.

[12] Wynne-Jones[7] gives this equation without proof. We find that in order to derive this expression it is necessary to assume that the *specific* conductances of the ionic species present in solution are additive and that they vary linearly with concentration.

ments impossible at that temperature. Consequently nitroisopropane has been studied at 0 and 5° in light water, and only at 5° in D_2O.

TABLE II

THE NEUTRALIZATION OF NITROETHANE IN H_2O AND D_2O

Solvent	Temp., °C.	Run	Concn.	k_2
H_2O	0.00	8-A	0.0419	38.43
		26-A	.0415	39.02
		7-A	.0329	39.03
		26-B	.0299	39.32
		6-A	.0283	39.50
		7-B	.0251	38.88
		23-A	.0237	39.53
		22-A	.0237	39.32
		24-A	.0236	39.33
		24-B	.0193	39.23
		6-B	.0168	38.60
				39.11 ± 0.29
				± .74%
H_2O	5.00	53-A	.0310	57.88
		51-A	.0273	58.57
		54-A	.0244	58.27
		50-A	.0200	59.20
		50-B	.0157	58.84
		52-A	.0120	57.46
				58.37 ± 0.50
				± .86%
		First stage		
99.3% D_2O	0.00	45-A	0.0266	55.6
99.1% D_2O	5.00	46-A	.0266	81.69
		56-A	.0201	81.95
		57-A	.0175	81.00
		58-A	.0155	80.69
				81.33 ± 0.49
				± .60%
		Second stage		
99.3% D_2O	0.00	45-B	0.0207	20.7
99.1% D_2O	5.00	46-B	.0207	29.82
		48-B	.0169	29.58
		56-B	.0169	29.54
		57-B	.0150	29.21
				29.54 ± 0.16
				± .54%

Attention should be directed to the B runs in Table II. The results of these runs are evidence that the barium salt of nitroethane is stable, and that it can be reconverted *completely* to the nitro form by the addition of an equivalent quantity of sulfuric acid. The same can be said for Run 44-B in Table I. Although the result deviates from the mean, still it must be considered as satisfactory evidence, if the uncertainties of reagent addition, barium sulfate precipitation, and the high rate of the reaction be recognized.

No B runs could be made with nitroisopropane. Although the barium salt was stable, the free acid, liberated on addition of an equivalent quantity of sulfuric acid, decomposed partially to yield a

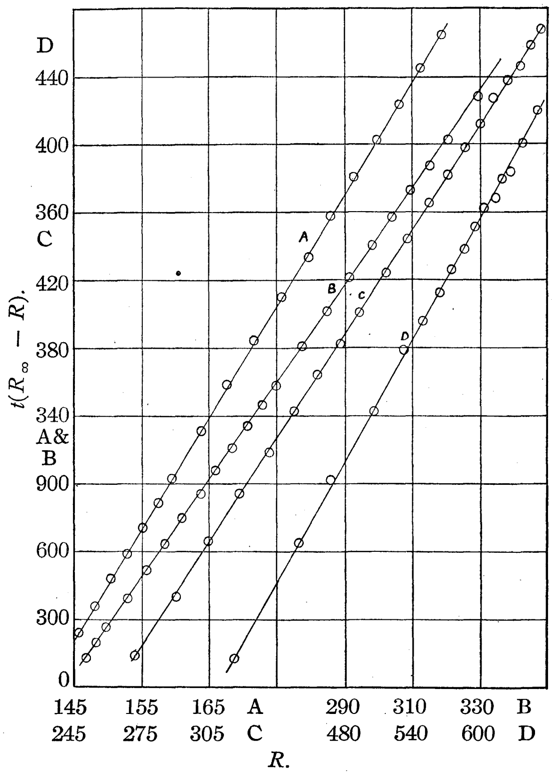

Fig. 1.—Plot of $t(R_\infty - R)$ *vs.* R at 5°: A, 0.0168 N nitroisopropane in H_2O; B, 0.0245 N nitroisopropane in D_2O; C, 0.0273 N nitroethane in H_2O; D, 0.0266 N nitroethane in D_2O.

TABLE III

THE NEUTRALIZATION OF NITROISOPROPANE IN H_2O AND D_2O

Solvent	Temp., °C.	Run	Concn.	k_2
H_2O	0.00	30-A	0.0349	2.08
		31-A	.0301	2.08
		32-A	.0265	2.05
		33-A	.0213	2.08
		34-A	.0165	2.09
				2.08 ± 0.01
				± .48%
H_2O	5.00	61-A	.0307	3.36
		64-A	.0263	3.37
		62-A	.0231	3.38
		65-A	.0206	3.35
		66-A	.0168	3.34
		63-A	.0116	3.34
				3.36 ± 0.01
				± .30%
99.1% D_2O	5.00	69-A	.0359	4.62
		67-A	.0310	4.59
		68-A	.0245	4.57
		70-A	.0150	4.54
				4.58 ± 0.03
				± .66%

TABLE IV

SUMMARY AND COMPARISON OF RESULTS IN H_2O

Substrate	Temp., °C.	k_2 Maron and La Mer (cond.)	Junell (brom.)	Wynne-Jones (cond.)
Nitromethane	0	237.6 ± 1.5	171 ± 3	..
Nitroethane	0	39.11 ± 0.29	35.2 ± 1.0	39.0 ± 2.0
	5	58.37 ± .50	..	..
Nitropropane	0	..	29.2 ± 0.2	..
Nitroisopropane	0	2.08 ± .01	1.94 ± .04	..
	5	3.36 ± .01	..	..

product or products other than the nitro form. In this respect Junell's[6c] (p. 110) experience is in accord with our own.

The nitroethane measurements in D_2O merit further explanation. Wynne-Jones[7] first called attention to the fact that it should be possible to study the kinetics of exchange of the H for D atoms on the carbon adjacent to the nitro group in nitroethane by the following series of reactions carried out in D_2O

$$CH_3CH_2NO_2 + OD^- \xrightarrow{k_1} CH_3CH{=}NO_2^- + HOD \tag{10a}$$

$$CH_3CH{=}NO_2^- + D_3O^+ \longrightarrow CH_3CHDNO_2 + D_2O \tag{10b}$$

$$CH_3CHDNO_2 + OD^- \xrightarrow{k_2} CH_3CD{=}NO_2^- + HOD \tag{11a}$$

$$CH_3CD{=}NO_2^- + D_3O^+ \longrightarrow CH_3CD_2NO_2 + D_2O \tag{11b}$$

$$CH_3CD_2NO_2 + OD^- \xrightarrow{k_3} CH_3CD{=}NO_2^- + D_2O \tag{12a}$$

The idea in this sequence of reactions is to remove the protons one at a time with OD^- and introduce deuterons instead of protons with D_3O^+, until finally only D atoms are attached to the alpha carbon. Further neutralization should involve the transfer of a deuteron to the OD^- ion (12a). By this simple artifice it should be possible to measure both the rate of proton transfer (10a) and deuteron transfer (12a) to the same ion, OD^-, in the same solvent D_2O. Reaction (11a) would proceed only as written if the rate of proton removal is considerably greater than that of the deuteron from CH_3CHDNO_2.

One such sequence of measurements with nitroethane was carried out by Wynne-Jones at 0°. We have repeated these experiments at both 0 and 5°. In Table II the constants designated first stage refer to reaction (10a), while those marked second stage refer to reaction (11a). Stage three, corresponding to (12a), could not be measured for reasons to be given below.

Comparison of Results with Previous Measurements

In Table IV are summarized all the known rate constants for the neutralization of nitroparaffins in light water. Inspection of these data shows that Wynne-Jones' result for nitroethane at 0° is in very good agreement with our value of 39.11. On the other hand, Junell's constants, obtained by a bromination method, are in every case *lower* than those of this paper.

The conductance method measures directly the rate of removal of hydroxyl ions from solution. Since the latter are removed in the reactions under discussion by taking on a proton from the substrate, we conclude that we are measuring directly the rate of proton transfer to hydroxyl ions. In the bromination method, however, the rate of proton transfer is arrived at indirectly through two fundamental assumptions. As used by Junell, the procedure consisted in neutralizing a nitroparaffin with sodium hydroxide up to a certain point, and then suddenly adding a large excess of strongly acid solution of bromine. The assumptions were (1) that the acid would neutralize the alkali and thus stop the reaction, and (2) that the bromine would react very rapidly with the aci acid present. From the quantity of bromine consumed the extent of neutralization at the time of addition of bromine could then be calculated.

Nothing definite can be said about the second of these assumptions. It is known that bromine is absorbed very rapidly by the aci form of a nitroparaffin, but just how rapidly is still an open question. To the first assumption, however, two serious objections can be raised. First, Nef[13] has shown that in the presence of excess mineral acid the aci salts are unstable and decompose to give various products. Secondly, Junell[14] has shown that in the presence of H_3O^+ the anions of the aci-paraffins isomerize rapidly to the nitro-forms.

(13) Nef, *Ann.*, **280**, 263-291 (1894).

(14) Refs. 6b; 6c, p. 79.

He has shown, further, that the reaction anion + acid is subject to general acid catalysis. We may expect that even with a very rapid bromination rate, an appreciable back reaction may set in on addition of a large excess of mineral acid, converting some aci to nitro-form before bromination is completed. The two factors mentioned should operate to give *low* results for the concentration of aci form, and hence for k_2. The error should be especially large with nitromethane, where the rate constant for the back reaction is known to be large, and smaller for the other nitro-paraffins under discussion.

This is actually the case, as may be seen from Table IV. The divergence between the rate constants of this paper and Junell's is 28% for nitromethane, about 10% for nitroethane, and about 7% for nitroisopropane.

It should be mentioned that Junell, in some preliminary experiments, tried out his method on nitroethane and found the error involved in the concentration determinations to be 0.5–4%, depending on the dexterity of operation. The error in the determination of the nitromethane concentrations would then be expected to be even larger, leading to greater error in the constants for nitromethane. These facts substantiate the above analysis of the bromination procedure.

In view of these considerations we consider the results of conductance to be more accurate and reliable than those obtained by the bromination method.

Table V gives a summary and comparison of the kinetic constants obtained in D_2O. The agreement between Wynne-Jones' value at 0° for the first stage and that of this paper is fair, but there is no agreement at all for the second. Wynne-Jones' $k_2 = 36$ is altogether too high in view of the constants measured at both 0 and 5°. For the third stage Wynne-Jones reported a rather unsatisfactory constant varying from 6 to 15. We have found that no satisfactory constants for this stage can be obtained because the $CH_3CD{=}NOO^-$ ion, although stable in the salt, is more sensitive to acid than the corresponding $CH_3CH{=}NOO^-$ ion, and undergoes some decomposition on addition of D_2SO_4. In the light of Nef's[13] work the decomposition product may be expected to be CH_3CDO. A test with 2,4-dinitrophenylhydrazine gave a positive reaction. This finding renders Wynne-Jones' measurement of the third stage too questionable to have any meaning in the calculation of ratio of proton to deuteron transfer.

TABLE V

COMPARISON OF RESULTS FOR NITROETHANE IN D_2O

	Temp., °C.	k_2 Maron and La Mer	k_2 Wynne-Jones
First stage	0	55.6	60
	5	81.33 ± 0.49	..
Second stage	0	20.7	36
	5	29.54 ± .16	..
Third stage	0	No result	6–15

Discussion

The rate of proton donation by a nitroparaffin to a base depends greatly on the nature of the atoms or groups attached to the α-carbon. An inspection of Table IV shows that the rate of neutralization is highest for nitromethane and least for nitroisopropane, *i. e.*, the greater the number of hydrogen atoms attached to the α-carbon the greater the rate of proton donation to a base. As the hydrogens are progressively replaced by alkyl groups, the rate decreases rapidly. Apparently the length of the substituent alkyl group is of relatively minor importance, since the rates of neutralization of nitroethane and *n*-nitropropane are not very different. On the other hand, the number of alkyl substituents is of importance, as is evidenced by the very large decrease in rate constants when two hydrogen atoms are replaced by methyl groups in nitroisopropane.

Qualitatively these observations are in accord with the "inductive effect" ascribed to methyl groups in particular and to alkyl groups in general. An alkyl group is considered to be more "electron repulsive" than a hydrogen atom. Consequently, on replacement of a hydrogen atom by an alkyl group, the carbon to which the attachment is made becomes more negative by induction, and exercises a greater attraction for the proton. This stronger attraction between hydrogen and carbon should be evidenced by a decrease in rate beyond that expected on purely statistical grounds. Such is actually the case. From Table IV it will be observed that the rate inhibiting effect of various alkyl groups is in the order

$$\begin{matrix}CH_3\\CH_3\end{matrix} > > CH_3CH_2 > CH_3 > H$$

This is the sequence found by Kharasch and Flenner[15] for the order of increasing electron repulsive character of alkyl groups, and is also the order

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[15] Kharasch and Flenner, THIS JOURNAL, **54**, 674 (1932).

given by Watson[16] for the relative magnitudes of the "inductive effect."

Again, the inductive influence of halogen, which is electron attractive, should be to increase the rate of prototropic change. This is in accord with Junell's measurements[17] which show that the rates of ionization of brominated nitromethane and nitroethane are faster than those of the corresponding unhalogenated nitroparaffins.

Quantitatively, the velocity constants for the neutralization of nitroisopropane, *n*-nitropropane, nitroethane and nitromethane are in the ratio 1:14:18:114, respectively. These figures are not explicable on purely statistical grounds. Again, the effect of the methyl groups is not additive. Although there is about a six-fold decrease in rate on going from nitromethane to nitroethane, the decrease in rate from nitroethane to nitroisopropane is 18-fold. These variations in rate, outside of statistical considerations, can be ascribed only to differences in force of binding of the hydrogen to the carbon produced from compound to compound by the substitution of alkyl groups.

The heavy water experiments add nothing to the above facts. The ratio of the velocity constants of nitroethane to nitroisopropane in D_2O is the same as in H_2O, 18. These experiments do show, however, that the rate of proton transfer from a nitroparaffin to OD^- in D_2O is *faster* than the rate for the transfer of a proton to OH^- in H_2O. The ratio of velocity constants is essentially constant, being 1.42 and 1.39 for nitroethane at 0 and 5° and 1.36 for nitroisopropane at 5°. Such accelerations in reactions involving OH^- and OD^- ions in the two media have been observed in the saponification of ethyl acetate,[18] the hydrolysis of diacetone alcohol,[19] and the hydrolysis of the monochloroacetate ion.[20] The ratios found there were in the order given 1.33, 1.22 (15°) and 1.2 (45°).

Since the substrates in the examples cited were the same in both H_2O and D_2O, the differences in rate in the two media may be ascribed to solvent effect and to differences in the OH^- and OD^- ions. It is doubtful whether the solvent alone would account for a 40% acceleration in rate observed here. These experiments indicate that the OD^- ion is a stronger base than the OH^- ion, and by virtue of its greater basicity accelerates the rate of proton removal from the substrate.

The ratios of the rates of proton to deuteron transfer could not be determined by the method suggested by Wynne-Jones. Nor do the results for the first and second stages for nitroethane in D_2O support Wynne-Jones' contention that the rate of removal of a proton from $CH_3CH_2NO_2$ is essentially twice that from CH_3CHDNO_2. This factor of two was explained on statistical grounds by the decrease in number of mobile protons present from two to one. His conclusion was based on a value of $k_2 = 36$ for the second stage, a value we believe to be considerably in error. The results of this paper show that the ratio of constants in the first and second neutralization stages is 2.7. There is no evidence for a simple quantitative statistical connection between rate constants and number of prototropic hydrogens in the molecule.

The rate constants reported in Tables II and III can be expressed as functions of the temperature by the equations

(a) Nitroethane in H_2O

$$\log_{10}k = -\frac{2640.5}{T} + 11.261$$

(b) Nitroethane in D_2O, first stage

$$\log_{10}k = -\frac{2513.7}{T} + 10.949$$

(c) Nitroethane in D_2O, second stage

$$\log_{10}k = -\frac{2341.0}{T} + 9.888$$

(d) Nitroisopropane in H_2O

$$\log_{10}k = -\frac{3163.0}{T} + 11.899$$

The units are equivalents per liter and minutes.

Columns (4) and (5) of Table VI summarize the energies of activation and the constant B in the Arrhenius equation: $\log_{10}k = B - (\Delta E^*/2.303RT$. All the reactions proceed with energies of activation somewhat lower than are usually encountered (*ca.* 20,000 cal.). The considerably lower rate for nitroisopropane in H_2O as compared with nitroethane in the same solvent is partially explicable by the difference of 2400 cal. in the energies of activation. The increase in rate of neutralization of nitroethane in D_2O over that in H_2O may be accounted for by the decrease in energy of activation of 600 cal. although this difference would call for a larger increase in rate than has been observed. However, no explanation can be advanced on this basis for the rate observed in the second stage for nitroethane in

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(16) Watson, "Modern Theories of Organic Chemistry," Oxford University Press, New York, 1937, p. 74.

(17) Junell, *Z. physik. Chem.*, **A141**, 71–90 (1929).

(18) Wynne-Jones, *Chem. Rev.*, **17**, 117 (1935).

(19) Hornel and Butler, *J. Chem. Soc.*, 1361–1366 (1936).

(20) Reitz, *Z. physik. Chem.*, **A177**, 85–94 (1936).

TABLE VI

ENERGIES AND ENTROPIES OF ACTIVATION

(1) Substrate	(2) Solvent	(3) Log $\frac{k_{5^\circ}}{k_{0^\circ}}$	(4) ΔE^*, cal.	(5) B min.$^{-1}$	(6) Log k (2.5°)	(7) $\frac{-\Delta E^*}{2.303RT}$	(8) $\frac{\Delta S^*}{2.303R}$	(9) ΔS^*
Nitroethane	H_2O	0.1738	12,100	11.26	1.70	− 9.58	−3.26	−14.99
Nitroethane								
First stage	D_2O	.1655	11,500	10.95	1.83	− 9.12	−3.59	−16.41
Second stage	D_2O	.1541	10,700	9.89	1.40	− 8.49	−4.65	−21.25
Nitroisopropane	H_2O	.2082	14,500	11.90	0.42	−11.48	−2.64	−12.06

D_2O. Although the energy of activation is lower than that for the first stage by about 800 calories the rate observed is also lower, though the exact opposite would be expected. The difficulty can be resolved by ascribing a part of the difference in rates observed to differences in entropy of activation of the reactions in question. The magnitude and variations in the B constant show that the entropy terms are appreciable.

According to the transition state theory of reaction velocity[21]

$$k = \frac{RT}{Nh} e^{-\Delta S^*/R} e^{-\Delta E^*/RT} \qquad (13)$$

or

$$\log_{10}k = \log_{10}\frac{RT}{Nh} + \frac{\Delta S^*}{2.303R} - \frac{\Delta E^*}{2.303RT} \qquad (14)$$

where R/N and h are the Boltzmann and Planck constants, respectively, and ΔS^* is the entropy of activation for all degrees of freedom.[22] By comparison with the Arrhenius equation

$$B = \log_{10}\frac{RT}{Nh} + \frac{\Delta S^*}{2.303R} \qquad (15)$$

Since ΔE^* was taken as constant for 0 and 5° in the calculation of B, ΔS^* values were calculated for the average temperature of 2.5°. At this temperature ΔS^* is given by

$$\frac{\Delta S^*}{2.303R} = B - \log_{10}\frac{RT}{Nh} = B - 14.54 \qquad (16)$$

when the time is expressed in minutes. The values are tabulated in columns (8) and (9) of Table VI, and show large negative values for the entropy of activation.

Columns (7) and (8) give the activation energy and activation entropy contributions to the logarithm of the velocity constant at 2.5° shown in column (6). The entropy contributions are in every case large fractions of the energy contributions. Comparison of nitroethane and nitroisopropane in H_2O shows that the decrease in rate observed for nitroisopropane is due primarily to increase in activation energy,[23] although an increase in the activation entropy of about three units mitigates the decrease in rate constants. On the other hand, the increase in rate in D_2O over that in H_2O for nitroethane is due to the fact that although the entropy decreases, the simultaneous decrease in the energy of activation outweighs the effect of the entropy, thus leading to a higher rate of reaction. For the second stage, however, just the reverse is true. Here the decrease in entropy of activation outweighs considerably the decrease in the activation energy, and consequently the rate constants *decrease* although from a consideration of activation energies alone they should increase.

Summary

1. The rates of neutralization of nitromethane, nitroethane, and nitroisopropane by OH^- ion in H_2O and by OD^- ion in D_2O have been studied by a conductance method. Measurements are given for nitromethane at 0° in H_2O and for nitroethane and nitroisopropane at 0 and 5° in both H_2O and D_2O.

2. The rate constants for these prototropic reactions in H_2O decrease as we pass from nitromethane to nitroethane, to nitroisopropane. A qualitative explanation of this change in rate with substitution is given in terms of the "inductive effect" of alkyl groups.

3. The rates for nitroethane and nitroisopropane are 40% faster in D_2O than in H_2O at the same temperature.

4. The results of this paper have been compared with previous measurements in the light of

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[21] Wynne-Jones and Eyring, *J. Chem. Phys.*, **3**, 492 (1935); Eyring, *Chem. Rev.*, **17**, 65 (1935).

[22] La Mer and Liotta, THIS JOURNAL, **60**, 1967 (1938); La Mer, *J. Franklin Inst.*, **225**, 709 (1938). See p. 729 for a more detailed discussion of difference between the entropy of activation as defined by Eyring (ΔS^*) and as defined by La Mer ($\Delta S_{\text{act.}}$) in *J. Chem. Phys.*, **1**, 289 (1933).

[23] By the term "increase in activation entropy" on passing from nitroethane to nitroisopropane we refer to the algebraic increase in the entropy of the activation process: $S^* = -15$ to 12 E. U. respectively. This means that the latter complex is more probable, *i. e.*, more states, in the statistical sense, exist for the isopropane than for the ethane complex. On the other hand the energy differences for the activation process represented by $\Delta E^*/2.3RT$ are higher for the former, namely, 11.48 and 9.58. Hence the rate of reaction is slower for nitroisopropane.

the methods employed. A critical discussion of the bromination method is given, and certain errors pointed out.

5. Wynne-Jones' attempt to determine the ratio of proton to deuteron transfer by progressive exchange of H for D in nitroparaffins is inapplicable to nitroethane and nitroisopropane because of the instability of the substrate at certain stages in the process.

6. Equations for rate constants as functions of temperature are given, and energies and entropies of activation calculated. It is shown that the differences in rates observed cannot be explained in terms of changes in the activation energy alone; the differences in the observed rates are caused by an interplay of variations in both energy and entropy of activation.

NEW YORK, N. Y. RECEIVED JULY 23, 1938

[CONTRIBUTION NO. 362 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Reactions of Trialkyl Phosphates, Alkyl Acetates, and Tertiary Butyl Hypochlorite in the Friedel–Crafts Syntheses[1]

BY NATHAN BERMAN AND ALEXANDER LOWY

The synthesis of alkylated substances by means of the Friedel–Crafts reaction has been extended widely from the original use of alkyl chlorides with aromatic hydrocarbons. An important advance in the alkylation reaction was the application of esters to the synthesis. Among the esters used were: alkyl borates, alkyl acetates, alkyl formates, *n*-butyl oxalate, tetraethyl silicate, and diethyl carbonate. The trialkyl phosphates gave phenol ethers with phenol.

The purpose of this investigation was to observe whether the use of esters might be extended to the alkyl esters of phosphoric acid, acetic acid, and tertiary butyl hypochlorite. These substances proved to be efficient alkylating agents. The conditions which influenced the yield of alkylated benzenes were observed, such as concentration of reagents, duration of heating, and reaction time.

Experimental

The apparatus employed for the alkylations was the usual one-liter three-necked Pyrex flask, into one neck of which extended a dropping funnel and thermometer. The central neck was fitted with a glass stopper and mercury seal, through which extended a motor-driven glass stirrer. The third neck was connected to a modified Hopkins-type reflux condenser. Fractionations were conducted with a seventeen-inch (43-cm.) Vigreux column, which was wrapped in asbestos paper.

The aluminum chloride used throughout was of 99.5% purity. The benzene was dried over sodium and distilled at 80–81°. The various esters were purified by distillation or by vacuum distillation before use.

Typical Experiment. Triethyl Phosphate.—Benzene (435 g.) was stirred with 68.5 g. (0.515 mole) of aluminum chloride in the Pyrex flask, surrounded by an ice-water bath; 25 g. (0.137 mole) of triethyl phosphate was added dropwise through a separatory funnel over a two-hour period. The mixture was then stirred for eight hours at room temperature (20–25°). Throughout this time there was a vigorous evolution of hydrogen chloride. The mixture was poured over cracked ice and allowed to hydrolyze overnight. The benzene layer was washed with aqueous sodium bicarbonate and water, dried over calcium chloride, filtered, and fractionally distilled. There was obtained 27 g. of ethylbenzene boiling at 134–137°; n^{20}_D 1.4951. There was also obtained 8 g. of a higher boiling fraction.

Preparation of Triisopropyl Phosphate.—The procedure analogous to that described in "Organic Syntheses" for the preparation of *n*-butyl phosphate[2] was followed. In the four-necked flask fitted with (a) a mercury-sealed stirrer, (b) a Hopkins-Cole type condenser, (c) a thermometer, and (d) a separatory funnel, there was mixed three moles (180 g.) of isopropyl alcohol with 3.3 moles of pyridine and 275 ml. of benzene as solvent. This mixture was stirred and cooled in an ice-salt bath to −5°. Through the separatory funnel, 153 g. of phosphorus oxychloride was added dropwise over six hours at such a rate that the temperature never exceeded 10°. The mixture was refluxed for two hours at 80°; 500 ml. of water was added to dissolve the pyridine hydrochloride; the benzene layer was washed with 100 ml. of water and dried over anhydrous sodium sulfate. On vacuum distillation, 100 g. of triisopropyl phosphate was collected, which represents a 44.7% yield. Its boiling point was 122–125°, at 15–16 mm. pressure.

The accompanying Table I gives the results of the experiments conducted with the various esters as alkylating agents. The experimental procedure was analogous to that followed in the experiment with triethyl phosphate, except as indicated below.

I. Alkylating agent = triethyl phosphate (b. p. 96–101° at 3–5 mm.). Product = ethylbenzene (b. p. 134–137°; n^{20}_D 1.4951).

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[1] Abstracted from a thesis presented by Nathan Berman to the Graduate School in partial fulfilment of the requirements for the Ph.D. degree.

[2] *Org. Syntheses*, **16**, pp. 9–12 (1936).

II. Alkylating agent = triisopropyl phosphate. Product = isopropylbenzene (b. p. 151–154°; $n^{20}D$ 1.4917; d 0.859 (20°)).

III. Alkylating agent = tributyl phosphate (b. p. 157–160° at 4 mm.). Product = *s*-butylbenzene (b. p. 171–175°; $n^{20}D$ 1.4884).

IV. Alkylating agent = isopropyl acetate. Product = isopropylbenzene.

V. Alkylating agent = *s*-butyl acetate. Product = *s*-butylbenzene (b. p. 173–177°; $n^{20}D$ 1.4889).

VI. Alkylating agent = methylamyl acetate (b. p. 143–146°). Product = isohexylbenzene.

VII. Alkylating agent = tertiary butyl hypochlorite. Product = *t*-butylbenzene (b. p. 165–170°; $n^{20}D$ 1.4963).

TABLE I

Expt.	Alkylating agent		$AlCl_3$		Temp., °C.	Time, hrs.	Alkylated benzene		High boiler g.
	G.	Mole	G.	Mole			G.	%	
I-A	50	0.274	130	0.977	20–25	28	24	27.5	15
I-B	25	.137	68.5	.515	20–25	10	27	61.5	8
II	25	.112	48.9	.368	10–15	4	21	52.1	8
					20–25	20			
III	25	.094	46.9	.353	20–25	2	27	71.5	4
					80	14			
IV-A	50	.49	71.7	.538	80	1	8	13.6	3.5
					20–25	9			
IV-B	50	.49	71.7	.538	80	20	6	10.2	3
IV-C	25	.245	71.7	.538	20–25	23	17	57.8	6
V-A	50	.431	126	.945	80	10	9	15.6	19
V-B	50	.431	36	.472	80	20	31	53.7	7
V-C	50	.431	4.7	.0428	80	10	None		..
VI-A	50	.347	102	.765	80	10	None[a]		..
VI-B	50	.347	25.5	.191	80	10	None[a]		..
VI-C	50	.347	51	.383	80	10	27[b]	48.0	9
VI-D	25	.174	25.5	.191	80	10	17[c]	60.4	4
VII-A	30	.277	33.7	.253	20–25	25	16	43.1	6
VII-B	25	.231	None		15	3	None		..
					80	48			

[a] No mercury. [b] Amount of mercury unknown. [c] 10 g. of mercury.

In the experiments conducted with *s*-butyl acetate, the 19-g. high boiling fraction (experiment V-A) showed the usual effect of a high concentration of aluminum chloride. The molar ratio of aluminum chloride to ester of approximately one to one (experiment V-B) was more favorable to the production of *s*-butylbenzene. Experiment V-C showed that the relatively small amount of aluminum chloride did not promote the reaction, from which it was assumed that the aluminum chloride plays an integral part in the reaction, and its role is not purely catalytic.

The formula given to methyl amyl acetate by the Carbon and Carbide Co. was: $CH_3COOCH(CH_3)CH_2CH(CH_3)_2$(2,4-dimethylbutyl acetate). It has been established that under the conditions of the experiments mercury is a necessary catalyst for the alkylation of benzene with methyl amyl acetate. The physical constants of the alkylated benzene were: b. p. 195–200°; $n^{15}D$ 1.4930; d = 0.866 (15°), which corresponds with β-methyl-δ-phenylpentane (b. p. 197°; $n^{15}D$ 1.4876; d 0.863 (15°)).

t-Butyl hypochlorite was supplied by the Pennsylvania Salt Manufacturing Co. The question was considered as to whether it would condense the alkyl or alkoxy group on to benzene. Under the conditions of experiment VII-B, aluminum chloride was found to be a necessary catalyst for the alkylation of benzene by tertiary butyl hypochlorite. Since no ether but *t*-butylbenzene was obtained exclusively, it was apparent that the alkyl–oxygen bond in the hypochlorite was split in the reaction.

Aluminum Chloride with Isopropyl Acetate.—For the elucidation of the mechanism of these syntheses, it is important to determine the behavior of the esters when treated with aluminum chloride. In the following experiment an attempt was made to isolate any isopropyl chloride which might be evolved in the reaction of isopropyl acetate with aluminum chloride. Twenty-five grams of isopropyl acetate was added dropwise to 71.8 g. of aluminum chloride at 15° in the reaction flask. The mixture was stirred for five and one-half hours at 15° and then for two hours at 50°. Some reaction was apparent due to the mixture becoming thick and dark with an evolution of hydrogen chloride. No isopropyl chloride (b. p. 39°) was obtained.

Under the conditions of the experiment, any alkyl halide which might be formed could react further at once and hence was not isolated.

Summary

1. It has been shown that the trialkylphosphates (ethyl, isopropyl and butyl), the alkyl acetates (isopropyl, *s*-butyl, and methyl amyl) and *t*-butyl hypochlorite will condense with benzene in the presence of aluminum chloride to give the corresponding alkylated benzene. These reactions may be summarized by the equations

$$(RO)_3PO + 3C_6H_6 + AlCl_3 \longrightarrow 3RC_6H_5 + AlPO_4 + 3HCl$$

$$CH_3COOR + C_6H_6 + AlCl_3 \longrightarrow RC_6H_5 + HCl + CH_3COOAlCl_2$$[3]

$$t\text{-}C_4H_9OCl + C_6H_6 + (AlCl_3) \longrightarrow t\text{-}C_4H_9C_6H_5 + HOCl$$

2. The preparation of triisopropyl phosphate has been described.

PITTSBURGH, PENNA. RECEIVED JULY 27, 1938

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(3) Groggins, *Ind. Eng. Chem.*, **23**, 152 (1931).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Hexamethylethane and Tetraalkylmethanes

BY RUSSELL E. MARKER AND THOMAS S. OAKWOOD

Because of the difficulty of preparing hexamethylethane and other tetraalkyl substituted methanes in quantity by following the methods given in the recent literature,[1] a practical method has been developed whereby a tertiary halide may be condensed with an alkylmagnesium halide giving yields of 11 to 20% of the desired hydrocarbon. This condensation has been brought about by the addition of cuprous iodide to a mixture of the straight chain Grignard reagent and a tertiary halide. This method also may be applied to the condensation of a branched chain Grignard reagent with a tertiary halide as shown in the case of hexamethylethane, obtaining a yield of better than 16% in a preparation of 1120 g.

Two series of hydrocarbons were prepared, the 2,2-dimethyl compounds from tertiary butyl chloride and RMgBr, and the 3,3-dimethyl compounds from tertiary amyl chloride and RMgBr. If the physical properties of each of these two series of hydrocarbons are arranged in order of increasing molecular weights, not only is there a regular increase in boiling points, but the refractive indices and densities exhibit the same regular increase in value for each series of similar hydrocarbons. The results obtained are summarized in Table I.

TABLE I

	Yield, %	B. p. (760 mm.) °C.	$n^{20}D$	d^{20}_4
2,2-Dimethylbutane	11	49.6	1.3709	0.6491
2,2-Dimethylpentane	21	79.0	1.3825	.6739
2,2-Dimethylhexane	14	106.2	1.3942	.6934
2,2-Dimethylheptane	17	130.4	1.4035	.7105
3,3-Dimethylpentane	22	86.0	1.3911	.6937
3,3-Dimethylhexane	17	112.0	1.4008	.7107
3,3-Dimethylheptane	16	137.2	1.4087	.7254
3,3-Dimethyloctane	11	161.2	1.4165	.7390

Experimental

As the preparations of the hydrocarbons were essentially the same, the details will be given only for 2,2-dimethylbutane and hexamethylethane. The remainder were made by the condensation of the suitable straight chain alkylmagnesium bromide with tertiary butyl chloride or tertiary amyl chloride in the presence of cuprous iodide. Their properties and yields from ten mole runs of Grignard reagents are given in the table.

2,2-Dimethylbutane.—The Grignard reagent was made from 144 g. of magnesium with 1200 cc. of dry ether and 654 g. of ethyl bromide. The flask was cooled in ice and 400 g. of tertiary butyl chloride added with stirring. This was followed by 20 g. of cuprous iodide. The mixture stood overnight, during which time it solidified to a hard cake. This was decomposed by water and dilute acid. The ether extract was dried over solid potassium carbonate and fractionated. The crude hydrocarbon was shaken twice with cold concentrated sulfuric acid, followed by water, then sodium carbonate solution and finally dried over sodium sulfate. It was then refluxed for six hours with sodium–potassium alloy and again treated with sulfuric acid.

Hexamethylethane.—To 6 moles of tertiary butylmagnesium chloride in 2 liters of dry ether with rapid stirring was added a mixture of one-half mole of tertiary butyl iodide and five and one-half moles of tertiary butyl chloride. Much gas came off. Twenty grams of cuprous chloride was then added in 2-g. quantities. The reaction mixture heated up considerably, giving off gas and soon formed a hard cake. After standing overnight it was heated on a steam-bath until no more ether distilled. Dilute acid was then dropped slowly into the flask, the ether and hydrocarbon distilling off during decomposition. After the solid had dissolved, the residue was steam distilled. The hydrocarbons then were separated roughly by distillation, obtaining a product boiling at 104–106°. This crystallized in the receiver. This product was then crystallized from ether at −50° and redistilled from sodium taking a fraction boiling at 105–106° at 735 mm. This product although not of extreme purity melted above 99° and the crystals were dry; yield, 1120 g. from 60 moles of *t*-butylmagnesium chloride.

Summary

A practical method is given for the preparation of hexamethylethane and other hydrocarbons containing a tertiary group by condensation of an alkyl Grignard reagent with a tertiary halide by means of cuprous iodide.

STATE COLLEGE, PENNA.

RECEIVED JULY 25, 1938

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[1] Flood and Calingaert, THIS JOURNAL, **56**, 1211 (1934); Whitmore, Stehman and Herndon, *ibid.*, **55**, 3805 (1933); C. R. Noller, *ibid.*, **51**, 594 (1929).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Chemical Studies of Certain Pathogenic Fungi. I. The Lipids of *Blastomyces dermatiditis*[1]

BY ROBERT L. PECK AND CHARLES R. HAUSER

This series of investigations has been undertaken with the purpose of studying the constituents of certain pathogenic fungi with the hope that more light may be thrown on the chemical nature of the factors responsible for their pathogenicity. Data on nonpathogenic fungi are available to afford comparisons.

In this paper are presented the results obtained from a study of the lipid fraction of *Blastomyces dermatiditis*. No previous chemical study of the lipid fraction of *Blastomyces dermatiditis* in the yeast-like form could be found in the literature. The present investigation is concerned with the isolation and identification of the constituents of the lipids extracted from this organism by a mixture of alcohol and ether and by chloroform. The isolation and purification of the fractions were in general carried out according to the methods developed by Anderson.[2] In all operations involving unsaturated lipids, an atmosphere of nitrogen or carbon dioxide was maintained as far as possible. All solvents were purified and freshly distilled before use. During extractions and concentrations special precautions were taken in order to avoid contamination of the fungus lipids with extraneous fatty materials.

In Table I are given the percentages of lipids extracted from the cells. Table II gives the proportions of the phosphatide and the acetone-soluble fractions. In order to form an idea as to the precision of our methods of extraction and estimation, two small batches of organisms were grown and extracted for one month with a mixture of alcohol and ether. The extracts and washings were worked up as described in the experimental part. The results are given in Tables I and II, batches III and IV. These results indicate that the methods of extraction and of separation of the phosphatide and acetone-soluble fractions are reproducible within about five per cent.

TABLE I

PERCENTAGES OF LIPIDS EXTRACTED FROM *Blastomyces dermatiditis*

Batch and wt., g.		Lipids extracted Alc.-ether	CHCl$_3$	Total
I	Grams	81.7	4.6	86.3
818.5[a]	Extd., %[b]	9.0	0.5	9.5
II	Grams	18.8	1.6	20.4
209.0[a]	Extd., %[b]	8.2	0.7	8.9
III	Grams	6.1		6.1
62.7[a]	Extd., %[b]	8.9		8.9
IV	Grams	5.6		5.6
60.4[a]	Extd., %[b]	8.5		8.5

[a] Weight of extracted cells after drying *in vacuo*. [b] Per cent. of weight of dried extracted cells plus weight of total extracted lipids.

TABLE II

PROPORTIONS OF THE PHOSPHATIDE AND ACETONE-SOLUBLE FRACTIONS OF *Blastomyces dermatiditis*

Batch		Phosphatide	Acetone soluble
I	Grams	21.0	65.3
	% of whole cell[a]	2.3	7.2
	% of lipids[b]	24.3	75.7
II	Grams	1.7	18.8
	% of whole cell[a]	0.7	8.2
	% of lipids[b]	8.2	91.8
III	Grams	2.1	4.0
	% of whole cell[a]	3.0	5.9
	% of lipids[b]	34.1	65.9
IV	Grams	1.9	3.7
	% of whole cell[a]	2.9	5.6
	% of lipids[b]	34.3	65.7

[a] The whole cell weight is assumed as that of the dried extracted cells plus extracted lipids.

[b] The lipids are the ether-soluble lipids extracted as in our experiments.

Batch I was grown on a medium[3] containing a small amount of blood. Batches II, III, and IV were grown on the same medium without blood. It can be seen from Table II that the composition of the lipids of batch I is essentially the same as that of batches III and IV; hence it would appear that the presence of blood in the medium does not greatly influence the lipid composition.

Batch II was left for two weeks in a preliminary killing solution of 1% aqueous phenol before ex-

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(1) *Blastomyces dermatiditis* [Gilchrist and Stokes (1898)] a yeast-like organism when grown at 37°, is the etiological agent of the human disease, blastomycosis. The disease may be either a skin infection or a fatal generalized condition. See Martin and Smith, *Am. Rev. T. B.*, in press.

(2) Anderson, *J. Biol. Chem.*, **74**, 525 (1927), and later papers.

(3) This medium was developed by Dr. Wm. H. Kelly of the Department of Medicine, Duke University. It consists of 10 g. of dextrose, 10 g. of peptone, 15 g. of agar-agar, 3 g. of beef extract, 0.5 g. of sodium chloride, and 1000 g. of distilled water. To this is added 20 cc. of laked blood (one part blood to three parts distilled water).

traction of the lipids, whereas the other batches were placed in alcohol and ether immediately after removal from the culture. It is evident from Table II that immediate extraction of the living organisms with alcohol and ether yields much more phosphatide than similar extraction of the organisms after allowing them to stand with aqueous phenol. It should be observed, however, that the total fat remains about the same in the two methods.

In Table III the data on the phosphatide fraction are presented. It can be seen that, although grown and extracted under somewhat different conditions, batches I and II yielded phosphatides of essentially the same composition. The phosphatide fraction is presumably a mixture containing substances resembling lecithin and cephalin. The nitrogen–phosphorus ratio is 1:1. On hydrolysis with aqueous sulfuric acid, glycerophosphoric acid, choline, ethanolamine and fatty acids were obtained. The first three compounds were isolated and identified. Evidence has been obtained which indicates that the following fatty acids were present: palmitic, stearic, oleic, and linoleic acids. It should be mentioned also that a small amount of carbohydrate was obtained on saponification of the phosphatide.

Tables IV and V give the data on the acetone-soluble fats. The acetone-soluble fraction obtained from batch I was qualitatively the same as from batch II, but certain quantitative differences appear; these are probably due to the differences in treatment of the cells before extraction. The acetone-soluble fraction appears to be a mixture containing free fatty acids and sterols. On saponification it gave glycerol, ergosterol, and palmitic, oleic and linoleic acids. These compounds were isolated and identified. Stearic acid was probably also present.

TABLE III

PERCENTAGE COMPOSITION OF PHOSPHATIDE FRACTIONS

	Blastomyces dermatiditis Batch I	*Blastomyces dermatiditis* Batch II	Tubercle bacilli[a]
Water soluble	32	32	34
Ether soluble	68	68	64.2
Unsaponifiable	3	3	1.8
Total fatty acids	65	65	62.4
Solid acids	12.4		30.5
Liquid acids	52.6 (iodine no., 96)		33.7 (iodine no., 30)
Liquid satd. acids	0		20.9
Palmitic acid	8.2[b]		30.5
Stearic acid	4.2[b]		Very small amount
Oleic acid	49.1[c]		12.8
Linoleic acid	3.5[c]		0 (?)
Carbohydrates	Present	Present	30.4
Glycerophosphoric acid	3.1	Present	5.4
Choline	Present	Present	Absent
Ethanolamine	Present	Present	Absent
Nitrogen	1.78	1.71	0.4
Phosphorus	3.89	3.61	2.3
Nitrogen–phosphorus ratio	1:1	1:1	2:5

[a] See ref. 4. [b] Calculated on assumption that solid acids were mixture of palmitic and stearic acids. [c] Calculated from iodine number (96) and weight of liquid acids.

TABLE IV

CONSTANTS[a] OF ACETONE-SOLUBLE FAT

	Blastomyces dermatiditis Batch I	*Blastomyces dermatiditis* Batch II	Tubercle bacilli[b]
Iodine number	106.1	101.2	52.6
Melting point	Oil	Oil	33°C.
Acid value	45.3	60.3	60.3
Saponification value	191.5	170.0	203.6
Ester value	146.2	109.7	143.2
Reichert–Meissl value	2.7		3.9

[a] These constants with the exception of iodine number and melting point were determined in the case of *Blastomyces dermatiditis* according to Assoc. Official Agr. Chem. "Methods of Analysis," Washington, D. C., 1936, 4th ed.
[b] See Anderson, *Physiol. Rev.*, **12**, 166 (1932).

TABLE V

PERCENTAGE COMPOSITION OF THE ACETONE-SOLUBLE FATS

	Blastomyces dermatiditis Batch I	*Blastomyces dermatiditis* Batch II	Tubercle bacilli[c]
Unsaponifiable matter	8.0	15.4	10.3
Water soluble	4.0	4.8	6.3
Fatty acids	88.0	79.8	83.3
Solid acids (satd.)	14.5	11.9	30.3
Liquid acids	73.5	67.9	50.6
Iodine no.	116	126	31
Liquid saturated acids	0	0	38.0
Oleic acid[a]	55.0	37.7	10.6
Linoleic acid[a]	18.5	30.2	?
Palmitic acid[b]	9.7		30.3
Stearic acid[b]	4.8		Traces
Sterols[d]	4	6	0

[a] Calculated from the weight and iodine number of the unsaturated acid. [b] Calculated from weight and mean molecular weight of the saturated acids. [c] See ref. 4. [d] Colorimetric analysis.

In a later paper the lipids of *Blastomyces dermatiditis*, together with those of another pathogenic fungus, *Monilia albicans*, will be compared with the lipids of certain non-pathogenic fungi.

In this paper it seemed of interest to compare the lipids of *Blastomyces dermatiditis* with those of the tubercle bacillus,[4] since the clinical picture of the disease caused by the fungus resembles in certain respects that caused by the bacillus,

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(4) R. J. Anderson, *Physiol. Rev.*, **12**, 166 (1932).

Data on the lipids of both organisms are listed in Tables III, IV and V.

It can be seen from Tables III and V that, while the lipids of *Blastomyces dermatiditis* and of tubercle bacilli have a number of similarities, certain striking differences appear. In the fungus are found a higher percentage of unsaturated acids and a lower percentage of saturated acids than are found in the tubercle bacillus, but, more significant, the latter organism contains a considerable amount of liquid saturated fatty acid, which appears to be entirely absent in the fungus. The phosphatide of the fungus (Table III) contains two nitrogenous constituents which apparently are not found in the tubercle bacillus, and the nitrogen–phosphorus ratio is different in the two organisms. Sterols (ergosterol) are present in the acetone-soluble fraction of the fungus (Table V) but this constituent apparently is not found in the tubercle bacillus. It is of interest that carbohydrates are present in the phosphatides of both organisms.

Experimental

Materials.—The culture medium was prepared from bacto-peptone, bacto-dextrose, and agar–agar purchased from Difco Laboratories, Detroit, Michigan, and beef extract from Armour and Company, reagent quality sodium chloride, and distilled water. In the media for batch I, laked sheep blood (one part blood to three parts distilled water) was used; no blood was in the media for batches II, III and IV. The medium was placed in liter prescription bottles which were then plugged with cotton and gauze and sterilized. The cultures were always checked for contamination; only pure cultures were used for the experiments.

Ether was dried over sodium; acetone and chloroform were dried over drierite. These were freshly distilled before use. Alcohol was freshly distilled from potassium hydroxide.

Growth and Extraction.—A virulent strain of *Blastomyces dermatiditis* (Strain F-2) was grown[5] for seven days on the solid media at 37° in the dark. The organisms (in the case of batches I, III, and IV) were washed from the media with 95% alcohol, collected in 5-gallon (19 liters) bottles, an equal volume of ether was added and the bottles were stoppered with corks covered with tin-foil and stored for one month at room temperature in the dark. They were shaken occasionally with a rotary motion. Control experiments have shown that no appreciable amounts of lipids were extracted from the media or the stoppers under the conditions used in this work. The cells were filtered off, washed with alcohol and ether, and reëxtracted for two weeks with a mixture of equal parts of alcohol and ether. After filtration and washing, the cells finally were extracted with chloroform for one month. The cells were filtered off, washed with chloroform, and dried *in vacuo* giving a cream-colored powder.

Batch II was washed from the culture with aqueous 1% phenol and allowed to stand under this solution for two weeks. The cells were then filtered off and placed in a mixture of equal volume of alcohol and ether. The procedure from this point was the same as in the extraction of the other batches.

Concentration of Extracts.—The alcohol–ether extracts and washings were concentrated under reduced pressure in an all-glass apparatus to a small volume. The resulting aqueous emulsion was thoroughly extracted with ether. The residual aqueous solution was treated as described in the next section. The ether extract, after drying over sodium sulfate, yielded on evaporation a clear red-brown oil (batch I, 81.7 g.; batch II, 18.9 g.). White crystals (batch I, 2.12 g.) appeared in this oil on standing overnight. These were separated and identified as ergosterol as described below.

The chloroform extract and washings, on concentration under reduced pressure, yielded a dark brown oil (batch I, 4.6 g.; batch II, 1.6 g.). This was similar to the alcohol–ether soluble material and was therefore combined with it.

The Residual Aqueous Solution.—The aqueous solution, remaining after the ether extraction of the lipids described in the previous section, was concentrated to small volume and treated with two volumes of 95% alcohol. A crude polysaccharide (batch I, 1.5 g.) was precipitated. The purified polysaccharide possessed biological activity and will be reported at another time. From the sirup obtained by concentrating the supernatant solution and washings, mannitol (batch I, 1.0 g.) melting at 164–165° was obtained. This was proved by the mixed melting point method, and by the preparation of the hexaacetate, melting at 121°, and of mannitol tribenzal[6] melting at 218–220°.

Separation of the Phosphatide and Acetone-Soluble Fractions.—On addition of acetone to the brown oil which formed the combined lipids, the phosphatide separated as a sticky brown residue on the bottom of the flask. This fraction was purified by repeated precipitation from ether solution by means of acetone. The phosphatide (batch I, 19.5 g., batch II, 1.5 g.) was a buff-colored hygroscopic powder. The acetone solutions and washing from the separation and purification of the phosphatide (about four liters) were concentrated under reduced pressure to a volume of approximately 300 cc. To this solution was added a small amount of saturated alcoholic strontium chloride. After standing overnight in the refrigerator, a further small amount of phosphatide had separated (batch I, 1.5 g., batch II, 0.2 g.).

The supernatant solution and washings from the separation of the phosphatide fraction yielded on concentration a clear red oil (batch I, 65.3 g., batch II, 18.8 g.). It contained only traces of phosphorus and nitrogen. This fraction was designated the acetone-soluble fat.

The Phosphatide Fraction.—The phosphatide, obtained as a pale buff-colored powder, softened at 100°, was fully liquid at 125°, and began to decompose at about 130°. It formed emulsions with water. The phosphorus–nitrogen ratio was 1–1.

Micro-Anal. Found: P, 3.89; N, 1.78.

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[5] The organisms were grown in the laboratories of the Department of Medicine, Duke University, by one of us (R. L. P.).

[6] Preus, Peterson and Fred, *J. Biol. Chem.*, **97**, 483 (1932).

Hydrolysis was carried out by refluxing the phosphatide with 5% aqueous sulfuric acid for eight hours. After extraction of the fatty acids with ether, the water solution was freed quantitatively from sulfuric acid with barium hydroxide. The water-soluble constituents were separated essentially as described by Newman and Anderson[7] and by Peterson and co-workers.[8] Barium glycerophosphate was isolated as a white powder and was purified by means of its lead salt. This was decomposed with hydrogen sulfide, reconverted to the barium salt and dried in air.

Micro-Anal. Calcd. for $C_3H_7O_6PBa \cdot 2H_2O$: Ba, 39.99; P, 9.03. Found: Ba, 39.48; P, 8.91.

Choline was isolated as the chloroplatinate, melting point 235–236° with decomposition.

Micro-Anal. Calcd. for $(C_5H_{14}ON)_2PtCl_6$: Pt, 31.68. Found: Pt, 31.57.

Ethanolamine was isolated as the picrolonate, melting point 224–226° with decomposition.

Micro-Anal. Calcd. for $C_{12}H_{15}O_6N_5$: N, 21.55. Found: N, 21.30.

The residual sirup from the water-soluble fraction gave a positive acrolein test and a positive Molisch test. A small amount of a sticky residue appeared on the walls of the flask when a sample of the phosphatide was hydrolyzed with alcoholic potassium hydroxide. This was soluble in water and gave a positive Molisch test for carbohydrate. The small amount of this substance obtained has prevented further study at present.

The fatty acids made up 65% of the phosphatide. They were separated in the case of batch I by means of the lead salt treatment into 12.4% solid and 52.6% liquid acids. The solid acids were a white crystalline mass melting at 54–55° and having a mean molecular weight of 266. On the assumption that the mixture of solid acids consisted only of palmitic and stearic acids, the relative proportions of each may be calculated from the neutral equivalent and the weight of the mixed acids. This would indicate a mixture composed of about two-thirds palmitic and one-third stearic acid. A sample of the liquid acids was reduced with hydrogen and platinum oxide.[9] On treatment of the reduced acids by the lead salt method, a very small amount of liquid acid was obtained, but this was shown to be unsaturated. No liquid saturated acids were found. The solid reduced acid, crystallized once from alcohol, was a white crystalline mass, melting at 70–71°. Admixture with pure stearic acid (m. p. 70–71°) did not lower the melting point. The neutral equivalent was 284.8. This shows that the reduced acid was stearic acid (neut. equiv. 284.3).

Micro-Anal. Calcd. for $C_{18}H_{36}O_2$: C, 75.95; H, 12.76. Found: C, 76.14; H, 12.79.

On bromination of the unsaturated acids only a trace of petroleum ether insoluble acids was obtained. The main product was a brown oil, probably dibromostearic acid.

Micro-Anal. Calcd. for $C_{18}H_{34}Br_2O_2$: Br, 36.15. Found: Br, 37.20.

The iodine number (96) and the amount of stearic acid isolated on reduction indicate that the liquid acids consisted mainly of oleic acid with a small amount of linoleic acid.

Analysis of the Acetone Soluble Fat.—This fraction was a red-brown oil containing only traces of phosphorus and nitrogen. It possessed a peculiar musty smell. Some of its constants are given in Table III.

The oil (batch I, 33.7 g.; batch II, 15.1 g.) was saponified by refluxing with 4% alcoholic potassium hydroxide for eight hours. After most of the alcohol was distilled off, the soap solution was diluted with water and the unsaponifiable material thoroughly extracted with ether. The remaining solution was resaponified for three hours and again extracted with ether. The soap solution was then acidified with hydrochloric acid and the crude fatty acids were extracted with ether. The aqueous acid solution was concentrated to dryness under reduced pressure and extracted with alcohol–ether solution (1:1). This extract was concentrated to a sirup. The sirup was extracted with warm absolute alcohol. The alcohol extract was evaporated, yielding a pale brown sirup. The sirup, which was evidently crude glycerol, gave a positive acrolein test. A sample was benzoylated, giving a very small yield of a crystalline derivative melting at 75–76°. This melting point was not lowered by admixture with glycerol tribenzoate (m. p. 76°). The presence of glycerol is thus established.

The unsaponifiable material was a brown semi-solid mass (batch I, 8%; batch II, 15.4% of the acetone-soluble fat). Since a colorimetric determination indicated that about one-half of this unsaponifiable material consisted of sterols, it was recrystallized from a mixture of alcohol and benzene (2:1). The white crystals obtained melted at 158–160° and were identified as ergosterol by the mixed melting point method and by conversion to the acetate. The latter melted at 169–171° and when mixed with the acetate from authentic ergosterol showed no depression. The ergosterol mentioned under the heading "Concentration of Extracts" was identified in the same manner.

The fatty acids were separated by the lead salt method into solid and liquid acids. The crude solid acids melted at 55–56° and gave a neutral equivalent of 266. They were thus similar to the crude solid acids of the phosphatide fraction. The methyl esters of a portion of the solid acids were prepared and fractionally distilled under 0.5 mm. pressure. The top fraction was saponified and the free acid was isolated. After repeated crystallization from methyl alcohol and acetone, an acid melting at 62–63° was isolated. This was proved to be palmitic acid by the mixed melting point method and by analysis.

Micro-Anal. Calcd. for $C_{16}H_{32}O_2$: C, 74.91; H, 12.58. Found: C, 75.27; H, 12.59.

A sample (2.408 g.) of the liquid acids in alcohol solution was reduced catalytically with hydrogen and platinum oxide. The reduced acids, a semi-crystalline buff-colored mass, were separated by means of the lead salt treatment into a main fraction of white crystals and a very small amount of liquid acid. The recovery was 95% (2.291 g.). Since the small amount of liquid acid was shown to be unsaturated, it appears that no liquid saturated acids were present. The solid crystalline acid melted at 69.5–70.5°

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[7] Newman and Anderson, *J. Biol. Chem.*, **102**, 229 (1933).

[8] Woolley, Strong, Peterson and Prill, THIS JOURNAL, **57**, 2589 (1935).

[9] Voorhees and Adams, *ibid.*, **44**, 1397 (1922).

and had a neutral equivalent of 283.8. Its melting point showed no depression on mixing with pure stearic acid (m. p. 70–71°, neut. equiv. 284.3); hence the reduced acid was stearic acid.

Anal. Calcd. for $C_{18}H_{36}O_2$: C, 75.95; H, 12.76. Found: C, 76.19; H, 12.82.

Oxidation of a small amount of the liquid acids with alkaline permanganate[10] yielded a mixture of dihydroxy- and tetrahydroxystearic acids. The dihydroxystearic acid was extracted from the crude mixed acids with chloroform. After crystallization from alcohol it melted at 129–130°. No depression was observed in the melting point on admixture with authentic 9,10-dihydroxystearic acid.

Anal. Calcd. for $C_{18}H_{36}O_4$: C, 68.26; H, 11.47. Found: C, 67.99; H, 11.48.

The acid insoluble in chloroform was crystallized from alcohol and melted at 171–172°. A mixed melting point with authentic tetrahydroxystearic acid showed no depression and established the substance as tetrahydroxystearic acid.

Anal. Calcd. for $C_{18}H_{36}O_6$: C, 61.99; H, 10.42. Found: C, 62.29; H, 10.21.

Another sample of the unsaturated acids was brominated in cold light petroleum ether. The precipitate which formed was crystallized from petroleum ether yielding a white crystalline acid melting at 113–114°. It was proved by the mixed melting point method to be tetrabromostearic acid.

Anal. Calcd. for $C_{18}H_{32}O_2Br_4$: Br, 53.29. Found: Br, 53.01.

The substance remaining in the petroleum ether after removal of the tetrabromostearic acid was a light brown oil. It was probably dibromostearic acid.

Anal. Calcd. for $C_{18}H_{34}O_2Br_2$: Br, 36.15. Found: Br, 38.21.

The above data show the presence in the acetone-soluble fat of both oleic and linoleic acids. Since no substance insoluble in ethyl ether was found on bromination, it appears that no higher unsaturated acids were present.

Acknowledgment.—This work was supported in part by grants from the Duke University Research Council. The expense of growing the fungi was also in part defrayed by a grant from the John and Mary R. Markle Foundation.

Summary

1. The chemical composition of the lipids of the pathogenic fungus, *Blastomyces dermatiditis*, has been determined. The lipids make up about eight to ten per cent. of the weight of the whole dried cells.

2. The lipids were separated into approximately one-third phosphatide and two-thirds acetone-soluble fat.

3. The phosphatide on hydrolysis with aqueous sulfuric acid gave glycerophosphoric acid, choline, ethanolamine, and fatty acids. These substances were isolated and the first three identified. The fatty acids probably consisted of palmitic, stearic, oleic and linoleic acids. A small amount of carbohydrate was obtained on saponification.

4. The acetone soluble fat gave on saponification glycerol, ergosterol, and palmitic, oleic and linoleic acids. These were isolated and identified. Stearic acid probably was present also.

5. These results are compared with the data on tubercle bacilli and certain striking differences noted.

DURHAM, N. C. RECEIVED AUGUST 22, 1938

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[10] Lapworth and Mottram, *J. Chem. Soc.*, **127**, 1628 (1925).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, SWIFT & COMPANY]

The Reversibility of the Reaction between Triglycerides and Glycerol

BY HARLAND H. YOUNG, JR., AND HOWARD C. BLACK

The fact that triglycerides react with glycerol at high temperatures has been known for several years. The products obtained by such a reaction have been described in the literature[1] and more recently have become of commercial importance as emulsifying agents for water-in-oil emulsions. Many of the products reported have been prepared from natural fats and oils and necessarily have been complex mixtures. The designation of these as mixtures of mono- and diglycerides has been based upon saponification numbers, acetyl values and their marked solubility in the lower alcohols.[1a,c] Grün[1b] reported the formation of di- and triglycerides when monoglycerides were heated but did not identify the products completely. Fischer[2] prepared α-dibenzoylglycerol by the vacuum distillation of α-monobenzoylglycerol. More recently Hurd[3] has described the formation of glycerol triphenyl-

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[1] (a) Bellucci, *Gazz. chim. ital.*, **42**, II, 283 (1912); (b) Grün, *Chem. Umschau Fette, Öle, Wachse, Harz*., **32**, 225 (1925); (c) Tsuchiya and Akiyama, *J. Soc. Chem. Ind. Japan*, **36**, Suppl. binding, 233 (1933).

[2] Fischer, Bergmann and Bäwind, *Ber.*, **53**, 1589 (1920).

[3] Hurd, *et al.*, THIS JOURNAL, **59**, 1952 (1937).

methyl di- and triethers by heating the α-monoether to 190 and 260°, respectively.

This research has resulted from the observation that commercial monoglycerides, as prepared from natural fats and glycerol, do not hydrolyze when deodorized with steam at high temperatures and reduced pressures, but lose glycerol and are converted into the original fat. In the present investigation, pure synthetic triglycerides have been treated with glycerol in the presence of catalysts. The reaction products have been separated and identified. Their behavior during vacuum distillation with and without the aid of steam has been studied.

Experimental

α-Monoglycerides.—Monolaurin, monopalmitin and monostearin were prepared by Fischer's method as described by King and co-workers.[4] In the purification of these compounds by numerous crystallizations, it was noted that rate of crystallization is an important factor in obtaining the high melting points reported by King. Saponification values were used as the best criterion of purity.

Triglycerides.—Trilaurin, tripalmitin and tristearin were prepared by the action of a slight excess of the fatty acid chlorides on anhydrous glycerol in the presence of quinoline or pyridine. This procedure is a modification of that described by King.[4] After one crystallization from ether and two from an alcohol–chloroform mixture (70:30 by volume) the white crystalline compounds melted sharply and had the theoretical saponification values.

Ethylene Dipalmitate.—Three and one-tenth grams (0.05 mole) of redistilled ethylene glycol and 16 g. of quinoline were placed in a glass-stoppered bottle and cooled in an ice-bath. Twenty-eight g. (0.10 mole) of palmityl chloride was added and the mixture shaken vigorously until it set to a hard mass. After standing at room temperature for two or three days, the product was taken up in 1200 cc. of ether and 400 cc. of 0.5 *N* sulfuric acid. Successive washings with additional 0.5 *N* sulfuric acid, 10% sodium bicarbonate and water removed most of the impurities. After drying over anhydrous sodium sulfate, the ether solution was allowed to stand at −26°. Light yellow plates separated which were redissolved in 500 cc. of ether, decolorized with carbon and recrystallized at −26°: yield 20.0 g.; m. p. 68.7–68.9°. This compound, as prepared in another way, has a reported m. p. of 68.7°.[5]

Reaction of Triglycerides with Glycerol.—The reaction between trilaurin and glycerol is described as typical of the procedure. Ten grams of glycerol, 10 g. of trilaurin and 0.2 g. of trisodium phosphate were refluxed for fifteen minutes at the boiling point of glycerol under anhydrous conditions in an atmosphere of nitrogen. One layer formed after five minutes of boiling. After the flask had cooled, some of the excess glycerol was held in solution in the solid fatty layer, but 4 g. of it separated into a clear liquid lower layer. The solid product was dissolved in 100 cc. of anhydrous ether, leaving behind all of the excess glycerol, most of the catalyst and a trace of soap. The ether solution was dried over anhydrous sodium sulfate, decolorized with carbon and crystallized at −26°. The gummy precipitate was recrystallized from 150 cc. of ether and then from 50 cc. of alcohol at −26°: yield 3 g.; m. p. 60.5–61.0°; sap. value 204.2, calcd. for monolaurin, 204.6; mixed m. p. with monolaurin was 60.5–61.0°. With no alkaline catalyst thirty minutes boiling was necessary for the formation of one layer and only 1.0 g. of pure monolaurin was isolated. A small quantity of another compound was separated from the uncatalyzed reaction mixture. This melted at 54.5–55.0°; reported melting point for α,α′-dilaurin 56.6°.[4] The amount obtained was insufficient for saponification value determination. When 0.2 g. of sodium carbonate was used as a catalyst, 0.5 g. of crystalline material was separated: m. p. 54.5–55.0°; sap. value 236.4, calcd. for dilaurin, 245.8.

Ten grams of tripalmitin treated in the same way gave 1.0 g. of crystals: m. p. 75.0–75.5°; mixed m. p. with pure monopalmitin 75.0–75.5°; sap. value 171.0, calcd. 169.8. With no alkaline catalyst, a five-hour boiling period failed to cause the formation of one layer and no crystalline product could be isolated. The amorphous nature of many of these products is probably due to the formation of polyglycerol ethers and their esters.

In the case of tristearin 0.5 g. of crystals melting at 79.5–80.0° was isolated when trisodium phosphate was used as catalyst: mixed m. p. with pure monostearin 79.5–80.0°; sap. value 156.0, calcd. 156.6.

Several recrystallizations were required in the isolation of pure reaction products from the reësterification of tripalmitin and tristearin. The low yields of pure monoglycerides obtained are not indicative of the completeness of the reaction. In every case, the saponification value of the reaction mixture, after complete removal of excess glycerol, was only slightly above the calculated value for the pure compound. The loss occurred in the several crystallizations necessary for the removal of last traces of di- and triglycerides.

Decomposition of α-Monoglycerides when Heated in Vacuo.—The distillation of α-monopalmitin is described as typical of this procedure. Five grams of monopalmitin was distilled at 0.5 mm. With an oil-bath temperature of 200°, material was distilled at 189–190°. Distillation stopped after half the material came over. Nothing more distilled even by raising the temperature to 225°. The non-volatile residue, when purified by successive crystallization from alcohol–chloroform mixtures, was tripalmitin and melted at 63.5–64.0°. The distillate was extracted with ether to separate the fatty material from glycerol. Seven-tenths gram of material was isolated from the distillate melting at 74.0–75.0°; mixed m. p. with pure monopalmitin 74.0–75.0°.

Similar treatment of α-monolaurin resulted in the distillation of a large portion of the monolaurin unchanged, b. p. 171–172° (0.5 mm.). A very small amount of glycerol was found in the distillate. The residue in the flask was purified and yielded 0.5 g. of trilaurin. α-Monostearin was transformed into tristearin with only a trace of the

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[4] Averill, Roche and King, This Journal, **51**, 866 (1929).

[5] Rutan and Roebuck, *Trans. Roy. Soc. Canada*, [3] **9**, June (1915).

monoglyceride distilling unchanged at 184–86 (0.3 mm.). An appreciable quantity of glycerol which distilled with the trace of fatty material made isolation of the small amount of monoglyceride impossible.

Reaction of Ethylene Dipalmitate with Ethylene Glycol.—Ten grams of ethylene glycol (redistilled and dry) was refluxed at its boiling point with 10 g. of ethylene dipalmitate and 0.2 g. of anhydrous trisodium phosphate. The reaction proceeded for fifteen minutes, one layer being formed after ten minutes of boiling. The esters were separated from excess ethylene glycol by means of dry ether extraction. Impure crystals were obtained by holding the ether solution at −26°. These, after being filtered, were dissolved in 250 cc. of hot alcohol. As the solution cooled to room temperature, crystals of unreacted dipalmitate separated, m. p. 68.6–68.9°; yield 2 g. The mother liquor, when cooled to 2°, yielded 5 g. of β-hydroxyethyl palmitate, m. p. 51.2–51.5°. Rutan and Roebuck[5] reported the melting point of β-hydroxyethyl palmitate and ethylene dipalmitate as 51.5 and 68.7°, respectively. This method for the preparation of the monoester is an improvement over earlier methods. With no alkaline catalyst the interesterification did not take place during three hours of refluxing at the boiling point of ethylene glycol.

Decomposition of β-Hydroxyethyl Palmitate when Heated in Vacuo.—Five grams of the palmitate was distilled as described previously for the α-monoglycerides. About half the material distilled at 155–160 (2 mm.). From the residue there was separated 1.5 g. of pure ethylene dipalmitate, m. p. 68.5–68.9°. The distillate was separated and purified by fractional crystallization from alcohol. A trace of the crude dipalmitate, melting at 66–67°, separated at room temperature. The mother liquor at 2° yielded 1.5 g. of pure β-hydroxyethyl palmitate, m. p. 51.5–52.0°.

Steam Distillation of α-Monoglycerides in Vacuo.—The distillation procedure already described was repeated with a rapid current of steam being used. A vacuum of 2 mm. was maintained. The same general reaction was obtained in every case; *i. e.*, some of the monoglyceride and glycerol distilled, the triglyceride remaining in the residue. At no time was there found more than minute traces of free fatty acid in the distillates from the steam distillation. This is noteworthy because much steam was used, and during the removal of glycerol and the transformation to triglyceride one might expect any free acyl groups to react with the steam as rapidly as with monoglyceride. In the presence of steam, decomposition of mixed monoglycerides, as prepared from natural fats, to triglycerides and glycerol takes place at a much lower temperature (140°) than under the condition of ordinary vacuum distillation (170°).

Discussion

The reaction between triglycerides and glycerol is reversible. The reaction between the higher diesters of ethylene glycol and the glycol is also reversible. Alkaline catalysts promote the formation of the monoesters but seem to have no accelerating effect upon their decomposition during vacuum distillation with or without steam. Temperatures required for formation of mono- from polyesters are appreciably higher than for the reverse decomposition. The catalytic effect of the alkaline salts used may be due either to the alkalies themselves or to the soaps formed during the reaction. Approximately 90–95% of the alkaline salt catalysts are recovered when anhydrous reactants are used, but small traces of soap are always found in the reaction mixture.

Summary

1. The products obtained by the interaction of triglycerides with glycerol have been isolated in pure state. These products are chiefly α-monoglycerides.

2. There has been effected the reverse of this reaction, namely, the formation of triglycerides from the mono- or diglycerides by distillation *in vacuo* with or without steam.

3. A new method of preparation for β-hydroxyethyl palmitate has been described as well as a method for its separation from ethylene dipalmitate.

CHICAGO, ILL.

RECEIVED AUGUST 11, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

Some Derivatives of *s*-Triethylbenzene

BY WINTHROP B. DILLINGHAM[1] AND E. EMMET REID

Mesitylene has been investigated thoroughly but its homolog, *s*-triethylbenzene, is comparatively little known; figures for its boiling point range from 200 to 220°. As the polyethylbenzenes are now readily available it seemed that this, the most abundant of the triethylbenzenes, merited further study.

Klages and Lickroth[2] found that *s*-triethylbenzene can be separated conveniently from its isomers by taking advantage of the facts that it is more difficult to sulfonate than its isomers and its sulfonic acid is hydrolyzed more readily. We have verified their observations and used their method for obtaining *s*-triethylbenzene from the proper fraction of the ethylation mixture.

The *s*-triethylbenzene used boiled at 211.2° at 760 mm. and had density 0.8772 0°/4° and 0.8568 25°/4°. The properties and analyses of the derivatives are given in Table I.

TABLE I

PROPERTIES AND ANALYSES OF DERIVATIVES OF *s*-TRIETHYLBENZENE

Name	B. p., °C.	Press.	M. p., °C.	d^0_4	d^{25}_4	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Sulfur Calcd.	Sulfur Found
s-Nitrotriethylbenzene	141.2	7	...	1.0550	1.0174	...	...	...	...	7.91	7.82	..	..
s-Triethylaniline	135.5	6	...	0.9492	0.9280	...	...	...	...	7.91	7.82	..	..
Acetyl derivative	...	..	149.5	....	....	76.65	76.63	9.65	9.54	..	..	..	..
Benzoyl derivative	...	..	181.3	....	....	...	...	...	...	..	..	..	..
s-Triethylthiocarbanilide	...	..	196.5	....	....	...	...	...	...	..	..	8.09	7.90
s-Triethylphenol[a]	126.5	5	...	.9716	.9504	80.84	80.91	10.18	10.08				
s-Triethylanisole	100.8	3	...	.9600	.9379	81.18	80.97	10.49	10.34	..	..	..	..
s-Triethylbenzonitrile	108.5	2	...	.9572	.9356								
Azo dye with β-naphthol	...	..	...	....	....	69.99	69.83	6.14	6.16				

[a] Since our work was done v. Auwers and Mauss, *Ann.*, **460**, 240 (1928), made this phenol by the reduction of 2,6-diethyl-4-acetylphenol and gave its b. p. as 244–246°.

Experimental

Into 200 g. (2.5 moles) of benzene and 50 g. of aluminum chloride 205 g. (7.4 moles) of ethylene was passed with stirring at 10,000 r. p. m. The temperature was about 60° at the start and was raised gradually to 85°. The absorption was slow at first but rose to 2500 cc. per minute. The products from several runs were fractionated and the fractions 190–230° united and refractionated. The triethylbenzene fraction was stirred for three hours at 60–70° with 2 parts of concentrated sulfuric acid. On cooling the mixture separated into 3 layers, the upper of which proved to be the desired *s*-triethylbenzene. The mixture of sulfonic acids was hydrolyzed by Armstrong's method.[3] At 110–125° the *s*-triethylbenzene was set free, while the liberation of the 1,2,4- did not occur until 160–175° was reached. The *s*-triethyl thus obtained was identical in all respects with the unsulfonated hydrocarbon above. This was proved by completely sulfonating a portion with 6 parts of sulfuric acid and converting the product into the amide which melted at 117–119°.[4]

It was nitrated with a mixture of 2 parts fuming to 3 concd. nitric acid at 25 to 30° for two hours which converts about half to the mononitro with a negligible amount of the dinitro which is obtained by stronger treatment. One part of the nitro derivative, 1 of water, and 3 of iron filings with a trace of acetic acid on the steam-bath for six hours gave the amino derivative which was purified by precipitation from benzene solution by hydrogen chloride. The acetyl and benzoyl derivatives were prepared by usual methods. The thiocarbanilide was prepared by adding 40% caustic soda solution to a cooled solution of the amine in carbon disulfide. The phenol was obtained through the diazo and methylated with dimethyl sulfate. The iodo derivative was made by the diazo. Its properties checked the data of Klages. It was converted into dichloride but this could not be isolated. The nitrile was obtained by the diazo reaction. The diazonium chloride was coupled with β-naphthol which gave a red azo dye.

Summary

A number of derivatives of *s*-triethylbenzene have been prepared and their properties determined.

BALTIMORE, MD.

RECEIVED AUGUST 1, 1938

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[1] Taken from Ph. D. dissertation of Winthrop B. Dillingham, Johns Hopkins University, June, 1926.

[2] Klages and Lickroth, *Ber.*, **32**, 1564 (1899).

[3] Armstrong, *J. Chem. Soc.*, **45**, 148 (1884).

[4] Klages[2] gives 118.5°.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

A Spectrophotometric Study of Certain Neutralization Indicators[1]

BY W. B. FORTUNE WITH M. G. MELLON

Various organic compounds have been used extensively as indicators in neutralimetry and for the colorimetric determination of the *p*H value of solutions. While the general nature of the absorption spectra of solutions of such indicators has been known for years, few reliable spectrophotometric data on the transmittancy curves at different *p*H values have been reported until recently.[2] The present availability of objective photoelectric spectrophotometers has led the authors to check some of the earlier data obtained with subjective visual instruments. In addition to the simple systems studied by other workers, the present work includes certain modified and mixed indicators used in titrimetry.

Experimental Work

Apparatus.—All measurements of transmittancies were made on a photoelectric spectrophotometer[3] with cells 1.000 cm. thick and a spectral band 10 mμ wide. The data were secured within fifteen minutes of the time the solutions were prepared, the transmittancy–wave length curves being recorded by the instrument.

Tristimulus values were obtained with a calculator[4] using 10 selected ordinates, a procedure shown to give a precision of 0.2%. The values are based on the I. C. I. illuminant C.

Solutions.—The indicator solutions were prepared by dissolving the purest obtainable commercial reagents in doubly distilled water, or ethanol, if necessary. Dilutions were made from the stock solutions to give the concentrations listed in Table I.

Clark and Lubs' buffer solutions were prepared,[5] with *p*H values ranging from 2.2 to 6.8 at intervals of 0.2 *p*H unit. The salts were recrystallized three times, and the solutions were checked with a glass electrode. An antiseptic was added to prevent the growth of mold.

In preparing a solution for measurement exactly 0.3750 ml. of the indicator solution was transferred to a 25-ml. volumetric flask by means of a micro-buret, buffer solution was added to the mark and the system was mixed. Specifications are given below for the solutions prepared to represent colorless end-points with modified indicators.

TABLE I

SYSTEMS STUDIED

Indicator	Concentration, g./l.	Solvent
Brom cresol green	0.4000	Water
Ethyl orange	.4000	Water
Methyl orange	.4000	Water
Methyl red	.4000	50% ethanol
p-Methyl red	.4000	Water
Propyl red	.4000	50% ethanol
Methyl red	.2000	50% ethanol
Brom cresol green	.2000	
Methyl orange	.0400	Water
Brom cresol green	.2000	
Methyl orange	.4000	50% ethanol
Xylene cyanole FF	.5600	
Methyl red	.2500	95% ethanol
Methylene blue	.1750	

Data and Discussion.—The indicators studied are of three general types, simple, modified and mixed. The various indicators in each group are discussed under the respective group headings.

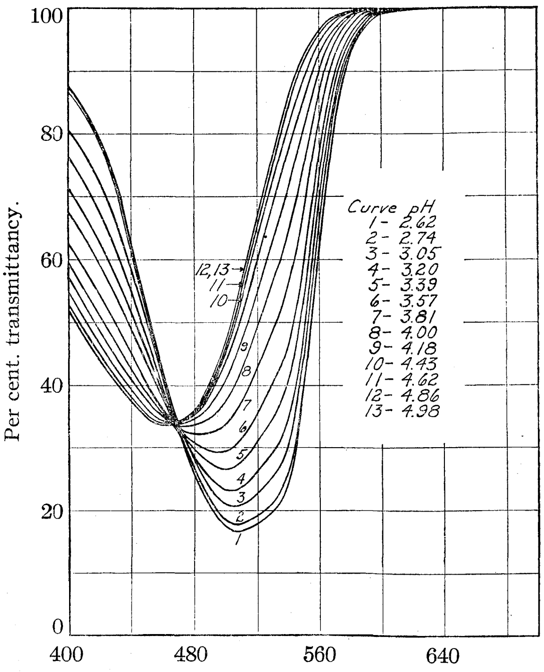

Fig. 1.—Spectral transmission curves for methyl orange solutions at different *p*H values: one cm. cell thickness and 0.375 ml. of a solution containing 0.4 g./l. diluted to 25 ml.

a. Simple Indicators.—The transmittancy curves for methyl orange are shown in Fig. 1. These exhibit a fixed isobestic point at 469 mμ,

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[1] Abstracted from a portion of a dissertation submitted by W. B. Fortune [present address, Eli Lilly and Co., Indianapolis, Ind.] to the Graduate School of Purdue University in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] Brode, THIS JOURNAL, **46**, 581 (1924); Uzumasa and Yamawaki, *J. Chem. Soc. Japan*, **58**, 721 (1937); **59**, 24 (1938).

[3] Michaelson and Liebhafsky, *Gen. Elec. Rev.*, **39**, 445 (1936).

[4] Swank and Mellon, *J. Optical Soc. Am.*, **27**, 414 (1937).

[5] Clark, "Determination of Hydrogen Ions," Williams and Wilkins Co., Baltimore, Md., 1928, p. 200.

together with a consistent change in intensity of absorption with increase of pH. The absorption band of this indicator, an azo compound, shows a definite shift of the wave length of the peak of the band through the transformation range. At pH 2.62 the peak is located at 507 mμ; with increase of pH the shift of the band is toward the blue, the peak being located at 472 mμ at pH 4.0. The shift of the peak follows approximately a hyperbolic spiral.

Ethyl orange, another azo compound, gave curves resembling those for methyl orange but bearing a mirror image relationship to them with respect to the relative heights of the absorption bands for the acidic and the basic forms of the indicator. In the curves for each of the two indicators a weak secondary band shows the same shift as the primary.

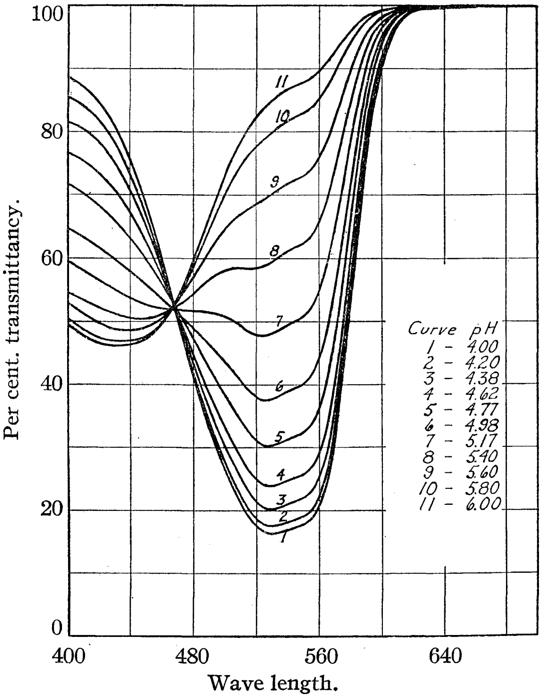

Fig. 2.—Spectral transmission curves for methyl red solutions at different pH values: one cm. cell thickness and 0.375 ml. of a solution containing 0.4 g./l. diluted to 25 ml.

The curves for methyl red are shown in Fig. 2. Although some earlier data[2] (p. 588) indicate that the peak of the absorption band apparently does not change in wave length through the transformation range, these curves, like those for methyl orange, show a shift toward the violet with increase in pH. The small secondary band shows a similar, but less obvious, shift.

Measurements on tropaeoline 00 gave results very similar to those for other azo indicators, the shift of the peak of the absorption band with change of pH being evident.

Unsuccessful attempts were made to secure curves for several other azo compounds. Solutions containing propyl red faded as much as 50% within two minutes after preparation. Paramethyl red precipitated from the buffer solution so rapidly that reliable curves were not obtainable. Dimethylaminoazobenzene gave reproducible curves on the acidic side of the transition point of the indicator; on the basic side fading occurred to the extent of more than 1% per minute. The curves for the acidic side showed a shift of the peak of the absorption band similar to that obtained for the other azo indicators studied.

Figure 3 shows the curves for brom cresol green, a sulfonphthalein type indicator. This is an example wherein the peak of the absorption band, at 615 mμ, does not change in wave length with change of pH of the solution. A good isobestic point is shown for this indicator also.

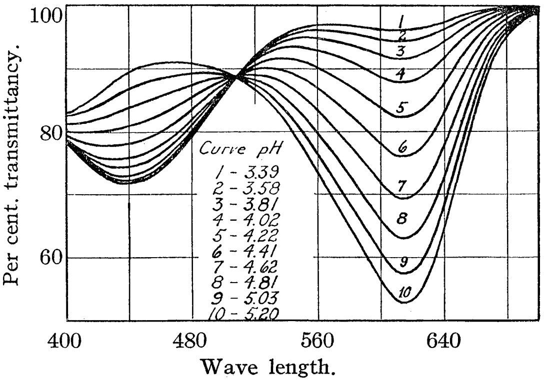

Fig. 3.—Spectral transmission curves for brom cresol green solutions at different pH values: one cm. cell thickness and 0.375 ml. of a solution containing 0.4 g./l. diluted to 25 ml.

Reference to Figs. 1 to 3 shows that a shift in the peak of the band is to be expected unless the slope of the top curve is nearly zero at the wave length of the minimum point of absorption for the bottom curve. Intermediate curves represent mixtures of the acidic and basic color forms of the indicator. The direction of the shift depends upon the slope of the top curve, that for methyl orange being toward the violet. In Fig. 3 the top curve for the primary band is nearly flat at 615 mμ while that for the secondary band at 436 mμ has considerable slope.

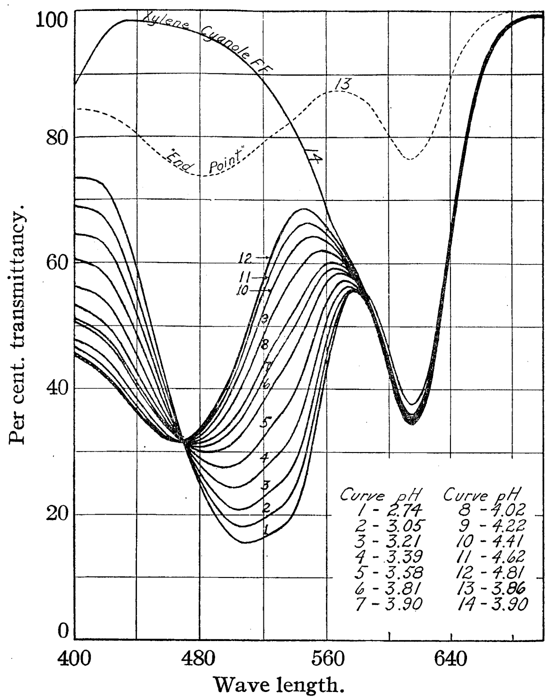

Fig. 4.—Spectral transmission curves for modified methyl orange at different *p*H values and the modifying agent at one value: one cm. cell thickness and 0.375 ml. of a solution containing 0.4 g./l. of methyl orange + 0.56 g./l. of xylene cyanole FF diluted to 25 ml. For the end-point curve 0.100 ml. of the indicator solution was diluted to 25 ml.

b. Modified Indicators.—A study was made of xylene cyanole FF and of methylene blue, modifying agents for methyl orange and methyl red, respectively. A curve for one concentration of each reagent is shown in Figs. 4 and 5. The curves do not show a shift in wave length of the peak with change of *p*H above 3.2. These curves represent the same concentration of modifying agent as that in the modified indicator discussed below.

Figure 4 shows the curves for methyl orange modified with xylene cyanole FF. The indicator was prepared according to the directions of Hickman and Linstead.[6] The characteristic shifting of the peak of the methyl orange absorption band is shown here, as with the simple indicator; also a definite isobestic point is exhibited with the modified indicator.

Curves for methyl red, modified with methylene blue, are given in Fig. 5. The solution was prepared according to recommendations of Johnson and Green.[7]

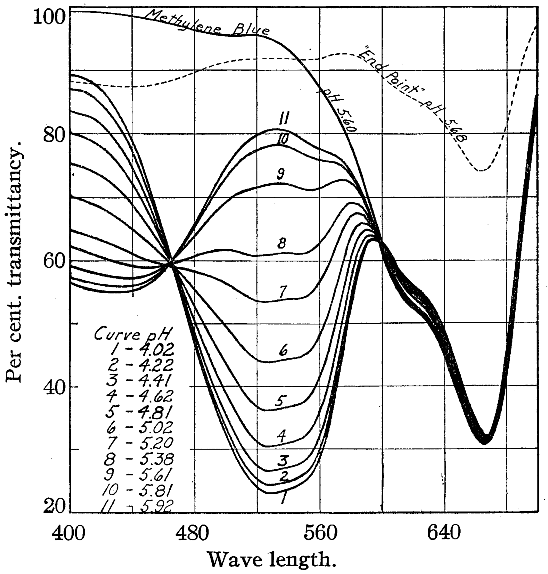

Fig. 5.—Spectral transmission curves for modified methyl red at different *p*H values and the modifying agent at one value: one cm. cell thickness and 0.375 ml. of a solution containing 0.25 g./l. of methyl red + 0.175 g./l. of methylene blue diluted to 25 ml. For the end-point curve 0.100 ml. of the indicator solution was diluted to 25 ml.

Curves for the colorless end-points obtainable in titrations using modified methyl orange or methyl red also are shown in Figs. 4 and 5. In each case 0.1000 ml. of the indicator solution (Table I) was diluted with a buffer to make 25 ml. of solution. This corresponds to about two drops of the stock solution in 125 ml. of solution to be titrated. Other concentrations gave similar curves.

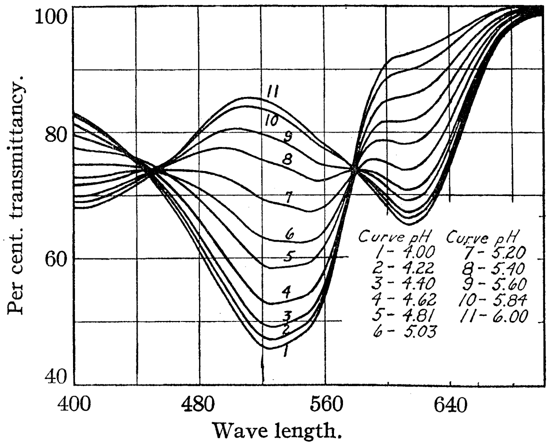

Fig. 6.—Spectral transmission curves for the mixed indicator methyl red + brom cresol green at different *p*H values: one cm. cell thickness and 0.375 ml. of a solution containing 0.2 g./l. of methyl red + 0.2 g./l. of brom cresol green diluted to 25 ml.

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(6) Hickman and Linstead, *J. Chem. Soc.*, **121**, 2502 (1922).

(7) Johnson and Green, *Ind. Eng. Chem., Anal. Ed.*, **2**, 2 (1930).

TABLE II

COLOR SPECIFICATIONS OF INDICATOR SOLUTIONS

Indicator		Trichromatic			Monochromatic		
		Red, %	Green, %	Violet, %	Dominant wave length mμ	Relative brightness, %	Colorimetric purity, %
Brom cresol green	(3-2)[a]	33.0	34.5	32.5	572.8	90.8	13.0
	(3-10)	27.3	29.8	43.0	484.8	71.1	15.4
Methyl orange	(1-1)	40.8	29.5	29.8	493.6[b]	56.2	27.0
	(1-11)	39.5	39.5	21.0	578.6	83.1	43.8
Methyl red	(2-1)	36.1	22.9	41.0	513.6[b]	42.0	44.6
	(2-11)	36.3	37.8	26.0	575.5	88.1	30.6
B-c. green +	(6-1)	34.4	28.4	37.2	503[b]	63.2	19.4
M. red	(6-11)	30.1	32.6	37.3	505	77.1	3.0
Modified	(4-1)	34.9	25.8	39.4	510.4[b]	35.0	30.6
M. orange	(4-11)	33.7	37.6	28.6	567.4	55.0	23.2
Modified	(5-1)	30.9	22.7	46.5	551.8[b]	38.3	35.8
M. red	(5-11)	29.8	35.8	34.3	532[b]	72.5	8.6
Methylene blue	(5-)	26.6	30.7	42.6	488.4	82.9	17.2
Xylene Cyanole FF	(4-)	25.2	28.0	46.8	483.0	69.0	25.0
Colorless mod. M. orange	(4-)	31.3	31.9	36.8	578	90.2	1.5
Colorless mod. M. red	(5-)	30.8	32.0	37.2	515	95.0	1.9

[a] Figure curve number.

[b] Dominant wave length of the complementary.

c. **Mixed Indicators.**—Since many mixtures of indicators, the individual compounds of which have contrasting hues, have been proposed, representative examples were studied. The results for one of them are included here.

Selected curves for the mixture proposed by Hähnel,[8] consisting of equal parts of methyl red and brom cresol green, are shown in Fig. 6. A definite isobestic point is exhibited at 580 mμ, and a diffuse crossing at 450 mμ.

Color specifications were determined for selected curves for each indicator. Values for one curve on the acidic side and one on the basic side of the indicator are presented in Table II.

Recently De Almeida[9] suggested the use of a graph coördinating dominant wave length with *p*H as a means of determining the *p*H of solutions. In the present work the dominant wave length of representative curves of several indicators was plotted against the *p*H of the solution, but the results have little practical value for indicators whose dominant wave length falls in the purple on one side of the transformation range. Since the dominant wave length of a purple is specified as that of its complementary, the curve consists of two widely separated parts—one for the true dominant wave lengths and one for the complementaries. With sulfonphthalein indicators which show no purple characteristics, the method may be used with some degree of accuracy. Relative brightness also was plotted against the *p*H of the solution, but the resulting curve seemed to have little practical value.

Summary

A spectrophotometric study has been made covering the transformation range of various simple, modified and mixed neutralization indicators. The spectral transmittancy curves show the characteristics of the absorption bands in the visual region at different *p*H values. Colorimetric specifications are included for selected curves for several indicators.

LAFAYETTE, INDIANA RECEIVED JUNE 18, 1938

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(8) Hähnel, *Svensk Kem. Tids.*, **47**, 4 (1935).

(9) Dissertation, Lisbon, 1937.

[CONTRIBUTION FROM THE MALLINCKRODT CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Conductance of Dilute Solutions of Alkali Iodides in Dimethylamine[1]

BY ELIJAH SWIFT, JR.

While solutions of electrolytes in solvents of low dielectric constant exhibit many of the properties of aqueous solutions, there are differences in these properties which have not been investigated fully because of the experimental difficulties involved. Kraus and Fuoss[1a] have shown that for mixtures of dioxane and water, as well as for other systems, as the dielectric constant of the mixture is lowered, the shape of the conductance–concentration curve for any salt changes continuously. These curves can be accounted for quantitatively on the basis of a combination of ion association and interionic attraction.

It was the purpose of this investigation to extend the generality of this theory by using salts with ions which are comparatively small. Since the particular salts chosen have small ions, they should be only very feebly dissociated in dimethylamine ($D = 3.3$). By comparing the members of a series of salts, such as the alkali iodides, it should be possible to decide whether there may be any solvation of these small ions by a solvent of low dielectric constant with an "unshared electron-pair."

The solvent used, dimethylamine, has been shown to be extremely useful in precise thermodynamic studies of alkali metal amalgams by means of concentration cells.[2,3] In the course of this investigation it was found that while sodium and lithium iodides are extremely soluble and form low-conducting solutions, potassium and cesium iodides (and probably rubidium iodide by inference) are too insoluble to be of use without highly refined methods of potential measurement, or concentration cells of extremely low cell constant. The specific resistance of a saturated solution of potassium iodide at 25° is approximately 7×10^6 ohms, and that of cesium iodide about 4×10^7 ohms,[4] while a specific resistance of 10^4 is readily obtained with either sodium or lithium iodide. This latter is a convenient value for these thermodynamic studies.

Experimental

Dimethylamine was prepared from dimethylamine hydrochloride obtained from the Eastman Kodak Company, dried over activated alumina and desiccated by dissolving sodium fluorenone in it.[5] It was then twice distilled in vacuum to remove the last traces of dissolved gases and high boiling impurities, and was thereafter kept in sealed Pyrex containers out of contact with air at all times.

The salts were Mallinckrodt Reagent grade chemicals, fused in a platinum boat at a pressure of less than 10^{-4} mm. The solutions were made up in a closed system without exposing the fused salts to the atmosphere.[3] The concentrations of the original solutions were found by measuring the volume of solution in a special sealed pycnometer before running it into the conductance cell. The amount of dissolved salt was measured after the completion of each series of measurements. The cells used have been described by Bent and Keevil,[6] and were designed so that a series of successive quantitative dilutions could be made on the original solution in the cell without opening the sealed system.

When calculating the equivalent conductances of the solutions which were measured at 0°, it was assumed that the molar concentration was the same as at 25°. This is, of course, not strictly true, due to a change in the density of the solution, but makes too small a difference to be of importance here. No correction was made for the change in cell constant with temperature.

The resistances were measured with a Leeds and Northrup student type bridge with parallel capacitances, using a Shallcross variable resistance box, reading up to 1 megohm, as an auxiliary resistance. The resistances and the slide wire were calibrated carefully, and no error as great as 0.1% was found. However, vaporization of the solvent out of the conductance cell during measurements, cumulative errors in concentration, and the large temperature coefficient of conductance contributed to cut down the accuracy of the measurements to 2–5%, a somewhat greater error being made in the most dilute solutions. The resistances measured ranged from 7.0 ohms to 1 megohm.

To see whether the precision of the resistance measurements in cells of as low cell constant as this could be bettered, which would be worth while in other solvents where errors could be better controlled, the measurements on lithium iodide were made with a bridge of the type described by Jones and Josephs.[7] Readings were usually made at 1000 and 2000 cycles, and a frequency correction applied to obtain the true resistances.

In order to apply the frequency correction, it was necessary to know whether the difference in the reactance at the two frequencies was due to a capacitance in the cell or

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[1] Presented before the 96th meeting of the American Chemical Society, Milwaukee, Wisconsin, Sept. 5–9, 1938.

[1a] C. A. Kraus and R. M. Fuoss, THIS JOURNAL, **55**, 21 (1933).

[2] H. E. Bent and E. Swift, Jr., *ibid.*, **58**, 2016 (1936).

[3] H. E. Bent and A. F. Forziati, *ibid.*, **58**, 2020 (1936).

[4] Private communication from A. F. Forziati.

[5] H. E. Bent and H. M. Irwin, THIS JOURNAL, **58**, 2072 (1936).

[6] H. E. Bent and N. B. Keevil, *ibid.*, **60**, 193 (1938).

[7] Grinnell Jones and R. C. Josephs, *ibid.*, **50**, 1049 (1928).

in the resistance, or a combination of the two. Measurements were made at one particular concentration, using four different frequencies. Applying the equation suggested by Jones and Josephs[8] and neglecting the higher terms, good agreement was found among the calculated resistances.

TABLE I

$$R_{\text{true}} = R_{\text{meas.}}(1 - R^2_{\text{measd.}}W^2C^2 + \ldots)$$

Frequency	$R_{\text{measd.}}$	$R_{\text{calcd.}}$
800	78485	78345
1000	78545	78325
1600	78920	78348
2000	79250	78344

It seems probable that if the other factors besides the electrical measurements can be controlled, measurements can be made in cells of this type which will be nearly as precise as those made in aqueous solutions with the best equipment.[9]

TABLE II

CONDUCTANCE OF SODIUM IODIDE IN DIMETHYLAMINE

Concn., moles/liter	Equiv. cond.	Concn., moles/liter	Equiv. cond.
Run I, 25°		Run II, 25°	
3.54×10^{-1}	1.56	1.82×10^{-2}	0.0943
7.17×10^{-2}	0.186	3.84×10^{-3}	.0647
1.46×10^{-2}	.0632	8.12×10^{-4}	.0854
2.95×10^{-3}	.0488	1.50×10^{-4}	.164
5.99×10^{-4}	.0778	3.63×10^{-5}	.361
1.21×10^{-4}	.160	7.68×10^{-6}	.865
2.46×10^{-5}	.450	1.62×10^{-6}	2.15
4.99×10^{-6}	1.40		
Run I, 0°			
1.46×10^{-2}	0.110		

TABLE III

CONDUCTANCE OF LITHIUM IODIDE IN DIMETHYLAMINE

Concn., moles/liter	Equiv. cond., 25°	Equiv. cond., 0°
6.58×10^{-2}	1.13	1.75
1.21×10^{-2}	0.199	0.452
2.22×10^{-3}	.171	.438
4.07×10^{-4}	.301	.789
7.47×10^{-5}	.652	1.70
1.37×10^{-5}	1.791	4.63
2.52×10^{-6}	5.248	13.53

TABLE IV

CONDUCTANCE OF POTASSIUM IODIDE IN DIMETHYLAMINE

Concn., moles/liter	Equiv. cond., 25°	Equiv. cond., 0°
	Run I	
3.69×10^{-4}	0.280	....
5.57×10^{-4}	.640	....
	Run II	
8.77×10^{-4}	0.164	....
1.63×10^{-4}	.352	0.731
3.03×10^{-5}	.737	1.58
5.64×10^{-6}	2.31	4.91
1.05×10^{-6}	5.63	18.32

An attempt was made to use d. c. in order to carry the measurements to lower concentrations, but this was not successful due to a small variable potential in the cell which could not be balanced out or removed by short circuiting.

It was unnecessary to correct for the conductance of the solvent, which has been found[2] to be about 3×10^{-12}, far too low to affect these measurements.

Results and Discussions

It is evident from examination of the figure that these systems are in accord with the Kraus and Fuoss theory, qualitatively at least. Both lithium iodide and sodium iodide exhibit minima in their conductance–concentration curves in the neighborhood of 0.005 *M*, and it is probable that potassium iodide would also if it were more soluble. Kraus and Fuoss[1a] state that, except for viscosity effects, the forms of conductance–concentration curves are dependent almost exclusively on the dielectric constant. If we compare the results of these measurements in dimethylamine ($D = 3.3$) with theirs in a dioxane–water mixture of $D = 3.5$, it is seen that for tetraisoamylammonium nitrate the minimum falls at almost exactly the same concentration. The minimum is also at this concentration for the same salt in a mixture of dioxane and ethylene dichloride ($D = 3.1$). It might be expected that the alkali iodides, having so much smaller ionic radii than tetraisoamylammonium nitrate, would show a stronger tendency to form triple ions, and that the minimum would occur at a lower concentration. It is evident, however, that the ionic size has little effect on the position of the minimum even in the extreme case of these small ions. This fact has been discussed by Kraus and Fuoss,[10] who have shown that, from a theoretical standpoint, the dielectric constant is the controlling factor in the position of the minimum, and that the ionic radius has little effect.

Below the minima the curves for all three salts show a slope of $-1/2$ within the limits of experimental error, corresponding to the association of two ions to form an ion-pair. It was not found possible to calculate Λ_0 and the dissociation constants of these equilibria, since the curves show no downward deviations from linearity in the low concentration region. However, we may estimate these constants by means of Walden's rule, using data obtained for aqueous solutions, but due to lack of necessary data on viscosities, it is

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[8] Grinnell Jones and R. C. Josephs, THIS JOURNAL, **50**, 1076 (1928).

[9] See, for example, Grinnell Jones and collaborators, *ibid.*, **56**, 602 (1934); **58**, 2561 (1936); **59**, 731 (1937).

[10] R. M. Fuoss and C. A. Kraus, *ibid.*, 55, 2387 (1933).

somewhat difficult to apply it in this case. If we assume the value of the viscosity of dimethylamine at 25° to be 0.002, as compared with water at 18° = 0.01, the three values of Λ_0 are as follows: LiI = 500, NaI = 550, KI = 650. Rough calculations of the dissociation constants from the data of this paper give for LiI, $K = 2.5 \times 10^{-10}$, for KI, $K = 1 \times 10^{-10}$ and for NaI, $K = 4 \times 10^{-11}$. These values are of course only approximate, but are probably correct within a factor of ten and, relative to each other, this discrepancy is doubtless even smaller. The degree of dissociation at the minimum is only about 10^{-4}, and the single ion concentration must be at least as low as 5×10^{-7}, which is an upper limit because of a considerable formation of triple ions.

Although the ionic diameters of the three positive ions in the crystalline state increase from lithium to potassium, the conductances at any given concentration do not occur in that order. We would expect that since the potassium ion is larger than the sodium ion, the conductance curve of its iodide would be lower than that of the sodium iodide because of its lower mobility. That this is not the case is probably because of the greater dissociation of the potassium salt due to its greater diameter. It is evident that the increase in dissociation is of more importance than the decrease in mobility, a fact that might be anticipated since the relationship between the dissociation and the ionic diameter is exponential in nature[11] and the mobility decreases only as the square of the ionic diameter.

On the other hand, these facts might be interpreted as showing that the sodium ion is solvated and hence has a lower mobility, as is the case in liquid ammonia solutions. If the sodium ion is solvated and hence low-conducting, the lithium ion should be even more so. That this is not true may be seen by comparison of these curves with that for lithium iodide which lies above them. It is highly probable that the difference in conductivity between the sodium and the lithium salts is not due to a difference in mobility, which would hardly amount to a factor of 3–4. Therefore we are led to the conclusion that the lithium salt is more highly dissociated due to solvation, which increases the size of the lithium ion greatly. This is in accordance with the fact that this solvent is a strong base; that is, it solvates a proton very readily.

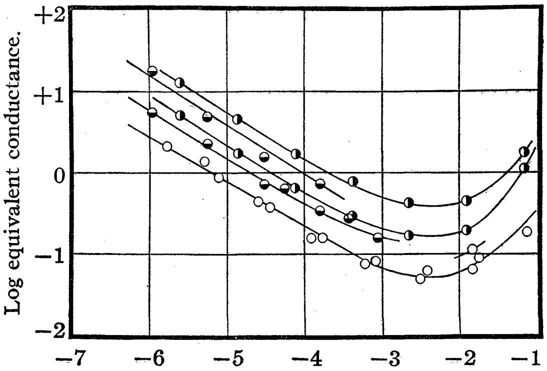

Fig. 1.—◑, LiI; ○, NaI; ◒, KI. The measurements at 0° lie *above* those at 25° in every case.

Additional evidence for an enhanced size of the lithium ion comes from consideration of the temperature coefficients of the resistance. These temperature coefficients are very large and positive; that is, the resistance is smaller at the lower temperature. This is the reverse of what is observed in aqueous solutions, but has often been observed in solutions of low dielectric constant. According to Coolidge and Bent,[12] since the process of separating two ions in solution requires work, the heat content of the system is increased thereby. During ionization, however, the molecules of the solvent are subjected to an electrostatic field which tends to orient them. This involves an entropy change which decreases the heat content of the system. ΔH (ionization) = ΔF (separation of ions, positive) + $T\Delta S$ (orientation, negative). Since the conductivity is greater at the lower temperature, it is evident that the dissociation is greater there and since K_{d}. is larger at the lower temperature, ΔH must be negative. Therefore for these systems the energy involved in the orientation of the solvent is greater than the work of separation of the two ions. Unfortunately there are no viscosity data available for dimethylamine except at the temperature of boiling ammonia,[13] and so it is impossible to calculate the values of ΔH and ΔS for these solutions. However, we can compare the three salts without knowing the absolute values. In Table V below, *r* represents the temperature coefficient of the resistance, written as $(R_{25} \times R_0)/R_{25}$.

In this table it is seen that the temperature coefficients fall in the order sodium iodide,

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[11] R. M. Fuoss and C. A. Kraus, This Journal, **55**, 1019 (1933).

[12] A. S. Coolidge and H. E. Bent, *ibid.*, **58**, 505 (1936).

[13] H. McK. Elsey, *ibid.*, **42**, 2454 (1920).

Table V

Concn. KI		Concn. NaI	r	Concn. LiI	r
......	..	......	..	6×10^{-2}	0.35
......	..	1×10^{-2}	0.43	1×10^{-2}	.56
......	..	......	..	2×10^{-3}	.61
1×10^{-4}	0.52	......	..	4×10^{-4}	.62
3×10^{-5}	.53	......	..	7×10^{-5}	.62
5×10^{-6}	.58	......	..	1×10^{-5}	.61
1×10^{-6}	.69	......	..	2×10^{-6}	.61

potassium iodide, lithium iodide, with lithium iodide having the largest coefficient. This in turn means that ΔH for lithium iodide has the largest negative value, indicating either that the entropy of orientation of the solvent is greater for this ion or that the free energy of ionization is smaller. Bent and Keevil[6] point out from their somewhat meager data on ether solutions that while ΔF varies somewhat with the distance of closest approach of the ions, the entropy change is relatively constant. If this is generally true, then the variation in ΔH is due to a difference in ΔF, rather than ΔS. Since the free energy of ionization decreases with increasing ion size, that is, larger salts are more easily ionized, it follows that the lithium ion has the largest ionic radius with the potassium ion next, as deduced previously. This again probably means that the lithium ion is solvated.

In a recent article,[14] Kelso and Felsing have reported finding negative partial molal volumes for lithium chloride in methylamine solutions. This probably indicates some solvation of this salt, while sodium nitrate has a positive partial molal volume, and probably is not solvated. These findings are in accord with the results of this research in a very similar solvent, and throw some light on the mechanism of the ionization process in solution. Since only an extremely small fraction of the lithium salt present is in the form of single ions in a solution of ordinary concentration such as those measured by Kelso and Felsing, the large negative partial molal volume observed must be caused by the ions in combination, rather than those existing as single ions. If these negative partial molal volumes are to be interpreted as indicating solvation, then the ions in the ion pairs are solvated and the greater dissociation of the lithium salt is due to the greater separation of the ions in the ion-pairs, resulting in a weakening of the coulombic force between them.

The author wishes to thank Professors H. E. Bent and Grinnell Jones for many suggestions and helpful criticisms.

Summary

1. The conductances of dilute solutions of sodium, potassium and lithium iodides in dimethylamine have been measured.

2. The results are qualitatively in accord with the Kraus and Fuoss theory.

3. It was found that the lithium ion is probably solvated by dimethylamine.

Knox College
Galesburg, Ill.

Received July 23, 1938

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(14) E. A. Kelso with W. A. Felsing, This Journal, **60**, 1949 (1938).

[Contribution from the Chemical Laboratories of the State University of Iowa]

Stable Sulfur Dithiocyanate

By P. A. Bond and G. A. Weaver, Jr.

In 1926, while investigating the solubilities of inorganic salts in sulfur monochloride, Baker[1] found that the thiocyanates of barium and potassium formed orange-red precipitates which were amorphous, insoluble in the strongest alkali, and stable in all except the most powerful oxidizing acids. Since the determination of the exact nature of this product did not come within the scope of the thesis, the reaction was not investigated further at that time. It seemed probable, however, that the orange-red powder belonged to the general class of "pseudo thiocyanates," upon which considerable research has been carried out.

In 1922, Lecher and Goebel[2] prepared the compound sulfur monothiocyanate, $S_2(SCN)_2$, by treating a mercuric thiocyanate in carbon disulfide with sulfur monochloride. The entire experiment was carried out at low temperatures in an apparatus described as being "practically completely protected from air."

Also, Lecher and Whittwer[3] prepared sulfur dithiocyanate, $S(SCN)_2$, by treating the free

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(1) Baker, "Solubilities of Inorganic Salts in S_2Cl_2," Thesis, State University of Iowa, 1926.

(2) Lecher and Goebel, *Ber.*, **55**, 1483–1495 (1922).

(3) Lecher and Whittwer, *ibid.*, **55**, 1481–1482 (1922).

thiocyanate, $(SCN)_2$, formed by the action of bromine on thiocyanates, with diethyl ether and dry hydrogen sulfide. Sulfur dithiocyanate was described as pearly yellow crystals which darkened upon standing, decomposed into an orange-red smoke at the temperature of the water-bath, and decomposed less rapidly in water or in alcohol.

Since Baker's product was prepared at reasonably high temperatures, it did not seem possible that the product could be sulfur monothiocyanate, which has a melting point of −3.3°; neither did the appearance of it correspond to the sulfur dithiocyanate of Lecher and Whittwer—although, as will be seen, its formula shows it to be sulfur dithiocyanate, $S(SCN)_2$, or some isomer.

Baker's work was repeated and somewhat extended to include the thiocyanates of mercury and ammonium. (Pure salts dried at 110° and purified sulfur monochloride were used.) The product formed by the reaction of each of these, as well as by the thiocyanates of potassium and barium, upon sulfur monochloride was identical in each case. The orange-red precipitate was purified by extracting three times with carbon disulfide, then by boiling with distilled water until the filtrate gave no tests for either the chloride or the metallic ions, and finally by extracting once again with carbon disulfide. Qualitative tests established the presence of only sulfur, nitrogen, and carbon.

Sulfur was determined by oxidation with nitric acid and precipitation as barium sulfate. Kjeldahl determinations were made for the nitrogen content. Carbon was determined as carbon dioxide by combustion in the presence of copper oxide, lead chromate, and potassium dichromate. From these analyses, as shown in Table I, the purified reaction product was found to be sulfur dithiocyanate, $S(SCN)_2$, or some polymerized form. On account of its insolubility, the molecular weight was not determined.

TABLE I

Element	% found in prepared samples		% calcd. for $S(SCN)_2$
S	64.81	64.88	64.91
N	18.98	19.01	18.90
C	16.22	16.29	16.19

The fundamental reaction between any metallic thiocyanate and sulfur monochloride, at high temperatures, appears to be

$$2MeSCN + S_2Cl_2 \longrightarrow 2MeCl + S(SCN)_2 + S$$

During the reaction, however, there was a considerable quantity of gas evolved which is not accounted for in the reaction as written. The gas, collected over mercury, is colorless and hydrolyzes in the air or in water, in which it is very soluble. It does not condense at room temperatures as would be expected were it a vaporized sulfur chloride, nor is it cyanogen.

Because the product differed in physical aspects from the sulfur dithiocyanate of Lecher and Whittwer, their preparation was repeated and the occurrence of pearly yellow crystals was verified. This crystalline form was found to change completely in approximately forty-eight hours to the orange-red form. When this was purified and analyzed, the results (as shown in Table II) were identical with those obtained by our reaction. Since Lecher and Whittwer found the crystalline form to have this composition also, it would appear that the change is a molecular rearrangement rather than a decomposition.

TABLE II

Element	% found in the purified product after rearrangement		% calcd. for $S(SCN)_2$
S	64.73	64.77	64.91
N	19.08	19.00	18.90
C	16.17	16.30	16.19

The stability of the final product, with respect to the high temperatures required for its decomposition, 500–600°, and its general insolubility taken in connection with its intense color, indicate the possibility of its use as a pigment.

Summary

1. Sulfur dithiocyanate, $S(SCN)_2$, has been prepared, at moderately high temperatures, by the action of pure sulfur monochloride upon metallic thiocyanates.

2. This compound is identical with the *final* product which Lecher and Whittwer obtained by the action of bromine and hydrogen sulfide upon thiocyanates.

3. It does not correspond to the sulfur monothiocyanate, $S_2(SCN)_2$, prepared by Lecher and Goebel by the action of sulfur monochloride upon thiocyanates in carbon disulfide solution at low temperatures.

IOWA CITY, IOWA RECEIVED AUGUST 8, 1938

[CONTRIBUTION FROM THE CHEMICAL AND OCEANOGRAPHIC LABORATORIES OF THE UNIVERSITY OF WASHINGTON]

Specific Gravities of Pure and Mixed Salt Solutions in the Temperature Range 0 to 25°[1]

BY RAYMOND W. BREMNER, THOMAS G. THOMPSON AND CLINTON L. UTTERBACK

In this paper are presented specific gravity data for aqueous solutions. The solutions are those of some of the various salts occurring in sea water. The concentrations of the binary solutions were in the same ratios that occur in the ocean waters.

Method of Procedure and Apparatus

Using the Archimedes principle, the weight of a given volume of solution was compared with that of an equal volume of pure water, the density of which was accurately known.[2] This method is more rapid than the pycnometer method and, with the refinements used, is capable of great precision.

A cylindrical glass bulb weighted with mercury and suspended by means of a piece of fine platinized platinum wire, was weighed when immersed in water and also in the solutions. For this purpose, the water and the solutions were contained in a cylindrical copper tank of suitable design, which was suspended in a water-bath. The temperature fluctuation in the water-bath varied from 0.01° at 0° to 0.002° at 25°. The weighings were made to 0.1 mg.

Check determinations were made with two different glass bulbs and two cylindrical copper tanks, using duplicate solutions. The approximate volumes of the bulbs were 250 and 260 ml., respectively. With the copper tank in position in the water-bath and the glass bulb suitably suspended in the solution at the desired temperature, consecutive weighings of the bulb were made at five-minute intervals until the change in weight during a five-minute interval was not greater than 0.1 mg. Observations were made in this way at 0, 5, 10, 15, 20, and 25°, respectively.

Immediately after making each observation, the weight of the support for the bulb was determined. The change in the buoyancy of the solution on the portion of the support immersed was negligibly small over the temperature range.

Solutions Measured

Materials.—Very pure potassium chloride and sodium chloride were prepared by well-known methods.[3] Purified magnesium sulfate was heated in air at 360° for sixteen hours. It was cooled in a vacuum desiccator charged with anhydrous magnesium perchlorate. It was then weighed in contact with dried air in a tared ground glass-stoppered weighing bottle.[4,5] The water used was similar to the equilibrium water described by Washburn.[6] The solutions were prepared according to the composition of sea water as reported by Thompson.[7]

The ions of the salts comprising the major constituents of sea water are chloride, sulfate, sodium, magnesium, calcium, and potassium. The ratio of the number of milligram atoms of any one of these to that of any other is a constant.[8] The concentrations of the elements comprising these ions for a sea water having a chlorinity of 19.00‰[9] are as follows:

	Mg. at./kg. of sea water
Chlorine	535.0
Sodium	454.0
Magnesium	52.30
Sulfur (sulfate)	27.63
Potassium	9.6

The solutions were prepared by taking a fixed mass of pure water, 1 kg., to which were added the various salts in the proper concentrations. It should be noted that this method differs from that in which the number of grams of salt per kilogram of solution is considered.

The constituents used were salts that are comparatively easy to purify and handle quantitatively in the dry condition. The sodium and potassium ions were introduced as chlorides, the sulfate and magnesium ions as magnesium sulfate.

TABLE I

SHOWING THE WEIGHT OF SALT ADDED TO 1 KG. OF WATER

Approximate chlorinity	19‰	14‰	8‰	4‰
	Sodium Chloride Solutions			
NaCl, g.	27.26159	19.94439	11.30020	5.61836
	Potassium Chloride Solutions			
KCl, g.	0.735220	0.537882	0.304756	0.151522
	Magnesium Sulfate Solutions			
$MgSO_4$, g.	3.41676	2.49969	1.41629	0.704166
	Sodium Chloride, Potassium Chloride Solutions			
NaCl, g.	27.26159	19.94439	11.30020	5.61836
KCl, g.	0.735220	0.537882	0.304756	0.151522
	Sodium Chloride, Magnesium Sulfate Solutions			
NaCl, g.	27.26159	19.94439	11.30020	5.61836
$MgSO_4$, g.	3.41678	2.49969	1.41629	0.704166

Sodium chloride was present in all of the solutions containing two salts. In preparing such solutions the approximate amount of a stock solution of the salt, other than sodium chloride, required to prepare about a liter of the desired solution was weighed accurately in a ground glass-stoppered flask. From this, the required weight of

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(1) Read before the Ninety-Fifth Meeting of the American Chemical Society at Dallas, Texas, April, 1938. For supplementary tabular data, order Document 1142, American Documentation Institute, 2101 Constitution Ave., Washington, D. C., remitting $1.00 for 6″ × 8″ photoprints or 28¢ for microfilm.

(2) "International Critical Tables," Vol. III, 1938, p. 25.

(3) Theodore Shedlovsky, THIS JOURNAL, **54**, 1417 (1932).

(4) G. H. J. Bailey, *J. Chem. Soc.*, **51**, 676–683 (1887).

(5) Adolph Schröder, *Ber.*, **4**, 471 (1871).

(6) Edward W. Washburn, THIS JOURNAL, **40**, 111 (1918).

(7) Thomas G. Thompson, *J. Chem. Ed.*, **13**, 203–209 (1936).

(8) Thomas G. Thompson, "Contribution to Marine Biology," Stanford University Press, 1930, p. 79.

(9) 19.00‰ means 19 parts per thousand by weight.

sodium chloride and of the desired solution was calculated. The calculated amount of dry sodium chloride was weighed out and added to the solution in the flask, which was then made up to the calculated weight by the addition of equilibrium water. All weights were corrected to vacuum for the purpose of computation and to the conditions pertaining in the laboratory for the purpose of weighing. The apparatus used for weighing has been described.[10] The solutions, as well as the equilibrium water used in their preparation, were kept in well seasoned and steamed Pyrex ground glass-stoppered bottles.

Experimental Results

The specific gravities of each of the following solutions were measured at 0, 5, 10, 15, 20, and 25°: sodium chloride, potassium chloride, magnesium sulfate, sodium chloride plus potassium chloride, and sodium chloride plus magnesium sulfate. Each of these was found by direct comparison with one of the values for water given in the "International Critical Tables." The experimentally determined data are accurate to five decimal places, the sixth being a close estimate in most cases. Duplicate values usually agreed exactly to five decimal places. A total of 120 determinations was made.

The specific gravities of the solutions were computed by the usual method. The volume of the bulb, its weight *in vacuo*, and its weight immersed in the solution at each temperature were redetermined several different times during the work, but no appreciable departure from the original values was observed.

The equation proposed by Root,[11] contains

$$D = D_0 + pN + qN^{3/2}$$

two constants p and q which are different for each type of solution and at each temperature. These constants were evaluated by the method of least squares at each of the six temperatures for each type of solution measured, and their values are listed in Table II. D and N are density and normality, respectively. Normalities were computed from the data in Table I, using the 1936 atomic weights.

After p and q were obtained for a particular type of solution, the specific gravities were calculated for the concentrations at which measurements were made and for concentrations at which specific gravity data were found in the "International Critical Tables."

TABLE II

CONSTANTS FOR THE ROOT EQUATION

Approx. no. mg. eq. wts. per 1 soln.	°C.	p	q
		Sodium chloride	
100 to 500	25	0.041916	−0.001853
	20	.042432	− .001990
	15	.042995	− .002052
	10	.043740	− .002204
	5	.044660	− .002391
	0	.045846	− .002684
		Potassium chloride	
2 to 10	25	.04570	.0211
	20	.04710	.0110
	15	.04802	.0050
	10	.04884	.0015
	5	.04949	.0023
	0	.05141	− .0088
		Magnesium sulfate	
10 to 60	25	.06340	− .00795
	20	.06331	− .00611
	15	.06423	− .00854
	10	.06440	− .00710
	5	.06476	− .00579
	0	.06631	− .00890
		Sodium chloride and potassium chloride	
100 to 500	25	.041983	− .001776
	20	.042467	− .001868
	15	.043042	− .001952
	10	.043759	− .002057
	5	.044728	− .002321
	0	.046004	− .002760
		Sodium chloride and magnesium sulfate	
100 to 500	25	.044213	− .002090
	20	.044658	− .002158
	15	.045240	− .002285
	10	.045968	− .002442
	5	.046880	− .002661
	0	.048054	− .002987

Table III is illustrative of the agreement between the observed and calculated values for two mixed solutions at two of the temperatures.

The agreement between the calculated and observed values, not given in Table III, is also in every instance within 5 in the sixth decimal place. Thus the equation proposed by Root is shown to reproduce the experimental results within the limit of experimental error in the case of mixed salt solutions as well as pure salt solutions in all the concentrations and at all the temperatures measured.

The most exact applicable data found in the "International Critical Tables" are for potassium chloride at 20°. They are reported to eight decimal places. These data and the values calculated from the constants given in Table II are consistent within the limits of experimental error.

[10] Raymond W. Bremner and Thomas G. Thompson, THIS JOURNAL, **59**, 2372 (1937).

[11] William C. Root, *ibid.*, **55**, 850–851 (1933).

TABLE III

SPECIFIC GRAVITIES OF MIXED SOLUTIONS

Mg. eq. wts. per kg. water		Mg. eq. wts. per 1 soln.	Sp. gr. obsd.	Sp. gr. calcd.	Difference (10^6)
SODIUM CHLORIDE AND POTASSIUM CHLORIDE					
Temperature 25°					
NaCl	KCl				
466.377	9.86172	470.805	1.016267	1.016266	1
341.198	7.21473	345.247	1.011206	1.011209	3
193.318	4.08775	196.147	1.005156	1.005155	1
96.116	2.03241	97.695	1.001123	1.001122	1
Temperature 0°					
466.377	9.86172	472.870	1.020725	1.020725	0
341.198	7.21473	346.627	1.015252	1.015251	1
193.318	4.08775	196.835	1.008679	1.008682	3
96.116	2.03241	98.004	1.004290	1.004292	2
SODIUM CHLORIDE AND MAGNESIUM SULFATE					
Temperature 25°					
NaCl	$MgSO_4$				
466.377	56.766	517.300	1.019167	1.019167	0
341.198	41.530	379.327	1.013359	1.013357	2
193.318	23.530	215.492	1.006391	1.006393	2
96.116	11.699	107.325	1.001746	1.001746	0
Temperature 0°					
466.377	56.766	519.609	1.023716	1.023718	2
341.198	41.530	380.865	1.017472	1.017468	4
193.318	23.530	216.257	1.009960	1.009960	0
96.116	11.699	107.666	1.004932	1.004936	4

Specific gravity values for sodium chloride solutions at 0, 10 and 25° are reported in the "International Critical Tables" to five decimal places. Using the concentrations listed and the above constants, these specific gravities were calculated by means of the equation proposed by Root. The deviations of the calculated values from those given in the "International Critical Tables" range from 0.00002 to 0.00023. These deviations are large considering that the data are reported to five decimal places. They are all negative but are considerably larger at 25 and 0° than they are at 10°. In some instances they increase with concentration while in others they decrease. It is evident that the "International Critical Tables" data for sodium chloride do not conform to the Root equation as well as those for potassium chloride.

Summary

1. The specific gravities of various solutions of salts occurring in sea water have been measured at 5° intervals from 0 to 25° inclusive.

2. The solutions were prepared to contain the pure and mixed salts in concentrations covering the range found in nature.

3. The specific gravity measurements, which are accurate to five decimal places and closely estimated to the sixth, were made by the method of weighing a weighted glass bulb suspended in the solutions.

4. Some of the data on the specific gravity of sodium chloride solutions reported to five decimal places in the "International Critical Tables" can be represented by the equation proposed by Root to only four decimal places. Certain more accurate data on potassium chloride solutions have been shown to be entirely consistent with the data reported in this paper.

5. The equation proposed by Root has been shown to reproduce the experimental results, within the limits of experimental error, at each of the six temperatures used. It applies equally well to solutions containing one solute and to those containing sodium chloride plus potassium chloride and sodium chloride plus magnesium sulfate. The constants for this equation have been calculated at six temperatures for each of the five types of solutions studied.

SEATTLE, WASHINGTON RECEIVED JULY 5, 1938

[CONTRIBUTION FROM THE AGRICULTURAL EXPERIMENT STATION AND DEPARTMENT OF PHYSICS, UNIVERSITY OF FLORIDA]

The Infrared Absorption Spectra of Some Sugars and Furans

BY LEWIS H. ROGERS AND DUDLEY WILLIAMS

In a previous paper,[1] the authors reported a study of the infrared absorption spectrum of Vitamin C. At that time a band was observed at 4 μ which, it was suggested, may have arisen from the lactone linkage. Additional studies on similar compounds are reported in this paper.

The infrared absorption spectra between 2 and 12 μ have been mapped for the following furans: furfural, tetrahydrofurfuryl alcohol, furfuryl alcohol and hydrofuramide. Spectra between 3 and 12 μ have been studied for the following sugars: *d*- and *l*-arabinose, *d*-lyxose, *l*-xylose, *d*-galactose, *d*-mannose, levulose and dextrose. Several studies of the Raman spectra of the furans have been reported,[2] while Coblentz[3] studied the infrared spectra of levulose and dextrose in approximately the same region as that studied here.

The spectrometer and experimental details have been described elsewhere;[1] the only change which has been made consists of the addition of a current amplifier employing two photocells. With the furans, rock salt absorption cells were used, which were of approximately 0.05 mm. thickness. The liquid furans were introduced directly into the cells; hydrofuramide, however, was melted onto the rock salt plates. The data are corrected for the absorption of the rock salt. The furans were contributed by the Quaker Oats Company.

Saturated water solutions of the sugars were used and fluorite cells of approximately 0.02 mm. thickness, together with a comparison cell of fluorite containing water. The sugars were obtained from Eastman Kodak Co.

In Fig. 1 are presented the transmission curves for the furans. Table I summarizes these data. In Table II, data are given on the sugars.

Discussion

The furans show considerable similarity in their absorption spectra in the region studied. In Fig. 1, it will be noted that the bands which occur in the 3–3.5 μ region are more pronounced in the alcohols than in the other two furans, a result which is to be expected, since no OH groups appear in furfural and hydrofuramide. From 5.6 to 6.6 μ there are several bands which arise from C═O, C═C or C═N. Tetrahydrofurfuryl alcohol, which contains none of these groups, exhibits no distinct bands in this region. Furfural contains a band at 5.9 μ which is characteristic of the C═O linkage. Again, in the 10 to 11 μ region, a band known to arise from the C—C linkage is found in all the furans.

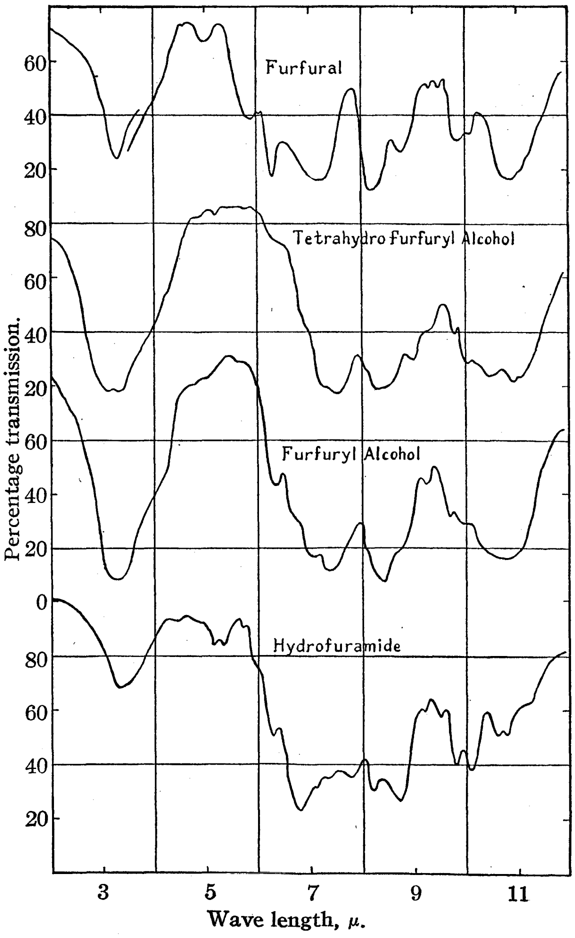

Fig. 1.

It will be seen that at 4 μ no band was observed in any of the furans. This would seem to indicate that the band observed at this wave length in Vitamin C was not due to a vibration involving the lactone linkage, as was previously suggested.[1]

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(1) D. Williams and L. H. Rogers, THIS JOURNAL, **59**, 1422 (1937).

(2) W. E. Catlin and H. A. Wilhelm, *Iowa State Coll. J. Sci.*, **10**, 135 (1936). A complete bibliography is given in this paper.

(3) W. W. Coblentz, *Carnegie Inst. of Wash.*, Pub. No. 65 (1906).

TABLE I

FREQUENCIES OF THE OBSERVED ABSORPTION MAXIMA OF SOME FURAN DERIVATIVES

Frequencies cm.$^{-1}$	Probable origin	Raman frequencies[2] cm.$^{-1}$
	Furfural	
3030	ν(C—H)	3142
2000		
1700	ν(C=O)	1691
1590	ν(C=C)	1569
1390		1395
1220		1223
1140		1156
1020		1024
925	ν(C—C)[a]	931
	Tetrahydrofurfuryl alcohol	
3120	ν(C—H), ν(O—H)	
1330		
1190		
1110		
1020		
1000		
950		
915	ν(C—C)[a]	
	Furfuryl alcohol	
3030	ν(C—H), ν(O—H)	3110
1590	ν(C=C)	1599
1430	δ(CH$_2$)	
1350		
1190		
1090		1091
1000		1015
925	ν(C—C)[a]	
	Hydrofuramide	
3030	ν(C—H)	
1960		
1890		
1590	ν(C=N)	
1470		
1280		
1220		
1150		
1020		
990		
933	ν(C—C)[a]	

[a] Barnes [*Rev. Sci. Instruments*, **7**, 265 (1936)] gives ν(C—C) as 980 cm.$^{-1}$; therefore the frequencies of 1000 cm.$^{-1}$ possibly should be assigned to ν(C—C) instead of those given.

TABLE II

FREQUENCIES OF OBSERVED ABSORPTION MAXIMA OF SOME PENTOSES AND HEXOSES

Frequencies cm.$^{-1}$	Probable origin	Frequencies cm.$^{-1}$	Probable origin
	d-Arabinose		*d*-Mannose
3030	ν(C—H), ν(O—H)	3030	ν(C—H), ν(O—H)
2040		2080	
1700	ν(C=O)	1725	ν(C=O)
1560		1350	δ(CH$_2$)
1390	δ(CH$_2$)	1040	
1220			
1090			
	l-Arabinose		*d*-Galactose
3030	ν(C—H), ν(O—H)	3030	ν(C—H), ν(O—H)
2040		2040	
1700	ν(C=O)	1725	ν(C=O)
1370	δ(CH$_2$)	1590	
1220		1370	δ(CH$_2$)
1110		1125	
	l-Xylose		Dextrose
3030	ν(C—H), ν(O—H)	3030	ν(C—H), ν(O—H)
2080		2080	
1725	ν(C=O)	1670	ν(C=O)
1350	δ(CH$_2$)	1590	
1100		1370	δ(CH$_2$)
960		1100	
		1000	
	d-Lyxose		Levulose
3030	ν(C—H), ν(O—H)	3030	ν(C—H), ν(O—H)
2080		1890	
1750	ν(C=O)	1350	δ(CH$_2$)
1590		1100	
1350	δ(CH$_2$)		
1100			

In column 4 of Table I are given some of the Raman frequencies reported by Catlin and Wilhelm.[2] The agreement in the case of furfural is good with the exception of the 3030 cm.$^{-1}$ frequency. This discrepancy is to be expected, since the high frequency OH vibration is active in the infrared, but is inactive in the Raman effect. On account of the low resolution obtainable in the 3 μ region with a rock salt prism the C–H and O–H bands could not be separated. The other frequencies reported here are apparently not active in the Raman effect. Similarly, certain Raman frequencies do not appear in the infrared.

The data in Table II for the eight sugars studied are strikingly similar for each compound. Charlton, Haworth and Peat[4] have discussed the possibility of a lactone linkage occurring in some of these sugars; since no band was observed at 4 μ in these materials, there is no evidence indicating that a lactone linkage gives rise to a band at this point.

The data in Table II for dextrose are in partial agreement with Coblentz' data,[3] since he reported a broad absorption maximum between 3 and 4 μ and another maximum at 4.8 μ. Beyond 7 μ, however, Coblentz was unable to detect any transmission. In the present study, thinner

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[4] W. Charlton, W. N. Haworth and S. Peat, *J. Chem. Soc.*, 89–101 (1926).

cells permitted the extension of the data to longer wave lengths. Also, it should be noted that Coblentz made his measurements with melted samples while in the present study sugar solutions were used. Furthermore, small bands were found at 6.0 μ and 6.3 μ which were not reported by Coblentz. In the case of levulose, agreement between Coblentz' data and those reported here is still less satisfactory. There is agreement on the 3.3 μ band, but Coblentz reports a band at 5.85 μ which is not noted here, and another at 5.3 μ reported here is not shown by Coblentz. Again, thinner cells permitted the extension of this study to longer wave lengths.

The effect of the solvent on the absorption of the sugars is very slight; also, no variation of the spectra of the solutions with time was detected.

Summary

The infrared absorption spectra for four furan derivatives, four pentoses and four hexoses between 2 and 12 μ have been mapped and the results compared with Raman and infrared data from other sources. Several bands were common to all the furans. Data on sugar solutions are in fair agreement with earlier results obtained in studies of melted compounds. No pronounced differences occurred between the spectra of any of the sugars studied.

GAINESVILLE, FLA. RECEIVED JULY 28, 1938

[CONTRIBUTION FROM NAVAL STORES RESEARCH DIVISION, BUREAU OF CHEMISTRY AND SOILS, U. S. DEPARTMENT OF AGRICULTURE]

The Dihydroabietic Acids from So-called Pyroabietic Acids

BY E. E. FLECK AND S. PALKIN

In a previous paper it has been shown that so-called "α-pyroabietic acid" prepared from *l*-abietic acid by the catalytic method, was a mixture of dehydro-, dihydro- and tetrahydroabietic acids.[1] It was pointed out, however, with regard to the *di*hydro acid ($[\alpha]^{20}\text{D}$ $-3°$) isolated, that while the combustion data were in good agreement with those calculated for the dihydro compound, the rotation did not conform to that indicated by the Biot relationship[2] in that the latter pointed to a dihydroabietic acid of high positive rotation.

This compound ($[\alpha]^{20}\text{D}$ $+108°$) has now been isolated by first removing the tetrahydroabietic acid as the insoluble ammonium salt and then the dehydroabietic acid as the crystalline methyl ester. The non-crystalline residue of methyl esters was saponified with 10% *n*-butyl alcoholic potassium hydroxide to obtain the new dihydroabietic acid.

Another dihydroabietic acid ($[\alpha]^{20}\text{D}$ $+ 9.0°$, m. p. 193–194°) from α-pyroabietic acid mixture prepared by heat, without catalyst has been reported recently by Ruzicka *et al.*[3]

Further work on the previously reported dihydro compound ($[\alpha]^{20}\text{D}$ $-3°$, m. p. 130–131°), which was isolated by partial sulfonation of the non-crystalline portion of the mixed methyl esters and subsequent hydrolysis of the unsulfonated part, has now been found to be a lactone, as it took up no alkali on direct titration. This lactone was found to be identical with that reported by Hasselstrom, *et al.*,[4] who also obtained it as a sulfonation by-product, and with that reported earlier by Ruzicka, *et al.*,[5] who prepared it by the action of hydrobromic acid on dihydroabietic acid.

By treatment with butyl alcoholic potassium hydroxide, the lactone yielded hydroxytetrahydroabietic acid, m. p. 164–165°, identical with that reported by the above authors.

Experimental Part

Fifty grams of *l*-abietic acid was converted into "pyroabietic" acid mixture at 225° as previously described.[1] The yield was 47 g. of a product that melted at 166–168° and showed $[\alpha]^{20}\text{D}$ $+62°$ in absolute alcohol. This mixture was dissolved in 180 cc. of alcohol and 425 cc. of 0.4 *N* ammonium hydroxide. On standing overnight at room temperature fine needles separated which consisted chiefly of tetrahydroabietic acid. These were removed by filtration. A second and third crop of crystals was obtained from the mother liquor at intervals of several days. The crystalline ammonium salts were recrystallized and the mother liquors were united with the original filtrate. The combined mother liquors were evaporated to dryness on the

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(1) Fleck and Palkin, THIS JOURNAL, **60**, 921 (1938).

(2) *Ibid.*, citation 11, p. 924.

(3) Ruzicka, Bacon, Sternbach and Waldmann, *Helv. Chim. Acta*, **21**, 595–596 (1938).

(4) Hasselstrom, Brennan and McPherson, THIS JOURNAL, **60**, 1267 (1938).

(5) Ruzicka, Meier, Waldmann and Hösli, *Helv. Chim. Acta*, **5**, 333 (1922); **16**, 139 (1933).

steam-bath. The residue was taken up in ether and shaken, first with dilute hydrochloric acid, and then with water. The ether was distilled and the residue (19.5 g.) was esterified with diazomethane in the usual manner.

The solvents were removed under reduced pressure and the residue was taken up in methyl alcohol. The solution was cooled to 0° and water was added until the solution became cloudy. On standing several days at 0° the crystalline methyl ether of dehydroabietic acid was deposited. By addition of more water to the filtrate a semi-crystalline deposit was obtained. The supernatant liquid was decanted and the methyl alcohol distilled under reduced pressure.

Nine grams of the resulting oil was refluxed for three hours with 90 cc. of *n*-butyl alcohol and 9 g. of potassium hydroxide. The butyl alcohol was removed by steam distillation. When the residue was cooled an amorphous potassium salt separated. Ether was added to the mixture and the aqueous layer was removed. This aqueous layer did not contain an appreciable amount of potassium salt of dihydroabietic acid. The ether solution was then shaken out with 0.25 *N* sodium hydroxide. The aqueous extract was shaken twice with fresh ether and then the dihydroabietic acid was isolated by addition of dilute hydrochloric acid, extraction with ether and evaporation of the solvent.

Eight grams of this light yellow product was dissolved in 35 cc. of alcohol and 50 cc. of 0.4 *N* ammonium hydroxide. On standing overnight 1.3 g. of stout prisms separated. The free acid was liberated as outlined above and the residue was recrystallized from alcohol. The final product melted at 174–176° and gave a yellow color with tetranitromethane: $[\alpha]^{20}\text{D}$ +108°; *c*, 2.043% in absolute alcohol.

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.88; H, 10.60; neut. equiv., 304.3. Found: C, 78.70, 79.00; H, 10.55, 10.32; neut. equiv., 310.

52.1 mg. of substance was dissolved in 10 cc. of alcohol and directly titrated with 0.1 *N* sodium hydroxide against phenolphthalein: neutralization equivalent, 310; calcd., 304.3.

Hydroxytetrahydroabietic Acid.—A solution of 50 mg. of the lactone in 10 cc. of 10% *n*-butyl alcoholic potassium hydroxide was refluxed for five hours. The butyl alcohol was removed by steam distillation, the aqueous solution diluted with water and extracted three times with ether to remove any neutral material. The aqueous solution was then made acid to litmus and neutral to congo red by addition of dilute acetic acid. The crystalline precipitate which separated was extracted with ether, the ether solution washed with water and the solvent evaporated. The residue after recrystallization from dilute methyl alcohol had a melting point of 164–165°.

Anal. Calcd. for $C_{20}H_{34}O_3$: C, 74.47; H, 10.63. Found: C, 74.25; H, 10.88.

Summary

A dihydroabietic acid of high positive rotation has been isolated from so-called "α-pyroabietic acid" prepared by the catalytic method.

Another compound of the same elemental composition, previously thought to be a dihydro compound, was found to be a lactone.

WASHINGTON, D. C.

RECEIVED JULY 29, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Vinyl Halide Polysulfones. Peracetic Acid as a Catalyst for the Reaction between Sulfur Dioxide and Olefins[1]

BY C. S. MARVEL AND F. J. GLAVIS

Polysulfones have been obtained from many common olefins and olefin derivatives and sulfur dioxide by using various organic peroxides to catalyze the reaction. However, up to this time no descriptions of the polysulfones prepared from vinyl chloride and vinyl bromide have appeared. Solonina[2] and Staudinger and Ritzenthaler[3] report failures to obtain the addition reaction between vinyl chloride and sulfur dioxide. Recently Frey, Fitch and Snow[4] intimate that the reaction occurs readily although they do not give the details of the preparation or a complete description of the product.

We have found that vinyl chloride and vinyl bromide will combine with sulfur dioxide to give polysulfones which have two vinyl units for each sulfur dioxide unit. In this respect they differ from all other olefins, olefin derivatives, or acetylenes which have been examined previously.

The addition reaction appears to require an especially effective catalyst and in our early experiments could only be brought about in the presence of an unusually "active" sample of paraldehyde which contained peroxides.

A closer examination of the paraldehyde samples which were tried as catalysts showed that the ones which would cause the reaction to run smoothly not only contained peroxides but also were strongly acidic and showed absorption

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[1] Paper No. VIII. For the seventh communication see THIS JOURNAL, **60**, 1450 (1938).

[2] Solonina, *J. Russ. Phys.-Chem. Soc.*, **30**, 826 (1898); *Chem. Zentr.*, **70**, I, 248 (1899).

[3] Staudinger and Ritzenthaler, *Ber.*, **68B**, 455 (1935).

[4] Frey, Fitch and Snow, U. S. Patent 2,114,292 (1938).

in the ultraviolet at 2400 Å. Other samples of paraldehyde which did not show all of these properties were relatively non-effective as catalysts. This combination of properties suggested to us that the active constituent in the aged paraldehyde was peracetic acid.

A sample of peracetic acid in acetic anhydride was prepared by the method of Böeseken, Cohen and Kip[5] and without attempting to purify it was tested as a catalyst for the vinyl chloride–sulfur dioxide reaction. The reaction took place quickly and gave a good yield of polymer. This result is especially significant as it is now possible to bring about the addition reaction with a catalyst which can be prepared readily whereas previously it was necessary to examine many samples of paraldehyde before finding one that was effective.

Peracetic acid also proved to be an effective catalyst to bring about the addition of sulfur dioxide to allyl chloride as well as for the simple olefins and acetylenes which have been reported in earlier papers[1] as condensing when active paraldehyde was used as a catalyst. However, no polysulfones could be obtained from allyl bromide, 1,2,3-trichlorobutene or 1-bromoheptene.

Several structural formulas seem quite possible for the vinyl chloride polysulfone but as yet it is impossible to decide which one is correct. The polymer is a white, amorphous, insoluble, high-melting compound. On heating it loses sulfur dioxide. When treated with liquid ammonia it is not degraded to a cyclic disulfone as are most of the polysulfones from the other olefins[1] which have been studied. Vinyl chloride polysulfone reacts with liquid ammonia to produce a nitrogen-containing polymer with the approximate composition $[(CH_2CHNH_3Cl)_2SO_2]_x$. Aniline also reacts with vinyl chloride polysulfone to yield a product which contains nitrogen. Treating the polysulfone with hot aqueous sodium hydroxide solution removes about one-third of the chlorine as hydrogen chloride, leaving a black insoluble polymer. Boiling the polysulfone with 7% sodium hydroxide and distilling with steam at the same time, causes the polymer to darken instantaneously and gives a distillate which contains very small quantities of an aldehyde. A 2,4-dinitrophenylhydrazone of this aldehyde melting at 127–129° has been isolated and analyzed. The analysis indicates that this derivative has one C_3H_5 unit for each dinitrophenylhydrazone residue. The product is apparently not the 2,4-dinitrophenylhydrazone of acetone (m. p. 128°).[6]

Further work must be done to characterize this compound and to establish the way in which the two vinyl chloride units are combined with one sulfur dioxide unit in the polymer. It should be mentioned that vinyl bromide polysulfone gives essentially the same reactions as the chloride in all cases which have been examined.

Some copolymers of vinyl chloride, 1-pentene and sulfur dioxide have been obtained using ascaridole as a catalyst although ascaridole will not cause vinyl chloride and sulfur dioxide to combine in a reasonable time. Benzoyl peroxide did not bring about the formation of a copolymer. Analysis of this copolymer indicated that the ratio of constituents may be one mole of vinyl chloride to one mole of 1-pentene to two moles of sulfur dioxide. A copolymer prepared from a mixture of vinyl chloride and phenylacetylene with sulfur dioxide seemed to have these constituents present in the ratio of two moles to one mole to two moles, respectively.

Some rather rough freezing point determinations of solutions of styrene, 1-pentene, 10-hendecenoic acid and vinyl chloride in liquid sulfur dioxide showed that there was apparently no compound formation in the absence of a catalyst in the first three cases. Styrene and sulfur dioxide mixtures showed a eutectic at 27 mole per cent. of styrene, and 10-hendecenoic acid and sulfur dioxide mixtures showed a eutectic at 4 mole per cent. of the acid. 1-Pentene and sulfur dioxide mixtures gave a complex melting point curve similar to that observed by Seyer and Hugget[7] in their careful study of the system 1-hexadecene–sulfur dioxide. On the other hand, vinyl chloride and sulfur dioxide mixtures showed eutectics at 37 mole per cent. of vinyl chloride and 98 mole per cent. of vinyl chloride and a peak indicating compound formation at approximately 40 mole per cent. of vinyl chloride. While it is impossible to relate this compound to the composition of the polysulfone which is obtained in the presence of a catalyst, it is of interest that only in the case of vinyl chloride was compound formation noted in the solution, and this is the only olefin derivative to combine in a two to one ratio with sulfur dioxide to yield a polysulfone.

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[5] Böeseken, Cohen and Kip, *Rec. trav. chim.*, **55**, 815 (1936).

[6] Curtius and Dedichen, *J. prakt. Chem.*, [2] **50**, 266 (1894).

[7] Seyer and Hugget, *Trans. Roy. Soc. Can.*, **18**, 213 (1924).

Experimental Part

Vinyl Chloride Polysulfone.—To a mixture of equal volumes of liquid vinyl chloride and liquid sulfur dioxide was added about a half volume of active paraldehyde and one-fifth volume of 95% ethanol. The ice-cold mixture was sealed in a pressure bottle and allowed to warm to room temperature. The reaction apparently was complete in one hour and longer standing did not increase the yield. The polymer separated as an insoluble powder as it formed. The reaction flask was cooled and opened and the contents were poured into ether. The polymer was isolated by filtration and was purified by repeated washing with alcohol. Unless the product was washed thoroughly it would turn dark on standing. The dark material had very nearly the same analysis as the white product. The yields varied with the effectiveness of the catalyst from about 5 to 30%. The reaction goes so quickly that practically the same yields are obtained by running the reaction in an open vessel. Addition of larger amounts of catalyst did not increase the yield, but when the reaction was carried out under conditions which permitted recovery of the unused vinyl chloride, it was found that the recovered material gave as good results as the original material when a fresh charge of catalyst was added.

When ascaridole and benzoyl peroxide were tried as catalysts for the addition reaction, no polysulfone was obtained in six hours. Over a longer period some dark colored material was obtained from reaction mixtures containing ascaridole. With benzoyl peroxide no product was obtained even after twenty-four hours. When 15 cc. of the solution of peracetic acid prepared from 97.3 g. of acetic anhydride, 20 g. of 30% hydrogen peroxide and 1 g. of *p*-toluenesulfonic acid[5] was used as a catalyst the polymer formed in 30% yields within one-half hour.

The polysulfone was a white amorphous powder. It darkened at 135–140° and melted at 250–275°. It was insoluble in common organic solvents except dioxane in which it was very slightly soluble.

Anal. Calcd. for $(C_4H_6Cl_2SO_2)_x$: C, 25.40; H, 3.17; S, 16.93; Cl, 37.57. Found: C, 26.42; H, 3.67; S, 17.62, 16.83, 16.53; Cl, 38.19.

Vinyl Bromide Polysulfone.—Using 10 cc. of liquid sulfur dioxide, 10 cc. of liquid vinyl bromide, 5 cc. of active paraldehyde and 2 cc. of 95% ethanol there was obtained 1–2.5 g. of polysulfone. It was isolated and purified as described for the chlorine analog. The product melted with decomposition at 200–225°.

Anal. Calcd. for $(C_4H_6Br_2SO_2)_x$: S, 11.51; Br, 57.55. Found: S, 10.92; Br, 54.13.

Reactions of Vinyl Chloride Polysulfone

With Liquid Ammonia.—When 1 g. of vinyl chloride polysulfone was dissolved in 100 cc. of liquid ammonia a deep blue solution formed. Evaporation of the ammonia left 0.5 g. of dark colored residue insoluble in organic solvents and acetic acid.

Anal. Calcd. for $(C_4H_{12}Cl_2N_2SO_2)_x$: C, 21.52; H, 5.38; S, 14.38; N, 12.55. Found: C, 23.19, 22.50; H, 6.09, 7.39; S, 13.32, 15.79, 15.42, 13.55, 15.32; N, 12.46.

With Aniline.—One gram of the polysulfone was dissolved in 25 cc. of aniline and the solution allowed to stand at room temperature for fifteen hours. Most of the aniline was removed by distillation under reduced pressure. When about 5 cc. of solution remained, the residue was poured into 100 cc. of 95% ethanol. The precipitate was collected on a filter and washed with ethanol. The residue weighed about 1 g.

Anal. Calcd. for $(C_{10}H_{12}NClSO_2)_n$: C, 48.9; H, 4.9; S, 13.1; Cl, 14.5. Found: C, 51.3; H, 5.5; S, 13.4; Cl, 14.0.

Action of Heat.—A weighed sample of vinyl chloride polysulfone was placed in 75 cc. of dioxane. A stream of air purified by leading it through an "ascarite" tube was led through the apparatus and then through standard potassium dichromate solution. The dioxane was heated to boiling for various lengths of time with different samples and the amount of sulfur dioxide liberated was determined by titration of the standard dichromate solution. In three hours using about 0.1 g. of polysulfone about 75–85% of the calculated amount of sulfur dioxide was given off. With five hours of heating the sulfur dioxide evolved amounted to 97%.

With Alkali.—When a weighed sample of polysulfone (about 0.1 g.) was suspended in standard sodium hydroxide solution and heated to boiling the mixture turned black. After six hours this mixture was acidified and titrated for chloride ion, and it was found that about one-third of the chlorine in the polymer had been removed. A reaction mixture which was refluxed for twenty-four hours gave the same result.

A mixture of 2 g. of the polymer with 75 cc. of 7% aqueous sodium hydroxide solution was distilled with steam. The distillate was collected in a solution of 2,4-dinitrophenylhydrazine. The distillate gave a positive test with fuchsin aldehyde reagent. A small amount of 2,4-dinitrophenylhydrazone was obtained. It melted at 127–129° after recrystallization from alcohol.

Anal. Found: C, 45.19; H, 3.85; N, 23.21, 23.35.

This product gave a depression in melting point when mixed with the 2,4-dinitrophenylhydrazone of acetone (m. p. 128°). While the analysis checks for $[(C_3H_5)(NNHC_6H_3(NO_2)_2)]_x$ it has not been identified further.

Vinyl Bromide Polysulfone and Liquid Ammonia.—This reaction was carried out exactly as described for the chloride analog. The product was analyzed for sulfur.

Anal. Calcd. for $(C_4H_{12}Br_2N_2SO_2)_x$: S, 10.25. Found: S, 9.25.

Freezing Point–Composition Diagrams of Solutions of Olefins in Liquid Sulfur Dioxide.—Freezing point curves were taken on solutions of styrene, 10-hendecenoic acid, 1-pentene and vinyl chloride in liquid sulfur dioxide. The olefin was introduced into a weighed glass tube and the amount thus introduced determined by weight difference. Liquid sulfur dioxide was then added and the tube weighed again. Temperature measurements were made by means of a copper–constantan thermocouple with the reference end held at 0° by an ice–water mixture. These measurements are not considered to be of great accuracy but do give some evidence of the nature of the mixtures. The freezing point–composition curves are given in Figs. 1–4.

Vinyl Chloride–1-Pentene–Sulfur Dioxide Copolymer.—An equimolecular mixture of vinyl chloride and 1-pentene

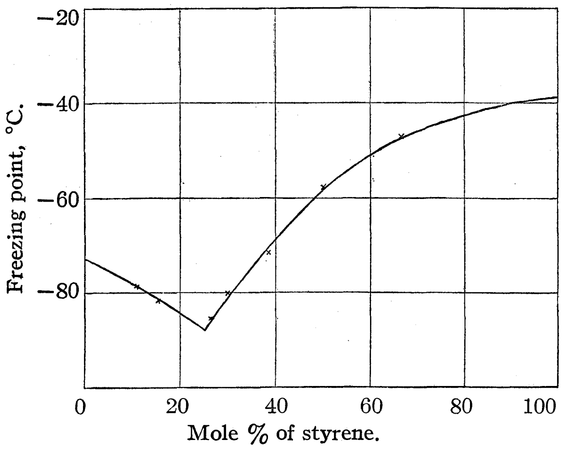


Fig. 1.—Sulfur dioxide–styrene freezing point–composition diagram.

was treated with an equal volume of liquid sulfur dioxide, catalyst and 95% ethanol and placed in a pressure bottle. The usual reaction mixture consisting of 10 parts of olefin, 10 parts of sulfur dioxide, $^1/_2$ part of catalyst and 2 parts of ethanol was used. Two catalysts, ascaridole and a mixture of ascaridole and active paraldehyde, were used without significant change in yield or properties of the product. The yield was about 50% of a polymer which melted with decomposition at 200–225°. The polymer was insoluble in common organic solvents.

Anal. Calcd. for $[C_5H_{10}C_2H_3Cl(SO_2)_2]_x$: S, 24.6; for $(C_5H_{10}SO_2)_x$: S, 23.88; for $(C_2H_3ClSO_2)_x$: S, 25.29. Found: S, 24.57, 24.07.

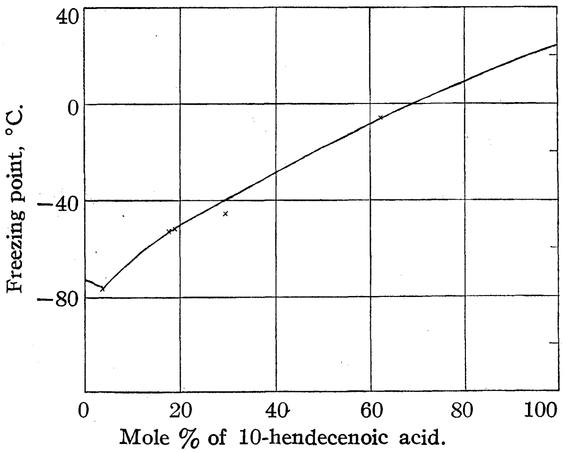


Fig. 2.—Sulfur dioxide–10-hendecenoic acid freezing point–composition diagram.

Vinyl Chloride–Phenylacetylene–Sulfur Dioxide Copolymer.—Two mixtures of vinyl chloride and phenylacetylene were treated with sulfur dioxide in the presence of ascaridole and alcohol in the usual ratios. Ten cubic centimeters of a mixture containing 13 moles of vinyl chloride for 5 moles of phenylacetylene gave 5.5 g. of a polymer which melted with decomposition at 280–285°.

Anal. Calcd. for $[(CH_2{=}CHCl)_2(C_6H_5C{\equiv}CH)(SO_2)_2]_x$: S, 18.03. Found: S, 17.97.

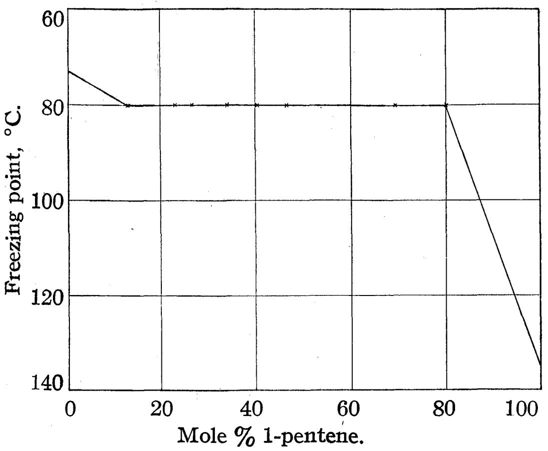


Fig. 3.—Sulfur dioxide–1-pentene freezing point–composition diagram.

Ten cubic centimeters of a mixture containing 8 moles of vinyl chloride for 5 moles of phenylacetylene gave 4 g. of polymer which melted with decomposition at 285–290°.

Anal. Found: S, 18.47.

Both polymers were insoluble in common organic solvents.

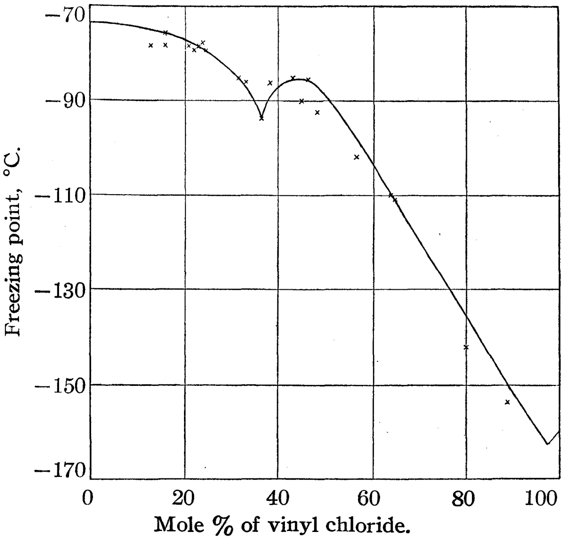


Fig. 4.—Sulfur dioxide–vinyl chloride freezing point–composition diagram.

Allyl Chloride Polysulfone.[4]—From 15 cc. of allyl chloride, 10 cc. of sulfur dioxide, 2 cc. of ethanol and 5 cc. of active paraldehyde, 2.5 g. of polymer was obtained in one hour. The polymer was slightly soluble in acetone and dioxane but insoluble in other common solvents. It melted at 185–215° and decomposed at 225–275°. Peracetic acid solution was equally effective as a catalyst for this preparation.

Anal. Calcd. for $(C_3H_4ClSO_2)_x$: S, 22.93. Found: S, 22.55.

Summary

1. The catalytic activity which certain samples

of aged paraldehyde have shown in promoting the reaction between olefins and sulfur dioxide can be obtained by use of peracetic acid solutions.

2. Vinyl chloride and vinyl bromide combine with sulfur dioxide in the presence of active paraldehyde or peracetic acid to give a polymer of the composition $[(CH_2{=}CHX)_2SO_2]_n$, rather than the usual one to one type of polymer. A preliminary study of the reaction of the vinyl halide polymer has not indicated its structural unit.

3. Freezing point–composition curves for solutions of styrene, 1-pentene and 10-hendecenoic acid in liquid sulfur dioxide offer no evidence of compound formation. But vinyl chloride and liquid sulfur dioxide form a compound containing approximately 40 mole per cent. of vinyl chloride.

URBANA, ILLINOIS RECEIVED AUGUST 1, 1938

[CONTRIBUTION OF THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Electronegativities of Highly Branched Aliphatic Groups

BY FRANK C. WHITMORE AND HERBERT BERNSTEIN

Since the well-known Kharasch table of relative electronegativities of univalent organic groups consists chiefly of aromatic groups,[1] we decided to place in the table some of the highly branched aliphatic groups available in this Laboratory. Following the method of Kharasch, the mixed dialkyl mercury compounds were treated with alcoholic hydrogen chloride.

$$R{-}Hg{-}R' + HCl \longrightarrow RHgCl + R'H$$

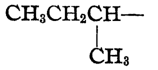
This result would place R′ above R in relative electronegativity. Of the fifteen mixed dialkyl mercury compounds used in the present study, four gave mixtures of R′HgCl and RHgCl. The groups involved in these cases are thus indistinguishable by Kharasch's method. With ten of the other compounds a clear distinction in the relative electronegativity of the groups was obtained.

The results are given in Tables I and II.

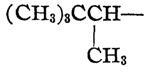
TABLE I

ORDER OF DECREASING ELECTRONEGATIVITY

Phenyl
Methyl
Ethyl
n-Propyl
$\left\{\begin{array}{l}n\text{-Butyl, }(CH_3)_3CCH_2CH_2{-}\\ n\text{-Hexyl, }(CH_3)_3CCH_2CH_2CH_2{-}\end{array}\right.$



$CH_3CH_2CH(CH_3){-}$



$(CH_3)_3CCH(CH_3){-}$

……

Benzyl
$(CH_3)_3C{-}$, $(CH_3)_3CCH_2{-}$

Groups on the same line or bracketed are not distinguishable by this method. The dotted line above the benzyl group indicates that its relation to the groups immediately above it has not been determined experimentally.

The most interesting feature of this table is the position held by the *t*-butyl and neopentyl groups. Both are less electronegative than the benzyl, which, according to Kharasch, is less electronegative than any alkyl group which he tested. Furthermore, their electronegativities approximate each other. This corresponds to the inertness of *t*-butyl chloride and neopentyl chloride in certain metathetical reactions.[2]

Also of interest is the relationship between the pinacolyl and the secondary butyl groups. The *n*-hexyl and *n*-butyl groups have the same relative electronegativity. However, the pinacolyl, a group very susceptible to rearrangement,[3] is distinctly less electronegative than the secondary butyl group.

Experimental

Neopentyl chloride was prepared by the chlorination of neopentane.[2]

1-Chloro-3,3-dimethylbutane was prepared by slowly adding 29.8 g. (0.25 mole) of thionyl chloride to a solution of 21.7 g. (0.21 mole) of neopentylcarbinol in 19.7 g. (0.25 mole) of pyridine cooled on an ice-bath. A thick white solid formed. When the addition was complete, the ice-bath was removed and the temperature of the flask raised. Decomposition of the solid occurred between 94–133°. The residue was added to a mixture of 45 g. of ice and 30 g. of concentrated hydrochloric acid, the organic layer was separated from the aqueous layer and the latter was extracted with ether. Upon distillation, 15.5 g. of

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[1] Kharasch and Marker, THIS JOURNAL, **48**, 3140 (1926); Kharasch and Flenner, *ibid.*, **54**, 685 (1932).

[2] Conant and Hussey, *ibid.*, **47**, 479 (1925); Whitmore and Fleming, *ibid.*, **55**, 4161 (1933).

[3] Whitmore and Rothrock, *ibid.*, **55**, 1106 (1933).

TABLE II

RHgR′	Melting points, °C. RHgCl pure	R′HgCl pure	HCl reaction product, crude	Mixture with RHgCl	Mixture with R′HgCl	Alkyl–HgCl formed by HCl
$(CH_3)_3CCH_2$–Hg methyl	117–118	167–168	117–117.5	117–118		Neopentyl
$(CH_3)_3CCH_2$–Hg butyl	117–118	126.5–127.0	105–112	113.5–116	82–98	Neopentyl
$(CH_3)_3CCH_2$–Hg benzyl	117–118	104–105	110–114	111–114	Below 80	Neopentyl
$(CH_3)_3CCH_2$–Hg $-CH_2CH_2C(CH_3)_3$	117–118	133.0–133.5	112–114	113–116.5	99–110	Neopentyl
$(CH_3)_3CCH_2$–Hg *t*-butyl	117–118	122–123, dec.	95–97[a]	105–115	100–117, dec.	Mixture
$(CH_3)_3CCH_2$–Hg *sec*-butyl	117–118	29–30	94–101			Neopentyl (?)
t-Butyl Hg *n*-butyl	122–123, dec.	126.5–127	119–123,[a] dec.	121–123, dec.	Below 95	*t*-Butyl
t-Butyl Hg benzyl	122–123, dec.	104.5–105	112–117,[a] dec.	117–119, dec.	Below 70	*t*-Butyl
t-Butyl Hg ethyl	122–123, dec.	193–193.5	117–118,[a] dec.	117–118, dec.	108–110, dec. 189–192	*t*-Butyl
s-Butyl Hg $-CH(CH_3)C(CH_3)_3$	29–30	89–91	83.5–88.5	87–91		Pinacolyl
s-Butyl Hg *n*-butyl	29–30	126.5–127	Liquid			*s*-Butyl
$(CH_3)_3CCH_2CH_2$–Hg *n*-butyl	133–133.5	126.5–127	89–109			Mixture
$(CH_3)_3CCH_2CH_2$–Hg $-CH_2CH_2CH_2C(CH_3)_3$	133–133.5	104.5–105	94–97	90–104	93–101	Mixture
$(CH_3)_3CCH_2CH_2$–Hg $-CH(CH_3)C(CH_3)_3$	133–133.5	88.5–90	84–90	85.5–90	75–106	Pinacolyl
$(CH_3)_3CCH_2CH_2CH_2$–Hg *n*-butyl	104.5–105	126.5–127	75–84			Mixture

[a] Dried *in vacuo* with no heat.

material (n^{20}_D 1.4161) boiling at 115° resulted. A small portion of the neohexyl chloride was converted to the Grignard reagent, the latter oxidized and the α-naphthylurethan prepared, m. p. and mixed m. p. with the α-naphthylurethan of neopentylcarbinol, 83°.

Pinacolyl chloride (2-chloro-3,3-dimethylbutane) resulted from the chlorination of neohexane.[4] 1-Bromo-4,4-dimethylpentane was made by the addition of hydrogen bromide to neopentylethylene under oxidizing conditions.[5]

Preparation of Alkyl Mercuric Chlorides.—The method used was essentially that of Marvel, Gauerke and Hill,[6] excess mercuric chloride reacting with a Grignard reagent. If the initial halide was a bromide, 70% alcohol and an equimolar quantity of silver chloride were added to the reaction mixture and the whole refluxed for five hours.

t-Butylmercuric chloride could not be recrystallized by the conventional methods, since it decomposed readily. Acetone was added to the reaction mixture at room temperature. After filtration water was added until the solution became cloudy. Enough acetone was added to clarify the solution. The acetone was then evaporated under vacuum at room temperature. The *t*-butylmercuric chloride precipitated out in long needles, m. p. 122–123° (dec.).

Analyses for mercury on the new alkylmercuric chlorides prepared were conducted by the method of Sobatzki.[7] The iodine solution was standardized against purified neopentylmercuric chloride.

TABLE III

Alkyl in RHgCl	M. p., °C. RHgCl	% Hg Found	% Hg Calcd.
t-Butyl, $(CH_3)_3C$—	122–123, dec.		
Neopentyl, $(CH_3)_3CCH_2$—	117–118	Ref. 2	
$(CH_3)_3CCH_2CH_2$—	133–133.5	62.5	62.5
Pinacolyl, $(CH_3)_3CC(CH_3)H$—	89–90	Ref. 4	
$(CH_3)_3CCH_2CH_2CH_2$—	104–105	59.5	59.8
n-Octyl, $CH_3(CH_2)_7$—	115–115.5	57.8	57.4

Preparation and Reactions of Dialkyl Mercury.—Neopentyl mercury *n*-butyl will serve as a typical example. *n*-Butylmagnesium bromide was prepared from 2.7 g. (0.02 mole) of *n*-butyl bromide and 0.48 g. (0.02 mole) of magnesium, and 3 g. (0.01 mole) of neopentylmercuric chloride was added to the Grignard reagent in small portions. The reaction was instantaneous and vigorous. The flask was surrounded by an ice-bath and the excess Grignard reagent was decomposed using 8 cc. of 0.5% sulfuric acid solution. The ether layer was decanted, shaken with 7 g. of anhydrous sodium sulfate and separated. The ether was then removed under vacuum at room temperature. The residue was divided into two portions.

To one portion of the dialkyl mercury was added 4 cc. of saturated alcoholic hydrogen chloride. After warming the flask for a minute the reaction proceeded vigorously. A portion of the resulting mixture was dried on a watch glass at 90–100°. No recrystallization was attempted, since this would change the ratio if two alkylmercuric chlorides had formed. Melting points and mixed melting points were taken (Table II).

To the second portion of the dialkyl mercury was added saturated alcoholic mercuric chloride until no more precipitate formed. The reaction was instantaneous. Neopentylmercuric chloride and *n*-butylmercuric chloride were isolated from the reaction products by fractional crystallization in aqueous alcohol, the latter precipitating first.

When the mixed dialkyl mercury compounds were treated with mercuric chloride and the products crystallized from aqueous alcohol, the following observations were made: if one of the alkyls is neopentyl the other alkylmercuric chloride separates first; if only one alkyl is normal its alkylmercuric chloride is least soluble; higher normal alkylmercuric chlorides show decreased solubility; in the case of related groups like the neohexyl and neoheptyl, the alkylmercuric chlorides could not be separated by crystallization.

Summary

1. Fifteen mixed dialkyl mercury compounds containing branched-chain groups have been treated with hydrogen chloride, the resulting alkylmercuric chlorides indicating the relative electronegativities. The *t*-butyl and neopentyl groups are the least electronegative, while the neohexyl

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[4] Whitmore, Bernstein and Mixon, THIS JOURNAL, **60**, 2539 (1938).

[5] Whitmore and Homeyer, *ibid.*, **55**, 4555 (1933).

[6] Marvel, Gauerke and Hill, *ibid.*, **47**, 3009 (1925).

[7] Whitmore and Sobatzki, *ibid.*, **55**, 1171 (1933).

and neoheptyl groups compare with the simpler straight chain groups.

2. Four new alkylmercuric chlorides have been reported. These are of use as derivatives for identifying the alkyl halides.

3. A method of recrystallizing tertiary alkylmercuric halides is given.

4. Neohexyl chloride (1-chloro-3,3-dimethylbutane) has been prepared.

STATE COLLEGE, PENNA. RECEIVED AUGUST 22, 1938

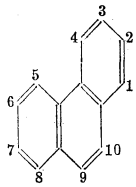
[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

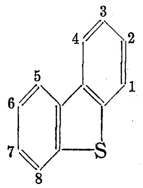
Isosteric Compounds. I. Acyl Derivatives of Dibenzothiophene

BY ALFRED BURGER, WILLIAM B. WARTMAN, JR., AND ROBERT E. LUTZ

The similarity between the physical characteristics of benzene and thiophene and their corresponding derivatives, and the agreement in the physiological behavior of certain of these compounds[1] have been subject to frequent speculation. In 1933 Erlenmeyer[2] advanced the theory that divalent sulfur contains a shell of orbit electrons similar to that of the group or "pseudoatom,"—CH=CH—, and that this similarity in electronic structure known as isosterism,[3] accounted for the formation of mixed crystals and the many like physical properties of the two series. In a few cases, isosteric compounds are interchangeable in serological reactions and cannot be differentiated by the precipitin reaction.[2a]

The present paper is the first in a series of studies on the physical and pharmacological changes effected by introducing a thiophene nucleus into condensed ring systems in place of an aromatic nucleus. The first case under investigation is dibenzothiophene (I) which may be regarded as a pseudophenanthrene. Amino alcohols derived from dibenzothiophene, characterized by the groups —CHOHCH$_2$NR$_2$ and CHOHCH$_2$CH$_2$NR$_2$, may be expected to resemble the corresponding alkamines of the phenanthrene series in analgesic action.[4] Their similarity to the corresponding alkamines derived from dibenzofuran[5] and carbazole[6] should be less marked, since oxygen and the imino group are not isosteric with the —CH=CH— group.





I

The preparation of acetyldibenzothiophenes as starting materials for the proposed dibenzothienyl alkamines is described in this communication. The direct introduction of the acetyl group by the Friedel–Crafts reaction was chosen as a suitable approach. The only ketone derived from dibenzothiophene known heretofore is stearoyl dibenzothiophene, prepared by the Friedel–Crafts reaction in boiling carbon disulfide.[7] No proof for the position of the stearoyl group has been offered, but the group is presumed to have entered position 3 which is known to be preferred in nitration, sulfonation, and halogenation.[8]

Friedel–Crafts reaction on dibenzothiophene with acetyl chloride at low temperature yielded a difficultly separable mixture of methyl ketones, from which one (II), melting at 111–112°, was separated by laborious fractional crystallization and was the major product. An isomeric monoketone, melting at 128–129°, was isolated in small amounts during this procedure. The structure of the major constituent of this mixture, 3-acetyldibenzothiophene (II), was proved by Beckmann rearrangement of its oxime. The resulting acetaminodibenzothiophene and the amine obtained from it by hydrolysis were

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(1) Steinkopf and Ohse, *Ann.*, **437**, 14 (1924); **448**, 205 (1926); Gilman and Pickens, THIS JOURNAL, **47**, 245 (1925); Hartmann and Wybert, *Helv. Chim. Acta*, **2**, 60 (1919); Jaffé and Levy, *Ber.*, **21**, 3458 (1888).

(2) (a) Erlenmeyer, Berger and Leo, *Helv. Chim. Acta*, **16**, 733 (1933); (b) Erlenmeyer and Leo, *ibid.*, **16**, 1381 (1933).

(3) Grimm, *Naturwissenschaften*, **17**, 536, 557 (1929).

(4) Mosettig, Shaver and Burger, THIS JOURNAL, **60**, 2464 (1938), footnote 2.

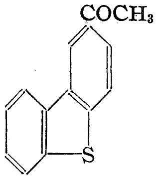
(5) Mosettig and Robinson, *ibid.*, **57**, 2186 (1935).

(6) Ruberg and Small, *ibid.*, **60**, 1591 (1938).

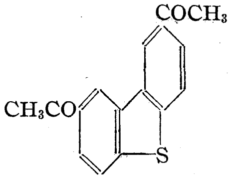
(7) Ralston and Christensen, *Ind. Eng. Chem.*, **29**, 194 (1937).

(8) (a) Courtot and Pomonis, *Compt. rend.*, **182**, 893, 931 (1926); (b) Courtot and co-workers, *ibid.*, **186**, 1624 (1928); **192**, 1667 (1931); **198**, 2003, 2260 (1934); (c) Cullinane, Davies and Davies, *J. Chem. Soc.*, 1435 (1936).

identical with 3-acetamino- and 3-aminodibenzothiophene, respectively, which had been prepared from 3-nitrodibenzothiophene.[8c]



II



III

When the Friedel–Crafts reaction was carried out in boiling carbon disulfide, the main reaction product was a diacetyldibenzothiophene. One of the acetyl groups must be attached in position 3, because the compound was formed in excellent yield by the action of acetyl chloride and aluminum chloride in boiling carbon disulfide on 3-acetyldibenzothiophene (II). The position of the second acetyl group was demonstrated when the dioxime was rearranged to 3,6-diacetaminodibenzothiophene, which on hydrolysis yielded 3,6-diaminodibenzothiophene.[8a] Our diketone must be therefore 3,6-diacetyldibenzothiophene (III).

The good yield of III obtained by drastic acetylation of dibenzothiophene and 3-acetyldibenzothiophene, respectively, suggests that the first acetyl group enters position 3 largely, and therefore II must be the chief product in the mixture of monoketones.

Experiments are under way to make more practicable the direct synthesis of dibenzothiophene ketones for preparative purposes. We are also studying the introduction of the succinoyl group. The mono- and disuccinoyl derivatives are expected to yield naphthobenzo- and dinaphthothiophenes, respectively, by the usual reactions. These compounds may exhibit carcinogenic properties similar to those of the analogous benzanthracenes and benzphenanthrene.

Experimental

Dibenzothiophene.—The dibenzothiophene used was prepared by heating diphenyl with sulfur in the presence of anhydrous aluminum chloride.[9]

Acetylation of Dibenzothiophene.—The action of acetyl chloride and anhydrous aluminum chloride on dibenzothiophene under widely varying conditions was investigated in a series of nine experiments. Carbon disulfide, nitrobenzene, tetrachloroethane, and a mixture of the latter two were employed as solvents, the reaction temperature ranging from 0 to 55°. The aluminum chloride was added to the mixture of dibenzothiophene and acetyl chloride in preference to the reverse order of addition to avoid a side reaction of the aluminum chloride with the starting material. Mixtures of methyl ketones were obtained in all cases, and only two of the experiments yielding the best results are described here.

3-Acetyldibenzothiophene.—A solution of 145 g. of aluminum chloride in 400 ml. of dry nitrobenzene was added dropwise to a well-stirred, ice-cold mixture of 95 g. of dibenzothiophene, 48 ml. of acetyl chloride, and 500 ml. of dry tetrachloroethane over a period of one hour. The mixture was stirred at 0° for two hours and allowed to stand at this temperature for twelve days. It was decomposed by pouring onto ice and hydrochloric acid. The solvent was removed by steam distillation, the brown oily residue was dissolved in benzene, the solution was filtered, and the benzene was evaporated. The crude reaction product obtained from three combined runs totalling initially 265 g. of dibenzothiophene was combined and distilled under reduced pressure, using an oil pump. The distillate was redistilled, and three fractions were collected. Treatment of the partly crystalline main fraction with methanol yielded crystals melting at 85–100°. Crystallization from benzene–petroleum ether, and purification through the semicarbazone which was hydrolyzed easily by the action of boiling dilute hydrochloric acid, failed to improve the melting point. At this stage, the yield of the purified mixture of monoketones was approximately 50%. The mixture was boiled out with two portions of 400 ml. of ether each for one half hour; the sparingly soluble portion was collected and recrystallized from methanol. Twenty grams of 3-acetyldibenzothiophene was thus obtained in colorless plates; m. p. 111–112°.

Anal. Calcd. for $C_{14}H_{10}OS$: C, 74.31; H, 4.46. Found: C, 74.10; H, 4.69.

3-Acetyldibenzothiophene semicarbazone was prepared by boiling the alcoholic solution of the ketone with a concentrated aqueous solution of the calculated amounts of semicarbazide hydrochloride and sodium acetate for ten minutes. It crystallized from ethanol as slightly yellow plates; m. p. 234–235° (dec.).

Anal. Calcd. for $C_{15}H_{13}N_3OS$: C, 63.58; H, 4.62. Found: C, 63.49; H, 5.01.

The oxime was formed by boiling 1.5 g. of 3-acetyldibenzothiophene, 1 g. of hydroxylamine hydrochloride, and 3.7 g. of barium carbonate in 75 ml. of ethanol under reflux for four hours. The barium salts were filtered, the alcoholic filtrate was concentrated and the oxime allowed to crystallize. Recrystallization from ethanol yielded colorless needles; m. p. 161–164°.

Anal. Calcd. for $C_{14}H_{11}NOS$: N, 5.81. Found: N, 5.86.

?-Acetyldibenzothiophene.—The ether extracts of the less soluble 3-isomer deposited on cooling 1 g. of a more soluble ketone as rhombic prisms. It was recrystallized from methanol; m. p. 129–130°.

Anal. Calcd. for $C_{14}H_{10}OS$: C, 74.31; H, 4.46. Found: C, 74.29; H, 5.06.

The semicarbazone formed much slower than that of the isomeric 3-acetyldibenzothiophene. It was necessary to

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(9) Private communication by A. L. Jacoby through the courtesy of Dr. Henry Gilman. See also Chapiro and Gach, *C. A.*, **27**, 2696 (1933); I. G. Farbenindustrie A.-G., *C. A.*, **28**, 1053^7 (1934).

boil the mixture for thirty minutes. It crystallized as slightly yellow plates; m. p. 302–304° (dec.).

Anal. Calcd. for $C_{15}H_{13}N_3OS$: N, 14.83. Found: N, 14.81.

Beckmann Rearrangement of 3-Acetyldibenzothiophene Oxime.—Dry hydrogen chloride was passed into a solution of 1 g. of 3-acetyldibenzothiophene oxime in 4 ml. of glacial acetic acid and 2 ml. of acetic anhydride for one hour, and the mixture was allowed to stand for twenty hours. Water was added; the crystals which had formed were filtered and recrystallized from methanol. The substance appeared as colorless needles; m. p. 181–183°.

Anal. Calcd. for $C_{14}H_{11}NOS$: C, 69.68; H, 4.60. Found: C, 69.86; H, 5.02.

A mixture melting point with 3-acetaminodibenzothiophene of the same melting point, obtained by acetylation of 3-aminodibenzothiophene with acetic anhydride in pyridine solution, showed no depression.

Hydrolysis of 3-Acetaminodibenzothiophene.—A mixture of 0.3 g. of 3-acetaminodibenzothiophene, 1.5 ml. of glacial acetic acid, and 1.5 ml. of 6 *N* hydrochloric acid was boiled under reflux for one hour. On cooling, the amine hydrochloride separated out. It was converted to the base by treatment with dilute sodium hydroxide solution, and the amine was recrystallized from alcohol. It appeared as colorless needles, m. p. 131–133°.

A mixture melting point with 3-aminodibenzothiophene of the same melting point, prepared by reduction of 3-nitrodibenzothiophene[8c] with stannous chloride and hydrochloric acid in ethanol solution showed no depression.

3,6-Diacetyldibenzothiophene.—Anhydrous aluminum chloride (3.7 g.) was added to a solution of 5 g. of dibenzothiophene and 2.1 ml. of acetyl chloride in 75 ml. of dry carbon disulfide at 10° with vigorous stirring over a period of thirty minutes. The mixture was stirred for forty-five minutes, and then boiled under reflux for five hours. It was poured onto ice and hydrochloric acid, the solvent was driven off with steam, and the brown oily residue was extracted into chloroform. The solution was evaporated, and the crystalline residue was extracted with cold benzene. The insoluble portion was recrystallized from ethanol and obtained as colorless needles; m. p. 208–209°; yield, 1.4 g.

Anal. Calcd. for $C_{16}H_{12}O_2S$: C, 71.62; H, 4.51. Found: C, 71.02; H, 4.94.

The portion soluble in benzene also contained ketones as shown by its conversion into a mixture of semicarbazones. Hydrolysis of these semicarbazones yielded a mixture of ketones, m. p. 85–100°.

3,6-Diacetyldibenzothiophene was formed in 90% yield when a solution of 1 g. of 3-acetyldibenzothiophene and 1 ml. of acetyl chloride in 20 ml. of dry carbon disulfide was treated with 1 g. of aluminum chloride, and the mixture was boiled under reflux for six hours and worked up as described above.

3,6-Diacetyldibenzothiophene Dioxime.—A mixture of 1 g. of diacetyldibenzothiophene, 1 g. of hydroxylamine hydrochloride, 3 g. of sodium acetate, and 50 ml. of ethanol was boiled under reflux for seven hours. A precipitate formed and was filtered and washed with alcohol and water. Recrystallization from ethanol yielded colorless crystals; m. p. 272–274° (dec.); yield, 1 g.

Anal. Calcd. for $C_{16}H_{14}N_2O_2S$: N, 9.38. Found: N, 8.99.

Beckmann Rearrangement of 3,6-Diacetyldibenzothiophene Dioxime.—A solution of 1 g. of the dioxime in 6 ml. of glacial acetic acid and 3 ml. of acetic anhydride was saturated with dry hydrogen chloride and allowed to stand for sixteen hours. The diacetamino compound separated out. Water was added and the product was filtered and purified by sublimation in a high vacuum and crystallization from methanol. It appeared as colorless crystals, melting at 253–255°. Courtot and Pomonis[8a] describe 3,6-diacetaminodibenzothiophene as brown crystals, m. p. 237–239° (dec.).

The diacetamino product was hydrolyzed in the same manner as the 3-acetamino compound described above. 3,6-Diaminodibenzothiophene appeared as grayish needles, m. p. 178° (dec.). This is in good agreement with the data of the French authors. However, our product could be purified by sublimation in a high vacuum and recrystallization from ethanol. It appeared then as colorless needles, m. p. 193–194° (dec.).

Summary

A Friedel–Crafts reaction with acetyl chloride on dibenzothiophene at low temperatures yields a mixture of methyl ketones from which two isomeric monoketones have been isolated. One of these ketones has been shown to be 3-acetyldibenzothiophene by degradation to 3-aminodibenzothiophene. At higher temperatures, the reaction furnishes mainly 3,6-diacetyldibenzothiophene, which could be converted to 3,6-diaminodibenzothiophene.

UNIVERSITY, VIRGINIA
RECEIVED AUGUST 8, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Substitution Reactions of Dehydroabietic Acid

BY LOUIS F. FIESER AND WILLIAM P. CAMPBELL[1]

In our paper[2,3] reporting the first preparation of the partially aromatic dehydroabietic acid, obtained from abietic acid by hydroxylation with selenium dioxide and dehydration, we advanced the hypothesis that the so-called pyroabietic acids of the literature are not isomerization products of abietic acid but mixtures of hydro and dehydro acids resulting from the disproportionation of the doubly unsaturated acid. This conception of the pyro acids, based at the time merely on the recognition that the substances contain dehydroabietic acid, as revealed in Pd-treated acid by spectroscopic data and nitration and in heat-treated acid by nitration, was promptly established by Fleck and Palkin,[4] who obtained the first conclusive evidence of disproportionation. From their Pd-treated pyroabietic acid,[5] these investigators succeeded in isolating pure dehydroabietic acid, identical with our material, a tetrahydro acid, and a substance having the composition of a dihydro acid and later identified[6] as an isomeric (known) lactone; in the recent work[6] another dihydro acid was isolated. Littmann[7] also isolated dehydroabietic acid from Pd-treated material and obtained evidence of the presence of a tetrahydride, and Ruzicka and co-workers[8] have reported experiments showing that Pd-treated and heat-treated acids are mixtures. Although heat-treated acids have been characterized less extensively than material prepared by the method of Fleck and Palkin,[5] evidence is available showing that disproportionation also occurs on heating. Hasselstrom and co-workers,[9] in an investigation of the action of sulfuric acid on a heat-treated pyro acid, obtained a crystalline sulfonic acid having the composition of a dehydroabietic acid derivative, and isolated a lactone known to be an isomerization product of a dihydroabietic acid. This is the lactone which Fleck and Palkin[6] subsequently isolated from Pd-treated acid. Ruzicka and co-workers[8] fractionated a heat-treated acid and isolated another dihydro acid and a substance corresponding in properties and spectrum to our dehydroabietic acid.

It is evident that the acid mixtures obtained by heating abietic acid either alone or with a dehydrogenation catalyst constitute a potential and abundant source of dehydroabietic acid. Since the method of preparing the pure acid previously described[2] does not provide a ready means of obtaining the acid in quantity, as required for our projected research,[2] we investigated this possible source. Probably the material richest in dehydroabietic acid is that prepared

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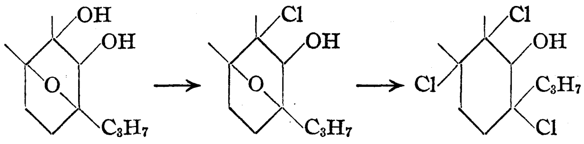
[1] Squibb Research Fellow.

[2] Fieser and Campbell, THIS JOURNAL, **60**, 159 (1938).

[3] The position regarding the structures suggested in this paper[2] for abietic acid and levopimaric acid is not altered by recent work from other laboratories. The new degradation of levopimaric reported by Wienhaus and Sandermann, *Ber.*, **71**, 1094 (1938), can be explained just as well with our formula (Δ: 7, 8; 14, 13) as with that employed for illustration by these authors (Δ: 5, 6; 7, 8), the reaction of their dihydroxy oxide with hydrogen chloride at 0° being represented as follows



The ready cleavage of the oxide bridge without disturbance of the acetylatable hydroxyl group is indeed better understandable on the assumption that the bridge is linked at each end in a tertiary rather than secondary condition. The degradations of Steele's "abietic acid" and of levopimaric acid by Ruzicka and Sternbach, *Helv. Chim. Acta*, **21**, 565 (1938), and by Ruzicka, Bacon, Lukes and Rose, *ibid.*, **21**, 583 (1938), can be interpreted, as these investigators show, with the formulas suggested. Ruzicka and Sternbach raise an interesting question concerning the validity of the evidence of conjugation in abietic acid furnished by our observation that the compound enters into the diazo coupling reaction but accept the view that conjugation is indicated by the absorption maximum. They point out, however, that some of their degradation products obtained in small amounts from the Steele acid mixture may have arisen from companion substances and not from the conjugated acid responsible for the selective absorption. This does not alter conclusions based upon results obtained with suitably purified (Palkin) abietic acid. Raudnitz, Lederer and Kahn, *Ber.*, **71**, 1273 (1938), have expressed the view that even this acid may not be homogeneous, their evidence being that purified acid and Steele acid were both found to give about 3% of acetone on prolonged treatment with ozone. Since Ruzicka, Meyer and Pfeiffer, *Helv. Chim. Acta*, **8**, 637 (1924), found that Steele acid yields isobutyric acid on ozonization as in the permanganate oxidation, it appears that ozone is capable of breaking the carbon chain as well as adding to the double bonds. The isolation of a small amount of acetone therefore seems of questionable significance. While Schultz, *Bull. inst. pin*, **38**, 25 (1938), regards the isolation of oxalic acid in good yield on oxidation of abietic acid with permanganate as an argument for the Δ: 13, 5; 6, 7-structure, this seems to us less convincing than the evidence against such a formulation, particularly since oxalic acid may arise from various parts of the molecule.

[4] Fleck and Palkin, THIS JOURNAL, **60**, 921 (1938).

[5] Fleck and Palkin, *ibid.*, **59**, 1593 (1937).

[6] Fleck and Palkin, *ibid.*, **60**, 2621 (1938).

[7] Littmann, *ibid.*, **60**, 1419 (1938).

[8] Ruzicka, Bacon, Sternbach and Waldmann, *Helv. Chim. Acta*, **21**, 591 (1938).

[9] (a) Hasselstrom, Brennan and McPherson, THIS JOURNAL, **60**, 1267 (1938); (b) Hasselstrom and McPherson, *ibid.*, **60**, 2340 (1938).

according to Fleck and Palkin[5] by heating pure abietic acid with palladium charcoal at a high temperature (250°), but there are difficulties in the way of effecting a practical recovery of pure acid by fractionation as acid or ester. We investigated the sulfonation of this pyro acid and found that sulfodehydroabietic acid can be obtained easily from this source in 61–63% yield, the non-aromatic hydro compounds and companion substances being left completely in the water-insoluble residue. It was next found that the sulfonic acid group can be removed smoothly by acid hydrolysis at 135° to give, after a single crystallization, dehydroabietic acid of perhaps slightly higher purity than that obtained from hydroxyabietic acid. The entire process is rapid, and the over-all yield of pure material from abietic acid is 42–43%.

Our purified sulfodehydroabietic acid melts with decomposition at about 248°, depending upon the manner of heating, and the analytical data correspond most closely with the formula for a hemihydrate. Hasselstrom and McPherson,[9b] on the other hand, obtained a trihydrate, m. p. 224° (uncorr.) dec., and Fanica,[10] who probably had the same sulfonic acid in hand, reports the m. p. 214° (uncorr.), dec. The free acid does not appear suitable for identification or determination of the empirical formula, but Hasselstrom and McPherson[9b] found that the diesters and the diamide fulfil these purposes, and they showed that the acid indeed belongs to the dehydro series. Our sample of the sharply melting dimethyl ester, prepared with diazomethane, corresponded exactly with theirs and analyses of this derivative and of the *p*-toluidine salt confirmed their conclusion. We can also supply the further evidence that the acid is a derivative, specifically, of the known[2] partially aromatic dehydroabietic acid, for we obtained the same acid, identified as the diester, from the pure dehydro acid as from pyro acid, and converted it into the dehydro acid as described above.

Attempts to convert sulfodehydroabietic acid into the corresponding phenol were unsuccessful. The acid is resistant to the action of alkali until a critical temperature is reached at about 300°, and at this temperature complex changes occur. The fusion was conducted in an autoclave in an atmosphere of nitrogen to avoid oxidation, but the product was found to be a mixture of at least four substances. The top fraction gave a nicely crystalline substance (A) of constant melting point (196.5–197.5°), but analyses indicated the presence of 2.5 atoms of oxygen and the substance yielded two distinctly different anilides. One of these (m. p. 257°) corresponded in composition to the anilide of an acid $C_{19}H_{24}O_3$ or $C_{20}H_{26-28}O_3$. The substance evidently contains one oxygen atom beyond that coming from the carboxyl group and may be the anilide of the desired hydroxydehydroabietic acid, $C_{20}H_{28}O_3$. The analyses of the second anilide agree best with the formula $C_{19}H_{22}O_2$ for the acid; this would be dehydroabietic acid less one molecule each of methane and hydrogen (naphthalene nucleus?). The more soluble fraction from the alkali fusion yielded only crystallizates of varying melting point, and one of these (B, composition: $C_{19}H_{26}O_2$) gave two constantly melting products on reaction of the acid chloride with aniline. One of these corresponds to the anilide of an acid $C_{19}H_{26}O_2$ (compare dehydroabietic acid: $C_{20}H_{28}O_2$). The anilides are resistant to hydrolysis, and the corresponding acids were not isolated. The results show only that the alkali fusion of the sulfonic acid is accompanied by extensive side reactions involving considerable alteration of the original structure. The phenolic hydroxyl group, if produced, is largely lost, and the molecule seems to suffer dehydration, dehydrogenation, or loss of a carbon atom in the alkali melt. Since substance A, which appears to be a molecular aggregate, was found to yield retene in 68% yield on dehydrogenation with palladium catalyst, it is probable that the carbon atom lost is that of the angular methyl group at C_{12}. With the realization that a phenolic derivative is at least not easily obtainable in quantity from this source, a further study of the fusion was not pursued.

Nitration of sulfodehydroabietic acid with mixed acid at a low temperature gave dinitrodehydroabietic acid, identical with that obtained directly from the dehydro acid.[2] A mononitro compound has not been obtainable in either reaction, even under very gentle conditions, and the smooth introduction of two nitro groups must mean that they enter meta positions. Since the only such positions available are 6 and 8, the dinitro compound very probably is the 6,8-derivative, as previously formulated.[2]

Having been unable to establish the point of attack in monosubstitution from a study of the

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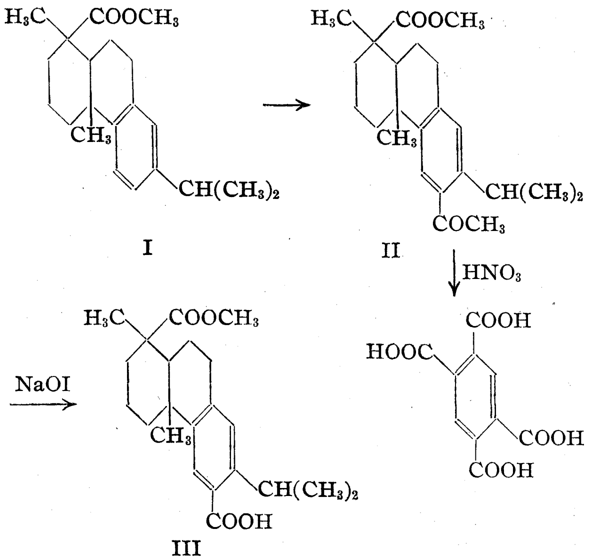
(10) Fanica, *Bull. inst. pin*, **44**, 151 (1933).



sulfonic acid, we investigated the Friedel and Crafts condensation of methyl dehydroabietate with acetyl chloride in nitrobenzene solution. This gave in good yield a beautifully crystalline and sharply melting monoacetyl derivative (II) which was characterized as the oxime and which yielded a crystalline acid on saponification. The structure was established by oxidation with dilute nitric acid, which gave a substance identified as pyromellitic acid. This proves that the acetyl group occupies the 6-position (II). Oxidation with hypoiodite in dioxane–alkali, following the procedure of Fuson and Tullock's[11] haloform test as used by Adelson and Bogert[12] for a similar oxidation of 6-acetylretene, gave methyl 6-carboxydehydroabietate, III. These and other substitution products are being investigated further.

Experimental Part[13]

Sulfodehydroabietic Acid.—One gram of the pyroabietic acid mixture of Fleck and Palkin[5] was sulfonated at −5° by a procedure similar to that of Fanica[10] and described in more detail below. The crystalline material separating from the filtered aqueous solution was crystallized once from glacial acetic acid, giving 0.76 g. (60%) of the sulfonic acid, m. p. 230° dec. After a second crystallization from this solvent the material was taken up in hot water and a small amount of insoluble resin was removed with Norite before crystallization. A further crystallization from glacial acetic acid gave very fine silky needles which when dried at 110° and 15 mm. over phosphorus pentoxide had the m. p. 247–248° dec., the temperature of decomposition varying considerably with the initial temperature of the bath and the rate of heating; $[\alpha]^{25}_{D}$ +72.4° (2.5% in alcohol[14]).

Anal. Calcd. for $C_{20}H_{28}O_5S \cdot {}^1/_2H_2O$: C, 61.68; H, 7.50; S, 8.22; neut. equiv., 195. Found: C, 61.03; H, 7.65; S, 7.85; neut. equiv., 194.

p-Toluidine Salt.—One-half gram of crude sulfonic acid, m. p. 230° dec., was dissolved in 20 cc. of water and the solution was freed from a trace of resin with Norite and treated with 0.18 g. of p-toluidine, brought into solution in 4 cc. of water with the use of the required amount of acetic acid. The mixture was heated to boiling and enough acetic acid was added to dissolve the gelatinous precipitate which initially separated. On cooling there was obtained 0.48 g. of crystalline salt, m. p. 271° dec. Recrystallization from alcohol gave fine silky needles of the same m. p.; $[\alpha]^{25}_{D}$ +57° (1.3% in alcohol).

Anal. Calcd. for $C_{27}H_{37}O_5SN$: N, 2.87. Found: N, 3.19.

Dimethyl Ester.—On adding excess diazomethane solution to a suspension of 0.5 g. of the pure sulfonic acid in ether the material rapidly dissolved, and after evaporating the filtered solution 0.34 g. of fine needles separated on cooling, m. p. 175–176°, $[\alpha]^{25}_{D}$ +76.2° (0.5% in alcohol). Further crystallization did not change the melting point.

Anal. Calcd. for $C_{22}H_{32}O_5S$: C, 64.69; H, 7.88. Found: C, 64.79; H, 8.06.

Sulfonation of Pure Dehydroabietic Acid.—A 0.5-g. sample of the dehydro acid prepared from hydroxyabietic acid[2] was sulfonated as before and the product crystallized once from glacial acetic acid. The yield of material, m. p. 230° dec., was 0.48 g. (73%). Esterified with diazomethane, 0.2 g. of this acid gave 0.15 g. of the dimethyl ester, m. p. 175–176°, and this did not depress the m. p. of the above sample.

Nitration of the Sulfonic Acid.—A solution of 0.6 g. of the sulfonic acid in 2.5 cc. of concentrated sulfuric acid was stirred in a salt–ice bath and treated with 0.1 cc. of concentrated nitric acid. After fifteen minutes the solution was poured into 300–400 cc. of water, giving a gelatinous precipitate containing a considerable amount of unchanged sulfonic acid. On bringing this into solution by heating there remained a small amount of water-insoluble precipitate. This was collected, washed well with water, and treated with excess diazomethane in ether. Crystallization of the product from hexane gave shiny, flat plates, m. p. 188–188.5°. A mixed melting point determination established the identity of this substance with methyl dinitrodehydroabietate[2] (m. p. 189–189.5°).

A mononitro derivative could not be obtained on nitration with mixed acids or in acetic acid solution.

Preparation of Pure Dehydroabietic Acid.—Pure abietic acid (47.5 g.) of the quality previously specified[2] was heated with palladium catalyst at 250° according to Fleck and Palkin[5] and the acidic product was extracted from an ethereal solution with 1% sodium hydroxide, precipitated with dilute acid, and crystallized once from aqueous alcohol, giving 38.5–40.5 g. (81–86%) of pyro acid. This acid (38.5–40.5 g.) was powdered and added rather rapidly (about ten minutes) with mechanical stirring to 200 cc. of concentrated sulfuric acid, keeping the tempera-

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[11] Fuson and Tullock, THIS JOURNAL, **56**, 1638 (1934).

[12] Adelson and Bogert, *ibid.*, **58**, 653 (1936).

[13] All melting points are corrected. Analyses by the Arlington Laboratories and Lyon Southworth.

[14] 95% Ethyl alcohol.

ture at −8 to −4°. After forty-five minutes the mixture was poured into 800 cc. of ice and water and the precipitated sulfonic acid was collected and washed with cold water until the wash water became cloudy on mixing with the mother liquor. Crystallization from water at this point was unsatisfactory, for the resin present formed an emulsion which could not be filtered, and the moist product was therefore crystallized from glacial acetic acid (about 200 cc.), giving 27.5 g. of satisfactory acid. The mother liquor was concentrated to a volume of about 50 cc. and poured into 800 cc. of water; some resin was removed by filtering through glass wool, and the sulfonic acid was precipitated by the addition of 200 cc. of concentrated hydrochloric acid and crystallized from glacial acetic acid, giving 3.6 g. of product. The total yield of material, m. p. 230°, dec., was 30.5–31 g. (61–63%).

A suspension of 31 g. of the powdered sulfonic acid in a mixture of 750 cc. of concentrated sulfuric acid and 1000 cc. of water was refluxed for ten hours, the temperature of the liquid being about 135°. The appearance of the suspended solid changes considerably during the heating and the progress of the hydrolysis is followed readily. After cooling, the solid was collected and washed with hot water. A solution of the dried material (19.1 g.) in 200 cc. of alcohol was clarified with a little Norite and water was added at the boiling point to incipient turbidity. On slow cooling there was obtained 17.3 g. (71%) of crystalline dehydroabietic acid, m. p. 173–173.5°,[15] $[\alpha]^{25}_D$ +62° (2.3% in alcohol[16]). The mother liquor and washings were combined and treated with 400 cc. of concentrated hydrochloric acid, and after standing overnight at 5° the crystalline sulfonic acid which separated was collected and dried; weight 5 g. Based on the amount of sulfonic acid consumed, the yield of dehydroabietic acid in the hydrolysis is 84% of the theoretical amount and the overall yield from abietic acid averaged 42–43%.

The melting point is slightly higher and sharper than observed with samples prepared by the earlier method. A further indication of the purity of the acid is that esterification with diazomethane gave an ester which crystallized at once and melted at 61–62.5° without further purification. For the pure ester Fleck and Palkin[4] give the m. p. 62–63°.

Alkali Fusion of the Sulfonic Acid.—In trial fusions carried out in the open at atmospheric pressure there was so much oxidation and decomposition that in subsequent experiments the fusion was run in an autoclave in an atmosphere of nitrogen. The acid was recovered entirely unchanged after heating with 25% potassium hydroxide solution under nitrogen at 280–285°, whether the heating was continued for fifteen minutes or for ten hours; fusion occurred, however, when the temperature was raised to 300°.

After heating 10.5 g. of sulfonic acid with 45 g. of potassium hydroxide and 90 cc. of water under nitrogen in an autoclave at 300° (thermocouple) for one hour, a solid layer separated on top of the aqueous solution on cooling. The solid was dissolved in water, acidified, and the precipitate washed, dried, and taken into ether. After filtering and concentrating, the ether was displaced by hexane, and on cooling 0.85 g. of solid, m. p. 183–187°, separated. The material in the mother liquor was distilled at 3 mm., and crystallization of the distillate from hexane gave a further batch of the above high-melting solid. The combined solid was distilled at 3 mm. and on crystallization from ether–hexane gave 0.75 g. of colorless prisms, m. p. 193–194.5°. The substance is moderately soluble in ether or methanol and slightly soluble in hexane. Repeated crystallization from methanol gave material melting constantly at 196.5–197.5° (Product A).

Anal. Found: C, 78.45, 78.77; H, 8.15, 8.28; neut. equiv., 301; mol. weight (Rast), 291.

An empirical formula calculated from the analytical data would contain 2.5 atoms of oxygen, which indicates that the material is a mixture or a molecular aggregate. The same substance was obtained on fusing the dimethyl ester of the sulfonic acid under similar conditions. The substance is slowly attacked by alkaline or neutral permanganate. Dehydrogenation by heating 0.4 g. of material, m. p. 194–195°, with 0.1 g. of 10% palladium charcoal under nitrogen at 290–300° for three hours gave, after extraction of the product and crystallization from methanol, 0.21 g. (68%) of retene, m. p. 99–99.5°. Treatment with sulfur at 300° also yielded retene.

No constantly melting substance could be isolated from the mother liquors remaining after removal of the high-melting product. The material is very soluble in all organic solvents. One fraction, m. p. 159.5–160.5°, had the neutralization equivalent 310; another, m. p. 167–169° (Product B), from a fusion of the dimethyl ester, gave the values: C, 79.45; H, 9.13. This corresponds to $C_{19}H_{26}O_2$ (Calcd.: C, 79.68; H, 9.15), and the result shows at least that no phenolic hydroxyl group is present.

Anilides from Fusion Product A.—One gram of material (m. p. 194–195°) was warmed on the steam-bath with 0.7 g. of phosphorus pentachloride, then stirred with 2.5 cc. of aniline, and the product washed in ether with water, acid and alkali. On concentrating the dried solution, a 0.32-g. crop of crystals, m. p. 250–255°, was obtained, and the mother liquor material on crystallization from methanol gave 0.38 g. of crystals, m. p. 110°. The higher melting anilide on crystallization from acetone gave diamond shaped leaves melting constantly at 255.5–257°. It is slightly soluble in ether and moderately soluble in acetone or methanol.

		C	H	N
Anal.	Calcd. for $C_{25}H_{29}O_2N$:	79.97	7.78	3.73
	$C_{26}H_{31}O_2N$:	80.17	8.02	3.60
	$C_{26}H_{33}O_2N$:	79.77	8.50	3.58
	Found:	80.29	8.06	3.78

The lower melting anilide, after removal of the less soluble product by partial solution in ether, was crystallized from methanol to the constant m. p. 114–114.5° (fine needles).

Anal. Calcd. for $C_{25}H_{27}ON$: C, 84.00; H, 7.61; N, 3.92. Found: C, 84.10; H, 7.81; N, 4.30.

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[15] Ruzicka and co-workers[8] comment on their observation that a sample of dehydroabietic acid prepared from the purified ester did not show a sharp melting point, as reported in our first description of the compound. We have obtained sharply melting samples by both the previous and present method of preparation on numerous occasions, and Fleck and Palkin's[4] sample of acid from the pure ester melted over a 1°-range.

[16] In stating that we did not specify the solvent used in determining the rotation, Ruzicka and co-workers[8] evidently overlooked Note 45 of our paper.

Anilides from Fusion Product B.—Material melting at 165° gave a mixture of anilides from which the following seemingly homogeneous products were isolated: fine needles from aqueous acetone, m. p. 214–215°; long flat needles from methanol, m. p. 147.5–148°. The second substance was analyzed as follows:

Anal. Calcd. for $C_{25}H_{31}ON$: C, 83.07; H, 8.63; N, 3.87. Found: C, 83.31; H, 8.87; N, 3.89.

Attempts to hydrolyze various samples of anilides were unsuccessful. The trials included treatment with boiling 10% butyl alcoholic potassium hydroxide (unattacked), aqueous alkali and ethylene glycol at 150° (unattacked), and sodium ethylate at 180° (acidic gum).

Methyl 6-Acetyldehydroabietate.—A solution of 9.4 g. of methyl dehydroabietate and 2.3 cc. of acetyl chloride in 50 cc. of nitrobenzene was stirred at 0–5° and treated with 8.25 g. of aluminum chloride. After this had gone into solution the mixture was allowed to stand for thirty-six hours at 5° and then poured onto ice and 20 cc. of concentrated hydrochloric acid and steam distilled. The residue, which solidified on cooling, was taken up in ether and after washing with aqueous bicarbonate the solution was dried over sodium sulfate and treated with Darco 6–60, which removed practically all of the color. After concentration the solution deposited in three crops 6.6 g. of long, heavy transparent prisms, often 2–3 mm. thick. On working the mother liquor as described below there was obtained 0.4 g. more of the prisms (pure); total yield of prisms, 66%. The acetyl compound was purified by crystallization from ether (prisms) and aqueous acetone (flat needles of the same m. p.) and melted sharply at 133.5–134°, $[\alpha]^{25}D$ +56° (0.9% in alcohol).

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.47; H, 9.03. Found: C, 77.49, 77.14; H, 8.84, 9.00.

For proof of structure 0.5 g. of the 6-acetyl compound was heated in a sealed tube with 1 cc. of concentrated nitric acid and 2 cc. of water at 190° for thirteen hours, and for twelve hours longer after adding 1 cc. of fresh acid. Evaporation of the clear solution to dryness gave a white solid which was stirred and washed with fuming nitric acid and sublimed at 250° (20 mm.) to yield pyromellitic anhydride, m. p. and mixed m. p. with an authentic sample, 282–285°.

The oxime was prepared by refluxing for one hour a mixture of 0.25 g. of the 6-acetyl compound, 0.5 g. of hydroxylamine hydrochloride, 0.7 g. of potassium acetate, 3 cc. of water, and 10 cc. of alcohol. The product was thrown out with water and crystallized from ether–petroleum ether to give needles, m. p. 151.5–152°; yield, 0.2 g. (77%); $[\alpha]^{25}D$ +83° (1.6% in alcohol). Using pyridine in place of potassium acetate solution the yield was 90%.

Anal. Calcd. for $C_{23}H_{33}O_3N$: N, 3.77. Found: N, 3.94.

From the ethereal mother liquor of the Friedel and Crafts reaction product there was obtained what appears to be a different crystalline modification of the 6-acetyl ester. After removal of the 6.6 g. of prisms, the solution on concentration deposited a crystallizate consisting largely of needles, which when crystallized twice from ether–petroleum ether gave 0.45 g. of fine needles, m. p. 117–119°. The remaining ethereal mother liquor when concentrated and treated with petroleum ether then gave crops consisting chiefly of the higher melting prisms, mixed with some needles, and purification by mechanical separation and crystallization gave 0.4 g. of pure prisms. After two recrystallizations of the more soluble, low melting material (0.45 g.) from ether–hexane, the substance was obtained as fine needles melting sharply at 119.5–120° (0.35 g.); $[\alpha]^{25}D$ +58 (0.7% in alcohol).

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.47; H, 9.03. Found: C, 77.48, 77.11; H, 8.57, 9.13.

Mixtures of this substance with the prism form melted at intermediate temperatures. The oxime, prepared as above from 0.1 g. of needles, melted at 150–150.5° and did not depress the m. p. of the other sample. A 0.1-g. sample of needles was oxidized as above but using only one charge of acid (seventeen hours) and the reaction product treated with excess diazomethane. The resulting ester when crystallized twice from methanol melted at 141–142°, with some previous softening, and a mixture of this with authentic pyromellitic acid tetramethyl ester, m. p. 142.5–143.5° (sharp) melted at 141–143°. The structure therefore is that of methyl 6-acetyldehydroabietate, and since the rotation, as tested on small samples, is practically the same for the needles as for the prisms, stereoisomerism is unlikely. Consequently, although an interconversion was not observed, it is believed that the two substances are different modifications of the same chemical individual.

6-Acetyl Dehydroabietic Acid.—One-half gram of the acetyl ester was refluxed for three hours with 15 cc. of alcohol containing 1 g. of potassium hydroxide. A small amount of white solid precipitated on adding water and was removed by filtration (plates from ether–petroleum ether, m. p. 117–117.5°). The alkaline filtrate was acidified and the precipitate dried in ether and crystallized from ether–petroleum ether (20–40°), giving fine, silky needles, m. p. 174.5–175° (0.2 g.); $[\alpha]^{25}D$ +74° (1% in alcohol).

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.14; H, 8.82; neut. equiv., 342. Found: C, 76.89; H, 9.05; neut. equiv., 344.

Methyl 6-Carboxydehydroabietate.—Iodine–potassium iodide solution was added to a solution of 2.5 g. of methyl 6-acetyldehydroabietate in 100 cc. of dioxane and 20 cc. of 10% sodium hydroxide solution until the color persisted for two minutes at 60° after a fresh addition. The solution was diluted with 600 cc. of water, filtered from iodoform, treated with a little bisulfite and acidified. The gummy yellow precipitate was extracted from ether into 1% alkali, and the substance then separated on acidification as a white solid. One crystallization from hexane gave 0.4 g. of material, m. p. 165–180°, and on three crystallizations from acetone the compound formed fine, silky needles melting constantly at 190–191.5°; $[\alpha]^{25}D$ +74° (0.9% in alcohol).

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.69; H, 8.44; neut. equiv., 358. Found: C, 73.38; H, 8.50; neut. equiv. (40-mg. sample), 344.

Summary

Pure dehydroabietic acid may be obtained readily in quantity by sulfonating the palladium-

treated pyroabietic acid of Fleck and Palkin and hydrolyzing the crystalline sulfonic acid. Fusion of the sulfonic acid with alkali results in extensive alteration of the molecule and under the conditions studied gives a mixture of several products.

Methyl dehydroabietate reacts smoothly with acetyl chloride in nitrobenzene solution in the presence of aluminum chloride and gives a sharply melting product characterized as the 6-acetyl derivative. This was hydrolyzed to the free acid and oxidized with hypohalite to methyl 6-carboxydehydroabietate.

CONVERSE MEMORIAL LABORATORY
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Hydroxy- and Methoxyphenyldihydroanthracenes

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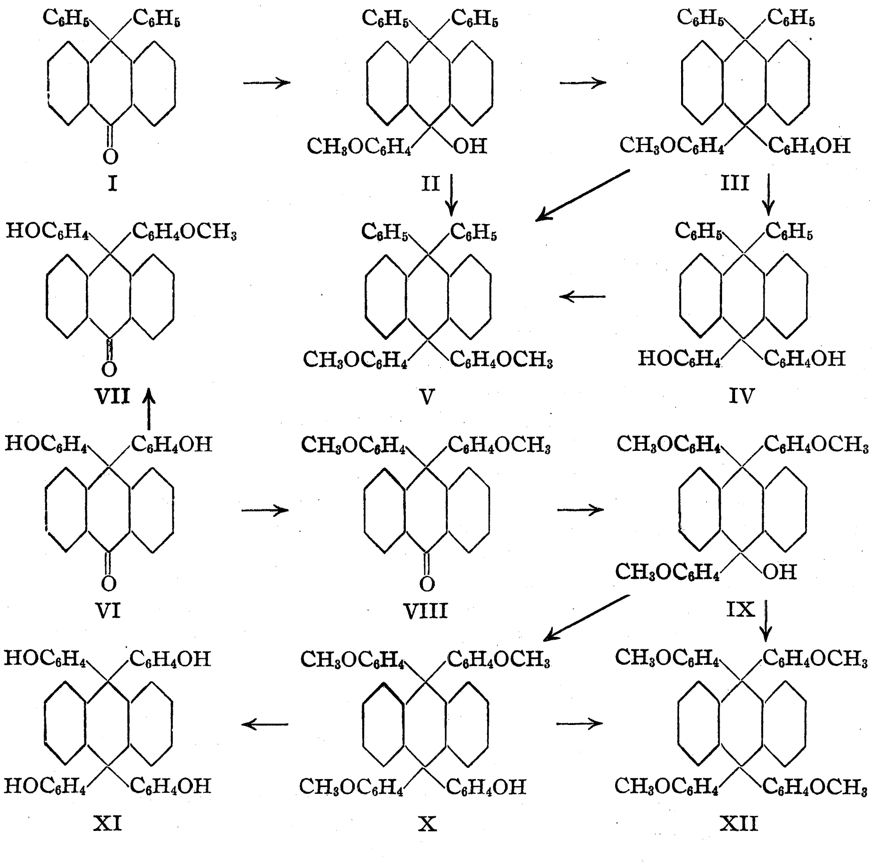
Very few substitution products of 9,10-dihydroanthracene are known in which aryl groups occupy *meso* positions and it seems that hydroxyaryl derivatives such as 9,9,10-tri- and 9,9,10,10-tetra-(*p*-hydroxyphenyl)-9,10-dihydroanthracene, compounds in which we were especially interested, have never been prepared.



Since the carbonyl group in a 9,9-diarylanthrone-10 reacts toward an arylmagnesium halide in the characteristic manner, it was possible to convert the carbonyl compound into a tertiary carbinol which represents a 9,9,10-triaryl-10-hydroxy-9,10-dihydroanthracene. The hydroxyl group of the latter proved to be especially reactive toward phenol and anisole in the presence of a small amount of sulfuric acid, hence the hydroxyl group could be replaced by the hydroxyphenyl and anisyl nuclei and in this way a tetraaryl-9,10-dihydroanthracene could be obtained. Demethylation, in the case of the anisyl compounds, yielded the desired hydroxy derivatives.

It has been found that 9,9-diphenylanthrone-10 (I) reacts with *p*-anisylmagnesium iodide to yield 9,9-diphenyl-10-hydroxy-10-(*p*-anisyl)-9,10-dihydroanthracene (II); this product was converted readily into its carbinol methyl ether by methyl alcohol and hydrogen chloride. Compound II condensed with phenol, in the presence of a small amount of sulfuric acid, to yield 9,9-diphenyl-10-(*p*-hydroxyphenyl)-10-(*p*-anisyl)-9,10-dihydroanthracene (III), and with anisole to produce 9,9-diphenyl-10,10-di-(*p*-anisyl)-9,10-dihydroanthracene (V). Compound V was obtained also by methylation of compounds III and IV. By demethylation of the last named

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substance (III) there was produced 9,9-diphenyl-10,10-di-(*p*-hydroxyphenyl)-9,10-dihydroanthracene (IV).

9,9-Di-(*p*-hydroxyphenyl)-anthrone-10 (VI) was converted by methyl sulfate into its monomethyl ether, 9-(*p*-hydroxyphenyl)-9-(*p*-anisyl)-anthrone-10 (VII), or into its dimethyl ether, 9,9-di-(*p*-anisyl)-anthrone-10 (VIII). Furthermore, the monomethyl ether (VII) was prepared by condensation of 9-hydroxy-9-(*p*-anisyl)-anthrone-10 with phenol in the presence of sulfuric acid.

Compound VIII reacted with *p*-anisylmagnesium iodide to form 9,9,10-tri-(*p*-anisyl)-10-hydroxy-9,10-dihydroanthracene (IX); condensation of the anthracene with phenol yielded 9,9,10-tri-(*p*-anisyl)-10-(*p*-hydroxyphenyl)-9,10-dihydroanthracene (X). Upon demethylation of compound X there was obtained 9,9,10,10-tetra-(*p*-hydroxyphenyl)-9,10-dihydroanthracene (XI).

9,9,10,10-Tetra-(*p*-anisyl)-9,10-dihydroanthracene (XII) was prepared by condensation of compound IX with anisole and by methylation of compound X.

Experimental Part

9,9-Diphenyl-10-hydroxy-10-(*p*-anisyl)-9,10-dihydroanthracene (II).—A solution of 30 g. of 9,9-diphenylanthrone (I)[2] in 100 cc. of dry benzene was added, gradually, to the Grignard reagent prepared from 35.4 g. of *p*-anisylmagnesium iodide, 3.7 g. of magnesium and 100 cc. of ether. The mixture was refluxed for five hours, decomposed with ice and ammonium chloride, the ether–benzene layer separated, filtered, steam distilled and the oily residue covered with methyl alcohol. After three days the product became crystalline; yield 22.5 g.; m. p. 142–144° after recrystallization from a mixture of ether and petroleum ether (30–60°).

Anal. Calcd. for $C_{33}H_{26}O_2$: C, 87.18; H, 5.77. Found: C, 86.88; H, 5.79.

In order to obtain the carbinol methyl ether, a methyl alcohol solution of the anthracene was partially saturated with hydrogen chloride and after one hour the solvent was removed and the ether recrystallized from acetic acid; m. p. 191–193°.

Anal. Calcd. for $C_{34}H_{28}O_2$: C, 87.14; H, 6.03. Found: C, 87.18; H, 6.09.

9,9-Diphenyl-10-(*p*-hydroxyphenyl)-10-(*p*-anisyl)-9,10-dihydroanthracene (III).—A mixture of 20 g. of compound II, 30 g. of phenol and five drops of concd. sulfuric acid was heated on a steam-bath for two hours, the product washed thoroughly with hot water and the colorless crystals recrystallized from methyl alcohol; yield 23 g.; m. p. 250–252°.

Anal. Calcd. for $C_{39}H_{30}O_2$: C, 88.26; H, 5.73. Found: C, 87.96; H, 5.68.

9,9-Diphenyl-10,10-di-(*p*-anisyl)-9,10-dihydroanthracene (V).—This product was obtained when a mixture of 1.0 g. of compound II, 3.0 g. of anisole and one drop of sulfuric acid was heated on a steam-bath for one hour. After recrystallization from acetic acid the colorless material melted at 233–235°.

Anal. Calcd. for $C_{40}H_{32}O_2$: C, 88.19; H, 5.94. Found: C, 88.26; H, 5.92.

In order to prepare compound V by methylation of compound III, 2.0 g. of the latter, 6.0 g. of sodium hydroxide and 30 cc. of 50% alcohol were refluxed and 5 cc. of dimethyl sulfate added gradually. The mixture was heated for one hour. The product obtained weighed 1.9 g. and melted at 233–235° after recrystallization from acetic acid.

9,9-Diphenyl-10,10-di-(*p*-hydroxyphenyl)-9,10-dihydroanthracene (IV).—A solution of 5 g. of compound III, 25 cc. of constant boiling hydrobromic acid and 150 cc. of acetic acid was refluxed for five hours, the precipitated material separated and the solution concentrated, whereupon more material separated; total yield 3.9 g.; m. p. 343–345° after recrystallization from acetic acid.

Anal. Calcd. for $C_{38}H_{28}O_2$: C, 88.33; H, 5.46. Found: C, 88.14; H, 5.52.

The di-3-bromobenzoyl derivative was prepared in the following manner: 2 g. of the anthracene and 5 g. of 3-bromobenzoyl chloride were heated for an hour at 190–200° and the mixture treated with hot alcohol. The ester was recrystallized from ethyl acetate; m. p. 231–233°.

Anal. Calcd. for $C_{52}H_{34}O_4Br_2$: Br, 18.13. Found: Br, 17.92.

The dimethyl ether was obtained when compound IV was methylated with dimethyl sulfate and alkali in dilute alcohol. It proved to be identical with compound V; mixed m. p. 233–235°.

9-(*p*-Hydroxyphenyl)-9-(*p*-anisyl)-anthrone-10 (VII).—A solution of 3.8 g. of 9,9-di-(*p*-hydroxyphenyl)-anthrone-10 (VI)[3] in 50 cc. of 20% sodium hydroxide solution was heated to 80° and treated, gradually, with 10 cc. of dimethyl sulfate. The precipitated product was recrystallized from acetic acid; m. p. 232–233°; yield 2.5 g.

Anal. Calcd. for $C_{27}H_{30}O_3$: C, 82.62; H, 5.14. Found: C, 82.51; H, 5.06.

We also prepared the anthrone by heating a mixture of 10 g. of 9-hydroxy-9-(*p*-anisyl)-anthrone-10 (XIII),[4] 25 g. of phenol and three drops of sulfuric acid for one hour on a steam-bath. The product was washed with hot water and recrystallized from acetic acid; yield 9 g.; mixed m. p. 232–233°.

9,9-Di-(*p*-anisyl)-anthrone-10 (VIII).—A mixture of 7.6 g. of 9,9-di-(*p*-hydroxyphenyl)-anthrone-10, 100 cc. of alcohol and 100 cc. of 10% sodium hydroxide solution was refluxed and 30 cc. of dimethyl sulfate added gradually. It was heated for one hour and the crystalline precipitate recrystallized from acetic acid; m. p. 208–209°.[5]

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[2] Barnett, Cook and Nixon, *J. Chem. Soc.*, 508 (1927).

[3] Scharwin and Kusnezof, *Ber.*, **36**, 2020 (1903); Scharwin, Naumof and Sandurin, *ibid.*, **37**, 3616 (1904).

[4] Blicke and Weinkauff, THIS JOURNAL, **54**, 1461 (1932).

[5] Scharwin, Naumof and Sandurin [*Ber.*, **37**, 3619 (1904)], who obtained the anthrone by another method, reported 208°.

The anthrone was prepared also by methylation of compound VII according to the procedure just described.

9,9,10-Tri-(*p*-anisyl)-10-hydroxy-9,10-dihydroanthracene (IX).—Sixteen grams of compound VIII, dissolved in 75 cc. of benzene, was added, gradually, to the Grignard reagent obtained from 18.9 g. of *p*-iodoanisole, 2.0 g. of magnesium and 75 cc. of ether. The mixture was refluxed for five hours, decomposed with ice and ammonium chloride, the ether–benzene layer filtered and the solution steam distilled. The crystalline residue was recrystallized from acetic acid; yield 15 g.; m. p. 226–228°.

Anal. Calcd. for $C_{35}H_{30}O_4$: C, 81.64; H, 5.91. Found: C, 81.42; H, 5.89.

The methyl ether was obtained when a methyl alcohol solution of the anthracene was partially saturated with hydrogen chloride; m. p. 205–206° after recrystallization from acetic acid.

Anal. Calcd. for $C_{36}H_{32}O_4$: C, 81.78; H, 6.11. Found: C, 81.52; H, 6.13.

9,9,10-Tri-(*p*-anisyl)-10-(*p*-hydroxyphenyl)-9,10-dihydroanthracene (X).—A mixture of 5 g. of compound IX, 20 g. of phenol and three drops of sulfuric acid was heated on a steam-bath for three hours, the material washed with hot water and recrystallized from acetic acid; yield 5 g.; m. p. 310–312°.

Anal. Calcd. for $C_{41}H_{34}O_4$: C, 83.35; H, 5.81. Found: C, 83.07; H, 5.84.

9,9,10,10-Tetra-(*p*-hydroxyphenyl)-9,10-dihydroanthracene (XI).—Two grams of compound X, 20 cc. of constant boiling hydrobromic acid and 300 cc. of acetic acid were refluxed for five hours. The mixture was concentrated to a volume of about 75 cc. and poured into 200 cc. of water. The precipitated product was recrystallized from dilute alcohol; m. p. 371–374°.[6] The compound dissolves readily in dilute alkali.

Anal. Calcd. for $C_{38}H_{28}O_4$: C, 83.18; H, 5.15. Found: C, 82.92; H, 5.14.

One gram of the anthracene was heated with 5 g. of *m*-bromobenzoyl chloride for one hour at 190–200°. The material was washed with hot alcohol, then dissolved in hot acetic acid. When the solution cooled a small amount of colored by-product precipitated. The filtered solution was diluted with three volumes of methyl alcohol; the colorless precipitate, which was the tetra-*m*-bromobenzoyl derivative, melted at 163–168°.

Anal. Calcd. for $C_{66}H_{40}O_8Br_4$: Br, 24.99. Found: Br, 25.18.

9,9,10,10-Tetra-(*p*-anisyl)-9,10-dihydroanthracene (XII).—A boiling solution, obtained from 1 g. of compound X, 3 g. of sodium hydroxide and 20 cc. of 50% alcohol, was treated, gradually, with 5 cc. of dimethyl sulfate. The mixture was heated for one hour and the product recrystallized from acetic acid; m. p. 329–331°.[6]

Anal. Calcd. for $C_{42}H_{36}O_4$: C, 83.40; H, 6.01. Found: C, 83.38; H, 6.07.

The same anthracene was obtained when 1 g. of compound IX, 3 g. of anisole and one drop of sulfuric acid were heated for one hour on a steam-bath; mixed m. p. 329–331°.

Summary

A number of 9,9,10-tri- and 9,9,10,10-tetraaryldihydroanthracenes have been prepared in which the aryl groups are phenyl, *p*-hydroxyphenyl and *p*-anisyl.

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[6] Determined in an air-bath with a 250–600° Palo–Myers mercury thermometer.

ANN ARBOR, MICHIGAN RECEIVED AUGUST 15, 1938

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Hydroxy- and Methoxyphenylanthrones. I.

BY F. F. BLICKE AND R. A. PATELSKI[1]

It is well known that interaction between phthalic anhydride and aromatic hydrocarbons or simple substitution products of the latter yields 2-acylbenzoic acids, diarylphthalides and anthraquinones; other products are formed also but their nature is not known.

It seems to us that in the reaction between phthalic anhydride and phenol, hydroxyphenylanthrones, such as 3,9-dihydroxy-9-(*p*-hydroxyphenyl)-anthrone-10, might be formed and that these anthrones, by further reaction with phenol, might be converted into hydroxy derivatives of diphenylanthrones, tri- and tetraphenyldihydroanthracenes. The hydroxyl groups can occupy either ortho or para positions in the phenyl nuclei and either a 1-, 2-, 3- or 4-position in the anthrone or anthracene nucleus. Since only a few representatives of such compounds have been described in the literature we have synthesized a number of them, often by several different procedures, in order to establish their structure definitely.

In many instances the desired substance has been prepared, with the aid of a Grignard reagent, in the form of its methyl ether; the hydroxy compound was then obtained by demethylation However, this procedure was not always successful since, occasionally, demethylation was accompanied by disruption of the molecule; hence

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[1] Monsanto–Pfizer Research Associate.

it became necessary to search for procedures by means of which the hydroxy compounds could be obtained directly.

Hitherto, we have obtained certain monoarylanthrones by interaction of an anthrone with an arylmagnesium halide,[2,3] by treatment of a diarylphthalin with sulfuric acid[3,4] or thionyl chloride[3] or by the action of phosphorus pentachloride on a diarylphthalide.[4] It should be mentioned that in some cases the action of sulfuric acid on a diarylphthalin yields a diarylbenzofuran or a mixture of a furan and an arylanthrone[2,3,4] (p. 276). In a paper which is to be published soon it will be shown that interaction of a diarylphthalin with zinc chloride yields an arylanthracene; upon oxidation of the latter an arylanthrone is produced.

Diarylanthrones, of the types in which we are interested, have been prepared by oxidation of a diaryldihydroanthracene; the latter were obtained by loss of water from 2-benzyltriphenylcarbinols.[5]

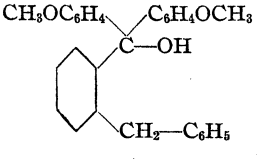
In order to obtain a triaryldihydroanthracene, a diarylanthrone was treated with an arylmagnesium halide.[6]

It was found that a tetra-(*p*-hydroxyphenyl)-dihydroanthracene could be synthesized by demethylation of 9,9,10-tri-(*p*-anisyl)-10-(*p*-hydroxyphenyl)-9,10-dihydroanthracene[6] (p. 2638).

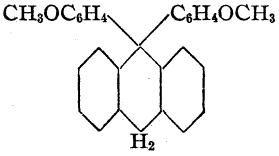
In this paper it has been shown that three different 2-benzyldimethoxytriphenylcarbinols can be converted into 9,9-dianisyl-9,10-dihydroanthracenes by loss of water. Subsequent oxidation and demethylation yielded, in each instance, the desired 9,9-di-(*p*-hydroxyphenyl)-anthrone-10.

It has been found that the ethyl ester of 2-benzylbenzoic acid reacts with two molecular equivalents of 4-anisylmagnesium iodide to yield 2-benzyl-4′,4″-dimethoxytriphenylcarbinol (I); the carbinol was prepared also from 2-(4″-methoxybenzoyl)-diphenylmethane and one molecular equivalent of the Grignard reagent.

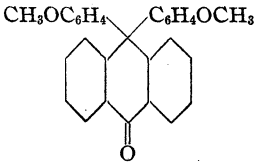
When the carbinol was treated with hydrogen chloride, water was eliminated with the formation of 9,9-di-(*p*-anisyl)-9,10-dihydroanthracene (II). Oxidation of the dihydroanthracene produced 9,9-di-(*p*-anisyl)-anthrone-10 (III) which can be converted into 9,9-di-(*p*-hydroxyphenyl)-anthrone-10 (IV) by demethylation with aluminum chloride. 9,9-Di-(*p*-hydroxyphenyl)-anthrone-10, prepared from anthraquinone, phenol and stannic chloride, according to the method of Scharwin and co-workers,[7] yielded compound III when methylated with dimethyl sulfate.



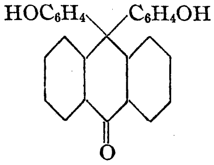
I



II



III



IV

When the ethyl ester of 2-(4′-methoxybenzyl)-benzoic acid was allowed to react with 4-anisylmagnesium iodide there was obtained 2-(4′-methoxybenzyl)-4″,4‴-dimethoxytriphenylcarbinol. This carbinol was converted, by loss of water, into 2-methoxy-9,9-di-(*p*-anisyl)-9,10-dihydroanthracene and the anthracene oxidized to 2-methoxy-9,9-di-(*p*-anisyl)-anthrone-10; upon demethylation 2-hydroxy-9,9-di-(*p*-hydroxyphenyl)-anthrone-10 was formed.

2-(2′-Methoxybenzyl)-4″,4‴-dimethoxytriphenylcarbinol was prepared from the ethyl ester of 2-(2′-methoxybenzyl)-benzoic acid and 4-anisylmagnesium iodide. Ring closure, by elimination of water, produced 4-methoxy-9,9-di-(*p*-anisyl)-9,-10-dihydroanthracene. 4-Methoxy-9,9-di-(*p*-anisyl)-anthrone-10, obtained by oxidation of the anthracene, was demethylated to yield 4-hydroxy-9,9-di-(*p*-hydroxyphenyl)-anthrone-10.

By interaction of ethyl 2-(4′-methoxybenzyl)-benzoate and 2-anisylmagnesium iodide there was obtained 2-(4′-methoxybenzyl)-2″,2‴-dimethoxytriphenylcarbinol which was converted, by ring closure, into 2-methoxy-9,9-di-(*o*-anisyl)-9,10-dihydroanthracene. So far we have been able to obtain the corresponding anthrone only in the form of a gum.

It was thought that 9,9-diarylanthrones might be prepared, easily, by condensation of anisole with a dibromoanthrone such as 3-methoxy-9,9-dibromoanthrone-10. However, we have not been able to effect this condensation. The dibromoanthrone reacts readily with mercury to

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[2] Blicke and Weinkauff, THIS JOURNAL, **54**, 1461 (1932).

[3] Blicke and Swisher, *ibid.*, **56**, 1406 (1934).

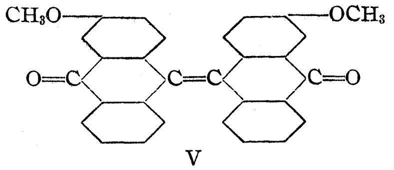
[4] Blicke and Patelski, *ibid.*, **58**, 274 (1936).

[5] Blicke and Patelski, *ibid.*, **58**, 560 (1936).

[6] Blicke and Patelski, *ibid.*, **60**, 2636 (1938).

[7] Scharwin and Kusnezof, *Ber.*, **36**, 2020 (1903); Scharwin, Naumof and Sandurin, *ibid.*, **37**, 3616 (1904).

yield 2,2′(or 2,7′)-dimethoxydianthraquinone (V).[8]



V

Experimental Part

9,9-Di-(*p*-anisyl)-9,10-dihydroanthracene (II).—To the Grignard reagent, prepared from 28.7 g. of 4-iodoanisole, 3.0 g. of magnesium, 50 cc. of ether and 50 cc. of benzene, there was added, gradually, a solution of 6 g. of the ether ester of 2-benzylbenzoic acid,[9] dissolved in 25 cc. of benzene. The mixture was refluxed for three hours, decomposed with ice and ammonium chloride, the solvents removed and the product submitted to steam distillation to remove anisole and other by-products. Since the crude, gummy 2-benzyl-4′,4″-dimethoxytriphenylcarbinol could not be obtained in crystalline form it was prepared by a second method.

Four grams of 2-(4″-methoxybenzoyl)-diphenylmethane,[10] dissolved in 40 cc. of benzene, was added, gradually, to the Grignard reagent prepared from 6.1 g. of 4-iodoanisole, 0.64 g. of magnesium, 30 cc. of ether and 30 cc. of benzene. The mixture was refluxed for three hours and treated as described above. In this instance, too, the carbinol was obtained as a gummy product.

The carbinols, obtained by both procedures, were dissolved in acetic acid or alcohol, the solutions partially saturated with hydrogen chloride and the red mixtures heated for three hours on a steam-bath. Upon dilution with water oils were obtained which crystallized after they had been covered with a small amount of acetic acid for twelve hours. After several recrystallizations from methyl alcohol and then from acetic acid the colorless, crystalline products, obtained from both gummy carbinols, melted at 166–167°. This material was 9,9-di-(*p*-anisyl)-9,10-dihydroanthracene.

Anal. Calcd. for $C_{28}H_{24}O_2$: C, 85.67; H, 6.17. Found: C, 85.52; H, 6.20.

9,9-Di-(*p*-anisyl)-anthrone-10 (III).—A mixture of 0.7 g. of 9,9-di-(*p*-anisyl)-9,10-dihydroanthracene, 1.0 g. of sodium dichromate and 15 cc. of acetic acid was heated on a steam-bath for four hours, diluted with water and the precipitated anthrone recrystallized from alcohol and then from acetic acid; m. p. 208–209°. Mixed with a sample of 9,9-di-(*p*-anisyl)-anthrone-10, obtained by methylation[6] (p. 2637) of 9,9-di-(*p*-hydroxyphenyl)-anthrone-10[11] with dimethyl sulfate, the mixture melted at 208–209°.

2-(4′-Methoxybenzyl)-4″,4‴-dimethoxytriphenylcarbinol.—A solution of 20.3 g. of the ethyl ester of 2-(4′-methoxybenzyl)-benzoic acid[2] (p. 1464) in 50 cc. of ether was added to the Grignard reagent obtained from 46.8 g. of 4-iodoanisole, 4.8 g. of magnesium and 120 cc. of ether. The mixture was stirred, refluxed for five hours, decomposed with ice and ammonium chloride and a crystalline, ether-insoluble product removed by filtration. After removal of most of the solvent from the filtrate a crystalline material, the desired carbinol, was obtained; yield 17 g.; m. p. 147–148° after recrystallization from a mixture of benzene and petroleum ether (90–100°).

Anal. Calcd. for $C_{29}H_{28}O_4$: C, 79.05; H, 6.41. Found: C, 78.88; H, 6.46.

2-Methoxy-9,9-di-(*p*-anisyl)-9,10-dihydroanthracene.—A solution of 9.5 g. of the above-mentioned carbinol in 40 cc. of acetic acid was partially saturated with hydrogen chloride and the deep red solution heated on a steam-bath for three hours. The solution then possessed a strong purple fluorescence and, when cooled, deposited the dihydroanthracene in crystalline form; m. p. 167–168° after recrystallization from acetic acid; yield 8.5 g.

Anal. Calcd. for $C_{29}H_{26}O_3$: C, 82.42; H, 6.21. Found: C, 81.92; H, 6.21.

2-Methoxy-9,9-di (*p*-anisyl)-anthrone-10.—A solution of 8 g. of sodium dichromate in 10 cc. of hot water was added to 10 g. of the dihydroanthracene, suspended in 50 cc. of acetic acid, and the mixture heated for three hours on a steam-bath. Upon dilution with water the anthrone was precipitated; yield 8.5 g.; m. p. 183–184°[2] (p. 1464) after recrystallization from acetic acid.

2-Hydroxy-9,9-di-(*p*-hydroxyphenyl)-anthrone-10.—Five grams of anhydrous aluminum chloride was added to a solution of 2 g. of 2-methoxy-9,9-di-(*p*-anisyl)-anthrone-10 in 100 cc. of dry benzene and the mixture refluxed for twenty-four hours on a steam-bath. After treatment with ice and hydrochloric acid the benzene layer was separated, the solvent removed, the residue dissolved in alcohol and the solution decolorized with charcoal. Upon dilution of the solution with water a colorless, crystalline product was obtained which was recrystallized from dilute alcohol; yield 0.9 g.; m. p. 312–314° with decomposition.

Anal. Calcd. for $C_{26}H_{18}O_4$: C, 79.16; H, 4.60. Found: C, 78.98; H, 4.72.

Two grams of the hydroxy-anthrone, dissolved in 50 cc. of hot 10% sodium hydroxide solution was treated gradually with 8 cc. of dimethyl sulfate and the mixture refluxed for three hours. The precipitated material, 2-methoxy-9,9-di-(*p*-anisyl)-anthrone-10, weighed 1.2 g. and melted at 183–184°.

The tri-(3-bromobenzoyl) derivative was obtained when 1.4 g. of the hydroxy-anthrone was heated with 6.5 g. of 3-bromobenzoyl chloride at 140–150° in an oil-bath for two hours. The brown oil was washed thoroughly with 10% sodium hydroxide solution, with water and then with alcohol. The product was covered with ether and, after it had become crystalline, was recrystallized from acetic acid; m. p. 174–176°.

Anal. Calcd. for $C_{47}H_{27}O_7Br_3$: Br, 25.44. Found: Br, 25.12.

Ethyl 2-(2′-Methoxybenzoyl)-benzoate.—A mixture of 90 g. of 2-(2′-methoxybenzoyl)-benzoic acid, 600 cc. of

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[8] 1,1′-Dimethoxydianthraquinone has been described by Attree and Perkin [*J. Chem. Soc.*, 163 (1931)] while 3,3′-dimethoxydianthraquinone was prepared by Barnett, Goodway and Savage [*Ber.*, **64**, 2193 (1931)] and by Perkin and Yode [*J. Chem. Soc.*, **127**, 1884 (1925)].

[9] Barnett, Cook and Nixon, *ibid.*, 508 (1927).

[10] Blicke and Swisher, This Journal, **56**, 925 (1934). We found the product melted at 78–79° instead of at 68–70° as reported previously.

[11] See ref. 7. These investigators obtained 9,9-di-(*p*-hydroxyphenyl)-anthrone-10 by demethylation of 9,9-di-(*p*-anisyl)-anthrone-10.

absolute alcohol and 25 cc. of concd. sulfuric acid was refluxed for twenty-four hours, one-third of the alcohol removed by distillation and the residue diluted with two liters of saturated sodium chloride solution. The precipitated oily ester was extracted with ether, the ether extract washed with sodium carbonate solution and then with water. The ether solution was dried with fused sodium sulfate and the solvent removed. The ester boiled at 268–270° under 14 mm. pressure; yield 70 g.

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.52; H, 6.72. Found: C, 75.29; H, 6.69.

2 - (2′-Methoxybenzyl)-4″,4‴-dimethoxytriphenylcarbinol.—The Grignard reagent, prepared from 46.8 g. of 4-iodoanisole, 4.8 g. of magnesium and 120 cc. of ether, was stirred and to it there was added, slowly, a solution of 20.3 g. of ethyl 2-(2′-methoxybenzoyl)-benzoate in 50 cc. of ether. The mixture was stirred and refluxed for three hours and then allowed to remain at room temperature for twelve hours. The mixture was decomposed with ice and ammonium chloride. The carbinol was recrystallized from a mixture of benzene and petroleum ether (30–60°); m. p. 139–140°; yield 22.7 g.

Anal. Calcd. for $C_{29}H_{28}O_4$: C, 79.05; H, 6.41. Found: C, 79.11; H, 6.58.

4-Methoxy-9,9-di-(*p*-anisyl)-anthrone-10.—Ten grams of the above mentioned carbinol was dissolved in 50 cc. of acetic acid, the solution partially saturated with hydrogen chloride and the red solution heated for six hours on a steam-bath. The solution, which possessed a strong purple fluorescence, was diluted with water, whereupon a light brown solid, 4-methoxy-9,9-di-(*p*-anisyl)-9,10-dihydroanthracene, precipitated.

A mixture of 10 g. of the dihydroanthracene, 50 cc. of acetic acid, 8 g. of sodium dichromate and 10 cc. of water was heated for three hours on a steam-bath, diluted with four volumes of water and the precipitated, crystalline anthrone recrystallized from acetic acid; m. p. 248–250°.

Anal. Calcd. for $C_{29}H_{24}O_4$: C, 79.78; H, 5.54. Found: C, 79.39; H, 5.52.

4-Hydroxy-9,9-di-(*p*-hydroxyphenyl)-anthrone-10.—Two grams of finely powdered 4-methoxy-9,9-di-(*p*-anisyl)-anthrone-10 and 3 g. of powdered aluminum chloride was heated for one hour at 100–105°, the mixture treated with ice and hydrochloric acid and the gummy product extracted with 10% sodium hydroxide solution. A dark green solid precipitated when the alkaline extract was acidified. The product was dissolved in alcohol and the solution diluted, gradually, with water. A dark brown gum, which precipitated first, was discarded. The light yellow, crystalline precipitate was recrystallized from dilute alcohol; yield 0.8 g.; m. p. 254–256° with decomposition.

Anal. Calcd. for $C_{26}H_{18}O_4$: C, 79.16; H, 4.60. Found: C, 78.89; H, 4.81.

A solution of 0.4 g. of the anthrone in 10 cc. of 10% sodium hydroxide solution was heated to 80° and treated, gradually, with 2 cc. of dimethyl sulfate. The mixture was heated for two hours and the precipitated 4-methoxy-9,9-di-(*p*-anisyl)-anthrone-10 recrystallized from acetic acid; m. p. 247–249°

A mixture of 0.14 g. of the anthrone and 0.65 g. of 3-bromobenzoyl chloride was heated for two hours at 140–150°, the brown oil washed with 5% sodium hydroxide solution and then with water. The product crystallized when rubbed under ether; m. p. 163–165° after recrystallization from acetic acid.

Anal. Calcd. for $C_{47}H_{27}O_7Br_3$: Br, 25.44. Found: Br, 25.01.

2 - (4′-Methoxybenzyl)-2″,2‴-dimethoxytriphenylcarbinol.—Twenty-three grams of ethyl 2-(4′-methoxybenzyl)-benzoate, dissolved in 50 cc. of ether, was added to 2-anisylmagnesium iodide prepared from 50 g. of 2-iodoanisole, 6.7 g. of magnesium and 150 cc. of ether. The mixture was stirred and refluxed for six hours, the crystalline precipitate removed by filtration and decomposed with ice and ammonium chloride. The crystalline product was recrystallized from petroleum ether (90–100°); yield 26 g.; m. p. 129–130°.

Anal. Calcd. for $C_{29}H_{28}O_4$: C, 79.05; H, 6.41. Found: C, 79.19; H, 6.27.

2 - Methoxy-9,9-di-(*o*-anisyl)-9,10-dihydroanthracene.—A solution of 23 g. of the carbinol described above in 75 cc. of acetic acid was partially saturated with hydrogen chloride and heated for five hours on a steam-bath. The solution, which possessed a high purple fluorescence, was diluted with four parts of water and the oily precipitate, which soon crystallized, was recrystallized from methyl alcohol; m. p. 154–155°.

Anal. Calcd. for $C_{29}H_{26}O_3$: C, 82.42; H, 6.21. Found: C, 82.17; H, 6.27.

3-Methoxy-9,9-dibromoanthrone-10.—Sixteen grams of bromine, dissolved in 100 cc. of carbon disulfide, was added to 11.2 g. of 3-methoxyanthrone-10[12] which was dissolved in 400 cc. of carbon disulfide, cooled to −5° and stirred. The mixture was then allowed to remain at room temperature for one hour, diluted with 500 cc. of petroleum ether (30–60°) and the light yellow crystalline precipitate recrystallized from benzene; yield 12 g.; m. p. 175–177° with decomposition.

Anal. Calcd. for $C_{15}H_{10}O_2Br_2$: Br, 41.88. Found: Br, 42.13.

When 3.0 g. of the brominated anthrone was treated with 20 cc. of water 1.8 g. of 2-methoxyanthraquinone was produced; mixed m. p. 195–196°.

2,2′(or 2,7′)-Dimethoxydianthraquinone.—A mixture of 15 g. of the dibromoanthrone, 200 cc. of dry benzene and 5 cc. of mercury was shaken for forty-eight hours, filtered, the benzene removed and the green amorphous solid recrystallized from acetic acid. The yellow crystals melted at 254–256° with decomposition.

Anal. Calcd. for $C_{30}H_{20}O_4$: C, 81.06; H, 4.54; mol. wt., 444. Found: C, 81.14; H, 4.44; mol. wt. (benzene, ebullioscopic procedure), 431.

Summary

A number of new triarylcarbinols, dianisyldihydroanthracenes, dianisylanthrones and di-(*p*-hydroxyphenyl)-anthrones have been described.

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(12) Also called 2-methoxyanthrone-9. See Barnett, Goodway and Savage, *Ber.*, **64**, 2191 (1931); ref. 2, p. 1460.

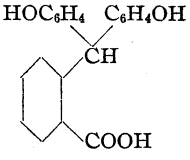
[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Hydroxy- and Methoxyphenylanthrones. II

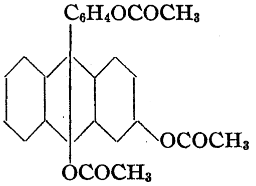
BY F. F. BLICKE AND R. A. PATELSKI[1]

A number of years ago it was stated by Baeyer[2] that phenolphthalin yields 3-hydroxy-9-(4′-hydroxyphenyl)-anthrone-10, or its tautomer, 3,10-dihydroxy-9-(4′-hydroxyphenyl)-anthracene, when treated with sulfuric acid and that the anthrone is converted, by oxidation, into 3,9-di-hydroxy-9-(4′-hydroxyphenyl)-anthrone-10. It has been shown,[3] however, that the two compounds actually obtained by Baeyer were 2,5-di-(*p*-hydroxyphenyl)-3,4-benzofuran and 2-(4″-hydroxybenzoyl)-4′-hydroxybenzophenone.

We have found that if phenolphthalin (I), or its diacetyl derivative, is treated with zinc chloride and acetic anhydride, instead of sulfuric acid, there is produced the triacetyl derivative of 3,10-dihydroxy-9-(4′-hydroxyphenyl)-anthracene (II) which, when oxidized, yields the diacetyl derivative of 3,9-dihydroxy-9-(4′-hydroxyphenyl)-anthrone-10 (III).



I



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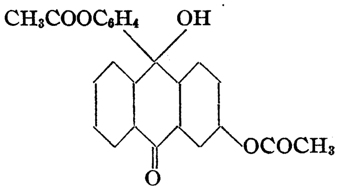

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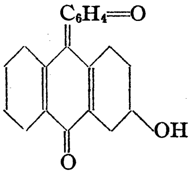

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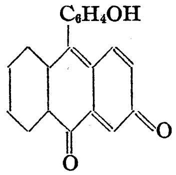
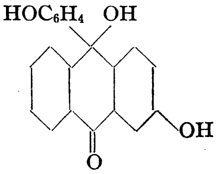
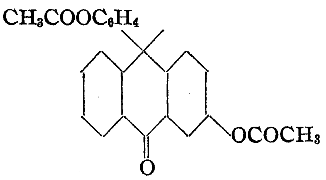


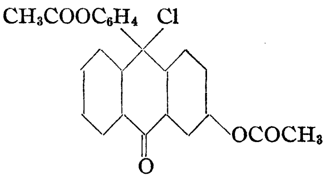
V



IV



VIII



VII

Upon hydrolysis the colorless trihydroxy compound (IV) is obtained. When heated or allowed to come into contact with mineral acids the hydroxy compound is converted into a highly colored fuchsone, either V or VI, or possibly a mixture of the two compounds. The diphenolic ether was obtained upon methylation of the trihydroxy compound (IV).

In order to supply proof of the structure of these compounds the carbinol III was converted into the carbinol chloride, the diacetyl derivative of 3-hydroxy-9-chloro-9-(4′-hydroxyphenyl)-anthrone-10, (VII). A solution of the chloride became deep red instantly when shaken with molecular silver due to the formation of the free radical 3-acetoxy-9-(4′-acetoxyphenyl)-anthronyl-10 (VIII); the red solution decolorized rapidly when exposed to air with the formation of the characteristic peroxide.

2,5-Di-(*p*-anisyl)-3,4-benzofuran (IX) was reduced to 2,5-di-(*p*-anisyl)-2,5-dihydro-3,4-benzofuran (X) with sodium amalgam. Reduction of 2-(4″-methoxybenzoyl)-4′-methoxybenzophenone (XIII) with the same reagent yielded 2-(4″-methoxy-α-hydroxybenzyl)-4′-methoxydiphenylcarbinol (XIV). When treated with zinc chloride in acetic acid solution both X and XIV were converted into 2-methoxy-9-(*p*-anisyl)-anthracene (XI). Upon oxidation the anthracene yielded 2-methoxy-9-hydroxy-9-(*p*-anisyl)-anthrone-10 (XII). The latter condensed with anisole to form 2-methoxy-9,9-di-(*p*-anisyl)-anthrone-10 (XV).

Experimental Part

Triacetyl Derivative of 3,10-Dihydroxy-9-(4′-hydroxyphenyl)-anthracene (II).—Twenty grams of phenolphthalin (I), or an equivalent amount of its diacetyl derivative, and 8 g. of anhydrous zinc chloride, dissolved in 35 cc. of acetic anhydride, were heated on a steam-bath for fifteen minutes and then poured into a mixture of water and ice which contained a small amount of hydrochloric acid. The crystalline product was digested with hot alcohol, filtered and recrystallized from a mixture of benzene and petroleum ether (90–100°); yield 19 g.; m. p. 188–189°.

Anal. Calcd. for $C_{26}H_{20}O_6$: C, 72.87; H, 4.71. Found: C, 73.04; H, 4.88.

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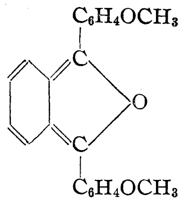
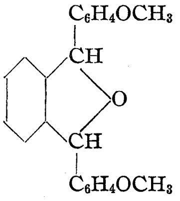
(1) Monsanto-Pfizer Research Associate.

(2) Baeyer, *Ann.*, **202**, 100 (1880).

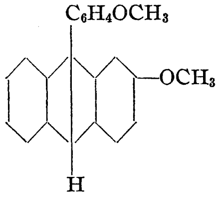
(3) Blicke and Weinkauff, THIS JOURNAL, **54**, 1454 (1932).



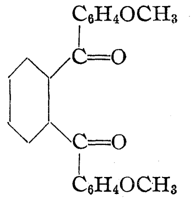
IX



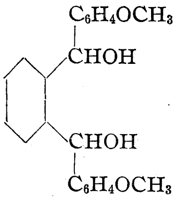
X



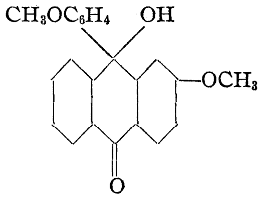
XI



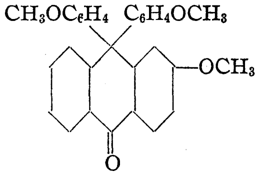
XIII



XIV



XII



XV

The compound exhibits an intense purple fluorescence when dissolved in organic solvents and a red-brown color when moistened with concd. sulfuric acid.

Diacetyl Derivative of 3,9-Dihydroxy-9-(4′-hydroxyphenyl)-anthrone-10 (III).—To 10 g. of the triacetate, dissolved in 50 cc. of acetic acid, there was added 7 g. of sodium dichromate, dissolved in 6 cc. of hot water. The mixture soon began to boil; after it had been heated on a steam-bath for two hours and poured into 500 cc. of water the crystalline product was recrystallized from benzene; yield 8 g.; m. p. 186–187°.

Anal. Calcd. for $C_{24}H_{18}O_6$: C, 71.61; H, 4.51. Found: C, 71.45; H, 4.67.

Solutions of this product in organic solvents do not fluoresce. The material turns purple when treated with concd. sulfuric acid.

3,9 - Dihydroxy-9-(4′-hydroxyphenyl)-anthrone-10 (IV).—A mixture of 5 g. of the diacetate, 20 cc. of 10% sodium hydroxide solution and 5 cc. of alcohol was heated on a steam-bath for five minutes, cooled, diluted with 25 cc. of water and 50 cc. of saturated ammonium chloride solution. The pale pink precipitate was dissolved in cold alcohol, treated with charcoal at room temperature, filtered and the solution diluted with water. After precipitation by water from an alcoholic solution the practically colorless, crystalline product melted at 127–128° with the formation of a deep red liquid. The compound, dried in a desiccator over calcium chloride for two weeks prior to analysis, contained water of crystallization.

Anal. Calcd. for $C_{20}H_{14}O_4 \cdot H_2O$: C, 71.43; H, 4.80. Found: C, 71.41; H, 4.87.

In addition to the development of the deep color, the loss of an amount of water which corresponds closely to that calculated for fuchsone formation demonstrates the conversion of IV into V or VI. Thus, when 0.5219 g. of the colorless anthrone was heated at 130° for twenty-four hours, the deep red sample obtained weighed 0.4669 g.; calcd. wt. 0.4660 g. ($C_{20}H_{14}O_4 \cdot H_2O - 2H_2O$).

The anthrone turns an intense purple when moistened with concd. sulfuric acid or a mixture of acetic and hydrochloric acid. When an acetic acid solution of the anthrone is warmed it turns bright red.

The 3,9-dimethyl ether of the anthrone was obtained when 3.2 g. of the anthrone, dissolved in 35 cc. of 20% sodium hydroxide solution, was treated with 8 cc. of dimethyl sulfate at 80–90°. After recrystallization from alcohol the ether melted at 155–156°.

Anal. Calcd. for $C_{22}H_{18}O_4$: C, 76.27; H, 5.24. Found: C, 76.01; H, 5.42.

The ether is colored an intense blue by concd. sulfuric acid.

Diacetyl Derivative of 3-Hydroxy-9-chloro-9-(4′-hydroxyphenyl)-anthrone-10 (VII).—A hot mixture of 3,9-dihydroxy-9-(4′-hydroxyphenyl)-anthrone-10 diacetate, 75 cc. of benzene and 5 cc. of acetyl chloride was treated with a stream of hydrogen chloride for two hours, the solvent removed under reduced pressure and the oily residue covered with petroleum ether (90–100°). After twelve hours the crystalline material was recrystallized from a mixture of benzene and petroleum ether; m. p. 128–129°.

Anal. Calcd. for $C_{24}H_{17}O_5Cl$: Cl, 8.43. Found: Cl, 8.25.

Peroxide of Free Radical 3-Acetoxy-9-(4′-acetoxyphenyl)-anthronyl-10 (VIII).—A mixture of 1.5 g. of the 9-chloro compound, 15 cc. of benzene and 4 g. of molecular silver was shaken for one hour. An intense red color developed immediately upon the addition of the silver. The mixture was filtered. The filtrate decolorized rapidly upon exposure to air and the peroxide precipitated upon the addition of petroleum ether; m. p. 195–200° with decomposition.

Anal. Calcd. for $C_{48}H_{34}O_{12}$: C, 71.79; H, 4.27. Found: C, 72.09; H, 4.42.

2,5-Di-(*p*-anisyl)-2,5-dihydro-3,4-benzofuran (X).—Ten grams of 2,5-di-(*p*-anisyl)-3,4-benzofuran was suspended in 600 cc. of absolute alcohol and 250 g. of 5% sodium amalgam added in portions. After the initial vigorous reaction had subsided, the mixture was heated for five hours on a steam-bath, filtered while hot and the precipitate of colorless, iridescent crystals recrystallized from alcohol; m. p. 115–116°; yield 7 g. Upon dilution of the mother liquor with water 2 g. more of material was obtained.

Anal. Calcd. for $C_{22}H_{20}O_3$: C, 79.17; H, 6.07. Found: C, 78.92; H, 6.12.

The colorless acetic acid solution becomes green when warmed and exhibits a green fluorescence.

When dissolved in acetic acid and oxidized with sodium dichromate, 2-(4″-methoxybenzoyl)-4′-methoxybenzophenone was produced; it was recrystallized from alcohol; mixed m. p. 157–159°.[4]

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[4] The same melting point was reported by Blicke and Weinkauff, THIS JOURNAL, 54, 1458 (1932).

2-(4″-Methoxy-α-hydroxybenzyl)-4′-methoxydiphenylcarbinol (XIV).—To 3.5 g. of 2-(4″-methoxybenzoyl)-4′-methoxybenzophenone, dissolved in 150 cc. of absolute alcohol, there was added 100 g. of 5% sodium amalgam. After several hours the reaction mixture was heated on a steam-bath for two hours, filtered while hot and the filtrate concentrated to one-half its original volume. Water was added gradually until the solution became turbid, the solution cooled and the crystalline precipitate recrystallized from alcohol; m. p. 139–140°; yield 2.8 g.

Anal. Calcd. for $C_{22}H_{22}O_4$: C, 75.39; H, 6.33. Found: C, 75.08; H, 6.39.

One and seven-tenths grams of the carbinol, dissolved in 20 cc. of acetic acid, was oxidized to 2-(4″-methoxybenzoyl)-4′-methoxybenzophenone with 2 g. of sodium dichromate, dissolved in 10 cc. of acetic acid; mixed m. p. 157–159°; yield 1.3 g.

2-Methoxy-9-(*p*-anisyl)-anthracene (XI).—To 1.5 g. of anhydrous zinc chloride, dissolved in a mixture of 7.5 cc. of acetic anhydride and 7.5 cc. of acetic acid, there was added 5.0 g. of 2,5-di-(*p*-anisyl)-2,5-dihydro-3,4-benzofuran. The furan dissolved with evolution of heat and the crystalline anthracene soon began to precipitate. After one hour the mixture was diluted with 50 cc. of water and the anthracene recrystallized from acetic acid; yield 3.9 g.; m. p. 177–179°.[5] Solutions of this compound exhibit a blue fluorescence.

Five grams of 2-(4″-methoxy-α-hydroxybenzyl)-4′-methoxydiphenylcarbinol was treated with zinc chloride in the manner described above. After one hour the crystalline anthracene was separated and recrystallized from acetic acid; yield 3.8 g.; m. p. 177–179°.

2-Methoxy-9-hydroxy-9-(*p*-anisyl)-anthrone-10 (XII).—Five grams of 2-methoxy-9-(*p*-anisyl)-anthracene, suspended in 25 cc. of acetic acid, was heated for two hours on a steam-bath with 4 g. of sodium dichromate, dissolved in 4 cc. of hot water. The mixture was diluted with an equal volume of water and the precipitated, crystalline anthrone recrystallized from acetic acid; yield 4.5 g.; m. p. 202–203°.[6]

2-Methoxy-9,9-di-(*p*-anisyl)-anthrone-10 (XV).—Two grams of 9-hydroxy-9-(*p*-anisyl)-anthrone-10, 6.0 g. of anisole and two drops of concd. sulfuric acid were heated for two hours on a steam-bath, the mixture treated with hot alcohol and the crystalline product recrystallized from acetic acid; yield 1.5 g.; m. p. 182–184°.[7]

Summary

It has been shown that a hydroxy- and a methoxyphenylanthrone can be obtained from a phthalin, from a benzofuran and from a benzoylbenzophenone.

A free radical of the anthraquinone type has been described.

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[5] Blicke and Weinkauff [THIS JOURNAL, **54**, 1463 (1932)] found 175–176°.

[6] Blicke and Weinkauff [*ibid.*, **54**, 1463 (1932)] reported 199–201°.

[7] Blicke and Patelski, [*ibid.*, **60**, 2640 (1938)] found 183–184°.

ANN ARBOR, MICHIGAN RECEIVED AUGUST 22, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BRYN MAWR COLLEGE]

The Introduction of Substituted Vinyl Groups. I. Isopropenyl Alkyl Malonic Esters

BY ARTHUR C. COPE AND EVELYN M. HANCOCK

The wide application of the malonic ester synthesis to organic preparations has resulted in the description of a large number of mono- and dialkyl malonic esters, containing both saturated and unsaturated groups. While β,γ-unsaturated (allyl) groups and groups with the double bond further removed from the point of attachment are readily introduced into malonic ester by the ordinary method, α,β-unsaturated (vinyl) groups cannot be introduced directly, because of the inactivity of the vinyl and alkyl substituted vinyl halides. Indirect methods for the introduction of vinyl groups are difficult and give poor yields,[1] and as a result very few vinyl substituted derivatives of malonic ester have been prepared. In this paper a practical method is described for preparing disubstituted malonic esters in which one of the substituent groups is the isopropenyl or 1-methylvinyl ($CH_2{=}C(CH_3)$—) group.

Kon and his associates,[2] in the course of their investigation of three-carbon tautomerism, methylated isopropylidene malonic ester, which forms a sodium derivative through migration of a hydrogen from the γ-carbon atom.

$$(CH_3)_2C{=}C(COOEt)_2 + NaOEt \longrightarrow$$

$$EtOH + \underset{(I)}{[CH_2{=}C(CH_3)C(COOEt)_2]^- Na^+} \xrightarrow{CH_3I}$$

$$CH_2{=}C(CH_3)C(CH_3)(COOEt)_2 + NaI$$

This reaction was employed to prove that the sodium enolate was derived from the isomeric β,γ-unsaturated ester $CH_2{=}C(CH_3)CH(COOEt)_2$, and was not extended as a possible synthetic method. The application of the reaction ap-

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[1] *Cf.* Cope and McElvain, THIS JOURNAL, **54**, 4311 (1932).

[2] Kon and Speight, *J. Chem. Soc.*, 2727 (1926).

peared to be limited, since the methylated ester undergoes alcoholysis readily in the presence of sodium ethoxide with the loss of a carbethoxy group as ethyl carbonate. The conditions of synthesis described by Kon and Speight,[2] therefore, induce alcoholysis, particularly since two treatments with alcoholic sodium ethoxide and methyl iodide were required to complete the methylation. The slow alkylations, to be expected with less active alkylating agents, would allow time for extensive cleavage during the synthesis.

We have found that the sodium enolate (I) can be prepared easily and almost quantitatively by reaction of isopropylidene malonic ester with sodamide, either in liquid ammonia solution or in an inert solvent. The resulting sodium derivative, preferably suspended in an inert solvent, can then be alkylated readily by the ordinary alkylating agents, such as the dialkyl sulfates or alkyl halides. Since the reaction mixtures are free from alcohol, the alkylations are successful even with the less reactive higher alkyl halides, some of which require long refluxing for appreciable reaction. The yields of pure isopropenyl alkyl malonic esters obtained by this method are as high as 90% when the more active alkylating agents are employed. Various primary alkyl groups have been introduced in good yield; the introduction of secondary groups is difficult. In cases in which the alkylation is not complete, the isopropenyl alkyl malonic esters may be purified conveniently by shaking with concentrated aqueous ammonia at room temperature. Like other dialkyl malonic esters, the isopropenyl alkyl derivatives are not affected by this treatment, while isopropylidene malonic ester is converted into acetone and malonamide.[3] The properties of nine isopropenyl alkyl malonic esters, prepared and purified in this manner, are described in the Experimental Part.

The sodium enolate (I) may also be prepared by the reaction of isopropylidene malonic ester with powdered sodium in an inert anhydrous solvent, such as ether or benzene. Unfortunately, a considerable amount of the isopropylidene malonic ester is reduced during the formation of the sodium enolate. Subsequent alkylation, therefore, produces a mixture of isopropenyl and isopropyl alkyl malonic esters which is difficult to separate.

Experimental Part

Ethyl Isopropylidene Malonate.—Improved yields of this ester were obtained by using an excess of acetone in a procedure otherwise similar to that described by Scheiber and Meisel.[4] A mixture of 1 kg. (6.25 moles) of ethyl malonate, 540 g. (9.3 moles) of acetone, 800 g. (7.8 moles) of acetic anhydride and 120 g. of freshly fused zinc chloride was heated under reflux in an oil-bath at 110° for twenty-four hours. The mixture was then cooled, and 800 cc. of benzene added. The nearly black solution was washed with four 500-cc. portions of water. The water washings were extracted with two 100-cc. portions of benzene, which were combined, washed with water and added to the main portion of the benzene solution. The wet benzene was removed by distillation under diminished pressure, and the remainder of the mixture was distilled in vacuum through a Vigreux column. A fore-run of acetic acid and acetic anhydride was collected, followed by 1200 g. of crude ester, b. p. 60–125° (18 mm.). The tarry residue amounted to 50 g. The crude ester was redistilled through an adiabatic, total reflux, variable take-off Fenske type column with a 70 × 1.2 cm. section packed with glass helices. The recovery of ethyl malonate, b. p. 81–83° (9 mm.), plus a small intermediate fraction was 411 g. (41%). A yield of 654 g. (52%) of ethyl isopropylidene malonate, b. p. 111–113° (9 mm.), was obtained, $n^{25}{}_D$ 1.4478, $d^{25}{}_{25}$ 1.0254, M_D calcd. 51.23, obsd. 52.42, exaltation + 1.19.

Alkylations of Ethyl Isopropylidene Malonate

A. Sodamide Procedure.—The ethylation will be described as a typical procedure. All apparatus was dried in an oven at 100 to 150° before use. A 1-liter, three-necked flask was equipped with an inlet tube, mercury-sealed stirrer and a reflux condenser attached to a soda lime tower. The tower was connected to a 3-liter bottle containing 1 liter of water (stirred with another mercury-sealed stirrer), and to the bottle was attached a water trap leading to the sink. Hydrated ferric nitrate (0.3 g.) was placed in the flask, which was then cooled in a dry ice–acetone bath while 300 cc. of anhydrous liquid ammonia was introduced through the inlet tube from an inverted ammonia cylinder. The cooling bath was then removed and 12.65 g. (0.55 mole) of sodium added in small pieces. One piece was added and the solution stirred until the blue color changed to gray, and the remainder added rapidly. Stirring was continued until the solution was gray (ten to thirty minutes), and fifteen minutes longer. All of the sodium should have reacted to form sodamide before the ester is added, since any sodium present will tend to reduce the ester. The solution was again cooled in the dry ice–acetone bath and the ethyl isopropylidene malonate (100 g. or 0.5 mole) added during ten minutes from a separatory funnel (introduced in the neck which originally held the inlet tube). The solution was stirred for ten to thirty minutes and 300 cc. of dry, sulfur-free toluene and 25 cc. of dry ether added. The solution was stirred until most of the ammonia had evaporated (one to two hours). The flask was then placed in an oil-bath which was gradually heated to 110°. During the heating the sodium derivative (I) precipitated as a gray solid and the last traces of the ammonia were distilled out through the reflux condenser

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[3] Kötz, *J. prakt. Chem.*, [2] **75**, 497 (1907).

[4] Scheiber and Meisel, *Ber.*, **48**, 247 (1915).

TABLE I

ETHYL ISOPROPENYL ALKYL MALONATES

Alkyl group	Alkylating agent	Hours refluxed[a]	Yield, %	Boiling point °C.	Mm.	$n^{25}\text{D}$	d^{25}_{25}	Mol. refraction Calcd.	Mol. refraction Found	Formula	Carbon, % Calcd.	Carbon, % Found[b]	Hydrogen, % Calcd.	Hydrogen, % Found
Methyl	Dimethyl sulfate	0	88	110–111	12	1.4370	1.0095	55.85	55.74	$C_{11}H_{18}O_4$	61.64	61.40	8.47	8.47
Ethyl	Diethyl sulfate	1	81	117–119	13	1.4402	1.0008	60.47	60.28	$C_{12}H_{20}O_4$	63.11	62.85	8.84	8.85
Allyl	Allyl bromide	3	82	122–123	10	1.4500	1.0036	64.62	64.50	$C_{13}H_{20}O_4$	64.96	64.96	8.39	8.45
Propyl	Propyl bromide	19	50	132–133	17	1.4418	0.9847	65.09	65.10	$C_{13}H_{22}O_4$	64.42	64.69	9.16	9.34
Isopropyl	Isopropyl iodide	5	10	114–116	10	1.4381	.9872	65.09	64.59	$C_{13}H_{22}O_4$	64.42	63.99	9.16	9.47
Butyl	Butyl iodide	10	59	137–138	13	1.4419	.9768	69.71	69.58	$C_{14}H_{24}O_4$	65.58	65.58	9.42	9.69
Isobutyl	Isobutyl bromide	58	40	131–132	12	1.4422	.9792	69.71	69.46	$C_{14}H_{24}O_4$	65.58	65.80	9.42	9.51
Amyl	Amyl bromide	9	50	147–148.5	12	1.4438	.9689	74.33	74.27	$C_{15}H_{26}O_4$	66.62	66.73	9.70	9.71
Isoamyl	Isoamyl bromide	25	36	140–141	11	1.4430	.9667	74.33	74.32	$C_{15}H_{26}O_4$	66.62	66.75	9.70	9.86

[a] The first three reaction mixtures were neutral after refluxing for the number of hours indicated; the remainder were from 70 to 90% neutralized. [b] We are indebted to Miss Corris Hofmann for these analyses.

with the ether. The oil-bath was removed and 101.6 g. (0.66 mole) of diethyl sulfate added during ten minutes. The oil-bath was then replaced and heated to 135°. After refluxing for one hour the reaction mixture was neutral. It was cooled in ice and washed with two portions of cold water. The washings were extracted with ether, and the ether and toluene distilled off in vacuum. The residue was shaken for twelve hours with 200 cc. of concentrated aqueous ammonia at room temperature. The ester layer was separated and the ammonia solution extracted twice with ether. The ether and ester were washed with water and the product was distilled in vacuum.

Variations of this procedure are less convenient but may be used in some cases. Ether or benzene may be employed as inert solvents. After the sodamide is formed, the inert solvent may be added and the excess ammonia expelled before adding the ester. This procedure is as convenient as that described above if the inert solvent is ether, but the ester reacts slowly with sodamide in benzene or toluene, probably due to the insolubility of both sodamide and the ester enolate. The methylation with dimethyl sulfate proceeds satisfactorily in ether, but the other alkylating agents require temperatures higher than the boiling point of ether for reaction at a satisfactory rate. With the higher alkyl halides, the reaction mixtures never become neutral. It is convenient in such cases to remove 2-cc. aliquots from time to time and determine the percentage reaction by titration with standard acid. If the reaction time is prolonged above that recorded in Table I, the yields are increased slightly in some cases, but in others increased amounts of high boiling material are formed. When the reaction mixtures do not become neutral, they should be neutralized with dilute hydrochloric acid before washing with water. Larger amounts of aqueous ammonia should be used to purify the product in such cases, and the treatment with aqueous ammonia may be prolonged to three or four days. In the alkylations giving poorer yields, it is convenient to distil the crude ester before shaking with ammonia in order to eliminate high boiling material. The esters were redistilled through a Widmer column. The yields of purified products, their physical constants and pertinent data concerning the preparations are recorded in Table I.

B. Sodium Procedure.—One-half mole of sodium was powdered under xylene and rinsed into a 1-liter, three-necked flask with 500 cc. of dry ether. Ethyl isopropylidene malonate (100 g. or 0.5 mole) was added during ten minutes with stirring and cooling in an ice-bath. The solution refluxed during the addition of the ester. The solution was stirred and refluxed for twelve hours, after which the alkylating agent was added and the reaction mixture treated as in part A. Methylation with dimethyl sulfate required two hours, and ethylation with diethyl sulfate twenty-four hours at the boiling point of ether. It is advantageous to replace the ether with benzene or toluene if less active alkylating agents are used. The sodium derivative may be prepared by this method in benzene or toluene, but, whereas in ether the sodium derivative separates as a flour-like solid and all of the sodium eventually reacts, in benzene and toluene stiff gels are formed and mechanical difficulties result.

C. Sodium Ethoxide Procedure.—In the methylation procedure described by Kon and Speight,[2] a large amount of the product is decomposed by alcoholysis, due to the long contact of the alkylated ester with alcoholic sodium ethoxide. The yields are improved if the ethyl isopropylidene malonate is treated once with sodium ethoxide and methyl iodide, and the unalkylated ester removed by shaking with aqueous ammonia as described in part A. Higher alkyl groups are not introduced in good yield by the sodium ethoxide procedure, even under conditions designed to minimize alcoholysis, as may be illustrated by the synthesis of ethyl butyl isopropenyl malonate.

A solution of sodium ethoxide was prepared in a 500-cc. three-necked flask by dissolving 5.75 g. (0.25 mole) of sodium in 200 cc. of absolute alcohol. The solution was cooled to −5° and 50 g. (0.25 mole) of ethyl isopropylidene malonate added with stirring at −5 to −10°. After stirring for thirty minutes at this temperature, 56 g. (0.30 mole) of *n*-butyl iodide was added in one portion and the solution was heated rapidly to the boiling point. After the vigorous reaction had subsided, the mixture was refluxed until neutral (one and one-half hours). The solution was cooled, diluted with water, and the ester extracted with benzene. Distillation gave 49 g. of crude ester, b. p. 110–128° (9 mm.), but after purification by shaking with concentrated ammonia for two days and redistilling, only 12 g. (19%) of ethyl isopropenyl *n*-butyl malonate was obtained.

Purity of the Alkylation Products.—The purity of the esters produced by the sodamide procedure (A) is indicated by the close correspondence of calculated and observed molecular refractions recorded in Table I. Several of the esters were hydrogenated quantitatively and the reduction products characterized as further proof of their purity and identity. The esters (0.01 to 0.03 mole) in 20 cc. of alcohol were hydrogenated at atmospheric pressure in the presence of 1 g. of palladinized charcoal,[5] containing 100 mg. of palladium. The reductions were carried out at room temperature in a 100-cc. mechanically shaken bottle attached to a large gas buret. Under these conditions the methyl, ethyl and allyl substituted isopropenyl malonic esters (described in Table I) absorbed 99.3, 99.6 and 97.8% of the theoretical quantity of hydrogen. The reductions required approximately one-half hour. The reduced esters were obtained in 85–90% yield by filtering the catalyst and distilling in vacuum. Ethyl methylisopropylmalonate, b. p. 100–102° (11 mm.), was identified by condensation with urea in the presence of alcoholic sodium ethoxide to give 5-methyl-5-isopropylbarbituric acid, m. p. 188–188.5°,[6] and by saponification with 10% barium hydroxide to methyl isopropylmalonic acid, m. p. 123.5–124.5°.[7] Ethyl ethylisopropylmalonate, b. p. 108–110° (11 mm.), was identified in a similar manner by conversion to 5-ethyl-5-isopropylbarbituric acid, m. p. 201.5–202.5°.[8]

The higher isopropenyl alkyl malonic esters are reduced very slowly with palladium at room temperature, but may be reduced rapidly and quantitatively at 150° over Raney nickel in the micro bomb described by Adkins.[9] Thus 0.02 mole of ethyl butyl isopropenyl malonate in 15 cc. of ethyl alcohol absorbed 99.7% of the theoretical quantity of hydrogen using 1 g. of catalyst. Ethyl butyl isopropyl malonate, b. p. 131–132° (11 mm.), was isolated as the reduction product in 90% yield by filtering and distilling in vacuum.

The esters obtained by the sodium alkylation procedure (B) contain a saturated impurity, which is presumably the corresponding isopropyl alkyl malonic ester, since it is not removed by long shaking with concentrated aqueous ammonia or by fractional distillation. Thus over palladium catalyst as previously described the methyl and ethyl substituted isopropenylmalonic esters prepared by sodium alkylation absorbed only 76 and 72% of the theoretical quantity of hydrogen, respectively.

Summary

Ethyl isopropylidene malonate, $(CH_3)_2C{=}C(COOEt)_2$, forms a sodium derivative (formula I) almost quantitatively by reaction with sodamide in liquid ammonia solution or in inert solvents. By alkylation of this sodium derivative in inert solvents, eight new isopropenyl alkyl malonic esters, $CH_2{=}C(CH_3)C(R)(COOEt)_2$, have been prepared. The sodium derivative has also been prepared by reaction of ethyl isopropylidene malonate with powdered sodium in inert solvents, but about 25% of the ester is reduced during the reaction.

If the sodium derivative is prepared and alkylated in alcoholic solution, the yields of alkylated esters are poor, due to extensive alcoholysis which occurs during the synthesis.

BRYN MAWR, PENNA. RECEIVED AUGUST 9, 1938

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[5] Hartung, THIS JOURNAL, **50**, 3372 (1928).

[6] Preiswerk, *Helv. Chim. Acta*, **6**, 192 (1923).

[7] Van Romburgh, *Rec. trav. chim.*, **5**, 236 (1886).

[8] Thorp, U. S. Patent 1,255,951; *C. A.*, **12**, 977 (1918).

[9] Adkins, THIS JOURNAL, **55**, 4272 (1933).

[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE]

Interaction between Grignard Compounds and Maleic Acid Derivatives

BY CH. WEIZMANN AND F. BERGMANN

Recently, Tarbell[1] reported on reactions between maleic and dimethylmaleic anhydrides with phenylmagnesium bromide: maleic anhydride reacted with two and three mols of the Grignard compound, respectively, giving phenylbenzoylpropionic acid (I) and desylacetophenone (II, R = C_6H_5). As we have studied some time ago the action of various Grignard compounds on maleic anhydride and dimethyl maleate, in continuation of previous work on other dicarboxylic acid anhydrides, we may be allowed to describe briefly our results. In accordance with Tarbell's results, neither ethylmagnesium bromide nor butylmagnesium bromide or benzylmagnesium chloride gave the expected unsaturated keto acids, $RCOCH{=}CHCOOH$, even when the organometallic compound was added to the anhydride; the keto acids formed apparently react more quickly with the Grignard compounds than maleic anhydride (or dimethyl maleate). The experiments to be described have been carried out, using a large excess (8 mols) of the magnesium derivatives.

Dimethyl maleate reacted under these conditions with 3 mols of each Grignard compound. The reacting products are 1,4-diketones of the general formula (II): they are saturated, do not contain hydroxyl groups, as shown by their negative response to the Zerewitinoff test, and give the pyrrole reaction characteristic for 1,4-diketones. The keto groups, although resistant against the attack of semicarbazide in aqueous ethyl alcohol solution, react upon phenylmagnesium bromide: 6-butyl-5,8-diketododecane (II, R = C_4H_9) gave a crystalline diol (IV), while the corresponding

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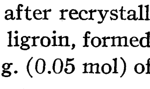
[1] Tarbell, THIS JOURNAL, **60**, 215 (1938).

3-benzyl-1,6-diphenyl-2,5-diketohexane (II, R = $CH_2C_6H_5$) took up only 1 mol of the Grignard compound, yielding (V); obviously, the second keto group is sterically hindered. The formation of the compounds (II) is completely analogous to the occurrence of desylacetophenone reported by Tarbell. The mechanism of the reaction leading to (II) is the following one: the methoxy groups are exchanged by the respective alkyl radicals, and subsequently 1 mol of the Grignard compound is added to the conjugated system, giving the enolate (III) of (II). The inverse order of the steps would not account for the formation of a diketone as primary addition to the conjugated system in dimethyl maleate would give the enolate (VI), which could undergo further alkylation only on one side of the maleate. Theoretically, the enolate (III) could react one-sided with the excess of the Grignard compound; but this reaction may be hindered for steric reasons.[2] In one case the unsaturated diketone, primarily formed according to the above mechanism, reacts with more Grignard compound in 1,2- and not in 1,4-position: from the interaction between dimethyl maleate and butylmagnesium bromide an isomeric tributyl product was secured in small amounts; it contained one hydroxyl group, was unsaturated and, therefore, has to be formulated as (VII). The same substance has been obtained from the analogous reaction with maleic anhydride.

The reaction of *maleic anhydride* upon the three Grignard compounds, in all cases, gave a mixture of acidic and neutral products. The acidic fractions proved homogeneous, they consisted of the respective γ,γ-dialkyl-γ-hydroxycrotonic acids (VIII), which have been characterized by their *p*-phenylphenacyl derivatives. The presence of the tertiary hydroxyl group was proved by the Zerewitinoff method; it causes the easy dehydration of these acids, which makes their purification somewhat tedious. It is rather surprising that phenylmagnesium bromide, according to Tarbell, introduced the two hydrocarbon radicals in a different manner (reaction at one carbonyl group and subsequently at the remaining conjugated system); our observations recall the behavior of phthalic and homophthalic anhydrides.[3] The neutral fractions, deriving from the interaction between maleic anhydride and the Grignard compounds, usually are complicated mixtures from which only the following individual reaction products have been secured: (a) in the case of benzylmagnesium chloride a hydrocarbon of the formula $C_{32}H_{28}$, therefore most probably (IX), the formation of which is analogous to that of tetraphenyldihydrofuran obtained by Purdie and Arup[4] in the case of phenylmagnesium bromide; (b) in the case of butylmagnesium bromide the same substance (VII) which had been isolated as by-product from the corresponding reaction with dimethyl maleate; (c) in the case of ethylmagnesium bromide, a compound $C_{12}H_{24}O_2$, which contains one hydroxyl group and therefore had to be formulated as (X). To the presence of a tertiary hydroxyl group points the inclination of the substance to spontaneous dehydration. The mechanism of the formation of (X) is self-explanatory.

In this connection, experiments on the interaction between butyrolactone (XI) and phenylmagnesium bromide may be mentioned briefly: 2 mols of the Grignard compound gave 1,1-diphenylbutane-1,4-diol (XII).[5]

I $C_6H_5COCH_2CH(C_6H_5)COOH$
II $RCOCH_2CH(R)COR$
III $RC(OMgX){=}CHCH(R)COR$
IV $(C_4H_9)(C_6H_5)C(OH)CH_2CH(C_4H_9)C(OH)(C_6H_5)(C_4H_9)$
V $(C_7H_7)(C_6H_5)C(OH)CH_2CH(C_7H_7)COC_7H_7$
VI $CH_3OOCCH(R)CH{=}C(OMgX)(OCH_3)$
VII $(C_4H_9)_2C(OH)CH{=}CHCOC_4H_9$
VIII $(R)_2C(OH)CH{=}CHCOOH$
IX $C_6H_5CH{=}C(C_7H_7)CH{=}CHC(C_7H_7){=}CHC_6H_5$
X $C_2H_5COCH_2CH(C_2H_5)C(OH)(C_2H_5)_2$
XI 
XII $(C_6H_5)_2C(OH)CH_2CH_2CH_2OH$

Experimental

Dimethyl Maleate and Benzylmagnesium Chloride.—The neutral reaction product boiled at 205–210° under 0.05 mm. pressure; on trituration with acetone it solidified and, after recrystallization from alcohol and subsequently from ligroin, formed leaflets, m. p. 136°; yield, 2.0 g. from 7.25 g. (0.05 mol) of dimethyl maleate.

Anal. Calcd. for $C_{25}H_{24}O_2$: C, 84.3; H, 6.7. Found: C, 84.6; H, 7.0.

3-Benzyl-1,6-diphenyl-2,5-diketo-hexane (II, R = $CH_2C_6H_5$) remained unattacked by concd. sulfuric acid, bromine and by hydrogen in the presence of platinum black

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[2] It is noteworthy that methyl maleate differs from other α,β-unsaturated esters, which add Grignard compounds preferentially in the 1,4-position. Compare Houben-Weyl, "Methoden der organische Chemie," Vol. IV, Leipzig, 1924, p. 840.

[3] *Cf.* ref. 2, p. 850; Weizmann and co-workers, *J. Chem. Soc.*, 1367 (1935); Komppa and Rohrmann, *Ann.*, **509**, 259 (1934).

[4] Purdie and Arup, *J. Chem. Soc.*, **97**, 1537 (1910).

[5] For the analogous reaction of coumarine, see Houben, *Ber.*, **37**, 489 (1904).

in glacial acetic acid solution; the absence of hydroxyl and methoxyl groups was indicated by the micro-Zerewitinoff and the Zeisel methods, respectively.[6]

Reaction with Phenylmagnesium Bromide.—The foregoing substance (0.6 g.) was dissolved in benzene and added to the Grignard solution (prepared from 0.15 g. of magnesium and 1 g. of bromobenzene); the mass was boiled for six hours and then decomposed with ice and dilute sulfuric acid. The reaction product was a viscous oil which crystallized on trituration with acetone and light petroleum. From ligroin (b. p. 130°) 2-hydroxy-5-keto-1,2,6-triphenyl-4-benzylhexane (V) separated in the form of longish plates, m. p. 202°; concd. sulfuric acid gave a brown-red color reaction; yield 250 mg.

Anal. Calcd. for $C_{31}H_{30}O_2$: C, 85.7; H, 6.9. Found: C, 85.7; H, 6.9.

Dimethyl Maleate and Ethylmagnesium Bromide.—The reaction product, 5-ethyl-3,6-diketo-octane (II, R = C_2H_5), boiled at 143° (25 mm.) and 110° (1 mm.).

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.6; H, 10.6. Found: C, 70.5; H, 10.7.

The colorless liquid had n^{21}_D 1.4538, d_{21} 0.9661, hence $MR = 47.63$, while (II, R = C_2H_5) requires 47.27. Hydroxyl and methoxyl groups were absent, the pyrrole test was strongly positive.

Dimethyl Maleate and Butylmagnesium Bromide.—From the neutral reaction product, two homogeneous fractions were obtained by careful fractionation. At 115–120° under 0.1 mm. pressure boiled 5-butyl-5-hydroxy-8-keto-dodecene-(*6*) (VII), which according to its boiling point, refractive index (n^{18}_D 1.4536) and analysis was identical with the neutral product obtained analogously from maleic anhydride.

Anal. Calcd. for $C_{16}H_{30}O_2$: C, 75.6; H, 11.8, active H, 0.394. Found: C, 75.0, 75.3; H, 11.4, 11.7; active H (micro-Zerewitinoff), 0.483.

The main product, 6-butyl-5,8-diketododecane (II, R = C_4H_9) boiled at 136° under 0.05 mm. pressure; yield 9 g. from 14.4 g. (= 0.1 mole) of dimethyl maleate. *Anal.* Calcd. for $C_{16}H_{30}O_2$: C, 75.6; H, 11.8. Found: C, 75.2; H, 11.6. It contained no hydroxyl or methoxyl groups, its diketone character was proved by reaction with phenylmagnesium bromide (see below), the 1,4-position of the carbonyl groups by the positive pyrrole test. The molecular refractivity, too, is in accord with (II, R = C_4H_9): n^{21}_D 1.4643; d_{20} 0.9267; hence $MR = 75.60$, while (II, R = C_4H_9) required $MR = 76.11$. **Reaction with Phenylmagnesium Bromide:** The diketone (6 g.) was added to the Grignard solution (from 5 g. of magnesium and 30 g. of bromobenzene). After two hours of boiling, the reaction product was worked up as usual; it distilled at 175–180° under 2.5 mm. pressure; it crystallized partly spontaneously (0.300 g.), from propyl alcohol as leaflets, from light petroleum (80–100°) as stout needles, m. p. 122–123°; concd. sulfuric acid gave an intensely yellow solution. The analysis pointed to formula (IV).

Anal. Calcd. for $C_{28}H_{42}O_2$: C, 81.9; H, 10.2. Found: C, 81.7; H, 10.2. The oily fraction, which has not been obtained analytically pure, is most probably a dehydration product of (IV).

Maleic Anhydride and Benzylmagnesium Chloride.—The acid fraction, boiling under 0.7 mm. at 210–220°, was inhomogeneous, due to partial spontaneous dehydration, but on treatment with *p*-phenylphenacyl bromide the phenylphenacyl ester[7] of γ,γ-dibenzyl-γ-hydroxycrotonic acid (VIII, R = C_7H_7) could be obtained; from propanol it crystallized in stout needles, m. p. 142–143°.

Anal. Calcd. for $C_{32}H_{28}O_4$: C, 80.7; H, 5.9; active H, 0.219. Found: C, 80.6; H, 5.9; active H, 0.211.

The neutral reaction product boiled at 215–220° under 1.5 mm. pressure. It crystallized on trituration with light petroleum and after recrystallization from ligroin (b. p. 130°) formed prisms, m. p. 184°. Combustion analysis proved that 1,6-diphenyl-2,5-dibenzylhexatriene-(1,3,5) (IX) had been formed; maleic anhydride gave no addition product; most probably the ethylenic double bonds are too highly and not asymmetrically enough substituted.[8]

Anal. Calcd. for $C_{32}H_{28}$: C, 93.2; H, 6.8. Found: C, 93.3; H, 6.8.

Maleic Anhydride and Butylmagnesium Bromide.—The acid product after many fractionations had b. p. 114° (0.05 mm.) and consisted of γ,γ-dibutyl-γ-hydroxycrotonic acid (VIII, R = C_4H_9).

Anal. Calcd. for $C_{12}H_{22}O_3$: C, 67.3; H, 10.3; active H, 0.935. Found: C, 67.2; H, 9.8; active H, 0.915. It was characterized by its *p*-phenylphenacyl ester, which after crystallization from light petroleum had m. p. 79°. *Anal.* Calcd. for $C_{26}H_{32}O_4$: C, 76.5; H, 7.8; active H, 0.245. Found: C, 76.0; H, 8.0; active H, 0.265. The neutral product (VII) distilled at 114° under 0.1 mm. pressure; $n^{22.5}_D$ 1.4568; d_{21} 0.9069; yield, 4 g. (from 9 g. of maleic anhydride). *Anal.* Calcd. for $C_{16}H_{30}O_2$: C, 75.6; H, 11.8; active H, 0.394. Found: C, 76.2; H, 12.2; active H, 0.450.

Maleic Anhydride and Ethylmagnesium Bromide.—γ,γ-Diethyl-γ-hydroxycrotonic acid (VIII, R = C_2H_5), could not be obtained in analytically pure state, due to spontaneous dehydration; the main part of the product distilled at 115° under 0.6 mm. pressure, n^{21}_D 1.4510; d_{21} 1.0170. *Anal.* Calcd. for $C_8H_{14}O_3$: C, 60.8; H, 9.0. Found: C, 62.6; H, 9.5. But this preparation gave a well-defined *p*-phenylphenacyl ester, silky needles from alcohol, m. p. 77–78°. *Anal.* Calcd. for $C_{22}H_{24}O_4$: C, 75.0; H, 6.8. Found: C, 74.7; H, 6.8. From the filtrate of this ester, a second substance, from light petroleum (b. p. 80–100°) as quadratic plates, m. p. 138°, was isolated in minute quantities; it probably is the *p*-phenylphenacyl ester of the corresponding unsaturated γ-ethylsorbic acid.

The neutral fraction had b. p. 75° (112°) under 1.5 (37) mm. pressure; it gave a brown-red color reaction with concd. sulfuric acid. According to the analysis, it consisted of 3-keto-6-hydroxy-5,6-diethyloctane (X). *Anal.* Calcd. for $C_{12}H_{24}O_2$: C, 72.0; H, 12.0; active H, 0.500. Found: C, 73.0; H, 11.3; active H, 0.592. In the same direction points the molecular refractivity: n^{21}_D 1.4574;

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(6) The reaction for 1,4-diketones, carried out according to Knorr [*Ber.*, **19**, 46 (1886)], was strongly positive.

(7) H. Meyer, "Nachweis und Bestimmung organischer Verbindungen," J. Springer, Berlin, 1933, p. 106.

(8) 1,2,3,4-Tetraphenylbutadiene, *e. g.*, does not add "philodienic" compounds. Unpublished results from our laboratories.

d_{21} 0.9269; hence $MR = 58.82$, while (X) requires $MR = 59.15$. We were unable to obtain this substance absolutely free from an impurity of diketonic character, which gave a positive response to the pyrrole test.

Butyrolactone[9] (VIII, 7.5 g.), in ethereal solution was treated with phenylmagnesium bromide (prepared from 2.1 g. of magnesium and 13.7 g. of bromobenzene); violent reaction took place. The reaction product, isolated as usual, crystallized spontaneously. By recrystallization from benzene, the needles of 1,1-diphenylbutane-1,4-diol (XII), m. p. 108°, were obtained; yield 2 g. *Anal.* Calcd. for $C_{16}H_{18}O_2$: C, 79.3; H, 7.4; active H, 0.827. Found: C, 78.9; H, 7.5; active H, 0.728.

Summary

The reaction between dimethyl maleate and maleic anhydride and Grignard compounds (benzylmagnesium chloride, butylmagnesium bromide, ethylmagnesium bromide) has been studied. Dimethyl maleate gives, by interaction with 3 mols of the organometallic compound, 1,4-diketones of the general formula $RCOCH_2CH(R)COR$, while from maleic anhydride γ,γ-dialkyl-γ-hydroxycrotonic acids and a variety of neutral products are obtained.

The reaction mechanism is discussed.

REHOVOTH, PALESTINE RECEIVED JULY 12, 1938

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(9) Johansson and Sebelius, *Ber.*, **51**, 4820 (1918), b. p. 104° at 19 mm.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Influence of α-Halogen Substitution on the Enolization of Ketones

BY E. P. KOHLER[1] AND H. M. SONNICHSEN

Halogen substitution in the α-position is known to promote the enolization of ketones in acid media,[2] but the effect of α-halogen substitution on the enolization of ketones in basic solution has been investigated less extensively. Bartlett's measurements of the rate of bromination and chlorination of acetone in basic solution[3] have indicated that enolization is the rate-controlling step in the reaction of ketones with halogens in the presence of bases, and if this mechanism is correct there can be no doubt that α-halogen substitution promotes enolization in basic media, for in practically every case[4] the only product which can be isolated from the alkaline halogenation of a methyl ketone is a trihalo methyl ketone or its cleavage products. Furthermore, if mono- and dihalomethyl ketones are prepared, they are found to react with halogens in the presence of bases more rapidly than the corresponding unsubstituted ketones.[5]

Direct chemical evidence for the theory that α-halogen substitution promotes enolization of carbonyl compounds is not plentiful. Watson observed that brominated acetones and acetophenones are acidic, but later proved that this acidity was to be ascribed to hydrolysis rather than enolization.[6] Fisher[7] found that several substituted dibromo acetophenones were markedly acidic, but like Watson did not attribute this acidity to enolization.

Thus, all discussion of the influence of α-halogen substitution on the enolization of carbonyl compounds in basic solution has been based on assumptions concerning the mechanism of bromination of ketones. In the experiments with α-bromo-β,β-diphenyl propionyl mesitylene described below, we have found direct chemical evidence in support of the theory that α-halogen substitution promotes the enolization of ketones in basic media, independent of any assumptions concerning the mechanism of the reactions of carbonyl compounds.

Investigations in this Laboratory and elsewhere[8] have indicated that the mesityl radical has a marked influence on the stability of enols; therefore it might be expected that α-bromo-β,β-diphenyl propionyl mesitylene would be a rather easily enolized ketone. One would not expect the influence of the mesityl radical to be strong enough, however, to produce any marked peculiarities in the behavior of a monoketone, so it

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(1) The investigations described in this paper were completed under the direction of Professor Kohler, but the manuscript was prepared for publication by the junior author after Professor Kohler's death.

(2) Watson and Yates, *J. Chem. Soc.*, 3318 (1931); 1207 (1932).

(3) Bartlett, THIS JOURNAL, **56**, 967 (1934).

(4) Fuson has been able to obtain stepwise halogenation in only one case [Bull, Ross and Fuson, *ibid.*, **57**, 764 (1935)].

(5) Fuson, Lewis and DuPuis, *ibid.*, **54**, 1114 (1932).

(6) Watson, Nathan and Laurie, *J. Chem. Phys.*, **3**, 170 (1935); Edwards, Evans and Watson, *J. Chem. Soc.*, 1942 (1937).

(7) Fisher and Walling, THIS JOURNAL, **57**, 1562 (1935).

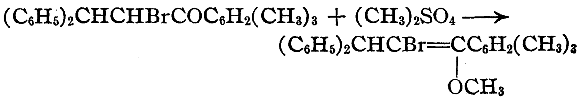
(8) (a) Kohler and Thompson, *ibid.*, **59**, 886 (1937); (b) Kohler, Tishler and Potter, *ibid.*, **57**, 2517 (1935); (c) Barnes and Green, *ibid.*, **60**, 1549 (1938); (d) Lutz and Wood, *ibid.*, **60**, 705 (1938); (e) Barnes, *ibid.*, **57**, 937 (1935); **60**, 1168 (1938).

was with considerable astonishment that we first observed that the above-mentioned bromoketone was extremely soluble in cold methyl alcoholic potassium hydroxide, so soluble in fact that it is extracted easily from benzene by alcoholic alkali.

The solubility of the bromide in ethanol is 0.214 g. per 100 cc. at 25°. In saturated ethyl or methyl alcoholic potassium hydroxide the solubility is at least 50 g. per 100 cc. The bromide could be recovered quantitatively from these solutions by acidification or dilution with water, but if they were allowed to remain for any length of time at room temperature, enough unsaturated ketone, $(C_6H_5)_2C{=}CHCOC_6H_2(CH_3)_3$, was formed to color the product yellow. The corresponding saturated ketone, $(C_6H_5)_2CHCH_2COC_6H_2(CH_3)_3$, although it is quite soluble in alcohol, shows no evidence of solubility in methyl alcoholic potassium hydroxide. The corresponding α-bromoketone in the phenyl series, $(C_6H_5)_2CHCHBrCOC_6H_5$, was soluble in methyl alcoholic potassium hydroxide, but to a much smaller extent, and the original compound could not be recovered by acidification. Instead, a new substance melting at 230–240° was obtained, which was not investigated further.

The presence of the enolic modification of α-bromo-β,β-diphenyl propionyl mesitylene in solutions in alcoholic potassium hydroxide was demonstrated by the formation of the enol methyl ether in alkaline solution. Dimethyl sulfate gave a 30% yield of $(C_6H_5)_2CHCBr{=}\underset{OCH_3}{C}C_6H_2(CH_3)_3$, and 65% of the bromide was recovered unchanged, along with traces of β-phenyl benzalacetomesitylene. Traces of the same ether were produced by methyl iodide.

α-Bromo-β,β-diphenyl propionyl mesitylene prepared by bromination of the Grignard addition product of phenylmagnesium bromide and benzalacetomesitylene often contains more bromine than the theoretical percentage. A large batch of crude bromide was methylated with dimethyl sulfate, yielding 20% of the ether and about 75% of unchanged starting material. The recovered bromoketone was then recrystallized and analyzed. Methylation of the analyzed sample gave the methoxyl derivative in 30% yield, leaving little doubt that only the bromoketone in the crude bromide underwent reaction as follows



$$(C_6H_5)_2CHCHBrCOC_6H_2(CH_3)_3 + (CH_3)_2SO_4 \longrightarrow (C_6H_5)_2CHCBr{=}\underset{\displaystyle OCH_3}{C}C_6H_2(CH_3)_3$$

Proof of the position of the bromine atom in α-bromo-β,β-diphenyl propionyl mesitylene was hardly necessary, since the same substance has been prepared by direct bromination of the saturated ketone, and the reactions of the Grignard reagent formed by treating the bromoketone with $C_2H_5MgBr^{8b}$ leave little doubt as to its structure. Further evidence of the position of the bromine atom was furnished by the bromination of benzhydrylacetomesitylene in alkaline solution according to Fuson's method for brominating acetomesitylene.[9] The dibromide obtained, $(C_6H_5)_2CHCBr_2COC_6H_2(CH_3)_3$, was identical with that formed by the alkaline bromination of α-bromo-β,β-diphenyl propionyl mesitylene.

To prove that the methoxyl compound did not have an indene structure, it was heated for forty-eight hours on the steam-bath with methyl alcoholic potassium hydroxide. The insoluble crystals gradually changed to a clear colorless oil, and potassium bromide was deposited. On acidification of the solution, the oil became bright yellow, and from the ether extract crystals of pure β-phenyl benzalacetomesitylene were obtained. Their identity was proved by hydrogenation to the corresponding saturated ketone and by their failure to depress the melting point of an authentic sample.

Experimental

α-Bromo-β,β-diphenyl Propionyl Mesitylene.—Twenty-five grams of benzalacetomesitylene in ether was added to a solution of phenylmagnesium bromide prepared from 5 g. of magnesium and 34 g. of bromobenzene. The solution was boiled for one hour, then cooled to −10° and stirred vigorously while 11 cc. of dry bromine was added dropwise, keeping the temperature below −5°. The magnesium derivative was decomposed immediately with ice and sulfuric acid and the precipitated bromoketone filtered off. The ether solution was washed with water, dried over calcium chloride and evaporated to recover the remainder of the bromoketone. The crude solid was recrystallized from benzene: yield of purified material, 80 to 90%, m. p. 172–173°.

Preparation of $(C_6H_5)_2CHC(Br){=}C(OCH_3)C_6H_2(CH_3)_3$.—α-Bromo-β,β-diphenyl propionyl mesitylene was dissolved in saturated methyl alcoholic potassium hydroxide by adding to the dry solid a number of cubic centimeters of the basic solution equal to twice the number of grams of solid. To prevent formation of unsaturated ketone, the bromide was ground finely and dissolved as rapidly as possible. Addition of 1 cc. of ether per 10 cc. of alcoholic alkali facilitated solution of the bromide, but if more than this was added the yield of methoxyl compound was reduced. After the solution became clear it was cooled in an ice-bath

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[9] Fuson and Walker, THIS JOURNAL, **52**, 3269 (1930).

and a number of cubic centimeters of dimethyl sulfate equal to the number of grams of bromide used was added with vigorous stirring and efficient cooling. The dimethyl sulfate was added as rapidly as possible without allowing the solution to boil. The maximum rate was three or four drops per second in runs on more than 25 g. of material and less in smaller runs. When about two-thirds of the dimethyl sulfate had been added, evolution of gas became noticeable, and the mixture became semi-solid. The gas evolved was the same as that produced when methyl alcoholic potassium hydroxide was treated with dimethyl sulfate; it was identified as dimethyl ether by its boiling point. The reaction mixture was allowed to stand at ice-bath temperatures for several hours, usually overnight, then thoroughly washed with water to remove sodium sulfate and filtered to remove the rather insoluble starting material. This recovered bromide was washed with ether to remove all traces of methoxyl compound. The ether filtrate contained the methoxyl compound, quite large amounts of bromide and barely enough unsaturated ketone to color the solution yellow. The ether solution, dried and evaporated to a small volume, deposited crystals of the bromide. The methoxyl compound separated from the filtrate, but, following this, a mixture of the reaction product and starting material was obtained, the bromide in fine needles and the methoxyl compound in large hexagonal plates. Separation of the mixture was effected by extracting the diluted ether solution with methyl alcoholic potassium hydroxide, thus removing the bromide completely. The crystals could also be separated mechanically.

The methoxyl compound, m. p. 115–116°, separates as hexagonal plates from ether, is slightly soluble in petroleum ether and quite soluble in acetone and benzene.

Anal. Calcd. for $C_{25}H_{25}OBr$: C, 71.3; H, 6.0; Br, 18.97; CH_3O, 7.36; mol. wt., 421. Found: C, 71.1; H, 6.2; Br, 19.1, 19.4; CH_3O, 7.0; molecular weight in boiling acetone, 410, 409, 403.[10]

The bromine determinations were carried out by the Carius method, but in order to decompose the sample completely it was necessary to heat the tubes for six hours at 250°, open them and boil out the spent acid, then add fresh fuming acid and heat above 300° for eighteen hours. Analyses by the Parr bomb method failed to decompose the sample.

α,α-Dibromo-β,β-diphenyl Propionyl Mesitylene.—β,β-Diphenyl propionyl mesitylene and α-bromo-β,β-diphenyl propionyl mesitylene both gave nearly quantitatively the same dibromide, $(C_6H_5)_2CHC(Br)_2COC_6H_2(CH_3)_3$, when shaken for one week with a solution of bromine in aqueous alkali.[9]

Anal. Calcd. for $C_{24}H_{22}OBr_2$: Br, 32.86. Found: Br, 33.0, 33.0.

The ether solutions of α,α-dibromo-β,β-diphenyl propionyl mesitylene rapidly became colored on standing and liberated bromine. The pure white solid dibromide, m. p. 135–136°, is stable at ordinary temperatures, but turns red on heating. When the dibromide was heated on the steam-bath for thirty hours with 20% aqueous potassium hydroxide, about 75% of the dibromide was recovered unchanged. The remainder was a yellow oil, which deposited crystals of β-phenyl benzalacetomesitylene. When 2 g. of the dibromide was boiled with 25 cc. of saturated methyl alcoholic potassium hydroxide for five hours, all of the bromine was removed, since the resulting oil, after it had been taken up in benzene and washed with water, no longer gave a Beilstein test. When the solvent was evaporated, crystals of β-phenyl benzalacetomesitylene were deposited.

Summary

α-Bromo-β,β-diphenyl propionyl mesitylene was shown to exist as the enolic modification in solutions in alcoholic potassium hydroxide by the preparation of the enol methyl ether in alcoholic alkali.

The ease with which α-bromo-β,β-diphenyl propionyl mesitylene is enolized by bases is attributed to the influence of the halogen atom in the α-position. This supports the theory that α-halogen substitution favors enolization in alkaline media.

Cambridge, Mass. Received August 23, 1938

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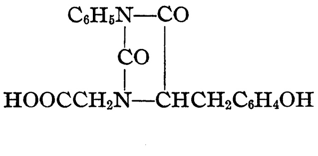
[10] These determinations were made by Mr. D. M. Bowen.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

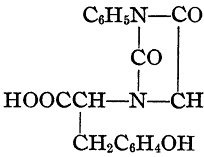
Hydantoins. LII.[1] The Synthesis of N-3-Phenyl-5-*p*-hydroxybenzylhydantoin-N-1-acetic Acid from Tyrosine-N-acetic Acid[2]

BY ELINOR WARE[3]

The purpose of this investigation was to study the effect of substituent groups on the cyclization of a derivative of hydantoic acid which might theoretically undergo ring closure to give either of two isomeric hydantoins. A large number of α-amino acids and the symmetrical imino dibasic acid, iminodiacetic acid, have been converted into hydantoic acid and hydantoin derivatives through the action of aryl isocyanates and isothiocyanates,[4] but similar reactions of an unsymmetrical imino dibasic acid of the type of tyrosine-N-acetic acid have not been studied. Reactions of isocyanates with unsymmetrical imino dibasic acids are of especial interest since, for example, the substituted hydantoic acid prepared from tyrosine-N-acetic acid by treatment with phenyl isocyanate might be expected to undergo cyclization to give either of two isomeric hydantoins: N-3-phenyl-5-*p*-hydroxybenzylhydantoin-N-1-acetic acid (I), or N-3-phenylhydantoin-N-1-*p*-hydroxybenzylacetic acid (II).



I

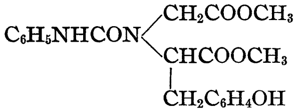


II

The fact that only one of these two isomeric hydantoins was isolated when this particular reaction was studied would appear to indicate that one of these hydantoins, because of the relative positions of its substituent groups, is formed much more readily from the corresponding acyclic hydantoic acid derivative than is its isomer.

When tyrosine-N-acetic acid was allowed to react with phenyl isocyanate in alkaline solution, the product obtained on neutralizing the cold alkaline reaction mixture was not the phenylureido derivative of tyrosine-N-acetic acid, but the closed hydantoin, N-3-phenyl-5-*p*-hydroxybenzylhydantoin-N-1-acetic acid (I). This result is quite in accordance with the work of other investigators, who found that certain substituted hydantoic acids were so unstable that they underwent spontaneous ring closure in cold neutral solutions.[5] An attempt to prepare the acyclic phenylureido derivative of tyrosine-N-acetic acid by decomposing its copper salt with hydrogen sulfide gave similar results, the closed hydantoin (I) again being obtained when the filtrate from the copper sulfide was concentrated under reduced pressure at room temperature.

While the free acyclic dibasic phenylureidic acid was not isolated because of its strong tendency to undergo ring closure, it was obtained in the form of its dimethyl ester (III).



$$C_6H_5NHCON\begin{cases}CH_2COOCH_3\\ CHCOOCH_3\\ \quad|\\ CH_2C_6H_4OH\end{cases}\qquad \text{III}$$

This ester was obtained by treating the dimethyl ester of tyrosine-N-acetic acid with phenyl isocyanate in ether solution. Since this substance is only slightly soluble in ether, it was precipitated in crystalline form from the reaction mixture. This dimethyl ester of the phenylureido acid could be made to undergo cyclization to a hydantoin derivative by either of two methods. When boiled for half an hour with 25% hydrochloric acid, it was completely converted into N-3-phenyl-5-*p*-hydroxybenzylhydantoin-N-1-acetic acid (I), the same compound which had been obtained when the alkaline reaction mixture of tyrosine-N-acetic acid and phenyl isocyanate was neutralized with mineral acid. Boiling of this ester in neutral aqueous solution for somewhat longer periods of time brought about the formation of the methyl ester of this same hydantoin-N-1-acetic acid.

The hydantoin prepared from tyrosine-N-acetic acid by the methods outlined above was proved

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(1) Previous papers of this series: L, Herbst and Johnson, THIS JOURNAL, **54**, 2463 (1932); LI, Haring and Johnson, *ibid.*, **55**, 395 (1933).

(2) Constructed from a dissertation presented in June, 1937, by the author to the Faculty of the Graduate School of Yale University in partial fulfilment of the requirements for the degree of Doctor of Philosophy.—T. B. Johnson.

(3) University Scholar in Chemistry, Yale Graduate School, 1936–37.

(4) Marckwald, Neumark and Stelzner, *Ber.*, **24**, 3278 (1891); Mouneyrat, *ibid.*, **33**, 2399 (1900); Neuberg and Manasse, *ibid.*, **38**, 2359 (1905); Bailey and Randolph, *ibid.*, **41**, 2505 (1908); Brautlecht, *J. Biol. Chem.*, **10**, 139 (1911); Bailey and Snyder, THIS JOURNAL, **37**, 935 (1915).

(5) Friedman, *Beitr. Chem. physiol. Path.*, **11**, 160 (1908); Brautlecht, *J. Biol. Chem.*, **10**, 139 (1911); Hahn and Endicott, THIS JOURNAL, **60**, 1040 (1938).

through synthesis to be N-3-phenyl-5-*p*-hydroxybenzylhydantoin-N-1-acetic acid (I). N-3-Phenyl 5-anisalhydantoin was prepared according to the method of Wheeler and Hoffman,[6] and then converted into ethyl N-3-phenyl-5-anisalhydantoin-N-1-acetate by allowing ethyl chloroacetate to react with its sodium derivative in alcohol solution. By treatment with hydriodic acid in the presence of red phosphorus, this unsaturated ester was transformed into N-3-phenyl-5-*p*-hydroxybenzylhydantoin-N-1-acetic acid (I), which proved to be identical with the substance obtained through the action of phenyl isocyanate on tyrosine-N-acetic acid. Therefore, in these particular experiments only one of the two theoretically possible isomeric hydantoins was obtained through the methods of ring closure employed.

This N-3-phenylhydantoin (I) will break down under alkaline hydrolysis to form tyrosine-N-acetic acid, carbon dioxide, and aniline. This decomposition follows the same course as that of the corresponding N-3-methyl derivative, which was found by Hahn and Renfrew to be converted by intensive alkaline hydrolysis into tyrosine-N-acetic acid, carbon dioxide, and methylamine.[7]

Experimental

N-3-Phenyl-5-*p*-hydroxybenzylhydantoin-N-1-acetic Acid (I).—Four grams of tyrosine-N-acetic acid was dissolved in 25 cc. of water containing three equivalents (2.8 g.) of potassium hydroxide, 2.0 cc. of phenyl isocyanate (a small excess) slowly added to the cold solution during a period of fifteen minutes, and the mixture mechanically stirred for seven hours while cooled in an ice-bath. The resulting milky solution was allowed to stand overnight at room temperature, a little diphenylurea was removed, and the alkaline filtrate was again cooled and neutralized with an amount of hydrochloric acid equivalent to the potassium hydroxide used. After all of the hydrochloric acid had been added, a gum precipitated and then slowly crystallized. This precipitate weighed 4.8 g. and melted at 198–201° to a clear oil. After recrystallization from 200 cc. of water, the melting point was raised to 202–203°. Additional quantities of this substance were obtained by concentration of the mother liquor, so that the yield was practically theoretical. This substance was shown to be N-3-phenyl-5-*p*-hydroxybenzylhydantoin-N-1-acetic acid through comparison with a sample of this substance prepared by another method, with which it proved to be identical.

Anal. Calcd. for $C_{18}H_{16}O_5N_2$: N, 8.24. Found: N, 8.25, 8.28.

This substance may be recrystallized most satisfactorily from boiling water, and can be made to separate in fairly large colorless crystals when its hot aqueous solution is cooled very slowly. It is quite soluble in alcohol and insoluble in ether.

This same hydantoin (I) was obtained by the decomposition of the copper salt of phenylureido-tyrosine-N-acetic acid with hydrogen sulfide. The copper salt was prepared by adding the theoretical amount of cupric chloride to an aqueous solution of the dipotassium salt of the phenylureido acid. Since it was almost insoluble in both alcohol and water, it was not recrystallized or analyzed. This blue copper salt was suspended in 95% alcohol, and gaseous hydrogen sulfide led into the mixture. After the removal of the precipitated copper sulfide, the filtrate was concentrated under reduced pressure at room temperature. When practically all the alcohol had been removed, the residue crystallized to give the same hydantoin (I) which previously had been obtained from solutions of the dipotassium salt of the phenylureido acid.

This hydantoin (I) was also prepared from the dimethyl ester of phenylureido-tyrosine-N-acetic acid (III) by boiling the latter with 25% hydrochloric acid. Two-tenths of a gram of the phenylureido ester was boiled for thirty minutes with 50 cc. of 25% hydrochloric acid. When the solution was cooled, a precipitate melting at 195–200° was obtained. After recrystallization from water it melted at 202–203°.

$CH_3OOCCH_2NHCH(CH_2C_6H_4OH)COOCH_3$, **Dimethyl Tyrosine-N-acetate.**—The hydrochloride of dimethyl tyrosine-N-acetate was prepared according to the method used by Hahn and Litzinger, through the treatment of tyrosine-N-acetic acid with a solution of dry hydrogen chloride in methyl alcohol.[8] In order to obtain the free ester, 2.0 g. of the ester hydrochloride was dissolved in 15 cc. of water and 0.55 g. of sodium bicarbonate, the amount necessary to free the ester from its hydrochloride, added to the aqueous solution. The free ester was then extracted with ether, the total volume used being about 100 cc. The ether extract was dried over anhydrous sodium sulfate, filtered, and concentrated to a small volume. When the ether was nearly evaporated and the free ester began to crystallize, water was added carefully in small portions to complete the crystallization of the ester. Dimethyl tyrosine-N-acetate is very soluble in both methyl alcohol and ether, but only slightly soluble in water. It was recrystallized by dissolving in a small amount of methyl alcohol and precipitating with water. It melts to a clear oil at 84–85°.

Anal. Calcd. for $C_{13}H_{17}O_5N$: N, 5.24. Found: N, 5.25, 5.02, 5.08.

Dimethyl Phenylureido-tyrosine-N-acetate (III).—The dimethyl ester of tyrosine-N-acetic acid was converted quantitatively into its phenylureido derivative by treatment with phenyl isocyanate in ether solution. One gram of dimethyl tyrosine-N-acetate was dissolved in 100 cc. of ether, and 0.8 cc. of phenyl isocyanate slowly added. The mixture was stirred in an ice-bath for three hours and then filtered from the precipitate which had begun to form at the end of twenty minutes. This precipitate consisted of the phenylureido derivative mixed with a small amount of diphenyl urea. It was purified by dissolving it in a small amount of methyl alcohol, filtering out the diphenyl urea, concentrating the alcoholic solution somewhat under

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[6] Wheeler and Hoffman, *Am. Chem. J.*, **45**, 375 (1911).

[7] Hahn and Renfrew, THIS JOURNAL, **47**, 147 (1925).

[8] Hahn and Litzinger, *ibid.*, **54**, 4664 (1932).

reduced pressure, and reprecipitating the phenylureido ester by the addition of ether. The melting point was 124–125° with evolution of a gas. This ester is very soluble in methyl alcohol, only slightly soluble in ether, and insoluble in water. The analyses of recently recrystallized samples indicate the presence of a molecule of methyl alcohol of crystallization.

Anal. Calcd. for $C_{20}H_{22}O_6N_2 \cdot CH_3OH$: N, 6.70. Found: N, 6.66, 6.79, 6.77.

Since heating will cause partial decomposition of this ester, it cannot be freed from solvents by this method. The methyl alcohol appears to be lost after long standing over dehydrating agents, as indicated by the analyses of a sample which had stood in a desiccator over calcium chloride for several months, although the melting point was unchanged.

Anal. Calcd. for $C_{20}H_{22}O_6N_2$: N, 7.26. Found: N, 7.33, 7.36.

$CH_3OOCCH_2NCON(C_6H_5)COCHCH_2C_6H_4OH$, **Methyl N-3-Phenyl-5-*p*-hydroxybenzylhydantoin-N-1-acetate.**—This ester could be prepared by either of two methods: (a) the esterification of the corresponding acid (I) with methyl alcoholic hydrogen chloride, or (b) the boiling of dimethyl phenylureido-tyrosine-N-acetate (III) in aqueous solution.

(a) Five-tenths of a gram of N-3-phenyl-5-*p*-hydroxybenzylhydantoin-N-1-acetic acid (I) was dissolved in 25 cc. of methyl alcohol, and the solution saturated with dry hydrogen chloride. The reaction mixture was then heated for several hours and finally evaporated to an oil. Treatment of this oil with methyl alcohol–water mixtures brought about the crystallization of the ester, m. p. 140–141°. It was recrystallized by dissolving in a few cc. of methyl alcohol and reprecipitating through the addition of water.

Anal. Calcd. for $C_{19}H_{18}O_5N_2 \cdot CH_3OH$: N, 7.25. Found: N, 7.19, 7.32, 7.19.

(b) The preparation of this ester by boiling the dimethyl ester of phenylureido-tyrosine-N-acetic acid (III) in neutral aqueous solution was not so satisfactory, since only partial conversion occurred even after several hours of heating. One gram of the phenylureido ester was boiled with 200 cc. of water for one hour, during which time a large amount of gummy precipitate was formed. By repeated extraction of this gum with boiling water, several precipitates of the methyl ester of the hydantoin-N-1-acetic acid (I) were obtained. The rest of the gum was converted into the corresponding acid (I) by boiling it with 25% hydrochloric acid.

$C_2H_5OOCCH_2NCON(C_6H_5)COC{=}CHC_6H_4OCH_3$, **Ethyl N-3-Phenyl-5-anisalhydantoin-N-1-acetate.**—In order to prove that the substance obtained through the action of phenyl isocyanate on tyrosine-N-acetic acid was N-3-phenyl-5-*p*-hydroxybenzylhydantoin-N-1-acetic acid (I), it was necessary to synthesize this compound by another method which could leave no doubt of the configuration of the compound. The first step in this synthesis was the preparation of N-3-phenyl-5-anisalhydantoin, $NHCON(C_6H_5)COC{=}CHC_6H_4OCH_3$, which was then converted into ethyl N-3-phenyl-5-anisalhydantoin-N-1-acetate. Five grams of N-3-phenyl-5-anisalhydantoin, prepared by the method of Wheeler and Hoffman[6] from N-3-phenylhydantoin,[9,10] was added to a solution of 0.43 g. of sodium in 50 cc. of absolute alcohol. The mixture was then heated for fifteen minutes, the phenylhydantoin dissolving as soon as the solution was hot, and 2.3 g. of ethyl chloroacetate (1.1 equivalents) added, together with 10 cc. more of absolute alcohol. The solution was now heated under reflux for three and a half hours. A heavy precipitate of sodium chloride began to separate at the end of one hour. At the termination of the heating period, the reaction mixture was poured into an equal volume of water, when a heavy precipitate was formed. This precipitate was extracted with chloroform in order to separate the reaction product from any unchanged N-3-phenyl-5-anisalhydantoin, and a residue of 2.5 g. of this hydantoin was obtained. The chloroform extract was evaporated almost to an oil and then treated with alcohol, when crystals of the reaction product, ethyl N-3-phenyl-5-anisalhydantoin-N-1-acetate, were obtained. After recrystallization from absolute alcohol, they melted at 89–91°.

Anal. Calcd. for $C_{21}H_{20}O_5N_2$: N, 7.38. Found: N, 7.22, 7.32.

This ester was converted by treatment with hydrogen iodide and red phosphorus into N-3-phenyl-5-*p*-hydroxybenzylhydantoin-N-1-acetic acid (I), reduction of the double bond, demethylation, and hydrolysis of the ester group taking place under the action of this reagent. Five-tenths of a gram of the unsaturated hydantoin ester was refluxed for three hours with 10 cc. of concentrated hydriodic acid in the presence of a small amount of red phosphorus. The mixture was then subjected to distillation under reduced pressure at 110–120° in order to remove the methyl iodide formed during the reaction, as well as the excess of hydrogen iodide. Small amounts of water were added from time to time, and the distillation continued until the distillate gave no test for iodide ions. The residue was dissolved in hot water, filtered from red phosphorus, and the solution concentrated to five cc. Crystals of N-3-phenyl-5-*p*-hydroxybenzylhydantoin-N-1-acetic acid (I), melting at 202–203° after recrystallization from hot water, were obtained from the cool solution. This hydantoin proved to be identical with the substance prepared from tyrosine-N-acetic acid and phenyl isocyanate, as shown by a mixed melting point determination, as well as by a comparison of their other properties.

Hydrolysis of N-3-Phenyl-5-*p*-hydroxybenzylhydantoin-N-1-acetic Acid with Barium Hydroxide.—Hot aqueous solutions of 1 g. of N-3-phenyl-5-*p*-hydroxybenzylhydantoin-N-1-acetic acid (I) and 3 g. of barium hydroxide were mixed and heated on a steam-bath for five hours, the total volume being kept between 10 and 15 cc. During the hydrolysis the odor of aniline could be detected and a white precipitate was formed. The hot mixture was filtered and the filtrate concentrated to a small volume, when a second precipitate was obtained by the addition of alcohol. The two precipitates were suspended in hot water, and the barium exactly neutralized with sulfuric

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(9) Paal, *Ber.*, **27**, 975 (1894).

(10) Mouneyrat, *ibid.*, **33**, 2399 (1900).

acid, the barium sulfate being subsequently filtered from the hot solution. After concentration of the filtrate, a precipitate of the imino dibasic acid, tyrosine-N-acetic acid, was obtained. This substance was identified by conversion into its characteristic hydrochloride, m. p. 212–213° with evolution of a gas, by treatment with 1:1 hydrochloric acid.[8]

Summary

Tyrosine-N-acetic acid, an unsymmetrical imino dibasic acid, will react with phenyl isocyanate to form a phenylureido dibasic acid which appears to be stable only in the form of its salts or esters. The free phenylureido acid undergoes spontaneous ring closure in cold aqueous solutions to give a trisubstituted hydantoin. Although the phenylureido derivative of tyrosine-N-acetic acid may theoretically undergo cyclization to give either of two isomeric hydantoins, only one of these isomers was obtained under the conditions studied.

NEW HAVEN, CONN. RECEIVED AUGUST 18, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

The Synthesis of 1,4-Di-(3',4'-dimethoxyphenyl)-butanone-2 (Veratrylhomoveratryl Ketone)[1]

BY RICHARD CARROLL AND PAUL E. SPOERRI

The importance of a new general synthesis of the papaverine type of alkaloid was pointed out by Allen and Buck[2] in 1930. The published methods for the synthesis of papaverine itself involve the preparation of homoveratroylhomoveratrylamine[3–5] through the condensation of homoveratrylamine with homoveratric acid. No attempt has been made to prepare homoveratroylhomoveratrylamine from the oxime of 1,4-di-(3',4'-dimethoxyphenyl)-butanone-2 by means of a Beckmann rearrangement.[6]

It was felt that the synthesis of this tetramethoxy ketone would furnish a new approach to the preparation of a benzylisoquinoline alkaloid as illustrated by the following equations

$$(CH_3O)_2C_6H_3CH_2COCH_2CH_2C_6H_3(OCH_3)_2 \longrightarrow$$
$$(CH_3O)_2C_6H_3CH_2C({=}NOH)CH_2CH_2C_6H_3(OCH_3)_2 \longrightarrow$$
$$(CH_3O)_2C_6H_3CH_2CONHCH_2CH_2C_6H_3(OCH_3)_2$$

In a first attempt to prepare this ketone, 1,4-di-(3',4'-dimethoxyphenyl)-butanone-2, a Friedel–Crafts reaction between 1-chloro-4-(3',4'-dimethoxyphenyl)-butanone-2 and veratrole was studied. The chloro ketone was made from 3,4-dimethoxydihydrocinnamoyl chloride by means of the Nierenstein[7] reaction. The desired coupling, as shown by the following equation, did not take place and the method was abandoned.

$$(CH_3O)_2C_6H_3CH_2CH_2COCH_2Cl + C_6H_4(OCH_3)_2 \longrightarrow$$
$$(CH_3O)_2C_6H_3CH_2CH_2COCH_2C_6H_3(OCH_3)_2$$

The ketone was finally prepared by the following series of reactions

$$(CH_3O)_2C_6H_3CH_2CN + (CH_3O)_2C_6H_3CH_2CH_2COOC_2H_5 \longrightarrow$$
$$(CH_3O)_2C_6H_3CH(CN)COCH_2CH_2C_6H_3(OCH_3)_2 \longrightarrow$$
$$(CH_3O)_2C_6H_3CH(CONH_2)COCH_2CH_2C_6H_3(OCH_3)_2 \longrightarrow$$
$$(CH_3O)_2C_6H_3CH_2COCH_2CH_2C_6H_3(OCH_3)_2$$

Ethyl 3,4-dimethoxydihydrocinnamate was condensed with 3,4-dimethoxybenzylcyanide to give 1-cyano-1,4-di-(3',4'-dimethoxyphenyl)-butanone-2. This ketonitrile was hydrolyzed to 1-carbamyl-1,4-di-(3',4'-dimethoxyphenyl)-butanone-2. This was further hydrolyzed and decarboxylated to yield 1,4-di-(3',4'-dimethoxyphenyl)-butanone-2.

The hydrolysis of the ketonitrile, 1-cyano-1,4-di-(3',4'-dimethoxyphenyl)-butanone-2, presented some difficulty. It was finally accomplished by prolonged treatment of the material with an acetic–hydrochloric acid solution. The resulting amide, 1-carbamyl-1,4-di-(3',4'-dimethoxyphenyl)-butanone-2, was decarboxylated to 1,4-di-(3',4'-dimethoxyphenyl)-butanone-2 by means of dilute hydrochloric acid.

During the course of attempts to hydrolyze the above-mentioned ketonitrile, a product, melting at 209°, was obtained whose analysis corresponded to the calculated values for 1-(3',4'-dimethoxy-

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(1) Presented before the Division of Organic Chemistry of the American Chemical Society at the Dallas meeting, April, 1938. This paper is an abstract of the thesis submitted by Richard Carroll to the Graduate Faculty of the Polytechnic Institute of Brooklyn in partial fulfilment of the requirements for the degree of Doctor of Philosophy in June, 1938.

(2) Allen and Buck, THIS JOURNAL, **52**, 310 (1930).

(3) Kindler and Peschke, *Arch. Pharm.*, **272**, 236 (1934).

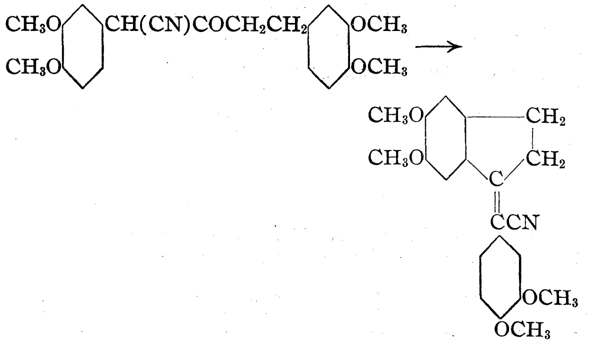
(4) Buck, Haworth and Perkin, *J. Chem. Soc.*, **125**, 2183 (1924).

(5) Sugasawa and Tsuda, *J. Pharm. Soc., Japan*, **55**, 194 (1935), *C. A.*, **31**, 6664 (1937), reduced dihomoveratroylamide.

(6) This reaction was suggested in a thesis by Ivey Allen, Jr., under J. S. Buck at Duke University, 1929.

(7) Bradley and Schwarzenbach, *J. Chem. Soc.*, 2904 (1928).

α-cyanobenzylidene)-5,6-dimethoxyindane. This material resulted from treatment of the ketonitrile with sulfuric acid. It could be formed in accordance with the following reaction



Experimental

3,4-Dimethoxydihydrocinnamoyl Chloride.—Thirteen grams of 3,4-dimethoxydihydrocinnamic acid[8] was treated with 6 g. of thionyl chloride. After standing for fifteen minutes the mixture was heated on a steam-bath for one hour and then distilled. The fraction boiling at 138–142° at 0.5 mm. was collected and redistilled. It solidified to a white solid melting at 40°[9,10] which was identified by conversion to the amide, melting at 121°.

1 - Chloro - 4 -(3',4' - dimethoxyphenyl) - butanone - 2.—Forty-eight cc. of nitrosomethylurethan was converted to diazomethane by the method of von Pechmann[11] and as used by Bradley and Robinson.[12]

To the ethereal solution (400 cc.) of diazomethane, cooled by ice, 27 g. of 3,4-dimethoxydihydrocinnamoyl chloride in 75 cc. of absolute ether was added slowly. There was a vigorous evolution of nitrogen during the addition. The solution was then placed in an ice chest overnight. After standing, dry hydrogen chloride was passed into the solution until the evolution of nitrogen ceased.

The solution was then evaporated to constant weight and allowed to stand. The chloro ketone crystallizes in rosets and has strong lachrymatory and vesicant properties. It can be recrystallized from alcohol and melts at 53°.

Anal. Calcd. for $C_{12}H_{15}ClO_3$: C, 59.38; H, 6.23; Cl, 14.60. Found: C, 59.04, 59.15; H, 6.14, 6.02; Cl, 14.71.

1 - Cyano - 1,4 - di - (3',4' - dimethoxyphenyl) - butanone-2.—Twenty-three grams of 3,4-dimethoxybenzyl cyanide, prepared by the method of Pfeiffer, Quehl and Tappermann,[13] was added to 32 g. of ethyl 3,4-dimethoxydihydrocinnamate and heated to 60°. This mixture was added to a warm solution of 3.1 g. of sodium in 50 cc. of absolute alcohol.[14]

The reaction mixture was refluxed[15] on a steam-bath for three hours and then allowed to stand for two days. During the heating, yellow colored crystals appeared. After standing, the solid material (sodio derivative of 1-cyano-1,4-di-(3',4'-dimethoxyphenyl)-butanone-2) was removed by filtration, washed with absolute alcohol and air dried. It was then dissolved in 400 cc. of water and the solution was extracted with ether. The aqueous layer was then placed under a vacuum to remove the dissolved ether. This was followed by the addition of 25 cc. of hydrochloric acid. The heavy gum which precipitated, crystallized in a few hours; yield 39 g. It was recrystallized from a dilute alcoholic solution and melted at 76°.[16]

Anal. Calcd. for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.27; N, 3.79. Found: C, 67.72, 67.60; H, 6.05, 6.14; N, 3.80, 3.86.

1 - Carbamyl - 1,4 - di - (3',4' - dimethoxyphenyl) - butanone-2.—Fifteen grams of 1-cyano-1,4-di-(3',4'-dimethoxyphenyl)-butanone-2 was dissolved in a mixture of 112 cc. of glacial acetic acid and 112 cc. of concentrated hydrochloric acid contained in a glass-stoppered flask. After standing for four days between 15 and 20°, the solution was poured into 1800 cc. of water and allowed to stand for twenty-four hours. A gum separated which clung to the walls of the beaker (if a crystal is added at the time of dilution a solid is obtained). The water layer was removed and the residue was dissolved in hot alcohol and filtered. The filtrate was evaporated to 10 cc. The product crystallized very slowly in buff colored plates. It gives a violet coloration with ferric chloride and dissolves in aqueous sodium hydroxide. It can be recrystallized from alcohol and melts at 123°; yield 4 g.

Anal. Calcd. for $C_{21}H_{25}NO_6$: C, 65.10; H, 6.50; N, 3.61. Found: C, 65.08, 65.18; H, 6.41, 6.58; N, 3.80.

1,4 - Di - (3',4' - dimethoxyphenyl) - butanone - 2.—Two grams of 1 - carbamyl - 1,4 - di - (3',4' - dimethoxyphenyl)-butanone-2 was added to 120 cc. of a solution of 12 cc. of concentrated hydrochloric acid in 138 cc. of water. This mixture was boiled for two hours. After cooling, the water solution was decanted and the remaining gum was dissolved in hot alcohol. This solution was filtered and evaporated to 4 cc. Buff colored crystals were deposited on standing; yield 0.90 g. The material was recrystallized from alcohol and melted at 76°.

Anal. Calcd. for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.45, 69.85; H, 7.04, 7.13.

Dinitro Derivative.—Nitration in acetic acid yields a dinitro derivative which can be recrystallized from acetic acid, and melts at 195°.

Anal. Calcd. for $C_{20}H_{22}N_2O_9$: C, 55.30; H, 5.10; N, 6.45. Found: C, 54.92, 55.09; H, 4.89, 5.03; N, 6.34, 6.27.

Compound Melting at 209°.—One-fifth gram of 1-cyano - 1,4 - di - (3',4' - dimethoxyphenyl) - butanone-2 was added to 5 cc. of a sulfuric acid solution (3 volumes H_2SO_4:2 volumes H_2O) and warmed on a steam-bath for ten minutes.

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(8) Perkin and Robinson, *J. Chem. Soc.*, **91**, 1080 (1907).

(9) After standing several weeks the material changed to a dark gummy paste.

(10) Pictet and Finkelstein, *Ber.*, **42**, 1985 (1909), prepared this chloride by using phosphorus pentachloride.

(11) Von Pechmann, *Ber.*, **28**, 856 (1895).

(12) Bradley and Robinson, *J. Chem. Soc.*, 1545 (1928).

(13) Pfeiffer, Quehl and Tappermann, *Ber.*, **63**, 1301 (1930).

(14) Pfeiffer, Quehl and Tappermann[13] used an alcoholic solution of sodium ethoxide for this type of condensation, while Haworth and co-workers, *J. Chem. Soc.*, 1426 (1934), employed a suspension of potassium ethoxide in benzene.

(15) All of the glassware was previously dried and the solution protected from moisture by a calcium oxide tube.

(16) A portion of this material was recrystallized after standing several months. It then melted at 122° and gave the following analytical results: C, 68.49, 68.66; H, 6.11, 6.05; N, 3.92, 4.04.

The solid first dissolved, this was followed by the appearance of yellow colored needles. After cooling, the solution deposited a curdy yellow precipitate. The solid was recrystallized from ethyl acetate and melted at 209°; yield 0.12 g.

Anal. Calcd. for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.76, 72.15; H, 5.85, 6.14; N, 4.32, 4.24.

Summary

1. Methods have been described for the preparation of 1-cyano-1,4-di-(3′,4′-dimethoxyphenyl)-butanone-2, 1-carbamyl-1,4-di-(3′,4′-dimethoxyphenyl)-butanone-2 and 1,4-di-(3′,4′-dimethoxyphenyl)-butanone-2.

2. Attempts to prepare 1,4-di-(3′,4′-dimethoxyphenyl)-butanone-2 by means of a Friedel–Crafts reaction were unsuccessful.

BROOKLYN, N. Y. RECEIVED AUGUST 17, 1938

[CONTRIBUTION NO. 175 FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, AND FROM THE CHEMICAL LABORATORY OF MCGILL UNIVERSITY]

The Influence of Branched Chains on Optical Activity. The Configuration of Propyl-*t*-butylcarbinol, with a Note on the Relation between Rotatory Power and Chemical Character

BY PHILIP G. STEVENS, W. EDWARD HIGBEE[1] AND ROBERT T. ARMSTRONG[2]

In a previous paper on this subject[3] the configuration of dextro methyl-*t*-butylcarbinol, as determined by Freudenberg's displacement rule, was found to be the same as dextro methyl-*n*-butylcarbinol. It was therefore apparent from their molecular rotations, +7.8° and +12.0°, respectively, that the *t*-butyl group did not cause as great a shift in the rotation as the isopropyl (+4.7°), or the cyclohexyl (+7.4°) group. This result was unexpected as it was felt that, if branching of the chain were responsible for the observed shift, the completely branched *t*-butyl group would cause a greater shift. Therefore the suggestion was made that the real effect of the singly branched group was due to the presence of a tertiary hydrogen atom. According to the theories advanced by Kuhn and Freudenberg,[6] this hydrogen atom might well bring about a shift in the rotation, since it represents another center of chemical reactivity close to the asymmetric carbon atom.

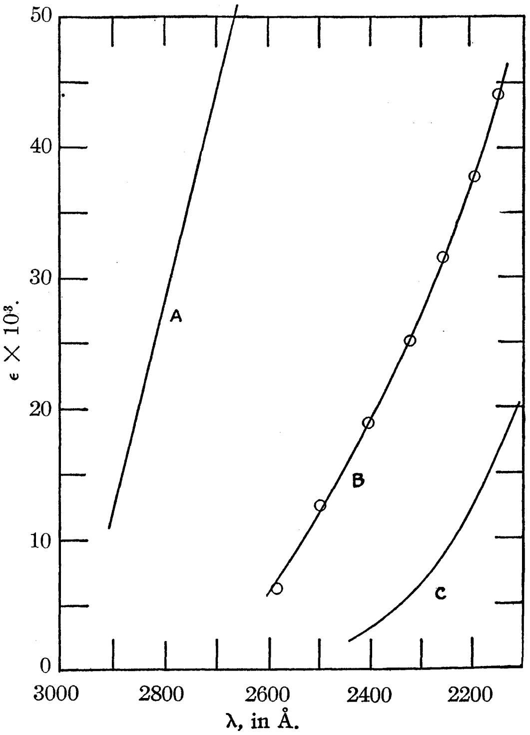

Fig. 1.—A, *n*-Butyl alcohol[4]; B, pinacolyl alcohol; C, ethyl alcohol.[5]

On the other hand, something may be abnormal about the *t*-butyl group. However, methyl-*t*-butylcarbinol shows no anomalous absorption bands in the near ultraviolet, and is similar to other carbinols as shown in Fig. 1. The high transmission of this carbinol as compared with other carbinols with a fewer number of carbon atoms may possibly be attributed to the high purity of the sample used.

Anomalous properties are often found in the lowest member of various series. This has been found to be true for the rotations of the isopropyl series.[7] A determination of the configuration of

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[1] Present address: Dennison Manufacturing Company, Framingham, Massachusetts.

[2] Present address: General Laboratories, U. S. Rubber Products Co., Passaic, New Jersey.

(3) Stevens, THIS JOURNAL, **55**, 4237 (1933).

(4) Bielecki and Henri, *Ber.*, **45**, 2819 (1912).

(5) Harris, *ibid.*, **55**, 1940 (1933).

(6) Kuhn, *Trans. Faraday Soc.*, **26**, 293 (1930); Kuhn, Freudenberg and Wolf, *Ber.*, **63**, 2367 (1930).

(7) Stevens, *ibid.*, **54**, 3732 (1932); Levene and Marker, *J. Biol. Chem.*, **101**, 413 (1933).

the third member of the *t*-butyl series, propyl-*t*-butylcarbinol, has now demonstrated that this is also the case here. This determination shows that levo propyl-*t*-butylcarbinol has the same configuration as dextro methyl-*t*-butylcarbinol on the basis of Freudenberg's displacement rule, for a dextro shift occurs in the rotations on passing from the acetates to the benzoates, and to the phthalates.

TABLE I

	$(M)_D$			
	Carbinol	acetate	Benzoate	Phthalate ($CHCl_3$)
$CH_3CHOHC_4H_9$-*t*	+ 7.8	+25.5	+93.4 +86.3 ($CHCl_3$)	+159.7
$C_3H_7CHOHC_4H_9$-*t*	−55.2[8]	−59.3	−19.9 −20.3 ($CHCl_3$)	+ 8.4

The *t*-butyl series belongs therefore to the same class as the isopropyl and cyclohexyl series, as shown in Table II.

TABLE II[9]

	$(M)_D$		
	CH_3	C_2H_5	C_3H_7
$CH_3CH_2CH_2CH_2CHOH$–	+12.0	+ 9.4	+ 0.95
$(CH_3)_2CHCHOH$–	+ 4.7	−16.7	−27.1
$C_6H_{11}CHOH$–	+ 7.4	−11.5	−17.0
$(CH_3)_3CCHOH$–	+ 7.8	....	−55.2

The high levo rotation of propyl-*t*-butylcarbinol shows that in cases where anomalies are avoided, the fully branched *t*-butyl group causes a much greater shift in the rotation than either of the other branched groups.[10]

It is therefore obvious that the controlling factor is not the tertiary hydrogen atom of the isopropyl and cyclohexyl groups, but rather the chemical character of the group as a whole. The chemical effect of branched chain groups is well established, as evidenced by the great difference in reactivity between primary, secondary and tertiary alcohols and halides. There is also a chemical effect of these groups when once removed from the hydroxyl group. This is shown by the marked tendency of carbinols containing these groups to undergo rearrangement when dehydrated or converted to halides.[11]

It is significant that only those carbinols which rearrange readily show a large shift in the rotation from the first to the next two higher members of the series. The sign of rotation is actually reversed in the latter two. Cyclohexylcarbinols, which show this large shift, have likewise now been found to rearrange. There seems therefore to be a connection between the chemical effect and rotatory effect of branched groups.

Table III shows the results on the conversion of several active carbinols to halides under standard conditions. The rotations and per cent. of rearrangement may be compared. There appears to be a relationship between the amount of rearrangement caused by each branched chain group, and the degree of rotatory shift, the order being cyclohexyl < isopropyl < *t*-butyl.

TABLE III

	Carbinol	Chloride		Rearrangement
	α_D	α_D	% *t*-Cl	%
$CH_3CHOHC_4H_9$-*n*	+ 7.11	−12.6	1.1	1[12]
$CH_3CHOHC_3H_7$-*i*	+ 0.90	− 0.01	92.5	92–93
$CH_3CHOHC_6H_{11}$	+ 4.59	+ .17	80.6	80–81
$CH_3CHOHC_4H_9$-*t*	+ 3.78	− .02	99.4	99–100
$C_3H_7CHOHC_4H_9$-*t*	+29.82	+ .72	94.2	94–95

We are indebted to Professor James F. Norris for the facilities of the Laboratories of the Massachusetts Institute of Technology where the major part of this work was done, and also to the Mallinckrodt Chemical Works for donating so generously the large amounts of strychnine necessary in this work.

Experimental Part

In this work, all rotations are for the homogeneous state unless otherwise stated.

Dextro Propyl-*t*-butylcarbinol.—The carbinol, prepared from *t*-butylmagnesium chloride and *n*-butylaldehyde, was converted into the acid phthalate, and resolved with strychnine in 95% alcohol. After twelve crystallizations, the salt was decomposed, the phthalate examined, $(M)^{24}_D$ ($CHCl_3$) −7.2° (max. −8.4°), and converted to the carbinol in the usual way, b. p. (36 mm.) 74.5–75.0°, n^{25}_D 1.4251, d^{25}_4 0.8215, $(M)^{25}_D$ +47.2°. The activity of the carbinol obtained from the corresponding unsaturated carbinol by reduction indicates that this value is not the maximum. By calculation the highest observed $(M)_D$ would be +55.2°. This is probably close to the maximum, and is tentatively therefore designated as the maximum.

Anal. Calcd. for $C_8H_{18}O$: C, 73.8; H, 13.9. Found: C, 73.9; H, 13.9.

Dextro Propyl-*t*-butylcarbinol Acetate and Benzoate.—These derivatives were prepared as described earlier for

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[8] Probably close to the maximum.

[9] Values from Pickard and Kenyon, *J. Chem. Soc.*, **99**, 45 (1911); **101**, 620 (1912); **105**, 830, 1115 (1914); Levene and Marker, *J. Biol. Chem.*, **97**, 379 (1932); Levene and Harris, *ibid.*, **111**, 723 (1935); Kuhn and Biller, *Z. physik. Chem.*, **B29**, 1 (1935).

[10] On this evidence the *t*-butyl group can be placed tentatively between the isopropyl group and the methyl group in Marker's configurational table [THIS JOURNAL, **58**, 976 (1936)].

[11] Michael and Leupold, *Ann.*, **379**, 271 (1910); Michael and Zeidler, *ibid.*, **385**, 227 (1911); Whitmore and Rothrock, THIS JOURNAL, **54**, 3431 (1932); **55**, 1106 (1933); Whitmore and Johnston, THIS JOURNAL, **60**, 2265 (1938).

[12] This value does not include the amount of rearrangement (presumably very small) resulting in isomeric secondary halides.

SUMMARY OF EXPERIMENTAL DATA[13]

	Carbinol		Carbinol αD	Time, days	Crude chloride αD	Crude chloride % tertiary Cl	Crude chloride $n^{25}D$
A	CH_3-C_4H_9-*n*	(1)	+ 7.11	1	−12.58	1.1 (2 hr.)	1.4148
		(2)	+ 7.11	19	−11.52	0.8 (2 hr.)	1.4140[a]
B	CH_3-C_3H_7-*i*		+ 0.90	2	− 0.01	92.5 (0.6 hr.)	1.4058[c]
C	CH_3-C_6H_{11}		+ 4.59	7	+ 0.17	80.7 (4 hr.)[d]	...
D	CH_3-C_4H_9-*t*		+ 3.78	2	− 0.02	99.4 (0.5 hr.)	1.4174
E	C_3H_7-*n*-C_4H_9-*t*		+29.82	3	+ 0.72	94.2 (3 hr.)	...

Distilled Chloride

	B. p. °C.	B. p. Mm.	αD	% tertiary Cl	$n^{25}D$	$d^{25}{}_4$	Total chlorine, % Calcd.	Total chlorine, % Found
A	122–123	760	..	....	1.4153[b]	..	..	..
B	84.5–86.0[f]	760	..	....	1.4051[c]	..	..	..
C	69.5–70.0	19	+0.09[e]	84.0 (3 hr.)	1.4636	0.9697	24.2	25.0
D	111.0[f]	750	..	....	1.4175	..	..	..
E	56.0–56.3	19	+0.72	94.3 (3 hr.)	1.4320	.8794	23.9	24.6

[a] $n^{21.5}D$ 1.4156.[14] [b] At 21.5°. [c] At 20°: *t*-amyl chloride before distillation, $n^{20}D$ 1.4054; *s*-isoamyl chloride, $n^{20}D$ 1.4095.[15] [d] Total chlorine, calcd. 24.2; found 24.2. [e] Distillation residue, $\alpha^{27}D$ +0.44°. [f] With slight evolution of hydrogen chloride.

methyl-*t*-butylcarbinol derivatives,[3] the acetate, b. p. (20 mm.) 73.0–73.5°, $(M)^{23}D$ +50.7° (max. +59.3°), $n^{25}D$ 1.4133, $d^{25}{}_4$ 0.8568.

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.7; H, 11.6. Found: C, 69.9; H, 11.8.

The benzoate, b. p. (4 mm.) 117.5–117. 8° $(M)^{23}D$ +17.0° (max. +19.9°), (max. $CHCl_3$, +20.7°), $n^{25}D$ 1.4873, $d^{25}{}_4$ 0.9570.

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.9; H, 9.4. Found: C, 77.1; H, 9.5.

Dextro Propenyl-*t*-butylcarbinol.—The highest rotation obtained with this carbinol, previously described,[16] was $(M)^{23}D$ +23.5°, with a phthalate of $(M)^{23}D(CHCl_3)$, −16.2°. Another sample, $\alpha^{22}D$ −0.60°, yielded the saturated carbinol, when reduced with Adams platinum catalyst in alcohol solution, with $\alpha^{22}D$ −1.41°.

Chloride Formation from Secondary Carbinols.—Seven to eleven cc. of each carbinol was sealed in a tube with 40–60 cc. of concentrated hydrochloric acid saturated with dry hydrogen chloride at −10°. The mixture was then allowed to warm up to 25°, shaking frequently. In all cases, except those of the octanols, the solution was homogeneous. In the latter, the carbinols did not dissolve in the hydrochloric acid, and the carbinol layer at first expanded, and then slowly contracted as the reaction proceeded. When the volume remained constant for a considerable length of time, the reaction was deemed complete. Generally, however, after one to two days, the chlorides had separated completely, and were then washed 2–5 times with concentrated hydrochloric acid, once each with ice water and iced sodium bicarbonate, and dried over anhydrous potassium carbonate. The chlorides were in every case free of olefins as shown by their failure to absorb bromine in either carbon tetrachloride or acetic acid. The chlorides were analyzed by Michael's method[11] for tertiary chlorides. This was carried out by shaking one gram of each with 250 cc. of water[17] until no more acid was evolved. This took about one-half to one hour, except in the cases of the more insoluble octyl chlorides which required three to four hours for hydrolysis to reach a standstill.[18]

Dextro Methyl-*t*-butylcarbinol.—The carbinol, b. p. 120° (760 mm.), $\alpha^{27}D$ + 3.78°, was redistilled in an all-glass apparatus before determining the absorption spectrum with a Hilger Spekker Photometer and E316 Quartz Spectrograph. The molal extinction coefficient, *e*, was calculated from the formula $e = \frac{1}{cd} \log \frac{I_0}{I}$ where *c* was 7.97, the concentration in moles per liter, and *d* was 2, the length of the cell in centimeters. The sample examined showed continuous absorption as indicated in Fig. 1. After standing for several weeks, the same sample showed an intense absorption band at 2800 Å., due no doubt to partial oxidation to pinacolone.

Summary

1. Dextro methyl-*t*-butylcarbinol is configurationally related, according to the displacement rule of Freudenberg, with levo propyl-*t*-butylcarbinol.

2. The *t*-butyl group, in the third member of that series, causes a greater shift in the rotation than either the isopropyl or cyclohexyl groups.

3. A relation between rotatory power and chemical character has been pointed out, and in a number of cases confirmed.

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MONTREAL, CANADA

RECEIVED MAY 23, 1938

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(13) The rotations were measured at 21–27°.

(14) Compare Zelinski and Przewalski, *Chem. Zentr.*, **79**, II, 1854 (1908).

(15) Whitmore and Johnston, THIS JOURNAL, **55**, 5020 (1933).

(16) Stevens, THIS JOURNAL, **57**, 1112 (1935).

(17) The chloride from *s*-isoamyl alcohol was shaken with only 50 cc. of water.

(18) Compare Woodburn and Whitmore, THIS JOURNAL, **56**, 1394 (1934).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY, UNIVERSITY OF MISSOURI, AND THE NEW MEXICO NORMAL UNIVERSITY]

"Glorieta" Monazite

BY O. B. MUENCH

Several years ago, Dr. A. C. Lane secured a large and almost perfect crystal of monazite from P. Krieger, who had obtained it from someone near Glorieta, New Mexico, and was under the impression that originally it had come from a deposit in that neighborhood. A small fragment of this crystal was sent by Lane to Dr. F. Hecht in Vienna. The microanalysis made by F. Hecht and Edith Kroupa is reported on page 44 of "The Report of the Committee on the Measurement of Geologic Time," of the National Research Council, April, 1935.

The Committee on the Measurement of Geologic Time is interested in obtaining a quantity of "thorium-lead," free from "uranium-lead" and common lead, for an atomic weight determination and other experimental purposes. Mr. Rufus C. Little of Albuquerque, who was in possession of twenty to thirty pounds of the monazite, kindly agreed to furnish specimens of the mineral which he had personally collected from the old Cribbenville Mica Mine near Petaca, New Mexico. It is quite possible that the crystal which Krieger had obtained came from the same deposit.

Monazite is suitable material to use for an age determination by the lead–uranium method. This particular monazite sample consisted of large pieces (crystal fragments, etc.) and besides smaller lumps, some fines. The fines were separated and not used in this analysis. The largest piece weighed 252 g. and all the better pieces used in this determination weighed over 100 g. The material was fresh, tan to reddish brown in color, most of it clear of any other adhering mineral and showing hardly any alteration.

The larger pieces were broken in a clean iron mortar and then finely powdered in a clean agate mortar to pass through an 80-mesh sieve. Precautions were taken to avoid contamination, especially by lead, not only during the preparation of the sample, but throughout the entire analysis.

Analysis

Fenner[1] has worked out a detailed method for the analysis of monazite. His method with several modifications was used in the decomposition of the sample and the lead determination. The details of analysis will not be included in this paper. Hecht[2] makes the statement, "By solution of monazite in sulfuric acid, one would find too little lead." A. C. Lane adds to this the following, "Possibly such an error has crept into many analyses heretofore."

The solution of the monazite was accomplished according to the method of Fenner by heating the powdered sample in a platinum dish for about six hours with a mixture of sulfuric and hydrofluoric acids. This treatment usually disintegrates the sample, but occasionally it was found that all was not decomposed completely. This residue was given further treatment till all of it was decomposed.

In the lead determinations, care was taken to test all residues and filtrates for traces of lead and add these when necessary. This is important, for in the hydrofluoric acid method of decomposition, much of the lead may be found in the residue after hydrofluoric and sulfuric acid treatment and even after the extraction with ammonium acetate. There is very little possibility of any lead being lost in this determination. All reagents used in this analysis were tested and found lead free. The lead was determined as the sulfate.

The iodate method as described with references in previous papers[3] was followed for the thorium determinations.

The uranium was determined as the pyrophosphate,[3] also described in detail in previous papers.

RESULTS OF ANALYSES

Lead

Sample, g.	$PbSO_4$, g.	Lead, %
30.0000	0.1475	0.336
30.0000	.1502	.342
30.0000	.1498	.341
30.0000	.1490	.339
	Average	.339

Thorium

Sample, g.	ThO_2, g.	Thorium, %
2.0035	0.1707	7.49
2.0024	.1720	7.54
3.0044	.2615	7.55

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(1) Fenner, *Am. J. Sci.*, **16**, 369 (1928).

(2) Report of the Committee on the Measurement of Geologic Time, Natl. Research Council, p. 45, April 27, 1935.

(3) Muench, THIS JOURNAL, **59**, 2269 (1937).

Thorium (*Concluded*)

Sample, g.	ThO_2, g.	Thorium, %
2.5011	.2131	7.49
2.0015	.1700	7.46
2.0550	.1762	7.52
	Average	7.50

Uranium

Sample, g.	$(UO_2)_2P_2O_7$, g.	Uranium, %
3.0044	0.0050	0.109
2.5011	.0038	.101
2.0015	.0033	.109
	Average	.106

Loss on ignition	0.838%
Loss at 110°, three hours	.14%

There were no indications of ordinary lead mineral associated with the sample. If we assume the absence of ordinary lead and make use of the conversion factor 0.36 for thorium, the lead-uranium ratio is

$$\frac{0.339}{0.106 + 0.36 \times 7.50} = 0.1208$$

The approximate age of the mineral is

$$\frac{0.121 \times 1.15 \text{ million years}}{1.57 \times 10^{-4}} = 886 \text{ million years}$$

With so old a mineral, the more exact or "logarithmic" formula for calculating age gives a materially different result from that found by the above "approximate" formula, and should be used in calculating the age of this material. Age, based on formula

$$\frac{\log(U + 0.36Th + 1.155Pb) - \log(U + 0.36Th)}{6.6 \times 10^{-5}} \text{ million years} = 858 \text{ million years}$$

As a pilot analysis for this work, Hecht made a complete microanalysis of a small piece from the crystal in Dr. Lane's possession. His results show, 9.36% thorium, 0.392% lead and give no figures for the uranium. Hecht obtains an age of 800 million years from his determination.

Acknowledgment.—The author is grateful to Mr. Rufus C. Little for the samples; to the Geological Society of America for financial assistance in part, for this research; to Dr. A. C. Lane for his constant interest in this work with helpful suggestions; and to the late Dr. Herman Schlundt and the University of Missouri for the use of the laboratories and other facilities.

Summary

This monazite is not a suitable source for pure "thorium-lead," as the analysis shows evidence of 0.106% uranium. The other analytical results are, 7.50% thorium and 0.339% lead. The age of the monazite is 858 million years, placing it in the Pre-Cambrian Age. Hecht, from his pilot analysis, obtains an age of 800 million years. It is probable but by no means certain that this material and the material Hecht used in his analysis came from the same deposit.

LAS VEGAS, N. M. RECEIVED AUGUST 22, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY, LYNCHBURG COLLEGE]

The Effect of the Triple Bond on the Rate of Reaction of ω-Chlorides with Potassium Iodide in Absolute Acetone

BY M. J. MURRAY

Conant and his students[1] have studied the rates of reaction of a variety of organic chlorides with potassium iodide in absolute acetone. The only triple bond compound they reported on, however, was $CNCH_2Cl$. Truchet[2] has shown qualitatively that chlorine attached directly to a triple bond carbon is very unreactive toward sodium iodide in acetone.

The present investigation was made because no study has been reported showing the effect of the acetylenic linkage on the reactivity of chlorine in the ω-position. The series selected was $C_6H_5C{\equiv}C(CH_2)_nCl$, all members of which were prepared from phenylacetylene. Cinnamyl chloride was available for comparison of the effect of the ethylenic linkage.

The method of measuring the velocity of the reaction and of calculating the constant for the reaction was essentially that given in detail by Conant and students.

The results are summarized in Table I. It is seen that in this series of acetylenic chlorides there is a definite alternation of reactivity, the order with respect to the triple bond being $\alpha > \gamma > \beta$. This order of reactivity is the same as that found

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[1] (a) Conant and Kirner, THIS JOURNAL, **46**, 232 (1924); (b) Conant and Hussey, *ibid.*, **47**, 476 (1925); (c) Conant, Kirner and Hussey, *ibid.*, **47**, 488 (1925).

[2] Truchet, *Ann. chim.*, [10] **16**, 309 (1931).

by Conant and Kirner[1a] for the simple C_6H_5 series without the triple bond ($C_6H_5CH_2Cl$, $K_{50} = 8.07 > C_6H_5CH_2CH_2CH_2Cl$, $K_{50} = 0.0713 > C_6H_5CH_2CH_2Cl$, $K_{50} = 0.0466$).

The inactivity of the chlorine attached to the triple bond carbon verifies Truchet's qualitative experiment and is to be expected in the light of the similar behavior of chlorine attached to an ethylenic carbon. Although chlorine α to a triple bond has somewhat smaller reactivity than when α to a double bond in the example studied, the order of activity is the same. The effect of the phenyl group in the 1-position can be evaluated approximately by the comparison of the values of the constants for allyl chloride[1c] and for cinnamyl chloride. It is apparent that the phenyl group extends its influence quite markedly by raising the value of the constant from 0.288 to 5.0. The effect of geometrical isomerism has not been studied, as only the *trans* form, cinnamyl chloride, was available.

TABLE I

REACTION VELOCITIES OF ω-CHLORIDES WITH POTASSIUM IODIDE IN ABSOLUTE ACETONE

Compound	K_{25}	K_{60}	Relative reactivity at 60°
$CH_3CH_2CH_2CH_2Cl$[1]	...	0.101	1
$C_6H_5C{\equiv}CCl$	...	0	0
$C_6H_5C{\equiv}CCH_2Cl$[a]	2.9	(79)	(782)
$C_6H_5C{\equiv}CCH_2CH_2Cl$	...	.048	0.48
$C_6H_5C{\equiv}CCH_2CH_2CH_2Cl$	...	.19	1.9
$C_6H_5CH{=}CHCH_2Cl$[a]	5.0	(138)	(1370)
$CH_2{=}CHCH_2Cl$[1]	0.288	(7.9)	(78)

[a] The values for K_{60} were calculated from the equation

$$\log \frac{K_{60}}{K_{25}} = 4000\left(\frac{1}{298} - \frac{1}{333}\right)$$

Experimental

Phenylethynyl Chloride (2-Chloro-1-phenylethyne).—This substance was prepared from sodium phenylacetylide and *p*-toluenesulfonyl chloride by the method of Truchet.[2] As he noted, phenylethynyl chloride begins to turn yellow very soon following distillation. After a few months, a sample of 9 g. yielded on distillation only 2 g. of the compound. Colorless crystals were found in contact with the viscous, dark brown resin. This resinification sets in so quickly that the first experiment carried out to determine the reaction velocity of this compound was misleading. The experiment was not started until three days after distillation of the chloride. As soon as the potassium iodide–acetone solution came into contact with the slightly yellow chloride, there was a gradual darkening of the solution; and after a short time a precipitate of potassium chloride began to form. At the end of seventeen hours the reaction was stopped, and titration showed that about 15% of the potassium iodide had disappeared. When the experiment was repeated immediately after distillation of the compound, the solution remained practically colorless; and after forty hours at 60° the difference between the "blank" and the reaction mixture was too small to be significant.

Chloromethylphenylacetylene (3-Chloro-1-phenylpropyne-1).—The compound was prepared by the action of phosphorus trichloride on phenylpropargyl alcohol in the presence of pyridine and ether. Tchao[3] prepared the corresponding bromide in an analogous way, using phosphorus tribromide. Into a flask containing 13.8 g. of phenylpropargyl alcohol dissolved in 10 ml. of dry ether and 1 ml. of pyridine, was slowly dropped 6.6 g. of phosphorus trichloride. The mixture was refluxed for two hours. A large volume of water was poured in, the layers separated, and the water extracted with ether. The ether layers were combined and washed with sodium bicarbonate solution, then with water, and dried over calcium chloride. The ether was driven off and the liquid distilled *in vacuo*. There was obtained 8 g. (51% yield) of purified product, b. p. 99° (7 mm.); d^{20}_{20} 1.112, n^{20}_D 1.5834.

Anal. Calcd. for C_9H_7Cl: Cl, 23.6. Found: Cl, 23.8.

Because of its great activity the reaction velocity of this compound was determined at 25° rather than at 60°.

β-Chloroethylphenylacetylene (4-Chloro-1-phenylbutyne-1).—This compound was prepared from the directions given by Johnson, Schwartz, and Jacobs:[4] b. p. 99° (3 mm.); d^{20}_{20} 1.085.

Anal. Calcd. for $C_{10}H_9Cl$: Cl, 21.6. Found: Cl, 21.5.

When the reaction velocity is as low as in the case of this compound, a saving in time can be effected by weighing the chloride directly into the reaction tube, adding the acetone–potassium iodide solution, sealing the tube at once, and placing it in the bath as soon as possible. The accuracy of estimating the time of starting is considerably greater than that of titration. The latter, according to Conant and Kirner,[1a] is subject to a variation of ±4%.

γ-Chloropropylphenylacetylene (5-Chloro-1-phenylpentyne-1).—This compound also was prepared according to the method given by Johnson, Schwartz, and Jacobs:[4] b. p. 125° (6 mm.); d^{20}_{20} 1.064.

Anal. Calcd. for $C_{11}H_{11}Cl$: Cl, 19.9. Found: Cl, 19.7.

Cinnamyl Chloride (3-Chloro-1-phenylpropene-1).—Eastman product redistilled, b. p. 106° (10 mm.).

Because the cinnamyl iodide, formed by the action of potassium iodide on cinnamyl chloride, liberates iodine during the titration of potassium iodide with potassium iodate in strongly acid solution, it is necessary to extract the mixture to be titrated before adding the potassium iodate. The liberation of iodine by cinnamyl iodide is especially rapid in sunlight but takes place too rapidly even in weak artificial light to permit titration without extraction.

All the chlorides were purified by distillation through a heated column 30 cm. long, packed with a spiral of No. 20 wire. A reflux ratio of at least 10 was used.

Acknowledgments.—This work was supported in part by a grant-in-aid from the Virginia Academy of Science from funds allotted it by the American Association for the Advancement of

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(3) Tchao, *Bull. soc. chim.*, [4] **53**, 1533 (1933).

(4) Johnson, Schwartz, and Jacobs, THIS JOURNAL, **60**, 1882 (1938).

Science. The writer wishes to thank Dr. John R. Johnson not only for suggesting the investigation but also for helpful advice.

Summary

1. The reaction velocity of a series of acetylenic chlorides has been measured according to the method of Conant.

2. A definite alternation in reactivity has been observed.

3. The most active acetylenic chloride measured has a somewhat lower activity than the corresponding ethylenic compound.

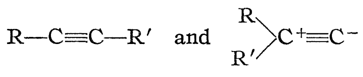
LYNCHBURG, VA. RECEIVED AUGUST 26, 1938

[CONTRIBUTION FROM THE CHEMICAL AND PHYSICAL LABORATORIES, LYNCHBURG COLLEGE]

Raman Spectra of Acetylenes. I. Derivatives of Phenylacetylene, $C_6H_5C{\equiv}CR$

BY M. J. MURRAY AND FORREST F. CLEVELAND

The Raman spectra of disubstituted acetylenes have been investigated by various workers, who have found that the characteristic acetylenic frequency in the region 2200–2300 cm.$^{-1}$ is usually double or triple, although in a few cases it is reported as a single, broad line.[1] Several explanations of this splitting have been given: Glockler and Davis[2] attribute the two strong lines in dimethylacetylene to symmetrical and asymmetrical vibrations. Gredy[3] suggests, as a working hypothesis, that two isomeric forms



$$R{-}C{\equiv}C{-}R' \quad \text{and} \quad {}^{R}_{R'}\!\!>\!C^{+}{\equiv}C^{-}$$

may exist simultaneously. Kohlrausch, Pongratz and Seka[4] regard the existence of two or more frequencies, if only one molecular form is present, as difficult to understand. Badger[5] attributes the doubling to a Fermi resonance interaction between the fundamental acetylenic frequency in this region and an overtone of a lower frequency near 700 or 1100 cm.$^{-1}$.

Gredy[3] found two lines for $C_6H_5C{\equiv}CCH_2OH$, while Faucounau[6] reported a single broad line for $C_6H_5C{\equiv}CCH_2CH_2OH$, and Bourguel and Daure[7] only a single frequency for $C_6H_5C{\equiv}CCl$. In view of these results and of the difference in opinion as to the cause of the splitting, it appeared worth while to investigate carefully the Raman spectra of disubstituted acetylenes in order to determine how the nature of the splitting varies for closely related molecules and to determine, if possible, whether there is a certain kind of substitution that yields only a single frequency. The present paper gives the results obtained for a series of compounds of the type $C_6H_5C{\equiv}CR$.

Experimental Procedure

The apparatus and experimental technique were essentially the same as previously described.[8] All the compounds were purified carefully by distillation in a heated column, using a high reflux ratio. Since the acetylenic compounds suffered photochemical decomposition when exposed to the exciting light and since the decomposition products were fluorescent and added greatly to the continuous background, it was necessary to redistill, from a flask attached to the scattering tube, at one-hour intervals during the exposures. In spite of these precautions, the continuous background was strong, especially in the case of the bromide.

The general procedure was to obtain several plates with both long and short exposure times, using both Hg 4047 Å. and 4358 Å. for excitation. The more intense lines could be measured with greater accuracy on the short exposure plates. In order to secure better definition of the stronger lines, the camera lens was stopped down to 5 mm. and a final exposure made. The time of this exposure was ten hours. The lines on these plates were exceedingly sharp and the acetylenic frequency in the 2200 cm.$^{-1}$ region, which on the other plates appeared as a single broad line, was resolved.

The comparator was illuminated with light from a yellowish-brown incandescent lamp, a practice which resulted in increased distinctness for the weaker lines.

Results

The results are given in the sections below, in which *k*, *f*, and *e* represent excitation by Hg 4047, 4347, and 4358 Å., respectively. Broad lines are designated by *b* and estimated intensities are given by the numbers in parentheses.

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(1) James H. Hibben, *Chem. Rev.*, **18**, 50–51 (1936).

(2) G. Glockler and H. W. Davis, *J. Chem. Phys.*, **2**, 881 (1934).

(3) Blanche Gredy, Thèses, Paris, 1935.

(4) K. W. F. Kohlrausch, A. Pongratz and R. Seka, *Sitzber. Akad. Wiss. Wien.*, Abt. IIb, **146**, 218 (1937).

(5) Richard M. Badger, *J. Chem. Phys.*, **5**, 178 (1937).

(6) Louis Faucounau, *Compt. rend.*, **199**, 605 (1934).

(7) M. Bourguel and P. Daure, *Bull. soc. chim.*, **47**, 1349 (1930); *Compt. rend.*, **190**, 1298 (1930).

(8) Forrest F. Cleveland and M. J. Murray, *Am. Phys. Teacher*, **5**, 270 (1937).

Brackets enclose those frequencies about which there is some question.

1. **3-Chloro-1-phenylpropyne-1** ($C_6H_5C{\equiv}CCH_2Cl$).—Synthesized by action of phosphorus trichloride on 3-phenyl-2-propynol-1 in the presence of pyridine and ether;[9] b. p. 99° (7 mm.); previous data, none.

$\Delta\nu$ = 257(1)*e*, 272(1)*e*, 294($^1/_2$)*e*, 316(2)*e*, 333(2)*e*, 363(1)*e*, 379(3)*e*, 471(3)*k*, 529(3)*ke*, 612(2)*ke*, 630(2)*ke*, 690(6b)*ke*, 718(4)*ke*, 756(3)*ke*, 903(1)*ke*, 980(8)*kfe*, 1006(2)*ke*, 1030(1)*ke*, 1159(3)*ke*, 1174(3)*ke*, 1251(8)*ke*, 1275(3)*ke*, 1380(1)*ke*, 1423(3)*ke*, 1443(3)*ke*, 1471(1)*ke*, 1491(4)*ke*, 1530(1)*ke*, 1600(9)*ke*, 2214(10)*ke*, 2231(10)*ke*, 2263(4)*ke*, 2956(3)*e*, 2969(2)*ke*, 3046(2)*ke*, 3064(4)*ke*.

2. **4-Chloro-1-phenylbutyne-1** ($C_6H_5C{\equiv}CCH_2CH_2Cl$).—Synthesized by two methods: (a) by action of thionyl chloride upon 4-phenyl-3-butynol-1 in the presence of pyridine,[6] b. p. 107–108° (7 mm.); (b) by action of β-chloroethyl *p*-toluenesulfonate, 2 moles, on phenylacetylenemagnesium bromide;[10] b. p. 104° (5 mm.); both products gave the same spectra; previous data, Faucounau.[6]

$\Delta\nu$ = 234(1)*ke*, 337(1)*ke*, 353(2)*ke*, 372(2)*ke*, 386(2)*ke*, 459(2b)*k*, 486(2b)*ke*, 520(4)*ke*, 535(4)*ke*, 550(1)*ke*, 624(3)*ke*, 646(3)*ke*, 665(4)*ke*, 700(3)*ke*, 754(5)*ke*, 912(1)*ke*, 987(2)*ke*, 1000(6)*ke*, 1032(3)*ke*, 1162(3)*ke*, 1181(3)*ke*, 1213(1)*ke*, 1244(5)*ke*, 1263(6)*ke*, [1329(1)*e*], 1424(3)*ke*, 1447(4)*ke*, 1491(4)*ke*, 1533(2)*ke*, 1603(9)*ke*, 2204(3)*ke*, 2221(10)*ke*, 2246(10)*ke*, 2293(2)*e*, 2842(1)*e*, 2909(4)*e*, 3010(1)*e*, 3034(1)*e*, 3050(3)*ke*, 3063(5)*ke*.

3. **5-Chloro-1-phenylpentyne-1** ($C_6H_5C{\equiv}CCH_2CH_2CH_2Cl$).—Synthesized by action of γ-chloropropyl *p*-toluenesulfonate upon sodium phenylacetylide in di-*n*-butyl ether;[10] b. p. 125° (6 mm.); previous data, none.

$\Delta\nu$ = 240(1)*ke*, 292(1)*e*, 373(3)*ke*, 408(1)*ke*, 440(3)*ke*, 521(3b)*ke*, 551(3)*ke*, 625(3)*ke*, 654(4)*ke*, 693(3)*ke*, 712(1)*ke*, 756(3)*ke*, 770(1)*ke*, 790(1)*ke*, 835(1)*ke*, 926(1)*ke*, 980(3)*ke*, 1000(7)*ke*, 1027(1)*ke*, 1062(1)*ke*, 1095(1)*ke*, 1154(3)*ke*, 1177(3)*ke*, 1241(4)*ke*, 1258(6)*ke*, 1276(2)*ke*, 1334(2)*ke*, 1435(4)*ke*, 1489(3)*ke*, 1528(1)*ke*, [1547(1)*ke*], 1580(2)*ke*, 1600(8)*ke*, 2220(10)*ke*, 2236(10)*ke*, 2900(3)*e*, 2923(3)*e*, 2956(2)*e*, 2984(2)*e*, 3049(3)*e*, 3063(5)*ke*.

4. **3-Bromo-1-phenylpropyne-1** ($C_6H_5C{\equiv}CCH_2Br$).—Synthesized by action of phosphorus tribromide upon 3-phenyl-2-propynol-1 in the presence of pyridine and ether;[11] b. p. 105–106° (5 mm.); previous data, none; continuous background very strong.

$\Delta\nu$ = 287(1)*e*, 304(1)*e*, 374(2)*e*, 518(1)*e*, 530(1)*e*, 609(6b)*e*, 710(2)*e*, 757(1)*e*, 968(3)*e*, 987(6)*e*, 1023(1)*e*, 1155(1)*e*, 1169(1)*e*, 1186(4)*e*, 1206(5)*e*, 1269(3)*e*, 1476(3)*e*, 1489(3)*e*, 1599(8)*e*, 2204(3)*ke*, 2226(10)*ke*, 2265(4)*ke*, 3064(3)*ke*.

5. **3-Phenyl-2-propynol-1** ($C_6H_5C{\equiv}CCH_2OH$).—Synthesized by action of formaldehyde on phenylacetylenemagnesium bromide;[12] b. p. 112° (5 mm.); previous data, Gredy.[3]

$\Delta\nu$ = [180(2)*e*], [195(2)*e*], 250(1b)*ke*, 270(2)*ke*, 282(2)*ke*, 302(1)*ke*, 336(1)*ke*, 350(2)*ke*, 366(3)*ke*, 382(4)*e*, 426(1)*ke*, 438(1)*ke*, 458(2b)*k*, 476(2b)*ke*, 512(2b)*ke*, 530(2)*ke*, 553(2)*ke*, 573(2)*ke*, 590(2)*ke*, 605(1)*ke*, 625(2b)*ke*, 648(1)*ke*, 663(1)*ke*, 703(1)*ke*, 721(2)*ke*, 743(3)*ke*, 761(3)*ke*, 789(2)*ke*, 956(3)*ke*, 985(2)*ke*, 1000(7)*ke*, 1028(3)*ke*, 1151(2)*ke*, 1164(4)*ke*, 1179(4)*ke*, 1238(4)*ke*, 1258(6)*ke*, 1285(1)*k*, 1331(1)*k*, 1439(3)*ke*, 1456(3)*ke*, 1496(3)*ke*, 1603(9)*ke*, 2202(3)*ke*, 2231(5)*ke*, 2242(10)*ke*, [2290(2)*e*], 2818(1)*ke*, 2951(2)*e*, 2978(1)*ke*, 3061(4)*ke*.

6. **4-Phenyl-3-butynol-1** ($C_6H_5C{\equiv}CCH_2CH_2OH$).—Synthesized by way of ethylene oxide on phenylacetylenemagnesium bromide;[13] b. p. 130° (7 mm.); previous data, Faucounau.[6]

$\Delta\nu$ = 248(1)*ke*, [265(3)*k*], 386(2)*ke*, 405(1)*ke*, 510(2)*ke*, 528(3b)*ke*, 558(2b)*ke*, 609(2)*ke*, 624(3)*ke*, 700(3b)*ke*, 730(1)*ke*, 747(2)*ke*, 759(3)*ke*, 847(2)*ke*, 874(1)*ke*, 893(1)*ke*, 936(1)*ke*, 980(3)*ke*, 1000(7)*ke*, 1027(2)*ke*, 1162(3)*ke*, 1181(3)*ke*, 1241(5)*ke*, 1259(5)*ke*, 1288(1)*k*, 1308(1)*k*, 1329(1b)*ke*, 1374(1)*ke*, 1432(3)*ke*, 1440(3)*ke*, 1469(1)*k*, 1492(3b)*ke*, 1530(1)*ke*, 1602(9)*kfe*, 2214(4)*ke*, 2233(10)*ke*, 2895(2)*ke*, 2918(2)*ke*, [2935(2)*ke*], 3053(3)*ke*, 3070(3)*ke*.

7. **3-Chloro-1-phenylpropene-1 (Cinnamyl Chloride,** $C_6H_5CH{=}CHCH_2Cl$).—Eastman product, redistilled in column; b. p. 94° (5 mm.); previous data, none.

$\Delta\nu$ = 248(2)*e*, 264(2)*e*, 302(2)*e*, 413(1)*ke*, 447(1)*ke*, 457($^1/_2$)*ke*, 507(2)*ke*, 605(4)*ke*, 619(3)*ke*, 670(5)*ke*, 678(4)*ke*, 699(3)*ke*, 746(1)*ke*, 814(2)*ke*, 823(1)*ke*, 849(3)*ke*, 915(2)*ke*, 924(2)*ke*, 963(1)*ke*, 1000(6)*ke*, 1033(2)*ke*, 1065(1)*ke*, 1080(2)*ke*, 1157(5)*ke*, 1184(3)*ke*, 1212(4)*ke*, 1251(7)*ke*, 1282(3)*ke*, 1303(4)*ke*, 1442(3b)*ke*, 1497(3)*ke*, 1538(1)*ke*, 1600(9)*ke*, 1660(10)*ke*, 2876(2b)*e*, [2944(1)*e*], 2967(2)*e* 3054(3)*e*, 3072(2)*e*.

Discussion of Results

The frequencies obtained agree quite well with those reported by Gredy[3] for $C_6H_5C{\equiv}CCH_2OH$ and with those reported by Faucounau[6] for $C_6H_5C{\equiv}CCH_2CH_2OH$ and for $C_6H_5C{\equiv}CCH_2CH_2Cl$, but the present results show many lines not listed by these earlier investigators. The compounds were prepared by essentially the same methods and were carefully purified. As a check upon the possibility that impurities might be the source of the additional lines, $C_6H_5C{\equiv}CCH_2CH_2Cl$ was prepared by a different method.[10] The resultant spectrograms were comparatively free from continuous background and showed not only the forty more prominent lines listed above but also forty-nine weaker ones which were quite generally checked by both Hg4047 Å. and 4358 Å.

It is possible that a few of these may be due to traces of impurities which were not removed by the careful fractionation, but the source of others cannot be laid to this as they occur in regions

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(9) M. J. Murray, THIS JOURNAL, **60**, 2662 (1938).

(10) J. R. Johnson, A. M. Schwartz and T. L. Jacobs, *ibid.*, **60**, 1882 (1938).

(11) Tchao, Y. L., *Bull. soc. chim.*, [4] **53**, 1533 (1933).

(12) "Org. Syntheses," Coll. Vol. I, 1932, p. 182, by adaptation.

(13) Danehy, Vogt and Nieuwland, THIS JOURNAL, **57**, 2327 (1935), reported a yield of 21% for this synthesis. However, by use of benzene as a diluent,[12] p. 299, and by allowing the rearrangement of the intermediate product to take place at 70–80°, yields of the alcohol approaching 70% were obtained in the present investigation.

where prominent lines are rare in organic compounds. Furthermore, a considerable number of the frequencies correspond to the weaker Raman lines in the spectra of benzene,[14] monosubstituted benzenes,[15] and compounds containing one or more —CH_2— groups. Because of certain remaining inconsistencies and difficulties in the measurement of the weaker lines, only the more prominent frequencies of the various compounds are listed at present.

The use of a low pressure mercury arc, with a consequent diminution in the amount of continuous radiation in the exciting light, and the method of illuminating the comparator are, without doubt, two of the factors contributing to the observance of so many lines. The number obtained is greater for some of the compounds than for others. This is due to the fact that some compounds decompose more readily when illuminated, resulting in the presence of small amounts of fluorescent materials. The consequent increase in the strength of the continuous background makes the measurement of weak lines extremely difficult.

Acknowledgment.—This work was aided in part by a grant from the Virginia Academy of Science from funds allotted it by the American Association for the Advancement of Science.

Summary

1. The principal lines in the Raman spectra of 3-chloro-1-phenylpropyne-1, 4-chloro-1-phenylbutyne-1, 5-chloro-1-phenylpentyne-1, 3-bromo-1-phenylpropyne-1, 3-phenyl-2-propynol-1, 4-phenyl-3-butynol-1, and 3-chloro-1-phenylpropene-1 (cinnamyl chloride) are reported.

2. Many other lines of very low intensity have been observed. Many of these are characteristic of benzene, monosubstituted benzenes, and compounds containing the —CH_2— group.

LYNCHBURG, VIRGINIA RECEIVED AUGUST 26, 1938

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[14] P. Grassmann and J. Weiler, *Z. Physik*, **86**, 321 (1933).

[15] J. W. Murray and D. H. Andrews, *J. Chem. Phys.*, **1**, 406 (1933); L. Kahovec and A. W. Reitz, *Akad. Wiss. Wien, Ber.*, **145**, 1045 (1936).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS AND THE WILLIAMS OIL-O-MATIC HEATING CORPORATION]

Hydrogen Bonds Involving the C–H Link. IV. The Effect of Solvent Association on Solubility

BY M. J. COPLEY, G. F. ZELLHOEFER AND C. S. MARVEL

In a series of papers,[1–3] by the authors, solubility data have been reported on a number of gaseous halogenated hydrocarbons (of the types CH_3X, CH_2X_2, CHX_3, CX_4, and C_2X_6) in a variety of solvents containing donor atoms (oxygen, nitrogen, and sulfur). The successive replacement of three of the hydrogen atoms of methane by halogen atoms results in each case in an increase of solubility, and for the type CHX_3 solubilities much in excess of the theoretical have been observed in many solvents; however, replacement of the fourth hydrogen produces an enormous drop in solubility compared to that shown by the haloform type. These results readily are interpreted by assuming that complex formation takes place through the bonding of a hydrogen atom of the halogenated hydrocarbon to an exposed pair of electrons on the nitrogen or oxygen atoms in solvent molecules. The presence of the strongly electron-attracting halogen atoms on the carbon activates the hydrogen atom and makes it available for coördination to the donor atom.

Latimer and Rodebush[4] first suggested the theory that a proton in certain cases is capable of forming a bond between two atoms. Since then numerous investigations have confirmed this theory and shown its great utility. The possibility that the hydrogen atom of a haloform molecule might be capable of forming such a bond to an oxygen or nitrogen atom in a molecule was proposed by Glasstone[5] to account for the dielectric behavior of binary mixtures, containing a haloform and either an ether, an ester, or an amine. The ease with which the large amount of solubility data[2] accumulated by the authors may be

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[1] G. F. Zellhoefer, *Ind. Eng. Chem.*, **29**, 584 (1937).

[2] G. F. Zellhoefer, M. J. Copley and C. S. Marvel, THIS JOURNAL, **60**, 1337 (1938).

[3] G. F. Zellhoefer and M. J. Copley, *ibid.*, **60**, 1343 (1938).

[4] Latimer and Rodebush, *ibid.*, **42**, 1419 (1920).

[5] Glasstone, *Trans. Faraday Soc.*, **33**, 200 (1937).

correlated on the basis of this idea affords strong support for it. Rodebush[6] has informed the authors that infrared absorption measurements on solutions in carbon tetrachloride of chloroform with an ether or amine show definite evidence of complex formation.

Although extremely high solubilities were observed for halogenated hydrocarbons of the haloform type in practically all solvents containing an effective donor atom (nitrogen or oxygen), an exception was found in the case of alcohols. These low solubilities in alcohols[2] are related to the intermolecular association through hydrogen bonding which takes place between alcohol molecules.[7,8] It was thought that a more extended study should be made of solvents where association between solvent molecules is known to occur. Such an investigation should furnish data to aid in stating more precisely the factors which are important in producing solubility and should also provide new information about the amount and type of association occurring in these liquids. For this purpose measurements were made of the solubility of monofluorodichloromethane ($CHCl_2F$) in a number of alcohols, ethers, acids, esters, amides, substituted amides, primary and tertiary amines, and oximes. The effect on solubility of each of the two factors (a) unsaturation and (b) chelation was studied also by measuring solubility of this haloform in compounds containing an aliphatic double bond and in compounds where chelation is known to exist.

Experimental

The method used in making the solubility measurements has been described previously in detail.[1] The solvents tested were all purified carefully and their boiling or melting points checked. The solubility measurements on the monofluorodichloromethane were made over a range of pressures at a temperature of 32.2°. While it is important that complete pressure–composition studies be made on the various mixtures, it is felt that at present it is more important to have partial data on a large number of combinations. The results of these measurements are shown in Figs. 1–3. To compare the solvents tested the mole fraction solubilities at a partial pressure of monofluorodichloromethane corresponding to its vapor pressure at 4.5° are used in the following discussion and given in Table I. The "ideal" or theoretical mole fraction stated at the top of Table I was calculated using Raoult's law, and it is the ratio of the vapor pressure (0.847 atm.) of monofluorodichloromethane at 4.5° to its value (2.221 atm.) at 32.2°. The statement in the table that the solubility is *very low* in the case of acetamide and diphenylamine, is based on the observation that when these solvents, which are solids at 32.2°, were melted, insufficient monofluorodichloromethane dissolved in the liquid in the pressure range used, to lower the melting point appreciably.

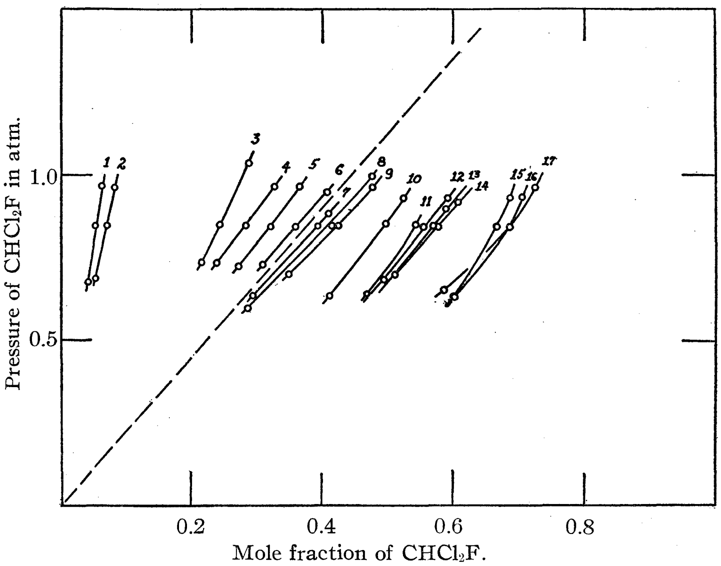

Fig. 1.—The solubility of monofluorodichloromethane as a function of pressure in alcohols, ethers, acids, and esters. The dotted line represents the "ideal" solubility: 1, ethylene glycol; 2, triethylene glycol; 3, phenol; 4, acetic acid; 5, propionic acid; 6, dimethyl sulfate; 7, phenyl vinyl ether; 8, anisole; 9, phenetole; 10, cyclohexylmethyl ether; 11, *n*-butyl butyrate; 12, diethyl oxalate; 13, 1,4-dimethoxycyclohexane; 14, dimethyl ether of ethylene glycol; 15, triethyl phosphate; 16, tributyl phosphate; 17, tri-(β-methoxyethyl) phosphate.

In a few cases a slow reaction was noted between the monofluorodichloromethane and the solvent used. This was particularly true with the amines and the values given for the solubility in these compounds are subject to a possible error of several per cent.

Discussion

Alcohols and Ethers.—In a preceding paper[2] the extremely low mole fraction solubilities of monofluorodichloromethane in ethylene glycol (0.055) and trimethylene glycol (0.073) were reported. In the present paper data are presented on the solubility of monofluorodichloromethane in phenol (0.197) and a similar low solubility compared to the theoretical (0.381) was observed.

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[6] Buswell, Rodebush and Roy, THIS JOURNAL, **60**, 2528 (1938); see also Gordy, *ibid.*, **60**, 605 (1938).

[7] Errera and Mollet, *Nature*, **138**, 882 (1936).

[8] Buswell, Deitz and Rodebush, *J. Chem. Phys.*, **5**, 84, 501 (1937).

TABLE I

SOLUBILITY OF MONOFLUORODICHLOROMETHANE IN ORGANIC SOLVENTS

Theoretical or "Ideal" mole fraction in saturated solution 0.381

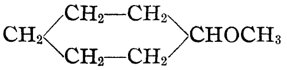
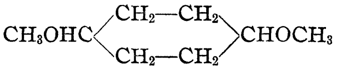
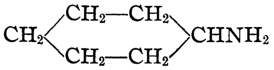
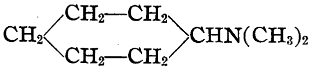
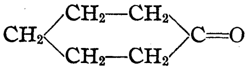
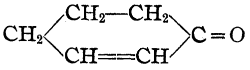
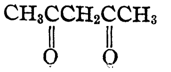
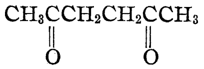
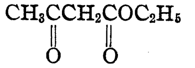
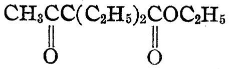
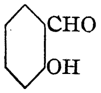
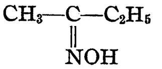
	Formula	Solubility	
		G./g.	Mole fr.
	Alcohols and Ethers		
Phenol	C_6H_5OH	0.269	0.197
Ethylene glycol	$HOCH_2CH_2OH$	.10	.055
Trimethylene glycol	$HOCH_2CH_2CH_2OH$	.106	.073
Anisole	$C_6H_5OCH_3$	.673	.415
Phenetole	$C_6H_5OC_2H_5$	.625	.425
Phenyl vinyl ether	$C_6H_5OCH{=}CH_2$	.559	.394
Dimethyl ether of ethylene glycol	$CH_3OCH_2CH_2OCH_3$	1.55	.576
Cyclohexyl methyl ether		0.900	.500
1,4-Dimethoxycyclohexane		0.941	.571
	Acids and Esters		
Acetic acid	CH_3COOH	0.688	0.286
Propionic acid	C_2H_5COOH	.665	.330
n-Butyl butyrate	$CH_3(CH_2)_2COO(CH_2)_3CH_3$	.870	.546
Diethyl oxalate	$C_2H_5OCOCOOC_2H_5$	.561	.556
Dimethyl sulfate	$(CH_3O)_2SO_2$	.463	.361
Triethyl phosphate	$(C_2H_5O)_3PO$	1.132	.666
Tributyl phosphate	$(C_4H_9O)_3PO$	0.842	.685
Tri-(β-methoxyethyl) phosphate	$(CH_3OCH_2CH_2O)_3PO$	.836	.687
	Amines and Substituted Amines		
Cyclohexylamine		1.070	0.506
Aniline	$C_6H_5NH_2$	0.385	.258
Quinoline	C_9H_7N	.633	.443
Diphenylamine	$(C_6H_5)_2NH$	(Very low)	...
Dimethylcyclohexylamine		0.807	.500
Dimethylaniline	$C_6H_5N(CH_3)_2$	.695	.425
Methyldiphenylamine	$(C_6H_5)_2NCH_3$	.357	.388
	Amides and Substituted Amides		
Formamide	$HCONH_2$	0.075	0.032
Acetamide	CH_3CONH_2	(Very low)	...
Methylformamide	$HCONHCH_3$	0.768	.303
N,N-Dimethylformamide	$HCON(CH_3)_2$	.931	.398
N-Methylacetamide	$CH_3CONH(CH_3)$	.955	.403
N,N-Dimethylacetamide	$CH_3CON(CH_3)_2$	1.87	.614
N-Tetraethyloxamide	$[CON(C_2H_5)_2]_2$	0.965	.651
N,N-Tetramethylsuccinamide	$[CH_2CON(CH_3)_2]_2$	1.180	.663
N-Methyl-N-cyclohexylacetamide	$CH_3CON(CH_3)C_6H_{10}$	1.140	.632
	Aldehydes and Ketones		
Benzaldehyde	C_6H_5CHO	0.750	0.436
Heptaldehyde	$C_6H_{13}CHO$	.979	.519
Paraldehyde	$C_6H_{12}O_3$	.888	.532
Cyclohexanone		1.278	.548
Δ^2-Cyclohexenone		0.903	.457
Acetylacetone	 $CH_3\underset{\underset{O}{\|}}{C}CH_2\underset{\underset{O}{\|}}{C}CH_3$	1.023	.499

TABLE I (*Concluded*)

	Formula	Solubility G./g.	Solubility Mole fr.
Acetonylacetone	 $\mathrm{CH_3\underset{\overset{\|}{O}}{C}CH_2CH_2\underset{\overset{\|}{O}}{C}CH_3}$	1.163	0.563
Ethyl acetoacetate	 $\mathrm{CH_3\underset{\overset{\|}{O}}{C}CH_2\underset{\overset{\|}{O}}{C}OC_2H_5}$	0.913	.536
Ethyl diethylacetoacetate	 $\mathrm{CH_3\underset{\overset{\|}{O}}{C}C(C_2H_5)_2\underset{\overset{\|}{O}}{C}OC_2H_5}$	.880	.614
Salicylaldehyde		.501	.372
	Oximes		
Ethylmethylketoxime	 $\mathrm{CH_3{-}\underset{\overset{\|}{NOH}}{C}{-}C_2H_5}$	.650	.338

When the hydrogen of the hydroxyl groups of alcohols is replaced by alkyl groups the resulting ethers show a high solvent power in excess of the theoretical as is illustrated by the examples in Table I and the results on a large number of ethers reported in a previous paper.[2] This difference in behavior of alcohols compared to ethers is to be traced to the association that exists in alcohols. Cryoscopic measurements[9] in non-polar solvents and analysis by Zachariasen[10] of X-ray data indicate that alcohols polymerize to form large linear or string polymers. This association takes place as first suggested by Latimer and Rodebush,[4] and later by Huggins,[11] through the bonding of a hydrogen of a hydroxyl group to the oxygen of a neighboring molecule. Recent infra-red absorption measurements[7,8] tend to confirm this picture of association. The low solubility of monofluorodichloromethane in alcohols is then due to the fact that a hydrogen bond formed by a hydrogen atom attached to a carbon atom with an oxygen atom, C–H ← O, is less stable than the O–H–O bonds already present in the alcohols. Hence the monofluorodichloromethane molecules are practically excluded from entering the large complexes present in the alcohol. Intermolecular association is blocked by the replacement of the hydrogen of the hydroxyl by an alkyl group, and then it is possible for C–H ← O bonds to form between the hydrogen of the monofluorodichloromethane and the oxygen atoms of an ether. The formation of this type of complex between the ether and the monofluorodichloromethane is responsible for the enormous solubilities observed for monofluorodichloromethane in ethers.

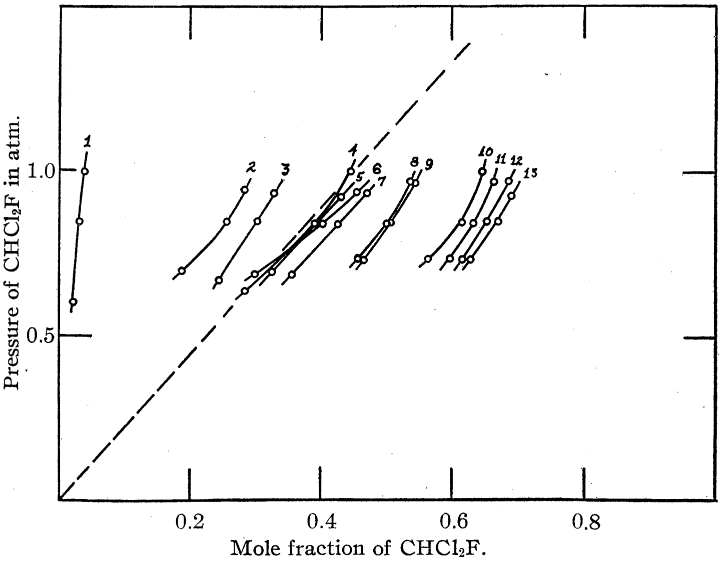


Fig. 2.—The solubility of monofluorodichloromethane as a function of pressure in amines and amides: 1, formamide; 2, aniline; 3, methylformamide; 4, methyldiphenylamine; 5, methylacetamide; 6, dimethylformamide; 7, dimethylaniline; 8, dimethylcyclohexylamine; 9, cyclohexylamine; 10, dimethylacetamide; 11, N-methyl-N-cyclohexylacetamide; 12, tetraethyloxamide; 13, tetramethylsuccinamide.

Acids and Esters.—The mole fraction solubility of monofluorodichloromethane is distinctly higher in the fatty acids (0.286 in acetic acid) than in the alcohols although an active hydrogen is present in the carboxyl group of these molecules. This result confirms the viewpoint that a different type of association takes place in the fatty acids than in the alcohols, which previously has been

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(9) Auwers, *Z. physik. Chem.*, **12**, 689 (1893); *ibid.*, **15**, 33 (1894).

(10) Zachariasen, *J. Chem. Phys.*, **3**, 158 (1935).

(11) M. L. Huggins, *J. Org. Chem.*, **1**, 407 (1936).

shown by the fact that the polymerization in acetic acid stops at the dimer stage. The existence of the dimers of acids is shown by numerous cryoscopic and distribution measurements. Recent vapor density,[12,13] and electron diffraction measurements[14] show the presence of these dimers in the vapor whereas there is no appreciable association in the vapor phase of alcohols. The association presumably takes place through hydrogen bonding and results in an eight-membered ring. The stability of the ring as suggested by Pauling and Brockway[14] probably is due to a resonance between the two structures (I and II) of equal energy.

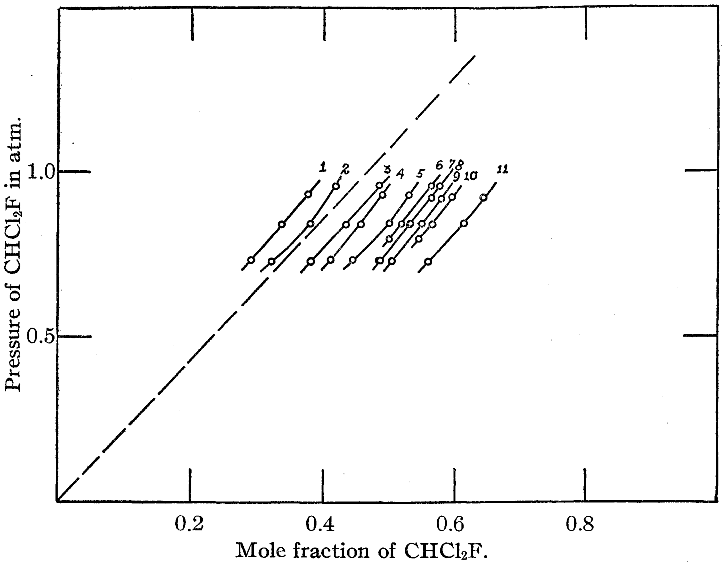
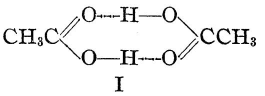
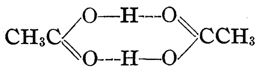


Fig. 3.—The solubility of monofluorodichloromethane as a function of pressure in aldehydes, ketones, and oximes: 1, ethylmethylketoxime; 2, salicylaldehyde; 3, benzaldehyde; 4, cyclohexenone; 5, acetylacetone; 6, heptaldehyde; 7, paraldehyde; 8, ethyl acetoacetate; 9, cyclohexanone; 10, acetonylacetone; 11, ethyl diethylacetoacetate.



I



II

When the mole fraction solubility of acetic acid is calculated using the molecular weight of the dimer instead of that of the monomer, its value (0.445) does not exceed the theoretical (0.381) to any marked extent. This result indicates that when an oxygen atom has shared one of its two exposed electron pairs its basic or donor properties are strongly reduced. Further evidence of this decrease in donor property of an oxygen atom after sharing one of its electron pairs will be given in the section on chelated compounds.

As in the case of alcohols the replacement of the active hydrogen of an acid by an alkyl group blocks association and extremely high solubility is observed for monofluorodichloromethane in esters. In general the solubility in an ester is of about the same magnitude as in an ether of similar structure although the ether has only one oxygen. Apparently this is due, as was shown in a previous paper,[3] to steric hindrance. The close proximity of the two oxygens prevents the simultaneous attachment of two monofluorodichloromethane molecules to the two oxygen atoms of the ester group.

Some measurements of solubility were also made using esters of phosphoric and sulfuric acids. The esters of phosphoric acid are extremely effective as solvents for monofluorodichloromethane but the one ester of sulfuric acid tested showed rather poor solvent power.

Amines and Substituted Amines.—Very high solubilities in excess of the theoretical were observed in cyclohexylamine (0.506) and dimethylcyclohexylamine (0.499). The almost equal solubilities of monofluorodichloromethane in these two compounds suggests that aliphatic amines are unassociated and that an aliphatic amine hydrogen is not sufficiently active to form hydrogen bonds. The failure to form bonds certainly cannot be due to any lack of donor properties on the part of the nitrogen atom since the high solubility of monofluorodichloromethane indicates ready sharing of the electron pair of the nitrogen to form C–H ← N bonds. This conclusion of lack of association in liquid amines from our solubility measurements is in accord with their cryoscopic[15] behavior in non-polar solvents. Also the substitution of a methyl group for the hydroxyl hydrogen of an alcohol causes a lowering of the boiling point, whereas the replacement of one or both hydrogens on the nitrogen of a primary amine raises the boiling point.

The considerably lower solubility of monofluorodichloromethane in aniline (0.258) than in dimethylaniline (0.425) suggests that in aromatic

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[12] Fenton and Garner, *J. Chem. Soc.*, 674 (1930).

[13] MacDougall, This Journal, **58**, 2585 (1936).

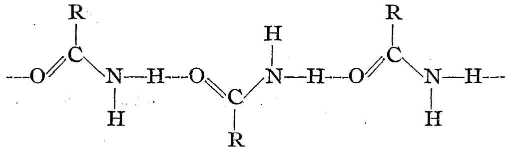
[14] Pauling and Brockway, *Proc. Nat. Acad. Sci.*, **20**, 336 (1934).

[15] E. N. Lassettre, *Chem. Rev.*, **20**, 259 (1937).

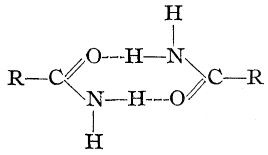
amines some association, probably of the linear polymer type, takes place.

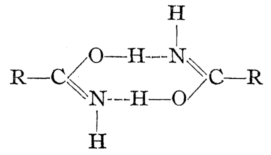
The almost equal solubilities observed in methylcyclohexyl ether (0.500), cyclohexylamine, and dimethylcyclohexylamine indicate that the donor properties of an aliphatic ether oxygen and an aliphatic amine nitrogen are almost equivalent.

Amides and Substituted Amides.—Extremely low solubilities were observed for monofluorodichloromethane in formamide (0.0318) and acetamide (*very low*). These much lower solubilities than those observed in the fatty acids suggest that dimers are not formed in amides but instead polymers of indefinite size. Cryoscopic measurements[15] on amides also indicate the formation of large polymers in non-polar solvents. A possible reason for the polymerization failing to stop at the dimer stage might be the formation of linear polymers as shown in structure III

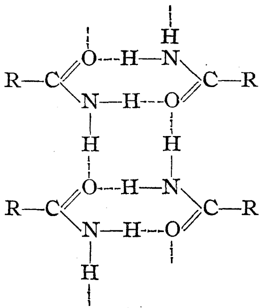

III

since the two resonating structures of the dimer illustrated in IV and V would be of unequal energy.


IV


V

On the other hand, the formation of linear polymers in alcohols does not lead to excessively high melting points, while amides melt much higher than alcohols containing the same number of carbon atoms. A different type of association is also indicated by the ease with which amides crystallize compared to alcohols which tend to form glasses. A type of association which might account for these differences in behavior of amides and alcohols is shown in structure VI where the association takes place through the fusing of dimers. It is true that the formation of such a polymer requires the sharing of the second pair of electrons on the oxygens; however, the behavior of acetic acid and chelated compounds indicates that this tendency while small is not negligible; also the numerous possible resonating structures in such a polymer would contribute to its stabilization. An association through the fusing of dimers would explain the intermediate solvent power for monofluorodichloromethane of a monosubstituted amide between that of the amide and the disubstituted amide (where no association exists) as is illustrated by the data in Table I. The substitution of an alkyl group for one of the hydrogens on the nitrogen would block the fusing of the dimers and should lead to a solubility comparable to that observed in the fatty acids. Chaplin and Hunter[16] have made some cryoscopic measurements on solutions of monomethyl and monoethyl acetamide in benzene which indicate that these compounds are associated, but the measurements are not complete enough to establish whether large polymers or only dimers are formed. Jenkins and Taylor[17] have investigated solutions of α-piperidone in benzene and find no evidence for polymerization proceeding past the dimer stage. It is recognized that the high dielectric constants of the amides and of the monosubstituted amides[18] appear to offer an objection to this latter picture of association, since the formation of such a symmetrical structure would apparently involve a neutralization of dipole moments of the amide molecules. However, it is possible that there are present in the liquid a sufficient number of the monomers to account for the observed dielectric constants.


VI

The solubility in N,N-dimethylacetamide (0.614) is extremely high and a similar high solubility has been observed in all completely substituted amides with the exception of N,N-dimethylformamide (0.398). This difference in behavior of dimethylformamide as a solvent may be caused by the existence of some polymerization involving the hydrogen on the carbon of the formic acid residue. The strong negative groups attached to

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(16) Chaplin and Hunter, *J. Chem. Soc.*, 1114 (1937).

(17) Jenkins and Taylor, *ibid.*, 495 (1937).

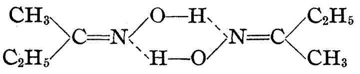
(18) Kumler, THIS JOURNAL, **57**, 600 (1935).

this carbon might be expected to cause its activation. If this is correct, a similar activity on the part of the hydrogen in formic acid would be expected, and indeed has already been suggested by Huggins[11] to account for the high dielectric constant of formic acid[18] compared to that of the other fatty acids.

A comparison of our solubility data in amines and amides shows that the tendency for hydrogen bonding is directly connected with the activity of the hydrogens on the nitrogen. However, the basicity of their solutions in water apparently is not related to the donor properties of the nitrogen in forming hydrogen bonds.

Ketones and Aldehydes.—The high solubilities observed for monofluorodichloromethane in aldehydes and ketones are in agreement with the well-known fact that these liquids are unassociated and suggest that the oxygen present in a carbonyl group is an excellent electron donor so that C–H ← O bonds readily form.

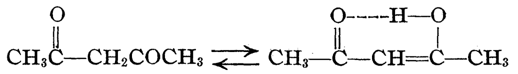
Oximes.—One oxime, methylethylketoxime, was tested. The almost normal solubility (0.338) of monofluorodichloromethane in this compound suggests that oximes form dimers similar in type to those formed by fatty acids and N-monosubstituted amides. A probable structure for this dimer is shown in formula VII.



VII

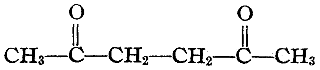
Cryoscopic measurements[15] on acetoxime and *d*-camphoroxime indicate that these compounds form either dimers or relatively small polymers in non-polar solvents.

Effect of Chelation.—The almost normal solubility observed in acetic acid dimers suggests, as was pointed out earlier, that when one pair of electrons on an oxygen is shared, its donor properties decrease. A study of the solubility of monofluorodichloromethane in compounds containing a chelate ring and a comparison of these solubilities with solubilities in compounds containing a similar structure but without chelation, gave further evidence on this point. Two pairs of compounds were tested. One of each pair is known to be chelated and in the other there is no opportunity for chelation. These compounds are shown in the four formulas below with the mole fraction solubility of monofluorodichloromethane in each.



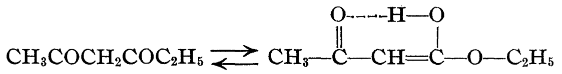
$$CH_3\overset{\overset{O}{\|}}{C}-CH_2COCH_3 \rightleftharpoons CH_3-\overset{\overset{O---H-O}{\|\qquad\quad|}}{C-CH=C}-CH_3$$

Acetylacetone
(0.499)



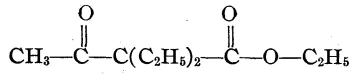
$$CH_3-\overset{\overset{O}{\|}}{C}-CH_2-CH_2-\overset{\overset{O}{\|}}{C}-CH_3$$

Acetonylacetone
(0.563)



$$CH_3COCH_2COC_2H_5 \rightleftharpoons CH_3-\overset{\overset{O---H-O}{\|\qquad\quad|}}{C-CH=C}-O-C_2H_5$$

Ethyl acetoacetate
(0.536)



$$CH_3-\overset{\overset{O}{\|}}{C}-C(C_2H_5)_2-\overset{\overset{O}{\|}}{C}-O-C_2H_5$$

Ethyl diethylacetoacetate
(0.617)

The results indicate an appreciable decrease in the formation of C–H ← O bonds by the compounds in which chelation occurs. A similar conclusion is obtained by comparing the solubility of monofluorodichloromethane in benzaldehyde (0.436) with that in strongly chelated salicylaldehyde (0.372).

Effect of Unsaturation.—A few compounds were examined to test the effect on solubility of an aliphatic double bond in the donor molecule. The solubility in phenyl vinyl ether (0.394) is so near that in anisole (0.415) and phenetole (0.425), as to indicate only a small effect. However, the effect is much more pronounced for Δ^2-cyclohexenone (0.457) when compared to cyclohexanone (0.548).

A phenyl group attached to an oxygen or a nitrogen atom markedly decreases its donor properties. This is clearly shown by the lower solubilities given in Table I for aromatic ethers and amines compared to aliphatic ethers and amines. On the other hand, the hydrogens of an aromatic amine are more active (leads to association) and hence the higher solubility of monofluorodichloromethane in dimethylaniline (0.425) compared to aniline (0.258).

Conclusion

The simple assumption of complexes formed through the medium of C–H ← O bonds in a remarkable manner correlates the large amount of solubility data that has been obtained. Furthermore, as stated earlier in this paper, recent infrared absorption measurements[6] on mixtures of chloroform with ethers, esters, ketones, and amines lead to the same conclusion. The strength of the C–H ← O or C–H ← N bond in the case of halogenated hydrocarbons of the CHX_3 type is less than that of N–H–O and O–H–O bonds, hence the addition of chloroform and monofluorodichloromethane does not cause dissociation in compounds associated by means of hydrogen bonding between two oxygen atoms, or a nitrogen atom and an oxygen atom. In this connection it should be recalled that it has been known for a long time that the haloforms behave essentially as non-polar solvents similar to benzene and hexane in cryoscopic measurements on alcohols, acids, and amides.

The considerations outlined above also should be applicable to the solution of solid organic compounds in monofluorodichloromethane, or other halogenated hydrocarbons of the type CHX_3, C_2HX_5, etc. (and to a lesser extent to the type CH_2X_2), and should allow the qualitative prediction of solubility in such cases.

Summary

The concept of $C–H \leftarrow O$ bonds between a hydrogen of a halogenated hydrocarbon and donor atoms in solvents has been shown readily to correlate solubility data on solutions of halogenated hydrocarbons in a large number of solvents of different types.

The most important factors governing the solubility of the types of compounds investigated are: (1) the donor properties of atoms in the solvent for forming $C–H \leftarrow O$ or $C–H \leftarrow N$ bonds; (2) the presence or absence of intermolecular association through hydrogen bonding in the solvent.

It has been shown that it is possible to predict the type of association occurring in a liquid by means of a solubility measurement. The presence of large linear polymers in the solvent inhibits the solution of monofluorodichloromethane but if the polymerization stops at the dimer stage nearly normal solubility is observed.

URBANA AND BLOOMINGTON, ILLINOIS
RECEIVED AUGUST 29, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF KENTUCKY]

The Reaction of Esters with Aluminum Isopropoxide

BY ROBERT H. BAKER

Aluminum alkoxides react with alcohols[1,2] and catalyze the alcoholysis of esters,[3] but their reaction with esters alone has been studied very little.[1,4]

For the simple esters the reaction is one of exchange of groups and possibly may be of use in the preparation of alkoxides whose alcohols themselves are either unstable or which fail to react with amalgamated aluminum. The reaction also may be used in the preparation of esters.

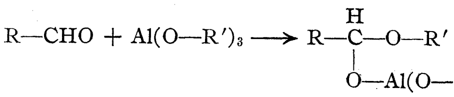
In this work the equilibrium

$$3R—COOR' + Al(O—i\text{-}Pr)_3 \longleftrightarrow 3R—COO—i\text{-}Pr + Al(O—R')_3$$

has been shifted as far to the right as possible by carrying out the reaction under a fractionating column which permits the removal of only the isopropyl ester. *t*-Butyl acetate failed to react completely, the reaction stopping when two of the isopropyl (or isopropoxide) groups had been replaced. This is in accord with the observations of Tischtschenko,[1] who found that the tertiary alkoxides reacted best with the alcohols.

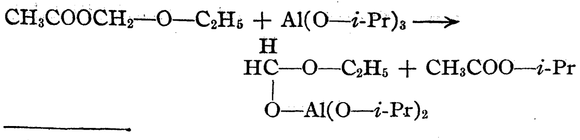
The isopropoxide, which is easily made and purified and which gives rise to low boiling esters, has been used exclusively in this work.

Only one ester, ethoxymethyl acetate, gave rise to reduction products similar to those which the simple esters give with sodium alkoxides.[5] This ester was used in an attempt to prepare an alkoxide of the type which Verley[6] postulated as an intermediate in both the Tischtschenko reaction[4] and in the reduction of aldehydes. This aluminate of a hemiacetal, which Verley claims is formed thus



$$R—CHO + Al(O—R')_3 \longrightarrow R—\overset{\displaystyle H}{\underset{\displaystyle O—Al(O—R')_2}{C}}—O—R'$$

was expected to be formed as follows



$$CH_3COOCH_2—O—C_2H_5 + Al(O—i\text{-}Pr)_3 \longrightarrow \overset{\displaystyle H}{\underset{\displaystyle O—Al(O—i\text{-}Pr)_2}{HC}}—O—C_2H_5 + CH_3COO—i\text{-}Pr$$

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[1] Tischtschenko, *J. Russ. Phys.-Chem. Soc.*, **31**, 694, 784 (1899); *Chem. Zentr.*, **71**, I, 10, 585 (1900).

[2] Adkins and Cox, THIS JOURNAL, **60**, 1151 (1938).

[3] Fehlandt and Adkins, *ibid.*, **57**, 193 (1935); Hatch and Adkins, *ibid.*, **59**, 1694 (1937).

[4] Tischtschenko, *J. Russ. Phys.-Chem. Soc.*, **38**, 355, 482 (1906); *Chem. Zentr.*, **77**, II, 1309, 1552 (1906).

[5] Magnani and McElvain, THIS JOURNAL, **60**, 813 (1938).

[6] Verley, *Bull. soc. chim.*, **37**, 537, 871 (1925).

TABLE I

			Aluminum alkoxide					
							Al, %	
Ester used	n^{20}D	Isopropyl ester, %[a]	%	M. p., °C.	B. p., °C.	Mm.	Calcd.	Found
n-Butyl acetate	1.3950	85	88[e]		280–284	12		
t-Butyl acetate	1.3838	66	98[b]	165–167	Subl. 160	14	11.64	11.64
s-Butyl formate	1.3865	81	57		165–166	3		
Allyl acetate	1.4050	95	100[c,e]	145–150	dec.			
n-Hexadecyl acetate	1.4438	100	98[e]	44			3.60	3.70
Ethyleneglycol diacetate	1.4184	80	120[d]	dec.			24.05	21.20

[a] Calcd. from fractions of isopropyl acetate n^{20}D 1.3770–1.3786 and of isopropyl formate n^{20}D 1.3720–1.3735. A dry refractionated synthetic sample of the latter had distillation range (Widmer) 66.9–67.0°; n^{20}D 1.3716; d^{20}_4 0.8726; *M*D calcd., 22.33, found 22.92. [b] Assumed to be aluminum di-*t*-butoxide monoisopropoxide, pure *t*-butyl acetate could be distilled from this even after heating together at 150° for two hours. [c] Attempts to purify this for analysis were unsuccessful. It begins to distill at 220° (5 mm.) and then decomposes violently. The crude product melts over a narrower range than that reported.[1] [d] A very light powder retaining ester even at 150° (2 mm.) for two hours. Completely insoluble in xylene, but retains xylene which is removed only at 150° (2 mm.). [e] These alkoxides gave a negative iodoform test after hydrolysis.

Such a compound was not isolated and no evidence for or against its formation[7] can be gained from the experiment, but it is of interest that the products of the reaction were those which one would expect from Tischtschenko reactions, reductions, and group exchanges between alkoxides and esters.

Experimental

Reagents.—Aluminum isopropoxide, b. p. 134° (5 mm.), m. p. 118°, was prepared in 91% yield by the method of Adkins.[8] Before each experiment the powdered material was tested for complete solubility, without opalescence, in dry benzene. The esters were prepared by the standard methods and distilled through a Widmer column, refractive index and boiling range rather than the boiling point being used as a criterion of purity. The esters were tested for moisture immediately before use by adding a few drops of a benzene solution of aluminum isopropoxide to a few cc. of the ester. If opalescence did not appear within a few minutes, the esters were considered to be dry. Ethoxymethyl acetate n^{20}D 1.3950, distillation range 129.5–130.0°, was prepared by the method of Farren[9] except that the final distillation was through the Widmer column.

The general procedure was to mix 0.4 mole of the ester with 0.1 mole of aluminum isopropoxide in a flask protected from moisture and fitted to a Widmer column equipped with a partial condensation head. Slow distillation was carried out collecting 1- or 2-g. fractions and following the fractionation by means of the refractive index. When all the isopropyl ester had distilled and the index corresponded to that of the starting ester, the remainder was distilled by diminished pressure to leave the alkoxide in weighable form. The results from several esters are found in Table I.

***n*-Butyl benzoate,** n^{20}D 1.5001, 53.4 g. (0.3 mole) and aluminum isopropoxide 20.4 g. (0.1 mole) were heated at 130° for two hours, cooled, poured into cold water containing 25 cc. of 6 *N* sulfuric acid, and extracted with ether. The ether solution was washed successively with water, saturated solution of calcium chloride, saturated solution of potassium carbonate, and then was dried over anhydrous magnesium sulfate. The ether solution gave upon fractionation through the Widmer column isopropyl benzoate n^{20}D 1.4975–1.4978, 27.0 g. (0.165 mole), and *n*-butyl benzoate n^{20}D 1.4998–1.5001, 18.9 g. (0.105 mole). This is a 90% recovery of the esters and, since the acidic hydrolysate gave negative tests for aldehydes and ketones, no reverse Tischtschenko reactions[5] take place.

Ethoxymethyl acetate, 35.4 g. (0.3 mole) and aluminum isopropoxide 20.4 g. (0.1 mole) were heated in an oil-bath from 50 to 150° over a period of eight hours. The reaction started quickly, as the odor of formaldehyde or acetaldehyde could be noticed. The exhaust gases were passed first through a drying tube and then through water. The water gave a positive Schiff test for aldehydes, but a negligible quantity of their 2,4-dinitrophenylhydrazones. Seven fractions, 36.2 g., distilling between 50 and 85° were collected and refractionated into fifteen fractions, b. p. 40–87°; n^{20}D 1.3570–1.3770. Four "flats" appeared in the refractive index–weight distilled diagram at n^{20}D 1.3640, 1.3680, 1.3730, and 1.3770. These constants, their respective distillation ranges, 56–58, 62–67, 71–75, and 80–87° and the fact that they were all saponifiable, were interpreted as indicating the presence of methyl acetate, isopropyl formate (possibly), ethyl acetate, and isopropyl acetate. The weights of the fractions in these "flats" were 4.4, 4.6, 6.6, and 7.7 g., respectively. Although acetone was found throughout the first six fractions, it was concentrated mainly, along with formate esters, in the first two, 3.7 g., from which it was identified (dibenzylideneacetone, m. p. 111–111.5°). The residue in the distilling flask, 16.5 g., was a mixture of alkoxides; when hydrolyzed it gave negative tests for aldehydes, esters, and acids.

Acknowledgment.—The author is indebted to Professor Charles Barkenbus for his coöperation and helpful suggestions.

Summary

The alkoxyl groups of esters and aluminum alkoxides are easily interchangeable and the resulting equilibrium has been shifted so as to prepare new alkoxides in good yield.

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(7) For more definite information concerning the probability of definite compound formation between aldehyde and catalyst see Child and Adkins, THIS JOURNAL, **47**, 798 (1925).

(8) Adkins, *ibid.*, **44**, 2175 (1922).

(9) Farren, Fife, Clark and Garland, *ibid.*, **47**, 2419 (1925).

The reaction of ethoxymethyl acetate with aluminum isopropoxide gave no isolable aluminate of the hemiacetal, but gave acetone, esters which were typical products of Tischtschenko reactions, and a mixture of methyl, ethyl, and isopropyl aluminates.

LEXINGTON, KY. RECEIVED SEPTEMBER 8, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CINCINNATI]

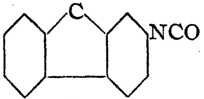
Fluorene Compounds. Nitrogen Derivatives

BY FRANCIS EARL RAY AND GEORGE RIEVESCHL, JR.

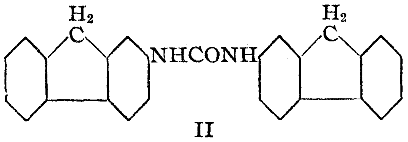
In the present work we undertook the preparation of new derivatives of 2-aminofluorene and of 9-N substituted 2-benzoylfluorene.

The preparation of 2-aminofluorene was first accomplished by Strasburger[1] from 4-aminodiphenic acid. A more convenient synthesis by the reduction of the normal mono-nitration product of fluorene is described in "Organic Syntheses."[2]

When we attempted to prepare 2-fluoryl-isocyanate, I, from the amine and phosgene, the *sym*-di-urea resulted, II.



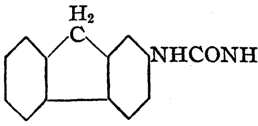
I



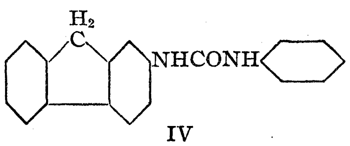
II

The isocyanate, I, was obtained by the modification of Hardy.[3] When dry it was quite stable but moisture caused its conversion into the di-urea, II. This di-urea was formed quantitatively when equimolar solutions of 2-aminofluorene and 2-fluoryl isocyanate were mixed.

When treated with ammonia, the mono-urea, III, was obtained. *sym*-Phenyl-2-fluorylurea, IV, was prepared in two ways: by treating 2-fluoryl isocyanate with aniline and by treating 2-aminofluorene with phenyl isocyanate.



III



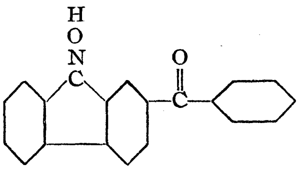
IV

Due to the sensitivity of 2-fluoryl isocyanate to water and the insolubility of the resulting di-urea in ether, acetone, etc., it may be a useful reagent to detect small amounts of water. The factor is 0.0464.

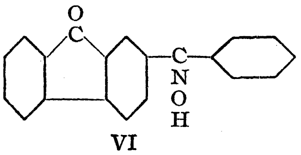
The methyl, ethyl and *n*-propyl urethans were prepared from 2-fluoryl isocyanate and the corresponding absolute alcohol.

Derivatives of 2-Benzoylfluorene

In 1902 Fortner[4] prepared a monoxime from 2-benzoylfluorenone which he described as bright yellow leaves from alcohol which sintered at 185° and melted at 199°. Fortner did not determine which of the configurations, V or VI, this compound possessed.



V



VI

As it seemed probable that the 9-position of the fluorene would be the more active, we set out to prepare V by methods that would leave no doubt as to its constitution.

Using Nenitzescu and Isăcescu's[5] method we condensed benzyl chloride with potassium 2-benzoyl-9-*aci*-nitrofluorene[6] and obtained an oxime melting at 207–208°.

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[1] Strasburger, *Ber.*, **16**, 2346 (1883).

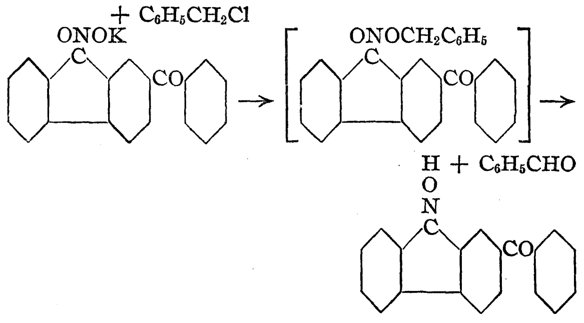
[2] *Org. Syntheses*, **13**, 74 (1933).

[3] Hardy, *J. Chem. Soc.*, 2011 (1934).

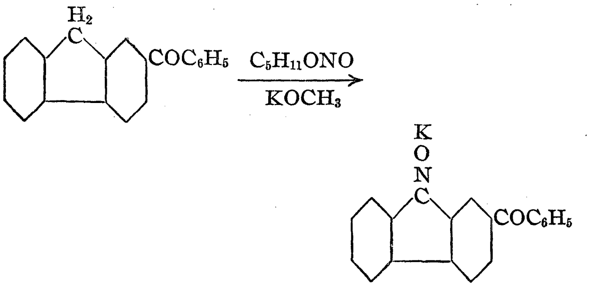
[4] Fortner, *Monatsh.*, **23**, 921 (1902).

[5] Nenitzescu and Isăcescu, *Ber.*, **63**, 2484 (1930).

[6] Ray and Palinchak, in press.



As this was somewhat troublesome to purify we also carried out the preparation by the method of Wislicenus and Waldmüller.[7]



In carrying out this reaction in an ether–benzene mixture some material seemed to precipitate out after standing several hours. On evaporating the filtrate to small volume and adding ether, a second batch of crystals was obtained.

Each was separately acidified and recrystallized. The first (insoluble), α, melted at 213–214° and was a pale yellow powder. The second, β, was obtained in long, golden needles melting at 207–208°.

As neither of these corresponded to the description of Fortner's compound we prepared some material by his directions. It is true that this material first melted at 198–199° but on repeated crystallization, first from benzene and then from alcohol, we obtained the compound in long needles melting at 207–208°, identical with our lower melting, β, oxime. We then mixed equal portions of our two oximes and on recrystallization the mixture melted at about 199°.

To characterize further these oximes the acetyl derivatives were prepared. That from the α-oxime (213–214°) melted at 144–145° while the acetyl derivative of the β-oxime (207–208°) melted at 150–151°. A mixed melting point mixture sintered at 116–126°. Which of these is *cis* and which *trans* remains to be determined.

Moore and Huntress[8] reported the melting point of *syn*-2-nitrofluorenone oxime, prepared in an alkaline solution, as 262.5–263°. Langecker,[9] preparing the oxime in a neutral solution, reported the melting point to be 249°. With this possible exception no other fluorenone oxime has been isolated in *cis* and *trans* forms.

Experimental

2-Aminofluorene was prepared by the method described in "Organic Syntheses."[2] It melted at 127°.

2-Fluoryl Isocyanate.—Eleven grams of 2-aminofluorene was dissolved in 250 cc. of warm toluene and dry hydrogen chloride was passed in until saturation was reached. The 2-aminofluorene hydrochloride separated as a cream-colored mass. The flask was heated to gentle reflux and a steady stream of carbonyl chloride was passed into the mixture. The precipitate gradually dissolved until at the end of one and one-half hours a clear liquid was obtained.

The solution was filtered and the toluene removed under diminished pressure. The tan colored product was recrystallized from ligroin. A pure white product was obtained melting at 69–70° which was readily soluble in most organic solvents. The yield was 11.2 g. or 89%.

Anal. Calcd. for $C_{14}H_9ON$: N, 6.76. Found: N, 6.85.

Methyl 2-fluorylcarbamate was prepared in the usual manner. It crystallized in shining laminae and melted at 118°.

Anal. Calcd. for $C_{15}H_{13}O_2N$: N, 5.85. Found: N, 5.92.

Ethyl 2-fluorylcarbamate was obtained as white plates from ligroin; m. p. 121–122°.

Anal. Calcd. for $C_{16}H_{15}O_2N$: N, 5.53. Found: N, 5.75.

***n*-Propyl 2-fluorylcarbamate** also crystallized in plates; m. p. 113°.

Anal. Calcd. for $C_{17}H_{17}O_2N$: N, 5.24. Found: N, 5.58.

2-Fluorylurea was prepared by passing dry ammonia gas into an ether solution of 2-fluoryl isocyanate. It was obtained as plates from alcohol. It did not melt at 360°.

Anal. Calcd. for $C_{14}H_{12}ON_2$: N, 12.49. Found: N, 12.67.

sym-Phenyl-2-fluorylurea was prepared from aniline and 2-fluoryl isocyanate and also by the reaction between 2-aminofluorene and phenyl isocyanate. White cottony fibers were obtained from dioxane, melting at 305° (block).

Anal. Calcd. for $C_{20}H_{16}ON_2$: N, 9.33. Found: N, 9.37.

sym-Di-2-fluorylurea was prepared from the isocyanate and 2-aminofluorene and also by treating the isocyanate with water. White cottony clusters were obtained from pyridine which did not melt at 360°. It is insoluble in most organic solvents.

Anal. Calcd. for $C_{27}H_{20}ON_2$: N, 7.21. Found: N, 7.37.

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(7) Wislicenus and Waldmüller, *Ber.*, **41**, 3334 (1908).

(8) Moore and Huntress, THIS JOURNAL, **49**, 1324, 2618 (1927).

(9) Langecker, *J. prakt. Chem.*, **132**, 145 (1931).

2-Benzoylfluorene was prepared by Perrier's[10] modification of the Friedel–Crafts reaction. It melted at 122°.

Potassium 2-benzoyl-9-aci-nitrofluorene was obtained by the method of Ray and Palinchak.[6]

2-Benzoyl-9-fluorenoneoxime.—Three and one-half grams of potassium 2-benzoyl-9-*aci*-nitrofluorene, 3.5 g. of benzyl chloride and 40 cc. of 95% alcohol were refluxed for eight hours. Potassium chloride slowly separated and the orange color faded to yellow. The solution was filtered and treated with water. An oil separated which solidified on stirring. After three recrystallizations from alcohol the melting point was 207–208° (β-form).

As this material was somewhat difficult to purify we condensed 27 g. of 2-benzoylfluorene with 13.7 cc. of isoamyl nitrite in the presence of 5.5 g. of potassium in 30 cc. of absolute methyl alcohol, 100 cc. of anhydrous ether and 200 cc. of pure benzene.

The product that precipitated weighed 16.1 g. It was separated, acidified and recrystallized from alcohol. This α-form of the oxime was obtained as a pale yellow powder melting at 213–214°.

Anal. Calcd. for $C_{20}H_{13}O_2N$: N, 4.67. Found: N, 4.66.

The acetyl derivative was prepared with acetyl chloride in pyridine–ether solution. Greenish-yellow fibers were obtained that melted at 144–145°.

Anal. Calcd. for $C_{22}H_{15}O_3N$: N, 4.11. Found: N, 4.31.

β-Oxime.—The filtrate from the α-potassium salt was evaporated to 50 cc. and 500 cc. of ether was added. The precipitate weighing 12.4 g. was separated, acidified and recrystallized three times from alcohol. Long, bright yellow crystals were obtained melting at 207–208°. These were identical with those prepared by Fortner's[4] method.

Anal. Calcd. for $C_{20}H_{13}O_2N$: N, 4.67. Found: N, 4.63.

This acetyl derivative crystallized in brilliant yellow plates that melted at 150–151°.

Anal. Calcd. for $C_{22}H_{15}O_3N$: N, 4.11. Found: N, 4.33.

Summary

The following new compounds of fluorene have been prepared: 2-fluoryl isocyanate; methyl, ethyl and *n*-propyl 2-fluorylcarbamate; 2-fluorylurea; *sym*-phenyl-2-fluorylurea; *sym*-di-2-fluorylurea; and the potassium salts and the acetyl derivatives of the α- and β-9-oximes of 2-benzoylfluorenone, as well as the free α- and β-oximes.

The compound obtained by the reaction between 2-benzoylfluorenone and hydroxyl amine reported by Fortner[4] is shown to have been a mixture of the α- and β-forms of the 9-oxime.

CINCINNATI, OHIO RECEIVED SEPTEMBER 2, 1938

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[10] Perrier, *Bull. soc. chim.*, [3] **31**, 859 (1904).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Analytical Separation of Various Classes of Sugars

BY CHARLES D. HURD AND SIDNEY M. CANTOR[1]

The purpose of this investigation was to develop a method for the separation of various classes of sugars, such as monosaccharoses from di- or trisaccharoses, or pentoses from hexoses. It was hoped that the method would achieve not only separation but also analysis of the mixture as well. The importance of a direct method of analysis is obvious, in view of the fact that most of the analytical methods which have been suggested for sugars are empirical and depend largely on a preëxisting knowledge of the identity of the sugar. Methods based on the reducing action of copper salts or on the preferential fermentation by specific microörganisms are obviously limited in scope.

Methylation and fractional distillation of sugar mixtures appeared to be the most promising plan of attack for several reasons: (1) the methyl ethers are known to distil *in vacuo* without decomposition, (2) sizable boiling point differences exist between the methyl ethers of the sugar classes, (3) the methylation procedure would be satisfactory on a wide variety of sugars since it brings about no serious structural changes, (4) the fact that physical constants of a large number of methylated sugars are known would be of help in subsequent identifications.

Preliminary experiments indicated the feasibility of the plan but they also demonstrated the inapplicability of the customary procedure of direct methylation of the sugar by Haworth's method. For example, glucose, lactose and sucrose were methylated by means of methyl sulfate and alkali and the methylated derivatives distilled. The yields, respectively, were 50, 45 and 46%. These results seemed acceptable but it was found that no such uniformity in yields was at-

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[1] Corn Products Refining Company Fellow, 1933–1936.

tainable when mixtures were taken at the outset. A 50:50 mixture of glucose and lactose gave an apparent per cent. value of 63:37. Such a preferential methylation of the monosaccharose demonstrated the inapplicability of Haworth's method of direct methylation as an analytical procedure. Although the yields in methylation reactions are far from quantitative, equivalence in the yields is the only requirement for a satisfactory analytical separation.

Two other disturbing features were revealed in these preliminary experiments. One was the fact that the glucose derivative, even upon repeated methylation, did not show the correct specific rotation for β-methyl tetramethylglucoside. A mixture containing about one-fifth of the α-isomer seemed to be indicated. A similar observation is known to occur with xylose[2] but glucose seems not to have been tested before. The specific rotation of the methylated glucose fractions, therefore, would have been useless for purposes of identification.

The other item concerned the methylation of sucrose. During this process there was found to be an appreciable hydrolysis, for which a correction factor would need to be applied to interpret the results on an unknown mixture containing sucrose. The yields, respectively, of methylated mono- and disaccharoses were 6 and 46%.

Attention was next directed to experiments on direct acetalization with a view to subsequent direct methylation of the methyl glycosides thus produced. The hemi-acetal hydroxyl of the reducing sugars seemed to promote the non-uniformity observed when Haworth's method was applied directly.

Glucose and methanol, when treated with 1–3% hydrogen chloride by Fischer's method, gave rise to 45% of crystalline α-methyl glucoside (A) and a sirup (B). Methylation by Haworth's method of A and B yielded, respectively, 60 and 67% of α-methyl tetramethylglucoside. It was evident, therefore, that separation of A from B was not necessary for the subsequent methylation.

Trouble was encountered with maltose, however, because some hydrolysis was noticed. α-Methylglucoside was isolated from the reaction mixture. This was substantiated later when a mixture (57:43) of glucose and maltose was methylated first by Fischer's method, then by Haworth's method. The products isolated on distillation indicated an apparent composition of 67:33. Therefore, this procedure also was poor from an analytical viewpoint.

Methylation in liquid ammonia[3] was tried and abandoned because the method required methyl glycosides or other derivatives wherein the hemiacetal hydroxyl was protected. The free sugars could not be used.

Feist[4] observed that methyl dibromoformal, $Br_2C(OCH_3)_2$, was a methylating agent toward sodium phenoxide or sodium acetate, yielding anisole and methyl acetate, respectively. It was thought that it might convert the monosodium derivative of glucose (prepared by glucose and sodium methoxide in methanol) into methyl glucoside but such a reaction was not observed.

Likewise, there was non-reaction when glucose, suspended in ether, was treated with diazomethane, although Schmid[5] has reported the methylation of starch in this way. Water or aluminum ethoxide[6] were not effective in catalyzing the reaction between diazomethane and glucose.

The plan of direct methylation, therefore, was changed to that of indirect methylation. Acetylation of the sugar by acetic anhydride and pyridine at 0° was the first step in a successful procedure. In the acetylation of glucose, Hudson and Dale[7] obtained an 88% yield of pure glucose pentaacetate. Maltose has not been acetylated in this manner, but in the present work it was found that a 90% yield of β-maltose octaacetate was isolable. One may infer that the acetylation reaction gives rise to practically quantitative yields of the acetyl sugars.

The problem, therefore, was to substitute uniformly the acetyl groups by methyl groups. To do this, the following steps were visualized and found to be satisfactory: replacement of the acylal[8] group by chlorine, substitution of this chlorine by methoxyl, hydrolysis of the ester groups without disturbing the acetal function, methylation of the alcoholic hydroxyl groups and separation by fractional vacuum distillation.

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[2] Phelps and Purves, THIS JOURNAL, **51**, 2443 (1929).

[3] Muskat, *ibid.*, **56**, 693, 2449 (1934).

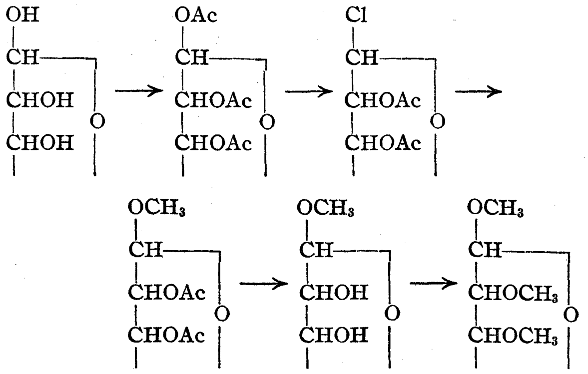
[4] Feist, *Z. angew. Chem.*, **35**, 489 (1922).

[5] Schmid, *Ber.*, **58**, 1964 (1925).

[6] Meerwein and Hinz, *Ann.*, **484**, 1 (1931).

[7] Hudson and Dale, THIS JOURNAL, **37**, 1264 (1915).

[8] If C, C′ and C″ represent, respectively, the states of oxidation of alcohol, aldehyde and acid, then C–O–C, C–O–C′, C–O–C″, C″–O–C″ represent the familiar functional groups of ether, acetal, ester and acid anhydride. No term exists for C′–O–C″ or C′–O–C′. The name "acylal" is proposed for the former and "aldal" for the latter.



Each of these steps will be discussed in turn.

Glucose pentaacetate may be converted into acetobromoglucose by the use of liquid hydrogen bromide[9] or by a mixture of hydrogen bromide in acetic acid.[10] It may be changed into acetochloroglucose by liquid hydrogen chloride, or phosphorus pentachloride[9] or by a mixture of phosphorus pentachloride and aluminum chloride[11] (but this method may bring about structural changes), or by titanium tetrachloride[12] in chloroform. The last method was far better than the others because of high yields and because of its freedom from causing structural changes. Pacsu's directions were followed for the preparation of tetraacetylglucosyl chloride with a resulting yield of 90%. In an analogous experiment with β-maltose octaacetate, not studied by Pacsu, heptaacetyl-α-maltosyl chloride was obtained in 86% yield. Also it was established that under comparable conditions there was no action between titanium tetrachloride and sucrose octaacetate or levoglucosan triacetate, neither of which contained acylal groups.

Maltose.—Five grams of β-maltose octaacetate, m. p. 157–158°, was dissolved in 35 g. of dry chloroform in a flask equipped with a reflux condenser and a dropping funnel. To the solution was added gradually 3 g. of titanium tetrachloride dissolved in 25 g. of chloroform. The reaction was carried out on a water-bath at 50° for two hours, then at 70° for one hour, at which time the original yellow, mushy precipitate had changed to a clear yellow solution. Crystallization of the product from ether and petroleum ether netted 2.2 g. of crystalline solid, and 2 g. of a sirup which was desiccated to a white powder. The crystals melted at 77–80°, and the specific rotation in chloroform, $[\alpha]^{20}_D$, was 151.8°. The rotation of the powder was 142.1°. From the viewpoint of an analytical procedure, the important item is the high yield of isolated product (86.5%) which suggests that the reaction itself was practically quantitative.

The melting point of heptaacetylmaltosyl chloride prepared by other methods is variously listed in the literature[13] as 88, 119, 125°. Both Foerg and Brauns reported 159.5° as the value of the specific rotation.

Sucrose.—Ten grams of sucrose octaacetate, m. p. 68°, dissolved in 150 cc. of dry chloroform was added to a solution of 5.6 g. of titanium tetrachloride in 50 cc. of chloroform. After three hours of refluxing and twelve more hours of standing it was possible to recover 9.6 g. of recrystallized sucrose octaacetate (m. p. and mixed m. p., 68°).

Levoglucosan.—Two grams of levoglucosan was prepared by pyrolysis of starch.[14] It was placed with 10 cc. of pyridine and 15 cc. of acetic anhydride and left at 0° for twenty-four hours. The solution was then poured into chloroform, washed thoroughly, first with acid then with sodium carbonate solution, then water, after which it was dried and the chloroform removed by distillation. The residual sirup was taken up in alcohol and water added until the acetylated material precipitated as a gum. Extraction of the gum with ether and decolorization of the solution finally yielded 0.2 g. of white crystals melting sharply at 108° and showing $[\alpha]^{20}_D$ $-58.6°$ in absolute ethyl alcohol. Pictet gives as the melting point 110°, while the rotation as determined by Vongerichten and Müller[15] is $-45.5°$ in alcohol, a value which may be questioned in view of the present work.

Rotation: sample, 0.0449 g.; ang. rotn., $-0.20°$; tube length, 1.89 dm.; volume solution, 25.0 cc.; $[\alpha]^{20}_D$ $-58.6°$.

A portion of this crystalline material, 0.138 g., was dissolved in chloroform and made up to exactly 25.0 cc. The rotation was then determined in a 2.00-dm. tube: ang. rotn., $-0.70°$; $[\alpha]^{20}_D$ $-63.6°$. To the chloroform solution was added approximately 0.5 g. of titanium tetrachloride in 5 cc. of chloroform. The resulting yellow solution was kept at 60–70° for ninety minutes. It was then poured into water, and the chloroform layer washed in the usual manner. After drying, it was made up again to 25.0 cc. and the rotation redetermined in the 2.00-dm. tube: ang. rotn., $-0.68°$; $[\alpha]^{20}_D$ $-61.8°$. The chloroform was then removed and the residue taken up in ether. On cooling, 0.1 g. of crystals, m. p. 107–108°, separated. A mixed melting point with the original material was also 107–108°.

Of the various methods for the replacement of the chlorine of the hemi-acetal chloride by methoxyl, the best was that which used methanol and silver carbonate. Koenigs and Knorr[16] discovered that hot methanol converted tetraacetylglucosyl bromide into β-methyl tetraacetylglucoside, but the beneficial effect of silver carbonate was discovered by Fischer and Armstrong.[9] It

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(9) Fischer and Armstrong, *Ber.*, **34**, 2985 (1901).

(10) Fischer, *ibid.*, **49**, 584 (1916).

(11) Brauns, THIS JOURNAL, **44**, 401 (1922); **45**, 833 (1923); Freudenberg, *Ber.*, **55**, 929 (1922).

(12) Pacsu, *ibid.*, **61**, 1508 (1928).

(13) Fischer and Armstrong, *Ber.*, **35**, 3153 (1902); Foerg, *Monatsh.*, **23**, 45 (1902); Schliephacke, *Ann.*, **377**, 186 (1910); Brauns, THIS JOURNAL, **51**, 1829 (1929).

(14) Pictet and Sarasin, *Helv. Chim. Acta*, **1**, 87 (1918).

(15) Vongerichten and Müller, *Ber.*, **39**, 245 (1906).

(16) Koenigs and Knorr, *ibid.*, **34**, 965 (1901).

was found that very satisfactory results were obtained in the present work if the reaction mixture was shaken for twelve to fifteen hours.

Alternative procedures for the chloride to acetal conversion were tried and found ineffective. For example, when tetraacetylglucosyl chloride was left for four hours with methanol and pyridine at 0°, the only result was crystallization of the acetochloroglucose. This is in contrast to the known conversion of heptaacetyl-α-maltosyl chloride[17] into β-methyl heptaacetylmaltoside under similar treatment. When the reaction with tetraacetylglucosyl chloride was performed at reflux temperatures, some β-methyl tetraacetylglucoside (21% yield) was formed but secondary reactions also were indicated. For a time, it was thought that sodium methoxide might be effective in introducing the acetal methoxyl and removing the acetyl groups concurrently. However, the method was discarded when it was found that no β-methyl glucoside was obtainable from tetraacetylglucosyl chloride and sodium methoxide. Thus, the silver carbonate method, although time-consuming, seemed to be the only one wherein yield and purity of product were satisfactory.

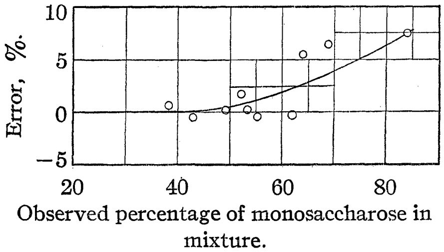

Fig. 1.—Correction curve.

Zemplén's method, namely, the use of sodium methoxide,[18] appeared to be the best means of removing the acetyl groups because of its simplicity and because of the high yields (nearly quantitative) obtained. The necessity of removing the acetyls prior to the final methylation was demonstrated in an attempted methylation of α-methyl tetraacetylglucoside. Only 2.7 g. of a sirup soluble in chloroform was obtained when 20 g. of it was treated with methyl sulfate and 20% aqueous sodium hydroxide solution for four hours at 70° followed by one-half hour at 100°.

For the final step of methylation of the methyl glycosides, Haworth's method was selected, although Muskat's liquid ammonia method might have served equally well. Simpler technique favored Haworth's method. It was recognized that this method would not give complete methylation in one operation, but this did not interfere with the analytical separation.

When glucose and maltose were carried separately through this procedure, the yield of methylated sirup from glucose was 38.3% and that from maltose 37.1%. Thus, no serious preferential action on the two classes of sugars was observed. Neither of the sugars was completely methylated but the sirup from glucose approached tetramethylglucose whereas that from maltose approached heptamethylmaltose.

The procedure was now standardized rigorously, and several duplicate runs were made on mixtures of glucose and maltose over a wide range of composition. The results, collected in Table I, showed that an error in favor of the monosaccharose existed which appeared to increase as the percentage of monosaccharose in the mixture was increased. To compensate for this error, a curve was constructed on the basis of known mixtures, and all unknown mixtures analyzed were corrected from this curve. Later results gave a better observation of the error involved so that the curve shown in Fig. 1 is based upon the average error of fourteen runs.

TABLE I

STANDARDIZATION RUNS ON THE PROCEDURE

Run	Sugars	Composition taken	% by weight, obsd.	Error, %
7A	Monosac.	30.0	29.9	−0.1
	Disacc.	70.0	70.1	.1
8A	Monosac.	30.0	32.2	2.2
	Disacc.	70.0	67.8	−2.2
7B	Monosac.	50.0	49.2	−0.8
	Disacc.	50.0	50.8	.8
8B	Monosac.	50.0	49.6	− .4
	Disacc.	50.0	50.4	.4
7C	Monosac.	70.0	64.4	−5.6
	Disacc.	30.0	35.5	5.6
8C	Monosac.	70.0	64.5	−5.5
	Disacc.	30.0	35.5	5.5

The efficacy of the curve is best demonstrated by the results on two mixtures whose composition was unknown to the observer. A mixture made up to contain 62% glucose and 38% maltose analyzed for a "corrected composition" of 64.3% glucose and 35.7% maltose. A second mixture containing 53.4% glucose and 46.6% lactose gave a "corrected composition" of 55.2% glucose and 44.8% lactose. The absolute error of the method

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[17] Freudenberg, *Ber.*, **55**, 929 (1922); Pacsu, THIS JOURNAL, **57**, 587 (1935).

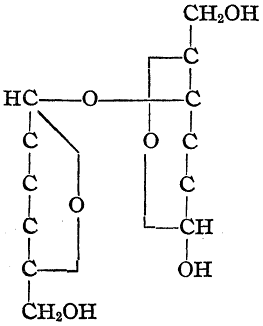
[18] Zemplén, *Ber.*, **56**, 1705 (1923).

varies considerably, but in only one observed case was greater than 3%.

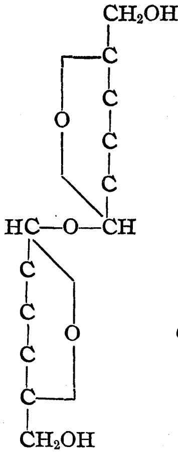
Types of Sugars Studied

Monosaccharoses.—Glucose was chosen as the representative aldohexose. Work with xylose showed that aldopentoses would respond equally well. That methylpentoses were also amenable was shown by results on a mixture of rhamnose (desoxy-*l*-mannose) and maltose. The standardization runs indicated that all such aldohexoses would undergo the procedure successfully. Attempts to apply the technique to mixtures containing fructose, a representative ketohexose, however, were unsuccessful.

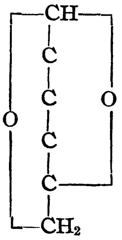
Disaccharoses.—Types of disaccharoses studied were necessarily more varied. The application to the maltose or reducing type of disaccharose was shown by the standardization runs. Further results with mixtures containing lactose and gentiobiose showed that such factors as the point of glucosidic attachment, alpha or beta modification of the parent sugar, or the nature of the hexose constituents of the disaccharoses were unimportant in the reactions listed. The chief factor concerned itself with the nature of the hydroxyl group, whether it was alcohol or acetal.



Maltose type
maltose (α at 4)
lactose (β at 4)
gentiobiose (β at 6)



Trehalose type
trehalose (αα at 1)
sucrose (α at 1)



Anhydrose type
levoglucosan

In the trehalose type all eight hydroxyl groups are alcoholic. The trehalose type would, therefore, be expected to undergo acetylation, hydrolysis of acetyl groups and methylation, but no other reactions. Results with sucrose, a trehalose type, indicated that sucrose octaacetate was stable to the action of titanium tetrachloride, but that hydrolysis occurred in the final methylation step, to the extent of 11% by weight. When this correction was applied the analytical data were satisfactory. Trehalose itself, being of a more stable configuration, acted normally and exhibited no hydrolysis.

Applicability to the third or anhydrose type of disaccharose depended upon the ability of the oxygen bridge to withstand the action of titanium tetrachloride. When the triacetate of levoglucosan (1,6-anhydro-*d*-glucose) was treated with the reagent under the conditions of the procedure, no hydrolysis occurred. Other investigators[19] have reported that hydrolysis will result from use of an excess of titanium tetrachloride.

Constants of the Sugars Studied

Monosaccharoses.—Evidence that monosaccharoses were unaltered through the procedure was obtained easily. For example, the methylated glucose fractions showed specific rotations near −20°. The specific rotation of pure β-methyl tetramethylgucoside is −22.4°. Further evidence was obtained by hydrolyzing a portion of the glucoside to tetramethylglucose and preparing the known aniline condensation product. In general, the evidence obtained from specific rotation, although not indicating absolute purity, was sufficient to demonstrate the nature of the fraction.

Disaccharoses.—Identification in the case of the disaccharoses was less clean cut. Derivatives of the methylated disaccharoses cannot be prepared since hydrolysis of the glucosidic methoxyl group always brings about concurrent hydrolysis of the disaccharose linkage. Thus the disaccharose fractions usually had to be remethylated and distilled in order to obtain a value for the specific rotation which approached the accepted value. The Purdie and Irvine method, involving silver oxide and methyl iodide,[20] was used. With only one remethylation of the maltose fraction a specific rotation of 68° was obtained. That for pure β-methyl heptamethylmaltoside is 79°. Several applications of this technique, accompanied by frequent distillation, would be necessary to obtain samples of optical purity.

Other Applications of the Procedure

Separation of a Pentose from a Hexose.—This separation was of interest to study since the two

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[19] Zemplén and Czurös, *Ber.*, **62**, 993 (1929).

[20] Purdie and Irvine, *J. Chem. Soc.*, **83**, 1021 (1903).

sugar types, which differ by only one carbon atom, give methylated derivatives boiling relatively close together. A sample run on a 1:1 mixture of *d*-glucose and *d*-xylose in which volume of distillate was plotted against temperature of distillation (Fig. 2) showed that separation was feasible. An almost quantitative separation of glucose and xylose bore this out. β-Methyl trimethylxyloside, the pentose fraction, was obtained crystalline, indicative of high purity.

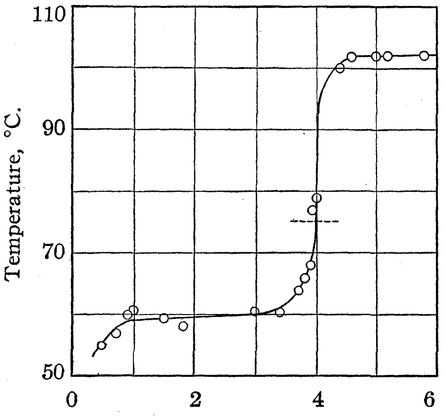

Fig. 2.—Separation of xylose–glucose mixture.

Analysis of Hydrols.—The application of the procedure to "hydrol," the mother liquor obtained after crystallization of glucose from the acid hydrolysate of corn starch, appeared to be an interesting extension of the problem since previous[21] investigators have shown that hydrol contains a mixture of disaccharoses as well as glucose. However, none of these investigators had ever analyzed a complete sample of hydrol, but had attacked the mixture after first fermenting away all fermentable sugars.

Three samples of hydrol were obtained from the Corn Products Refining Company which had various hydrolytic histories, but were alike in that they had all gone through a single crystallization of glucose after the final hydrolytic treatment. Subjection of these samples to the procedure gave the usual mono- and disaccharose fractions, but distillation of the disaccharose fraction after remethylation left a high boiling portion in each case. This material from molecular weight determinations was identified as partially methylated trisaccharoses. The results are shown in Table II.

TABLE II

	Original hydrol	Reconverted hydrol	Kansas City hydrol
Monosaccharoses, %	55.2	55.2	54.8
Disaccharoses	38.4	39.3	37.9
Trisaccharoses	6.4	5.5	7.3

The monosaccharose fraction was identified as glucose. Work is under way at the present time in this Laboratory on the separation and identification of the components of the disaccharose and trisaccharose fractions.

Apparatus for Analytical Vacuum Distillation.—In the standardized procedure (below), one of the steps is that of separation of methylated sugars by vacuum distillation. The details of this apparatus are shown in Fig. 3.

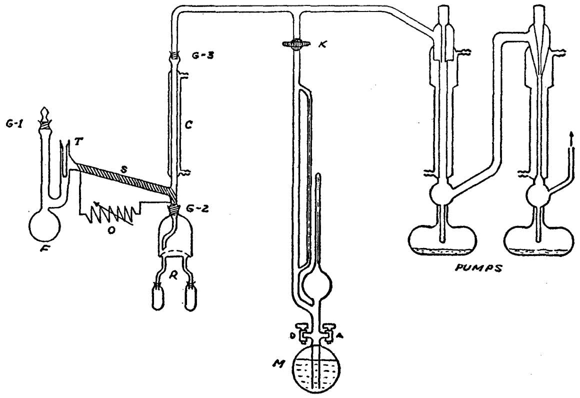

Fig. 3.—Distillation apparatus.

Low pressure was supplied by a set of two mercury vapor pumps connected in series and working against a back pressure of 10–20 mm., supplied by an ordinary water jet.[22] The first mercury pump was a high speed jet and the second was a diffusion pump. These pumps gave a minimum pressure of 1×10^{-5} mm., which was more than sufficient for the purpose.

The distillation flask, F (Fig. 3), was of the conventional Claisen type equipped with a thermometer well, T, and a ground glass stopper, G-1. Three of these flasks of capacities 125, 50 and 20 cc., were used interchangeably depending upon the amount of material to be distilled. The side-arm, S, connecting flask to receiver, was wrapped with nichrome wire surrounded by asbestos rope and was kept electrically heated by the introduction of a current controlled by the variable resistance, O. The temperature in the side-arm was usually kept at 80–90° during a distillation in order to avoid congealing the sirup and to bring to a minimum the holdover in the tubing. The receiver, R, was connected to the bent side-arm by a ground glass

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[21] Berlin, THIS JOURNAL, **48**, 1107, 2627 (1926); Coleman, Buchanan and Paul, *ibid.*, **57**, 1119 (1935).

[22] The use of mercury pumps backed by a water pump instead of an oil pump was a decided advantage in this work since it eliminated the necessity for a low temperature trap in the apparatus. Methylated sirups in chloroform solution could be transferred to the distillation flask and the solvent removed through the pumps without danger of corrosion or raising the pressure as is the case with oil pumps.

joint, G-2, and was of the multiple rotary type enabling five fractions to be taken. Two of the small receivers were later connected to the large receiver by ground glass joints which eliminated the necessity of breaking off and sealing on after each distillation. The condenser, C, prevented the entrance of any low boiling sugars into the connection tubing, and the ground glass joint, G-3, allowed removal of the distillation unit for cleaning. Pressures were read by means of the McLeod gage, M, connected to the system by a stopcock, K. The McLeod gage was of a modified variety. The mercury storage bulb was kept evacuated by a water pump at side-arm A. Opening side-arm D to the atmosphere resulted in the mercury rising into the gage from which the pressure was read off. The mercury could then be again lowered by evacuation of the storage chamber.

The Standardized Procedure

The anhydrous sample taken was always 25.0 g., for this quantity was found to give sufficient methylated material for the fractionation. Amounts of reagents were based upon the assumption that all of the material in the mixture was monosaccharose.

Step 1.—The mixture was treated with 120 g. of acetic anhydride and 156 g. of pyridine (dried over lime). This was 100% in excess of that required for complete acetylation if all of the material were monosaccharose. The reaction was allowed to proceed at 0° for forty-eight hours, then for four hours at 70°, which treatment usually completed the acetylation. Two hundred fifty cc. of chloroform was now added and the resulting solution washed twice with 300-cc. portions of 4 *M* hydrochloric acid, twice with 200-cc. portions of a dilute sodium carbonate solution and finally twice with 200-cc. portions of water. The chloroform solution was dried over anhydrous sodium carbonate.

Step 2.—The dried solution from (1) was treated with 28 g. of anhydrous titanium tetrachloride dissolved in 150 cc. of absolute chloroform. The mixture was heated at 70° for two hours on a water-bath, after which it was allowed to stand for five hours. A slight amount of pyridine or an excess of titanium tetrachloride often caused a darkening of this solution, but this effect apparently was not harmful. The resulting homogeneous solution was poured onto cracked ice, and the separated chloroform solution was washed until the washings showed no acid test. The solution was then dried over anhydrous sodium carbonate, and the chloroform removed on the steam-bath.

Step 3.—The sirup from (2) was taken up in 700 cc. of absolute methanol. Then, 25 g. of silver carbonate was added and the mixture shaken for twelve to sixteen hours. Upon completion the silver residues were filtered off.

The type of shaker for this step is sketched in Fig. 4. The box was rotated on its horizontal shaft at approximately 70 r. p. m. With the bottles set at an angle to the direction of rotation, and usually only two-thirds full, the mixing was very effective. The authors are indebted to Mr. Otto Stanger of the Miner Laboratories, Chicago, for suggesting this type of shaker.

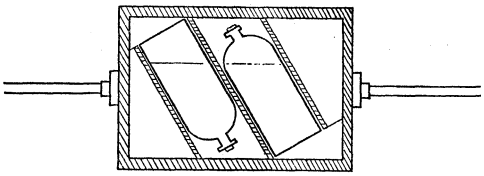

Fig. 4.—Shaking apparatus.

Step 4.—To the clear solution from (3) was added 200 cc. of dry chloroform and a solution made by dissolving 1 g. of sodium in 50 cc. of methanol. The mixture was allowed to stand at 0° for six hours and then diluted with an equal volume of water. The water layer was separated, made neutral to litmus with acetic acid, and reduced in volume to 30 cc. by distillation *in vacuo*. The glycoside sirup obtained at this stage was usually dark brown in color.

Step 5.—The sirup from (4) was transferred to the methylation apparatus, heated to 70° by means of a water-bath, and treated with 150 cc. (200 g.) of methyl sulfate and 140 g. of sodium hydroxide which was dissolved in 200 cc. of water. The reagents were added dropwise over a period of about three hours in an approximate ratio of two drops of methyl sulfate to three drops of sodium hydroxide solution. This kept the base slightly in excess and minimized the danger of hydrolysis. Upon completion of the addition, the mixture was heated with stirring for one-half hour at 100°. The cooled mixture was filtered, and the solid which separated was triturated four times with 25-cc. portions of chloroform. The filtrate was extracted four times with 100-cc. portions of chloroform. The extracts were combined with the washings and dried, without washing, over anhydrous sodium carbonate. Then, the chloroform was removed by distillation on the water-bath and the residual sirup transferred to the distillation apparatus. The chloroform was removed. Bumping under the high vacuum was

TABLE III

ANALYSIS OF MIXTURES OF GLUCOSE AND MALTOSE

Run		Original components (G or M), g.	Methylated derivatives, g.	Equivalent wt. of free sugar, g.	% Components		
					Obsd.	Corr.	Calcd.
7A		G 7.5	3.9	2.89	29.9	29.9	30.0
		M 17.5	8.9	6.80	70.1	70.1	70.0
	Total	25.0	12.8	9.69			
8A		G 7.5	4.5	3.34	32.2	32.2	30.0
		M 17.5	9.2	7.05	67.8	67.8	70.0
	Total	25.0	13.7	10.39			
7B		G 12.5	4.8	3.56	49.2	50.0	50.0
		M 12.5	4.8	3.67	50.8	50.0	50.0
	Total	25.0	9.6	7.23			
8B		G 12.5	6.1	4.52	49.6	50.0	50.0
		M 12.5	6.0	4.59	50.4	49.6	50.0
	Total	25.0	12.1	9.11			
7C		G 17.5	6.1	4.52	64.4	67.0	70.0
		M 7.5	3.3	2.52	35.6	33.0	30.0
	Total	25.0	9.4	7.04			
8C		G 17.5	6.0	4.45	64.5	67.0	70.0
		M 7.5	3.2	2.45	35.5	33.0	30.0
	Total	25.0	9.2	6.90			
12		G 19.0	8.4	6.21	69.3	72.8	76.0
		M 6.0	3.6	2.76	30.7	27.2	24.0
	Total	25.0	12.0	8.97			
14		G 23.0	7.6	5.54	84.8	92.0	92.0
		M 2.0	1.3	1.00	15.2	8.0	8.0
	Total	25.0	8.9	6.54			

relieved by means of small boiling chips. At pressures below 0.02 mm., the limit for removal of the monosaccharose fraction was 110°. If the sample contained only mono- and disaccharoses, the disaccharose fraction was not distilled but the residue was taken as disaccharose. When trisaccharoses were involved, the disaccharose fraction was distilled off and the residue was regarded as the trisaccharose. The fractions were then weighed directly, the weights calculated back to weight of free sugar using the correction curve (Fig. 1).

When glucose and maltose were carried through this procedure separately, the yield of methylated sirup from glucose was 38.3% and that from maltose 37.1%. Thus no serious preferential action on the two classes of sugars was observed. Neither of the sugars was completely methylated. The monosaccharose approached the tetramethyl stage and the disaccharose the heptamethyl. Macdonald[23] has shown that with a chloroform extraction of products obtained in the methyl sulfate methylation of glucose, less than 2% of the methyl dimethylglucoside passes into the chloroform. Hence the extracted material consists almost wholly of the methyl tri- and tetramethylglucosides (A and B). Carrying the analogy to the disaccharoses, one might expect that the chloroform extract would consist mainly of the methyl hexa- and heptamethylglycosides (C and D). From these considerations, it was decided to regard the separated fractions as equimolar mixtures of A and B, or C and D, and to correct the molecular weight accordingly. The molecular weights used for computation of the free sugar weights were thus 243 for the monosaccharose instead of 250, and 447 for the disaccharose instead of 454.

The procedure was now rigorously standardized. Some results on typical analyses of glucose–maltose mixtures are shown in Table III.

The glucose fractions from the first six runs were combined and identified as follows. The specific rotation in chloroform, $[\alpha]^{20}\text{D}$, was −20.5°, whereas that for pure β-methyl tetramethylglucoside is −22.4°. Ten grams of the liquid was hydrolyzed by heating for two hours at 100° with 7% hydrochloric acid, then neutralizing with calcium carbonate, evaporating to dryness and extracting with ether. In this way, 5.5 g. of tetramethylglucose was obtained. From this, by heating with aniline,[24] a good yield of tetramethylglucose-aniline, m. p. 135°, was obtained.

The maltose fractions were identified by refluxing 10 g. of the maltose residues (Table III) for six hours with 35 g. of silver oxide and 60 g. of methyl iodide. The silver residues were filtered off and the methyl iodide removed by distillation. The residual sirup was vacuum distilled. A fraction of 3.62 g., b. p. 158° (0.008 mm.), possessed a specific rotation in chloroform, $[\alpha]^{20}\text{D}$ of 67.7°. The specific rotation of β-methyl heptamethylmaltoside is accepted as 78.9°.

The method has been tested recently by Mr. P. J. Baker, Jr., of this Laboratory, who reported these data on a glucose–maltose mixture:

Components, g.		Methylated deriv., g.	Equiv. wt. of free sugar, g.	% Components		
				Obsd.	Corr.	Calcd.
G	17.5	11.75	8.70	67.7	70.7	70.0
M	7.5	5.42	4.15	32.3	29.3	30.0

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[23] Macdonald, THIS JOURNAL, **57**, 771 (1935).

[24] Greene and Lewis, *ibid.*, **50**, 2822 (1928).

Analysis of Other Mixtures

Details for glucose and sucrose are listed in Table IV. If the correction for the 11% hydrolysis of sucrose, noted above, is applied, then the weights of components would be changed from 12.5 g. apiece to 13.9 g. of glucose and 11.1 g. of sucrose. The methylated sucrose was characterized by refluxing it for eight hours with silver oxide and methyl iodide. After the usual procedure, 2.5 g. of liquid was secured: b. p. 130–140° (0.001 mm.), $[\alpha]^{20}\text{D}$ in chloroform +63.6°. The rotation of octamethylsucrose[25] is only reported with methanol as solvent, $[\alpha]^{20}\text{D}$ + 69.3°.

TABLE IV

ANALYSIS OF MIXTURES OF SUGARS

Components Name	G.	Methylated derivs., g.	Free sugar, g.	% Components Obsd.	Corr.	Calcd.
Glucose	12.5	6.8	5.04	52.4	53.4	56.0
Sucrose	12.5	6.0	4.59	47.6	46.6	44.0
β-Glucose Pentaacetate	35.7	12.6	9.34	63.2	..	62.6
β-Gentiobiose Octaacetate	19.5	6.8	5.20	36.6	..	37.4
Glucose	10.0	4.0	2.96	38.6	39.3	40.0
Trehalose	15.0	6.15	4.70	61.4	60.7	60.0
Glucose	13.3	7.34	5.43	52.5	53.5	53.3
Trehalose	2.77	6.40	4.90	47.5	46.5	46.7
Gentiobiose Octaacetate	17.6					
Rhamnose	11.1	5.54	4.03	43.5	43.9	42.5
Maltose	15.0	7.05	5.22	56.5	56.1	57.5
Glucose[a]	15.35	6.3	4.67	62.8	64.3	62.0
Maltose	9.41	3.6	2.76	37.2	35.7	38.0
Glucose[a]	13.9	6.0	4.45	54.2	55.2	53.4
Lactose	12.1	4.9	3.75	45.8	44.8	46.6

[a] These mixtures were supplied to the analyst as unknowns.

To include gentiobiose in the mixtures it was necessary to start at Step 2, since only gentiobiose octaacetate (Pfanstiehl's), $[\alpha]^{20}\text{D}$ in chloroform −5.3°, was available. Therefore, the correction curve was not applied to the data for this run in Table IV. The methylated gentiobiose fraction solidified on standing: $[\alpha]^{20}\text{D}$ −7.0° in chloroform. For β-methyl heptamethylgentiobioside, Haworth and Wylam[26] list −29.9° for the specific rotation in alcohol.

Anhydrous trehalose was obtained by heating Pfanstiehl trehalose monohydrate at 105° for three hours. After the analysis (Table IV), 10 g. of the methylated disaccharose fraction was refluxed for eight hours with 37 g. of silver oxide and 70 g. of methyl iodide. When the mixture was worked up, a 5-g. fraction was obtained: b. p. 165–168° (0.01 mm.), $[\alpha]^{20}\text{D}$ in chloroform +166.2°. The rotation given for octamethyltrehalose[27] in benzene is +199.8°.

In the mixture of glucose, trehalose and gentiobiose octaacetate, the weight of 17.6 g. of the acetate is equivalent to 8.9 g. of gentiobiose. This represents a total of 11.67 g. of gentiobiose plus trehalose.

In the mixture of rhamnose and maltose, the rhamnose fraction was collected to 110°; $[\alpha]^{20}\text{D}$ +12.0° in chloroform. The specific rotation of β-methyl trimethylrhamnoside[28] in water is given as −15°.

The methylated lactose fraction (Table IV) was remethylated with 20 g. of silver oxide and 50 g. of methyl iodide for eight hours. Three grams was obtained: b. p. 170–175° (0.02 mm.), $[\alpha]^{27}\text{D}$ +6.19° in chloroform, $[\alpha]^{27}\text{D}$ +3.00 in methanol. The specific rotation of β-methyl heptamethyllactoside[29] in methanol is listed at −13.04°.

Separation of a Pentose–Hexose Mixture

Ten grams each of xylose and glucose were mixed and treated by the analysis procedure. The mixture of methylated derivatives obtained in the last step was distilled at a rate of 3–5 drops per minute in the vacuum apparatus. The height of the side-arm on the distillation flask was approximately 10 cm. One of the receivers was previously calibrated in cc., so that temperature of distillation could be plotted against volume of distillate. The curve shown in Fig. 2 was obtained. The pressure was 0.03–0.04 mm.

In a second run 12.5 g. of xylose $[\alpha]^{20}\text{D}$ +17.7° and 12.5 g. of glucose were mixed and treated by the standardized procedure. The methylated sirup obtained in the final step was distilled, the cut being made at 75° as indicated by the curve. The pressure was 0.005 mm.

Components	Methylated deriv., g.	Free sugar, g.	% Components Obsd.	Corr.	Calcd.
Pentose	5.63	4.10	49.3	50.1	50.0
Hexose	5.85	4.21	50.7	49.9	50.0

Pentose.—A portion, 3.5 g., of the methylated pentose, crystallized during the distillation. The rotation was determined in chloroform. Sample: 0.1205 g.; ang. rotn., −0.64°; $[\alpha]^{20}\text{D}$ −69.9°; volume solution, 25.0 cc.; tube length, 1.89 dm. The melting point of the crystals was 45°. The recorded constants of β-methyl trimethylxyloside are: melting point 51°; $[\alpha]^{20}\text{D}$ −69.5° in chloroform.[2]

Hexose.—The specific rotation of the sirupy hexose portion was determined in chloroform. Sample, 0.9276 g.; ang. rotn., −1.75°; $[\alpha]^{20}\text{D}$ −33.7°; tube length, 1.89 dm.; volume solution, 25.0 cc. The specific rotation of β-methyl tetramethylglucoside is −22.4° in chloroform.

Analysis of Hydrol

The Drying of Hydrol.—The hydrols used in this work were obtained through the courtesy of Mr. W. B. Newkirk of the Corn Products Refining Company. Hydrol is the term used to represent the mother liquor after glucose has been crystallized from the acid hydrolysis of starch. Ordinarily, starch is hydrolyzed by 0.25 to 0.5% hydrochloric acid under pressure of about 40 pounds (3 atm.) of steam. It is then neutralized, filtered, clarified, concentrated and crystallized. Ordinary hydrol is the residue obtained from one such hydrolytic conversion and crystallization. If the hydrol is again subjected to a second hydrolytic conversion and crystallization, the mother liquors are the so-called Reconverted Hydrol. The material which had undergone two crystallizations for glucose after but one hydrolytic conversion is called Kansas City Hydrol.

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(25) Haworth and Law, *J. Chem. Soc.*, **109**, 1314 (1916).

(26) Haworth and Wylam, *ibid.*, **123**, 3120 (1923).

(27) Schlubach and Maurer, *Ber.*, **58**, 1178 (1925).

(28) Purdie and Young, *J. Chem. Soc.*, **89**, 1194 (1906).

(29) Haworth and Leitch, *ibid.*, **113**, 195 (1918).

All of the hydrols used for analysis by the procedure were dried in the following manner. One part of the hydrol was taken up with an equal volume of toluene and distilled at 11–15 mm. from an ordinary Claisen flask surrounded by a water-bath at 95°.

Five such operations usually served to remove almost all of the water, leaving the hydrol as a hard glassy mass. By continued warming on the water-bath the sirup could be softened and poured from the flask. Samples were weighed in this manner. That most of the water was eliminated by this procedure was indicated by a water analysis on dried hydrol. A sample weighing 6.151 g. lost 0.020 g. after four hours of heating at 110–120° in an air-bath; final weight 6.131 g.; % water, 0.32.

Application of the Procedure to Hydrol

The size of the original samples was in all cases 25.0 g. Acetylation with pyridine and acetic anhydride proceeded normally as in other sugar samples. It was found, however, that if the pyridine–hydrol mixture was warmed slightly before adding the acetic anhydride an appreciable amount of the sirup dissolved and hastened the reaction. In this way complete acetylation was usually accomplished in forty-eight hours at 0°.

In the final distillation, after removal of the low boiling fraction, as much as possible of the residual material was distilled by taking the bath temperature to 250°. Conditions for the distillation were substantially the same in all of the runs. The pressure varied from 0.001 to 0.008 mm. All material up to 110° was regarded as monosaccharose; the disaccharose distilled was collected between 160–190° at these pressures.

The weights of the fractions collected in the final distillations of the runs with the hydrols are listed in Table V.

TABLE V

METHYLATED PRODUCTS FROM HYDROLS

Run	Hydrol, g.				Reconverted hydrol, g.		Kansas City hydrol, g.	
	1	2	3	4	1	2	1	2
Fraction 1	5.40	6.44	5.94	4.88	4.94	5.90	5.12	4.86
Fraction 2	3.19	3.50	2.34	3.22	3.29	3.09	2.67	2.58
Residue	1.34	1.66	2.31	0.96	0.83	1.67	1.52	1.45
Calculated to basis of free sugars, g.								
Monosacch.	4.00	4.76	4.40	3.62	3.68	4.37	3.79	3.55
Disacch.	3.02	3.39	2.78	2.88	2.88	3.08	2.70	2.60
Trisacch.	0.45	0.56	0.78	0.32	0.27	0.56	0.51	0.49
Observed percentages of components								
Monosacch.	53.6	54.7	55.3	53.1	53.9	54.6	54.2	53.5
Disacch.	40.4	38.9	36.2	42.2	42.2	38.5	38.6	39.2
Trisacch.	6.0	6.4	8.5	4.7	4.9	6.9	7.2	7.3

Treatment of the Residue: Presence of Trisaccharoses.—To determine the nature of the residue, comparable experiments were performed on the methylated residues from maltose and from hydrol. About 10 g. of undistilled methylated maltose was dissolved in a minimum of chloroform, placed in a 500-cc. bottle, and 250 g. of methyl iodide and 25 g. of silver oxide added. The mixture was heated to boiling, the bottle stoppered and insulated with an asbestos wrapper. The bottle was now shaken mechanically for three days, the shaking being interrupted and heat applied as described about every six hours during the day.

The residues from the four runs of hydrol were treated in exactly the same manner. Upon completion of the shaking, the solutions were filtered, dried and the solvent removed. The sirups obtained were distilled *in vacuo* up to a bath temperature of 250°. Under this condition only would the disaccharose distil; any higher boiling fraction would remain. Upon completion, the distilled portion and the residues were weighed. The results with maltose and hydrol are summarized.

	Maltose	Hydrol
Distilled portion or disaccharose, g.	7.12	3.40
Residue, g.	0.92	2.64
Total, g.	8.04	6.04

The molecular weights of the residues were now determined in camphor:

	Maltose	Hydrol
Wt. camphor	0.0946	0.0907
Wt. sample	.0274	.0397
M. p. camphor, °C.	179.4	179.4
M. p. mixture, °C.	153.0	151.0
Difference, °C.	26.4	30.4
Constant for camphor	407.6	407.6
Molecular weight	429	587

Calculated for fully methylated disaccharose, 454
Calculated for fully methylated trisaccharose, 658

Although the molecular weights did not agree exactly with calculated values, they were different enough to signify that a portion of the original hydrol residues was trisaccharose.

Calculated from the weights obtained by fractionation of the residues, this appeared to be:

Disaccharoses	56.3%
Trisaccharoses	43.7%

The weights of residues obtained in the original fractionation were now corrected using these figures. The weights of methylated sugars were calculated back to the weights of free sugars as was done with the known mixtures, and the percentages of components thus obtained (Table V). The correction from the correction curve was applied only to the mono- and disaccharose fractions.

Molecular Weights Used

Monosaccharose	180	Methylated monosaccharose	243
Disaccharose	342	Methylated disaccharose	447
Trisaccharose	506	Methylated trisaccharose	658

The corrected percentages of components are summarized in Table VI. The whole analysis, including water and ash which were determined in the usual way, for each hydrol is also included.

Only glucose seemed to be present in the monosaccharose portion from hydrol. In two of the runs, the specific rotations taken in chloroform at 20° were −19.5 and −18.1°. This is reasonably near the rotation (−22.4°) for pure β-methyl tetramethylglucoside. Furthermore, glucose crystals separated from hydrol on standing.

Work is being continued on the identification of the sugars in the disaccharose portion. These specific rotations were obtained in chloroform on the methylated disaccharose fractions: hydrol, $[\alpha]^{20}\mathrm{D}$ +38.7°; reconverted hydrol, $[\alpha]^{20}\mathrm{D}$ +30.8°; Kansas City hydrol, $[\alpha]^{27}\mathrm{D}$ +66.7°.

TABLE VI

PERCENTAGE COMPOSITION OF HYDROL

	Monosacch.	Disacch.	Trisacch.	Water	Ash
		Hydrol			
Mean (Table V)	54.2	39.4	6.4	..	..
Corrected mean	55.2	38.4	6.4	..	..
Whole analysis	43.2	30.8	5.0	19.8	1.96
		Reconverted Hydrol			
Mean	54.2	40.3	5.5	..	..
Corrected mean	55.2	39.3	5.5	..	..
Whole analysis	40.1	28.5	4.0	21.60	5.83
		Kansas City Hydrol			
Mean	53.8	38.9	7.3	..	..
Corrected mean	54.8	37.9	7.3	..	..
Whole analysis	40.7	28.2	5.2	20.1	5.60

Summary

A procedure has been developed for the direct analysis of sugar mixtures of these types: mono- and disaccharoses; mono-, di- and trisaccharoses; pentoses and hexoses. The procedure involves indirect methylation, vacuum distillation of the methylated derivatives, and weighing of the fractions thus obtained. An accuracy of 3% was attained. Since the various fractions are separated from each other, they may be used for purposes of identification.

The indirect methylation is necessary to obtain uniformity in yields. Direct methylation of a mixture of mono- and disaccharoses gives results in the fractional distillation which are not indicative of the original percentage composition. The following steps are involved in the standardized procedure: acetylation at 0° by acetic anhydride and pyridine, replacement of the acylal function by chlorine by means of titanium tetrachloride, substitution of the chlorine by methoxyl by prolonged shaking with methanol and silver carbonate, hydrolysis of the remaining acetyl groups by sodium methoxide in methanol, methylation by one treatment with methyl sulfate and sodium hydroxide, and finally fractional distillation *in vacuo* of the methylated sirups.

Monosaccharoses such as xylose, rhamnose, glucose and levoglucosan undergo the procedure successfully. In its present form it does not apply to fructose. The disaccharoses studied included the maltose type (maltose, lactose, gentiobiose) and the trehalose type (trehalose, sucrose).

The procedure has been applied to three types of hydrol and the presence of trisaccharoses in these hydrols has been established.

EVANSTON, ILLINOIS RECEIVED JULY 18, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

The Mechanism of the Aqueous Hydrolysis of β-Butyrolactone

BY A. R. OLSON AND R. J. MILLER

In 1896 Walden[1] showed that *d*-malic acid was obtained when silver oxide was suspended in an aqueous solution of *d*-chlorosuccinic acid. Treatment of the chloro acid with potassium hydroxide yielded an *l*-malic acid. Holmberg[2] explained these results by assuming the primary formation of a lactone from the chloro acid, the lactone then hydrolyzing in several different ways, depending upon the hydrogen ion concentration. He[3] later succeeded in isolating the lactone. The generality of lactone formation from β-halogenated acids has been proved by Johansson's[4] work.

Holmberg[5] and Rørdam[6] studied the hydrolysis of the (+) malolactonic acid which was obtained from the (−) halogenosuccinic acids. They found that in dilute aqueous acids the hydrolysis was first order, and that the product contained a preponderance of (−) malic acid. In stronger acids, up to 2 *N* nitric acid and in basic solutions, the product was largely (+) malic acid. These results were confirmed and extended by Long and Olson,[7] who determined both rates and optical relations using buffered solutions. Their results are summarized in Figs. 1 and 2. The interpretation of these results is complicated by the difficulty of determining the total concentration of lactone and also by the possible existence of an α-lactone as well as a β-lactone. We have therefore turned to β-bromobutyric acid which readily yields a pure β-lactone. We have been able to show that this lactone hydrolyzes in neutral

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[1] Walden, *Ber.*, **29**, 133 (1896).

[2] Holmberg, *ibid.*, **45**, 1713 (1922).

[3] Holmberg, *Svensk. Kem. Tids.*, **30**, 190 and 215 (1918), through *Chem. Zentr.*, **90**, I, 223 (1919).

[4] Johansson, *Lunds Universitets Årsskrift*, N. F., Part 2, **12**, No. 8 (1916).

[5] Holmberg, *J. prakt. Chem.*, **88**, 553 (1913).

[6] Rørdam, *J. Chem. Soc.*, **2**, 2931 (1932).

[7] Long and Olson, unpublished work in this Laboratory.

aqueous solution to yield one optical form of hydroxybutyric acid exclusively and reacts with hydrogen ion and hydroxide ion by two other mechanisms to form the other optical isomer.

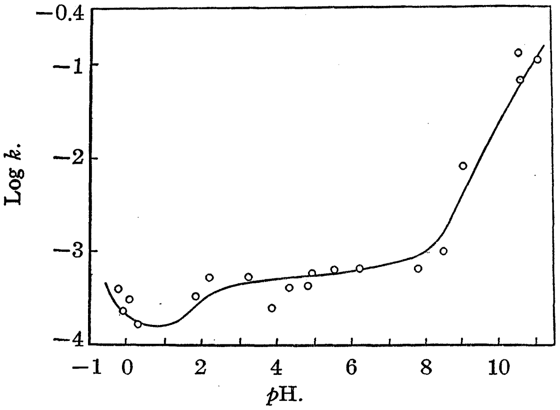

Fig. 1.—Velocity of hydrolysis of malolactonic acid.

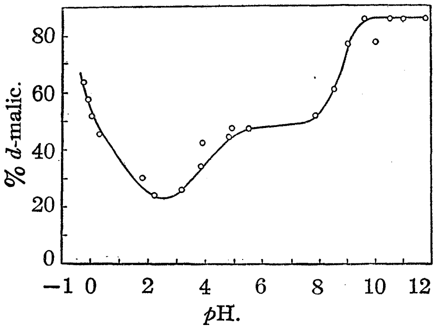

Fig. 2.—Optical form of malic acid produced by hydrolysis of (+) malolactonic acid.

The β-bromobutyric acid was prepared by Johansson's[8] method. The acid was resolved with morphine in methyl alcohol. Repeated recrystallization of the acid yielded a product which had a molar rotation of +116.5° in 2 *N* perchloric acid. This solution was 0.1632 *M* with respect to the β-bromobutyric acid. In water alone less than 1% decrease was observed. A 0.2361 *M* solution of the sodium salt had a molar rotation of 106.6°. The melting point of the purest acid was 44°. The β-butyrolactone was prepared from this acid by Johansson's procedure.

Hydrolysis of the β-Butyrolactone.—The lactone was weighed in volumetric flasks which then were filled to the mark with the solvent used for hydrolysis. The change of optical rotation with time and the final value reached were then observed using the polarimeter[9] described previously. This was a Bellingham and Stanley instrument designed so that 30-cm. polarimeter tubes in a thermostat with glass windows could be placed in the optical path. The thermostat was held at 25.0 ± 0.05° by means of a mercury regular and heaters. Light from a mercury lamp filtered through copper sulfate glass and a Wratten No. 77 filter was used for the readings with the Hg 5461 line. Unfiltered light from a sodium lamp was used for the sodium D lines. All readings were made to the nearest hundredth of a degree, and, except for the faster kinetic runs, the mean of six to ten readings was taken as an observation.

Results and Discussion.—It was known from the work of Johansson[4] that the hydrolysis of the lactone involves not only a first order reaction with water but also a second order reaction with hydroxide ion. In those solvents, therefore, where a change in the hydrogen ion concentration was apt to prove troublesome, we used buffers. In Table I we have collected the rate constants in various solvents. Those marked with an asterisk are copied from Johansson, who used a titration method for following the rate. In Fig. 3 we have plotted the rates which have been determined in this Laboratory, against the *p*H. For the 7.87 *N* sulfuric acid the activity of the hydrogen ion was taken arbitrarily as 7.87. The solid line in Figure 3 is the plot of the total rate at various hydrogen ion concentrations as calculated from the well-known equation for the catalytic catenary

$$-\mathrm{d}\log_e(\text{lactone})/\mathrm{d}t = k = k_{\mathrm{H_2O}} + k_{\mathrm{H}}(\mathrm{H}^+) + k_{\mathrm{OH}}(\mathrm{OH}^-)$$

where $k_{\mathrm{H_2O}}$ and k_{OH} were determined by Johansson and k_{H} was determined in 2 *N* perchloric acid.

TABLE I

EXPERIMENTAL RATES

Solvent	Molar concn. of lactone	First order $k \times 10^4$
7.87 *N* H_2SO_4	0.288	72
2 *N* $HClO_4$	.1685	12
Water	.789	7
0.665 *M* $H_2PO_4^-$, 1.00 *M* $HPO_4^=$, *p*H 6.8	.1890	29
0.60 *M* HCO_3^-, 2.18 *M* $CO_3^=$, *p*H 10	.207	800
Water*	.608	8.0
Water*	.0600	8.8
Water*	.00600	9.1
0.604 *M* HNO_3*	.603	9.2
0.0601 *M* HNO_3*	.0599	8.7
0.00600 *M* HNO_3*	.00600	9.0
		Second order
0.00400 *M* NaOH*	.00400	$C = 49$
0.00200 *M* NaOH*	.00200	$C = 49$

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[8] Johansson, *Ber.*, **48**, 1256 (1915).

[9] Olson and Long, THIS JOURNAL, **56**, 1294 (1934).

The lack of agreement between some of our points and the solid line will be discussed in a later section in connection with salt effects. The details of the calculation of the solid line are found in Table II. The last column in the table is useful in connection with the discussion in a later section.

TABLE II

CALCULATED RATES

$$-\frac{\mathrm{d}\log_e[\text{lactone}]}{\mathrm{d}t} = k = k_{\mathrm{H_2O}} + k_{\mathrm{H}}(\mathrm{H}^+) + k_{\mathrm{OH}}(\mathrm{OH}^-)$$

or $k = 8.5 \times 10^{-4} + 2 \times 10^{-4}(\mathrm{H}^+) + 49(\mathrm{OH}^-)$.

pH	$k_{\mathrm{H}}(\mathrm{H}^+) \times 10^4$	$k_{\mathrm{OH}}(\mathrm{OH}^-) \times 10^4$	$k \times 10^4$	$\frac{k_{\mathrm{H_2O}}}{k} \times 100$
− 2	200		208.5	4.2
− 1	20.0		28.5	29.8
− 0.5	6.3		14.8	57.4
0	2.0		10.5	81.0
1	0.2		8.7	97.0
2	.02		8.52	99.7
3	.002		8.502	100.0
4			8.5	100.0
5			8.5	100.0
6		0.0049	8.505	99.9
7		.049	8.55	99.4
8		.49	9.0	94.5
8.5		1.5	10.0	85.0
9		4.9	13.4	63.5
9.5		15.0	23.5	36.0
10		49.0	57.5	14.8
11		490	498.5	1.7
12		4900	4908.5	0.2

A change in the hydrogen ion concentration of the solvent in which the β-butyrolactone is hydrolyzed produces not only a change in the rate of hydrolysis as discussed above, but produces also a change in the ratio of the amount of (+) hydroxybutyric acid to the amount of (−) hydroxybutyric acid in the product. In order to determine this ratio the observed final rotation for each run must be corrected for the optical purity of the initial lactone. The corrected final rotation must then be compared with the molar rotation of pure hydroxybutyric acid in the same solvent. The correction was obtained by comparing the molar rotation of the bromobutyric acid from which the lactone was made with the rotation of the highly resolved bromobutyric acid. In Table III we enumerate the correction factors for the four preparations of bromobutyric acid which were used in this work. In Table IV we list the molar rotations of an optically impure sample of hydroxybutyric acid in the various solvents. Since the molar rotation of this sample of hydroxybutyric acid in water was only 18.5° we have multiplied all the experimentally determined molar rotations by a factor to obtain the rotation of pure hydroxybutyric acid. In Table V we have collected the data from the runs concerned with the optical form of the product. The first column indicates the preparation of bromobutyric acid from which the lactone was made, the second

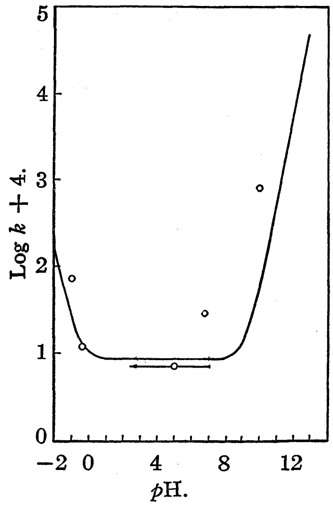

Fig. 3.—Rate of hydrolysis of β-butyrolactone.

TABLE III

Prepn. of β-bromobutyric acid from which lactone was made	Molar rotation of this acid in 2 N $\mathrm{HClO_4}$	116.5 divided by this molar rotation or correction factor to rotation
I	50.4	2.31
II	86.8	1.343
III	104.0	1.120
IV	100.7	1.158

TABLE IV

ROTATION[10] OF β-HYDROXYBUTYRIC ACID IN VARIOUS SOLVENTS

Free acid in aqueous solution, $[\mathrm{M}]^{25}_{\mathrm{D}}$ 25.9°. Sodium salt, c = 0.13 M, $[\mathrm{M}]^{25}_{\mathrm{D}}$ 17.5° Hg 5461 calibration using 5 cc. of 0.789 M acid solution of $[\mathrm{M}]^{25}_{\mathrm{D}}$ 18.5° diluted to 25 cc. with solvent, giving the concentration of β-hydroxybutyric acid = 0.789/5 = 0.1578 M in all solvents except water where the original 0.789 M solution was used.

Solvent	α	$[\mathrm{M}]^{25}_{5461}$	$[\mathrm{M}]^{25}_{5461} \times \frac{25.9}{18.5}$
7.87 N $\mathrm{H_2SO_4}$	1.12	23.6	33.1
Acetate buffer Ac$^-$ = 0.8 M, HAc = 3.2 M, pH 3.85	1.03	21.7	30.4
Water	5.10	21.5	30.1
Phosphate pH 6.8, 0.665 M $\mathrm{H_2PO_4^-}$, 1.0 M $\mathrm{HPO_4^=}$	0.77	16.2	22.7
Carbonate pH 9, 2.00 M $\mathrm{HCO_3^-}$, 0.72 M $\mathrm{CO_3^=}$	.77	16.2	22.7
Carbonate pH 10, 0.6 M $\mathrm{HCO_3^-}$, 2.18 M $\mathrm{CO_3^=}$	.76	16.0	22.4
6 N NaOH	.62	13.1	18.4

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[10] McKenzie, *J. Chem. Soc.*, **81**, 1402 (1902).

TABLE V

Prepn.	Solvent	Initial molar concn. of lactone	Obsd. final rotation of soln.	$[M]^{25}_{5461}$	Corrected $[M]^{25}_{5461}$	Rotation of pure β-hydroxybutyric acid in solvent	Corrected [M] × 100 divided by rotation of pure hydroxybutyric acid	Per cent. (+) form
I	7.87 N H_2SO_4	0.288	−0.65	− 7.5	−17.3	33.1	−52	24
III	2 N $HClO_4$	.1685	.13	2.6	2.9	(30.1)[a]	10	55
I	Formate buffer, pH 2.8	.363	1.36	12.5	28.8	(30.1)[a]	96	98
III	Acetate buffer, HAc = 3.2 M, Ac = 0.8 M, pH 3.8	.1319	1.02	27.0	30.2	30.6	98.7	99.4
I	Water	.113	0.40	11.8	27.0	30.1	90	95
II	Water	.789	5.10	21.5	28.9	30.1	96	98
			4.37[b]	18.5	24.8	25.9	96	98
III	Water	.1932	1.54	26.4	29.7	30.1	98.7	99.3
			1.32[b]	22.7	25.4	25.9	98.0	99.0
III	0.665 M $H_2PO_4^-$, 1.0 M $HPO_4^=$, pH 6.8	.1890	1.14	20.0	22.4	22.7	98.6	99.3
I	2.00 M HCO_3^-, 0.72 M $CO_3^=$, pH 9	.118	0.00	0.0	0.0	22.7	0	50
III	0.60 M HCO_3^-, 2.18 M $CO_3^=$, pH 10	.207	− .40	− 6.4	− 7.2	22.4	−32	34
III	0.140 M NaOH	.140	− .63[b]	−15.0	−16.8	17.5	−96	2
I	6 N NaOH	.308	− .65	− 7.0	−16.1	18.4	−88	6
IV	6 N NaOH	.249	−1.07	−14.3	−16.5	18.4	−90	5

[a] In the absence of experimental data rotation in water was used.

[b] Indicates runs made with sodium light.

the solvent in which the lactone was hydrolyzed, the third the initial molar concentration of lactone, and the fourth was observed final rotation. The percentages of (+) hydroxybutyric acid in the product as calculated from the corrected rotations are shown in the last column of Table V and plotted against the pH in Fig. 4. Where an unbuffered solution was used an arrow shows the change in pH during hydrolysis.

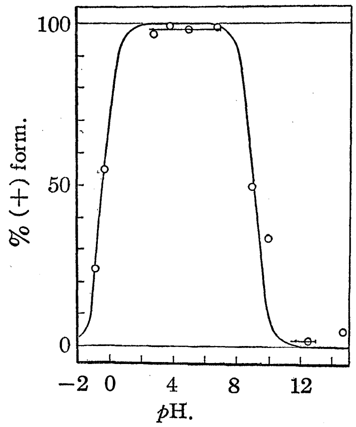


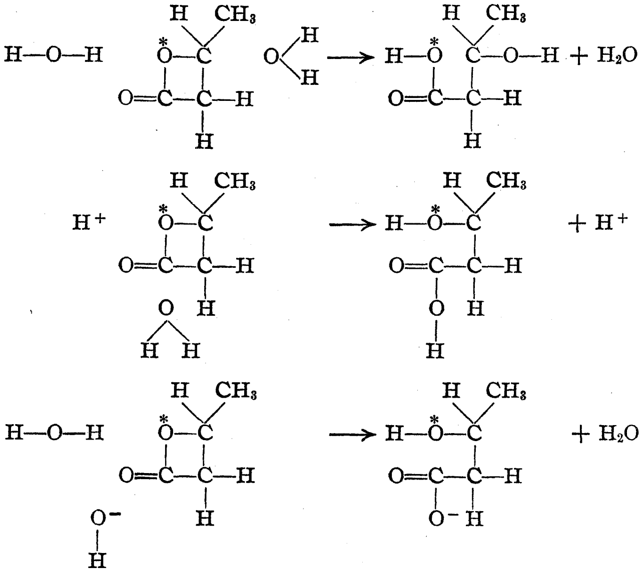
Fig. 4.—Optical form of hydroxybutyric acid produced by the hydrolysis of (+) β-butyrolactone.

If we assume that (+) β-butyrolactone reacts with water molecules to form only (+) hydroxybutyric acid and with hydrogen ions or hydroxyl ions to form only (−) hydroxybutyric acid, and if we combine these assumptions with the rates as determined in the preceding sections, we can calculate the percentage of (+) hydroxybutyric acid formed in the various solvents. This we have done with the aid of the last column in Table II and have plotted the results as the solid line in Fig. 4. The agreement between the experimental and calculated percentages is quite satisfactory except for the point at pH of 10 and the point in 6 N sodium hydroxide. The agreement for the point corresponding to 7.87 N sulfuric acid is of course due to our arbitrary selection of an activity for the hydrogen ion. If we had calculated the activity from the mean activity rule of Lewis and Randall,[11] the point would have come to the right of that for 2 N perchloric acid. This procedure of course neglects a specific contribution to the rate by the acid sulfate ion. That this ion contributes to the rate is made very plausible by the work to be discussed later in connection with carbonate ion.

The low rotation in the 6 N sodium hydroxide may be due to reactions producing unsaturated compounds such as is observed with bromobutyric acid in alkaline solutions.

(11) Lewis and Randall, "Thermodynamics," McGraw-Hill Book Co., Inc., New York, N. Y., 1923, pp. 328 and 357.

Postponing for the present the discussion of the point at *p*H 10, we can conclude that the composite reaction is the resultant of the three reactions.



These reactions are written in conformity with the principle that inversion occurs for every substitution. The formation of the lactone from the bromobutyric acid must have involved an inversion even though there is no change in rotation, for the action of phosphorus pentachloride on (−) hydroxybutyric acid or its ester produces a (+) chlorobutyric acid[12] or its ester, respectively. It is of interest to recall in this connection that (+) bromosuccinic acid produces a lactone with negative rotation. The lactone is in reality an inner ester. The breaking of the carboxyl oxygen bond under acid or alkaline conditions is in agreement with the hydrolysis of esters under similar conditions.[13] The hydrolysis of the lactone by molecular water is fast enough to be observed. In this case it is the alcohol oxygen bond which is broken. Due to the fact that we used optically active materials, we see that the big speeding up of the reaction by hydrogen ions and hydroxyl ions therefore does not necessarily involve a catalysis of the water reaction, but rather the acceleration of independent, competing reactions. In view of these results we must disagree with Waters,[14] who states "Without exception hydrolyses are ionic reactions..."

In Fig. 3 the point corresponding to the hydrolysis of a 0.789 *M* solution of the lactone in pure water shows a slower rate than that calculated for a 0.15 *M* solution. This is in agreement with Johansson's work in which it was found that the first order rate constants decreased as the concentration of the lactone increased. We already have mentioned the difficulty of assigning an activity to the hydrogen ion in the 7.87 *N* sulfuric acid. In addition to this the rate also should deviate from that calculated for a dilute solution due to the changes of the activity of water and of lactone as we go to such a concentrated solution. These effects are likewise very prominent in the runs with phosphate and carbonate buffers where the salt concentrations are several moles per liter. Thus the velocity of the run in the phosphate solution is about three times the calculated rate. A distribution experiment using dibutyl ether as the second solvent showed that the activity of the lactone in the phosphate solution was about twice as great as it was in water solution, accounting for the major portion of the rate change. The run in the carbonate buffer cannot be explained in this way, for here we get not only a thirteen-fold increase in the composite rate but also a change in the optical ratio of the product. This ratio would not be changed by a change in the activity of the lactone. Therefore, even after allowing for a two-fold change in the activity of the lactone by the salt, we find a five-fold increase in the rate of the reaction with hydroxide ion and fifteen-fold increase in the water reaction rate. If we think of the carbonate ion in solution as hydrated and write a structure for it $:\underset{\cdot\cdot}{\ddot{O}}:\overset{:\ddot{O}:}{\underset{\cdot\cdot}{C}}:\underset{\cdot\cdot}{\ddot{O}}:H:\underset{\cdot\cdot}{\ddot{O}}:H$, we see that the water in this complex is intermediate between molecular water and hydroxide ion since the hydrogen which forms the bond is no longer completely the property of the water. Assuming that the behavior of such a particle is intermediate between that of hydroxide ion and molecular water, we would expect the observed changes in the rates and products.

Reactions of β-Bromobutyric Acid.—The disappearance of β-bromobutyrate ion in aqueous solution at 25° gave a first order rate constant of 1.09×10^{-3} min.$^{-1}$. Runs which were followed by Volhard titration or by change of optical rotation gave identical results. The rate of this re-

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[12] Fischer and Scheibler, *Ber.*, **42**, 1219 (1909).

[13] (a) Holmberg, *ibid.*, **45**, 2997 (1912), and (b) Polanyi and Szabo, *Trans. Faraday Soc.*, **30**, 508 (1934).

[14] Waters, "Physical Aspects of Organic Chemistry," Routledge and Sons, Ltd., London, p. 262.

action at 38° was found by Johansson[8] to be 0.0093. Combining these results we get $k = 1.3 \times 10^{17}e^{-29,800/RT}\text{sec.}^{-1}$. Later Johansson[15] found that at 32° about 15% of the β-bromobutyrate decomposed into propylene, carbon dioxide, and bromide ion. At 25° we found a 17% discrepancy between the production of bromide ion and of acid after the hydrolysis of sodium β-bromobutyrate was complete, indicating about the same amount of decomposition. If all of the hydrolysis of the sodium bromobutyrate proceeds through the lactone intermediate, the optical activity of the product should be the same as that which is obtained from the hydrolysis of the lactone. Correcting for the 15% decomposition reaction this was found to be the case.

An aqueous solution of sodium bromobutyrate and thiosulfate ion shows an induction period when the rate is followed by titration of the thiosulfate ion. The induction period becomes shorter the greater the initial concentration of thiosulfate ion. The limiting value for the rate appears to be the same as the rate of production of bromide ion when thiosulfate ion is absent. The reaction therefore probably involves the preliminary production of lactone and bromide ion. In corroboration of this, the rate of the bimolecular reaction between lactone and thiosulfate ion was determined by following the change in concentration of thiosulfate ion and found to be 0.05 liter per mole-minute. The results therefore are completely analogous to those obtained by Long and Olson[16] with sodium bromosuccinate.

In solution by itself or with 2 N perchloric acid the β-bromobutyric acid loses its optical activity only very slowly, the rotation in 2 N perchloric acid being 55% of the beginning rotation after two months at 25°. In basic solution, however, a fast bimolecular reaction with hydroxide ion occurs, producing an optically inactive substance, probably crotonate ion, such as Fischer and Scheibler[12] found with sodium β-chlorobutyrate. The rate constant as determined by the decrease in optical activity with time was about 0.08 liter per mole-minute at 25°.

The racemization by bromide ion was followed in approximately 0.2 N β-bromobutyric acid and 2 N hydrobromic acid by the decrease in optical activity. The rate constants, uncorrected for decrease in optical activity due to other causes, since this correction was small and known only in the case of the lower temperature, were 1.27×10^{-5} minute^{-1} at 25° and 9.2×10^{-5} minute^{-1} at 39.3° as the results of a single run at each temperature. The rate constant can then be expressed as $k = 4.2 \times 10^{11}e^{-24,900/RT}\text{sec.}^{-1}$ as a preliminary result.

Summary

Pure optically active β-bromobutyric acid has been prepared. Its molar rotation, $[M]^{25}_{5461}$, in acid solution is 116.5°. In aqueous solution the salt gave $[M]^{25}_{5461}$ equal to 106.6°.

The rates of hydrolysis of optically active β-butyrolactone prepared from optically active β-bromobutyric acid have been measured over a range of hydrogen ion concentrations.

From the rates and the optical activity of the final hydrolysis products it has been shown that the mechanisms of hydrolysis by water, by hydrogen ion, and by hydroxide ion are distinct.

It has been shown that the addition of an ion, such as carbonate ion, has a big influence on both the water rate and the hydroxide ion rate. An explanation is advanced for this behavior.

Tentative values of the heats of activation for the reaction by which β-bromobutyrate ion produces lactone and for the reaction by which bromide ion racemizes β-bromobutyric acid have been determined.

The rate of the bimolecular reaction between β-bromobutyrate ion and hydroxide ion was determined to be about 0.08 liter per mole-minute.

The reaction between β-bromobutyrate ion and thiosulfate ion has been shown to involve the unimolecular formation of lactone as a primary step.

BERKELEY, CALIF. RECEIVED JULY 15, 1938

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[15] Johansson, *Ber.*, **55**, 647 (1922).

[16] Long and Olson, *J. Phys. Chem.*, **41**, 267 (1937).

[CONTRIBUTION NO. 138 FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF TEXAS]

The Heats of Solution of Gaseous Di- and Trimethylamines

BY ANDREW PATTERSON, JR., WITH W. A. FELSING

Object of the Investigation.—In a previous paper[1] there were reported calorimetrically determined values for the heats of solution of gaseous monomethylamine in water at different concentrations of methylamine produced. Since the di- and trimethylamines have been investigated[2] partially in this Laboratory with the view of determining their value in refrigerating systems of the absorption type and since it would be desirable to complete the heats of solution for this series of amines, this investigation was undertaken.

Existing Data.—Very few data on the heat of solution of these amines are recorded in chemical literature.

Bichowsky and Rossini[3] estimated the heat of solution of dimethylamine gas to be 12,700 cal. Other values, estimated in various ways, are due to Bonnefoi[4] (14,635 cal.), to Moore and Winmill[5] (12,290 cal.), and the "International Critical Tables"[6] (14,581 cal.), based upon data by Bonnefoi.[7] In no instance was there specified the concentration of the dimethylamine solution produced.

The values for the heats of solution for gaseous trimethylamine are also discordant. Berthelot[8] gives the value of 12,900 cal. when one mole of the amine is dissolved in 270 moles of water (*i. e.*, at $N = 270$). Other values are those of Moore and Winmill[5] (12,820 cal.), of the "International Critical Tables"[6] (12,908), and of Colson,[9] who gave a value of 8750 cal. for the heat of solution of *liquid* trimethylamine. This value may be combined with the molal heat of vaporization of 5540 cal./mole at 30°, based upon the data of Felsing and Phillips,[2] yielding a value of 14,290 cal./mole for the heat of solution.

Berthelot[8] cites some values for the heats of dilution of a saturated trimethylamine solution (410 g./1000 g. of water at 19°) and of some solutions ranging in concentration from near saturation to about one-half molar, the solutions in each case being diluted to approximately one-fourth molar.

Experimental Procedure.—The total heat of solution of these gaseous amines was determined by passing the dry gas into distilled water, observing the temperature effect, and determining the concentration of the amine solution produced. The method of procedure is that of Felsing and Wohlford;[1] only minor modifications were introduced.

The energy equivalent of the calorimeter system was determined by the usual electrical energy input method. Approximately 200 g. of distilled water measured to 0.001 g. was used for each of the seven determinations. The maximum deviation (a single determination) from the *mean* was 0.32 cal. (0.14%), whereas the average deviation was only 0.147 cal. (0.067%). The international calorie was used, 1 calorie being 4.1833 international joules.

No radiation corrections were applied to the heat of solution determinations since: (1) the time of a calibration run (the energy equivalent determinations) was made, by actual trial, the same as the time of a heat of solution determination; (2) the temperature rise of the calibration runs was made the same as the *average* rise of a heat of solution determination; (3) the stirring rate was held constant throughout; (4) the calorimeter vessel (a special Dewar flask) was highly evacuated and silvered; and (5) the surroundings were kept constant at 30 ± 0.05°. The initial temperature of each run was exactly 30°.

The gaseous amines were generated from the Eastman C. P. hydrochlorides by treatment with 50% potassium hydroxide in the apparatus of Felsing and Wohlford. The gases were dried by passing through tubes filled with pellet potassium hydroxide and were completely dried by storage over sodium wire. These dried gases (mixed with a very small amount of hydrogen resulting from the sodium wire drying process) were allowed to pass into the water of the calorimeter, the temperature rise was noted on a calibrated 2° Beckmann thermometer, and two samples (approx. 50 cc.) of the resulting solution were removed by

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(1) Felsing and Wohlford, THIS JOURNAL, **54**, 1442 (1932).

(2) Felsing and Phillips, *ibid.*, **58**, 1973 (1936).

(3) Bichowsky and Rossini, "Thermochemistry of Chemical Substances," Reinhold Publishing Corp., New York, N. Y., 1936, p. 50.

(4) Bonnefoi, *Ann. chim. phys.*, [7] **23**, 367 (1901).

(5) Moore and Winmill, *J. Chem. Soc.*, **101**, 1667 (1912).

(6) "I. C. T.," Vol. V, p. 182.

(7) Bonnefoi, *Compt. rend.*, **127**, 576 (1898).

(8) Berthelot, *Ann. chim. phys.*, [5] **23**, 247 (1881).

(9) Colson, *ibid.*, [6] **19**, 407 (1890).

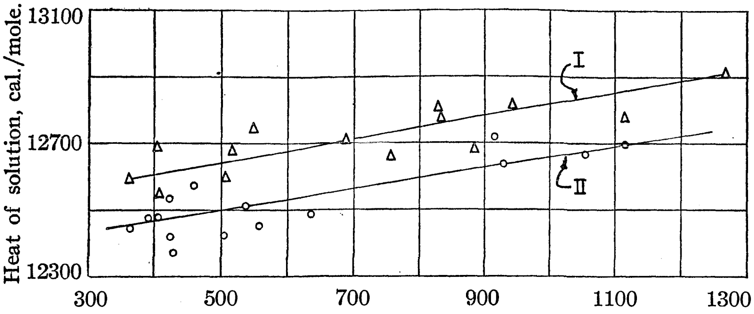

Fig. 1.—*N*, Moles water/moles amine; I, Dimethylamine; II, Trimethylamine.

means of a sampling pipet. From this pipet the sample was added to a weighed quantity of standard sulfuric acid, containing one drop of methyl red indicator, until faint alkalinity was indicated. To this essentially neutral solution was added the standard sulfuric acid to produce a slightly acid solution. This excess was then titrated with standard sodium hydroxide, the whole procedure being that of Moore and Winmill.[5] The use of methyl red as indicator has been recommended by Treadwell and Hall[10] and by Thompson.[11] All titrations and standardizations were made by weight; duplicate determinations always were made and the usual precautions for highest accuracy were observed.

A. DIMETHYLAMINE

Δt, °C.	$(CH_3)_2NH$, g.	H_2O, g.	*N* (moles H_2O/moles amine)	Heat of solution (cal./mole) Obsd.	Calcd. by Eq. (1)
0.514	0.4008	203.069	1267	12,912	12,915
.580	.4609	204.774	1111	12,765	12,860
.686	.5348	201.401	941	12,815	12,800
.703	.5363	197.407	920	12,863	12,793
.725	.5883	207.655	882	12,660	12,780
.776	.5872	208.649	832	12,779	12,763
.777	.6266	194.723	829	12,824	12,761
.853	.7064	212.061	750	12,646	12,733
.934	.7506	206.393	687	12,713	12,711
1.025	.8565	211.229	505	12,588	12,647
1.171	.9199	202.112	549	12,761	12,662
1.232	.9401	194.537	517	12,690	12,651
1.564	1.2659	205.094	405	12,543	12,612
1.592	1.3145	212.232	403	12,693	12,612
1.747	1.4066	204.550	363	12,586	12,597

Maximum deviation, 0.93%; average deviation, 0.43%.

B. TRIMETHYLAMINE

Δt, °C.	$(CH_3)_3N$, g.	H_2O, g.	*N* (moles H_2O/moles amine)	Heat of solution (cal./mole) Obsd.	Calcd. by Eq. (2)
0.574	0.6067	207.225	1123	12,700	12,697
.607	.6471	207.928	1053	12,653	12,697
.687	.7117	201.516	928	12,653	12,637
.833	.8763	207.921	913	12,724	12,632
.994	1.0572	204.613	634	12,498	12,544
1.128	1.2285	208.853	557	12,435	12,520
1.186	1.2617	205.783	538	12,510	12,514
1.225	1.3554	208.138	583	12,402	12,503
1.357	1.3898	197.689	466	12,579	12,491
1.455	1.6003	209.814	430	12,363	12,480
1.466	1.6238	212.323	428	12,412	12,479
1.506	1.6222	208.259	421	12,540	12,477
1.550	1.6187	200.385	406	12,489	12,472
1.620	1.7343	206.106	390	12,499	12,467
1.745	1.8104	199.712	361	12,533	12,458

Maximum deviation, 0.93%; average deviation, 0.43%.

The Data.—The data are listed in the table, in the order of increasing amine concentration; this is not necessarily the order of determination. A plot of the heat of solution against *N* (the ratio of moles of H_2O to moles of amine) was made for each amine. A straight line represents best the variation of the total heat of solution with change in the concentration of the solution produced for each of the amines. These functional relations are given by

$$\text{Dimethylamine:}\quad -\Delta H_1\ (\text{cal./mole}) = 12{,}470 + 0.35149N \qquad (1)$$

$$\text{Trimethylamine:}\quad -\Delta H_2\ (\text{cal./mole}) = 12{,}344 + 0.31645N \qquad (2)$$

These relations apply only to the range of concentrations investigated.

The rate of change of the total heats of solution per mole with change in concentration of amine solution produced, for any concentration over the limited range investigated, is given by

$$d(-\Delta H_1)/dN = 0.35149, \text{ for dimethylamine}$$
$$d(-\Delta H_2)/dN = 0.31645, \text{ for trimethylamine}$$

The data of Berthelot[8] on trimethylamine apply only to the dilution of concentrated solutions up to a concentration which is even greater than the most concentrated of this investigation. Hence his data cannot be compared with the results of the heat of dilution relations of this investigation.

Summary

1. The total heats of solution for gaseous di- and trimethylamines have been determined at 30° for various concentrations of amine solution produced.

2. The relation between $-\Delta H$ (heat of solution in cal./mole of amine) and *N* (moles water/mole amine) is given by two linear equations:

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(10) Treadwell and Hall, "Analytical Chemistry," Vol. II, 7th Ed., 1928, p. 470.

(11) R. T. Thompson, *Analyst*, **53**, 315 (1928).

$-\Delta H_1$ (dimethylamine) $= 12{,}470 + 0.35149N$ and $-\Delta H_2$ (trimethylamine) $= 12{,}344 + 0.31645N$. The experimental values agree with the values calculated by these relations on the average to 0.43%; the maximum deviation is 0.93%.

AUSTIN, TEXAS RECEIVED JULY 25, 1938

[CONTRIBUTION FROM THE LABORATORY OF PHYSICAL CHEMISTRY, THE STATE COLLEGE OF WASHINGTON]

The Densities of Fine Powders. II

BY J. L. CULBERTSON AND MARTIN K. WEBER

In a recent study of the apparent densities of fine powders made in this Laboratory[1] the differences in values obtained when different liquids were used as the buoying fluids were noted and conclusions were reached which were somewhat at variance, in their detail, from those reached by previous investigators. In a second study[2] there was evident a rough correlation between apparent density values and the heats of wetting of the powders when wetted by the same liquids. Further studies seemed desirable in order to test the conclusions reached in that work, and it was proposed that these should be developed along two lines, namely, (a) density determinations should be made of the fine powders used in the previous work (silica gel and active, practically ash-free, charcoal) using a number of liquids not yet investigated and (b) a study should be made of apparent densities of a non-porous powder in liquids of different types.

In the previous work[1] the conclusion was reached that variations in the apparent density of a porous powder might be due either to differences in the degree of penetration of the porous solid by the liquids or to differences in the degree of compression of the liquids at the solid–liquid interface. In either case the density differences noted must have been due primarily to the differences in surface energy decrease on wetting the solid, though in the second case differences in the compressibilities of the liquids would have been a conditioning factor. The measurements on a non-porous powder were proposed with the hope that by such means the first of these possible explanations might be confirmed or disproved.

Experimental.—In the previous work[1] a modification of the method of Harkins and Ewing[3] was used. Since this method requires considerable time, the method used by Tschapek[4] was investigated. This in brief consists of weighing a sample of the solid into a suitable specific gravity bottle and adding to the sample liquid sufficient to submerge it. The bottle is then placed in a vessel provided with suitable means of air-tight closure and a connection to a vacuum pump. This vessel is then evacuated to a pressure slightly below the vapor pressure of the liquid used on the sample. With such a pressure the adsorbed air is removed rapidly from the surface of the solid particles and after a sufficient time period (determined by increasing to time intervals yielding constant value determinations) the vacuum is broken, the specific gravity bottle filled, brought to the standard temperature and weighed. After making the necessary buoyancy corrections, the density is calculated directly. Tests of this method in comparison with that used in the previous work[1] demonstrated a satisfactory agreement, and, since it is considerably faster than the one formerly used, it was adopted for the present investigations.

Results and Discussion.—In the first study, samples of the same solid materials as were used previously[1] were employed. These were powdered silica gel and active ash-free charcoal. The methods for their preparation have been described.[1] Water, benzene, nitrobenzene, carbon disulfide, acetone, ethyl alcohol, and *n*-butyl alcohol were purified carefully by standard methods and used in the density determinations. The density values for each of the solids in each liquid are given in Table I(a). It is of interest also to add to these values those of Table I(b) taken from the previous work.

TABLE I(a)

Liquid used	Density values, g./cc. at 25° SiO_2	C
Acetone	2.310	2.047
Ethyl alcohol	2.248	2.012
Water	2.247	1.861
Nitrobenzene	2.239	2.011
n-Butyl alcohol	2.236	1.976
Carbon disulfide	2.216	2.029
Benzene	2.183	2.005

TABLE I(b)

Carbon tetrachloride	2.13	1.86
Petroleum ether	2.12	2.08

Harkins and Ewing found charcoal density to be a function of the compressibility of the liquid

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[1] Culbertson and Dunbar, THIS JOURNAL, **59**, 306 (1937).

[2] Culbertson and Winter, *ibid.*, **59**, 308 (1937).

[3] Harkins and Ewing, *ibid.*, **43**, 1787 (1921).

[4] M. W. Tschapek, *Kolloid-Z.*, **63**, 343 (1933).

used in the determination and in consideration of the fact that the charcoals were of different origins the data above are in satisfactory agreement with their values. As noted in the previous paper,[1] however, the observed values of the density of silica do not agree with such a concept. It appears significant that those liquids possessing the greatest compressibility yield the greatest values for the density of charcoal, while those with polar groupings, as indicated by high electric moment, show the greatest values for the density of silica; considering specific cases, the dipole moment of acetone is high and its compressibility is comparatively high. The density values of both charcoal and silica are high when determined by means of acetone. Water with high dipole moment and low compressibility yields a high density for silica and low density for charcoal, while petroleum ether with high compressibility and zero dipole moment yields a low density for silica and a high density for charcoal. The reader will of course observe that the extreme cases have been mentioned in illustrating the point made, and further that in some cases, particularly that of the density of charcoal in carbon tetrachloride and perhaps that of silica in carbon disulfide, the suggested relationship is not apparent. The data, however, offer considerable support for the generalization made. To the writers this would seem to indicate that on the silica surface polar groups are oriented to the interface and the large force of attraction causes compression of the liquid. Non-polar liquid molecules under the influence of less attractive force and feeble orienting influence even though of high compressibility fail to show such high densities for this solid. Generally speaking, opposite orientations and large forces of attraction between solid and non-polar groups and molecules seem to be indicated for the charcoal.

The data may, however, be explained on the basis of penetrability of the porous solids by the various liquids and the second series of determinations appear to be significant in this connection. For this study selected crystals of clear quartz were crushed and then ground in a pebble mill. The charge was removed from the mill at frequent intervals and screened. All material passing a 200-mesh sieve was retained and the rest returned to the mill. When approximately two pounds (1 kg.) of the 200-mesh material had been accumulated, the coarse fraction was discarded and the fine powder mixed and sampled. The fine material was then returned to the mill and the grinding continued for a period of five hundred hours, samples being taken at intervals. After approximately one hundred and twenty-five hours grinding, caking of the charge became so troublesome that the grinding was continued with the charge in the form of a slurry. The samples taken from the slurry were dried for twenty-four hours at 110°. Using the same method as was used in obtaining the data of Table I, the densities of these samples were determined using pure water and benzene. The results are given in Table II.

TABLE II

DENSITY OF GROUND QUARTZ

G./cc. at 25°

Grinding time, hours	Determination made in Water	Benzene
0	2.643	
4	2.642	
12	2.644	
24	2.641	
48	2.642	2.643
96	2.636	2.636
136	2.632	2.636
204	2.615	2.614
300	2.602	2.592
375	2.585	2.561
500	2.553	2.535

In the interpretation of these data cognizance must first be had of the falling trend of values as grinding is continued. This effect has been observed with ground quartz by Martin, *et al.*,[5] and the explanation has been offered that a part of the surface layer of the particles has been converted into amorphous material of lower density than the quartz crystal.[6] If this be the correct interpretation, then the relation between the two series of values becomes significant. Until well past two hundred hours of grinding, the density measurements in the two liquids show no appreciable differences, but from three hundred hours onward, the measurements in benzene fall definitely below those made in water. If it may be assumed that this material is non-porous, then only one of the suggested explanations will be applicable; *i. e.*, the water must be more strongly compressed at the interface than the benzene, the effect becoming evident only when a high

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(5) Alexander, "Colloid Chemistry," Vol. III, The Chemical Catalog Co., New York, N. Y., p. 305.

(6) That the effect cannot be due to attrition of the pebbles in the mill seems assured from the fact that the mean density of the pebbles was 2.577 g./cc. which, though much less than that of the original quartz, is appreciably greater than the final values obtained.

degree of subdivision is attained. Positive assurance can be had, however, only when the surface structure of the quartz particles is definitely known.

Summary

Density measurements of silica and charcoal, using a series of liquids as the buoying fluid, indicate that polar liquids yield high density values for silica, non-polar yield low values. The more compressible liquids yield the higher density values for charcoal. Polar liquids having large compression coefficients yield high density values for both solids.

Density measurements of ground quartz of varying degrees of fineness were made by means of benzene and water as the buoying fluids. These measurements confirm the foregoing statements and indicate that a different degree of penetration of different liquids into the surface of the solid is probably not a factor of significance in the variations of apparent density.

PULLMAN, WASH. RECEIVED AUGUST 22, 1938

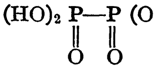
[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 652]

An Attempted Exchange of Phosphorus between Phosphorous and Phosphoric Acids

BY J. NORTON WILSON

The hydration of hypophosphoric acid, which takes place according to the equation

$$H_4P_2O_6 + H_2O \longrightarrow H_3PO_3 + H_3PO_4 \qquad (1)$$

has been shown[1,2] to proceed at a rate which is first order with respect to hypophosphoric acid and increases with increasing hydrogen ion concentration. It has been suggested[1] that this reaction is irreversible, but it seems probable that an equilibrium may be reached in which the concentration of hypophosphoric acid remaining is too small to be detected readily by chemical methods. If the structure of hypophosphoric acid is such that the phosphorus atoms are equivalent, as in the structure  $(HO)_2\underset{\underset{O}{\|}}{P}-\underset{\underset{O}{\|}}{P}(OH)_2$ which has been suggested on the basis of X-ray absorption spectra and chemical properties by Nylen and Stelling[3] and by Hantzsch,[4] the reverse of reaction (1) should lead to an exchange of radioactive phosphorus between phosphorous and phosphoric acids according to the following mechanism (the radioactive phosphorus atom is denoted by an asterisk)

$$H_3P^*O_4 + H_3PO_3 \rightleftarrows H_2O_3P^* - PO_3H_2 + H_2O \rightleftarrows H_3P^*O_3 + H_3PO_4 \qquad (2)$$

An attempt has been made to detect this exchange using radioactive phosphorus[5] obtained as a by-product of the formation of radio-sulfur by bombardment of sulfur with fast deuterons. The material was separated from most of the accompanying sulfur and oxidized to phosphoric acid; a small amount of ordinary phosphoric acid was added as a carrier. The phosphate was precipitated as magnesium ammonium phosphate and converted to lead phosphate which was treated with hydrogen sulfide to liberate radioactive phosphoric acid. The reaction mixtures were made up from this material and "C. P." phosphorous and phosphoric acids. The phosphorous acid used was found to contain a small amount of phosphoric; this was determined and corrected for.

In order to determine whether exchange had occurred the mixture was diluted and the phosphate precipitated as magnesium ammonium phosphate; this was dissolved in acid and reprecipitated to remove co-precipitated phosphite. The phosphate precipitate was dried and its electroscopic activity measured. The phosphite contained in the filtrates was oxidized with bromine and similarly precipitated; the electroscopic activity of this precipitate was determined as before. Occurrence of activity in the latter precipitate would be evidence either of exchange or faulty separation.

The reaction mixtures were made up in duplicate; one of the pair, used as a blank, was subjected immediately after mixing to the separation process and radioactivity measurements described above; the other was sealed in a glass

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[1] Van Name and Huff, *Am. J. Sci.*, **45**, 103, 18 (1918).

[2] Blaser, *Z. physik. Chem.*, **A167**, 441 (1934).

[3] Nylen and Stelling, *Z. anorg. allgem. Chem.*, **212**, 169 (1933); *ibid.*, **218**, 301 (1934).

[4] Hantzsch, *ibid.*, **221**, 63 (1934).

[5] This material was supplied through the generosity of Professor Edwin McMillan of the Radiation Laboratory of the University of California.

ATTEMPTED EXCHANGE OF PHOSPHORUS BETWEEN PHOSPHOROUS AND PHOSPHORIC ACIDS: EXPERIMENTAL RESULTS

No.	(H_3PO_4)	(H_3PO_3)	Other reagents	t, min.	T, °C.	Activity PO_3, div./min.	Activity PO_4, div./min.	β/α_0	β/α_0, blank
I	0.76	0.72		1440	100	$+0.004 \pm 0.005$	0.79	$(5 \pm 6) \times 10^{-3}$	$\pm 6 \times 10^{-3}$
II	.46	.43	NaOH, 2.86	1400	100	$-.002 \pm .005$	0.92	$(-2 \pm 5) \times 10^{-3}$	$\pm 5 \times 10^{-3}$
III	.60	.68	HCl, 5.31	11,500	100	$+.006 \pm .006$	4.85	$(1 \pm 1) \times 10^{-3}$	$\pm 1 \times 10^{-3}$
IV	.62	.70	HCl, 5.51	21,200	20–25	$+.013 \pm .006$	4.20	$(3 \pm 1) \times 10^{-3}$	$\pm 1 \times 10^{-3}$
V	.36	.35	HCl, 5.63	18,900	25	$+.010 \pm .010$	49.0	$(2 \pm 2) \times 10^{-4}$	$(1 \pm 1) \times 10^{-4}$
VI	.36	.35	HCl, 5.63	37,900	25	$+.006 \pm .004$	24.8	$(2 \pm 2) \times 10^{-4}$	$(1 + 1) \times 10^{-4}$

ampoule and allowed to stand for a convenient time before separation.

The probability of error due to faulty separation was greatly decreased in experiments V and VI in which after the precipitation and separation of the radioactive phosphate some inactive phosphoric acid equal in amount to that originally present in the solution was mixed with the phosphite in the filtrates and precipitated in the same way. This treatment should remove practically all of any radioactive phosphoric acid left in solution after the first precipitation. Measurement of the activity of the resulting precipitate indicated that about 0.1% of the radiophosphoric acid originally present was left in solution after the first precipitation. After the extra precipitation the phosphite in the filtrate was oxidized and precipitated as in the earlier experiments.

From the observed extent of an exchange occurring during the time t in accordance with the mechanism suggested in (2), one can calculate the rate at which reaction (1) and its reverse proceed at equilibrium. If the first order rate constant k_1 for the hydration of hypophosphoric acid is known, one can calculate from this result the equilibrium constant K, defined as $K = (H_4P_2O_6)/(H_3PO_4)(H_3PO_3)$. It may be shown that for the case where exchange occurs to a very small extent over a long time a good approximation is

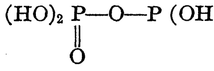
$$K = \frac{2}{(H_3PO_4)k_1t}\frac{\beta}{\alpha_0} \qquad (3)$$

where α_0 is the fraction of phosphoric acid initially radioactive corrected for radioactive decay to the time t and β is the fraction of phosphorous acid radioactive at time t.

In the following table are listed the concentrations, in formula weights per liter, of the reagents used in the experiments; the time t between the original mixing of the solutions and the separation of the phosphate; the temperature; the electroscopic activities of equal weights of the precipitates from the phosphite and phosphate fractions, corrected for radioactive decay and for the normal leak of the electroscope; and the values of β/α_0, which has been taken as the ratio of these activities. The values of β/α_0 for the "blank" experiments are also included. The normal leak of the electroscope was about 0.07 division per minute; fluctuations about this value were large enough to make a comparatively large uncertainty in the value of the activity of the phosphite precipitate. This uncertainty was estimated from the root mean square deviation from the mean of a number of alternate measurements of the normal leak and the phosphite activity. The results of experiments V and VI are the most reliable because of the care used to eliminate the error due to faulty separation.

It is apparent that in no case was definite evidence of exchange obtained. It can be stated, however, that the extent of exchange was less than a certain value determined by the estimated uncertainty; on the basis of the assumptions made a limit can then be placed on the value of the equilibrium constant K. Thus in experiment VI, β/α_0 was very probably less than 5×10^{-4}; k_1 for the given conditions may be estimated from the data of Van Name and Huff[1] to be 1.0×10^{-3} min.$^{-1}$. Then $K < 8 \times 10^{-5}$ mole^{-1} liters at 25° in 5.6 formal hydrochloric acid.

Unfortunately, an alternative conclusion is possible: that the phosphorus atoms in hypophosphoric acid are not equivalent, as for instance in the structure



$(HO)_2\underset{\overset{\|}{O}}{P}—O—P(OH)_2$

proposed on the basis of some slight chemical evidence by Blaser and Halpern.[6] If this is the case it is unlikely that the reverse of reaction (1) would lead to exchange. According to the evidence at present available,[1,2] however, it seems quite probable that the molecule contains two equivalent phosphorus atoms bonded to one another.

The author is grateful to Professor R. G. Dickinson for his advice, criticism and encouragement in connection with this investigation.

Summary

No exchange of radioactive phosphorus between

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[6] Blaser and Halpern, *Z. anorg allgem. Chem.*, **215**, 33 (1933).

phosphorous and phosphoric acids in acid or alkaline solution was found to occur beyond the limits of experimental error. The results indicate that if the phosphorus atoms in hypophosphoric acid are equivalent, the equilibrium constant for the formation of hypophosphoric acid from phosphorous and phosphoric acids is less than 8×10^{-5} mole^{-1} liters at 25° in 5.6 formal hydrochloric acid.

PASADENA, CALIF. RECEIVED JUNE 13, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY]

The Instability of Liquid Isobutene

BY EDWIN E. ROPER

In the course of measurements of the vapor pressure of a number of unsaturated hydrocarbons, the results of which are to be presented in a later paper, it was found that the vapor pressure of originally pure isobutene (2-methylpropene) decreases over a period of time and from this aged material a relatively high-boiling liquid was isolated. The most probable explanation of this instability of isobutene is that a polymer is formed. Since there appears to be no mention in the literature of any such uncatalyzed polymerization of isobutene, although it is well known that in the presence of certain catalysts isobutene is converted into polymers,[1] and since we do not plan to continue the study of this behavior further, it appears worth while to present our findings at this time.

Experimental

Apparatus.—A simple static system was used, consisting of a small (*ca.* 5 cc.) vapor pressure tube immersed in an ice-bath, which was maintained at 0.000 ± 0.001° for the observations. The washing procedure required to establish this temperature reproducibility in the ice-bath has been described.[2] The pressure was measured on an absolute manometer, of 15-mm. inside diameter Pyrex tubing, by a high grade cathetometer; meniscus corrections were determined for each observation and the pressure converted to international millimeters[3] (int. mm.) of mercury. Accessory apparatus included vacuum line, fore and condensation pumps, McLeod gage and a system of stopcocks; the manometer had a reservoir sealed on at the bottom, allowing the U to be used as a mercury cut-off, which was the only access to the vapor pressure system, so that no stopcocks were exposed to the vapor for long periods of time.

Material.—Four samples of isobutene were available. Sample D was from Dr. Harold S. Davis; it had been prepared by the dehydration of *t*-butyl alcohol by means of oxalic acid and purified in a Davis[4] low-temperature fractionating column. The boiling point range of this sample was given as ±0.05°. Sample R was one we had prepared by the method described by Davis,[4] with a boiling range of *ca.* 0.5°. Sample K, obtained from Professor Kistiakowsky of these Laboratories, had been highly purified for a determination of the heat of hydrogenation;[5] the consistent value of this heat of reaction for different fractions from the distillation,[5] the method of distillation,[5] the value of the freezing point,[5,6] and our vapor pressure measurements in conjunction with isothermal vaporization, gave indication of exceptional purity of the sample, of the order of 99.9%. Sample F was presented to us by Professor Forbes of these Laboratories; it had been prepared by the same investigators as had sample K and was the remnant of the material used in the photochemical investigation of Forbes and Nelson.[7] The boiling range was the same as that for sample K, namely, 0.02°. Samples K, F and R were dried by a physical method, which consisted of a filtration of the liquid through glass wool held at low temperatures;[8] this effectively dried the hydrocarbon and possibly removed some of the polymer. The samples were stored in the liquid phase in all-Pyrex glass containers, fitted with a glass internal break-off seal, externally operated by an electromagnet. High vacuum technique was used in all operations of filtering and transferring.

Procedure.—Immediately previous to the vapor pressure determinations, a distillation from the storage container at −80°, to a bulb on the vapor pressure line, via the manometer-cutoff, at −188° was carried out; this operation required some time, because of the low vapor pressure of the hydrocarbon at −80° (12 mm.). The first few tenths of a cc. that distilled was discarded, as was the last portion. In the subsequent examination of the latter, the container having been removed from the vacuum line, it was noticed that a small amount of residue, with a distinctive odor, was left after the admixed isobutene had been allowed to vaporize into the atmosphere; this residue was liquid at −80° and crystalline at −188°. It was obvious that the residue had formed during the several months of storage in the glass container, for during the

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(1) (a) Ellis, "The Chemistry of Petroleum Derivatives," The Reinhold Publishing Co., New York, N. Y., Vol. I, 1934, pp. 315, 378, 600; Vol. II, 1937, p. 641; (b) Whitmore and Wrenn, THIS JOURNAL, **53**, 3136 (1931); (c) Tongberg, Pickens, Fenske and Whitmore, *ibid.*, **54**, 3706 (1932).

(2) Roper, THIS JOURNAL, **60**, 866 (1938).

(3) Burgess, *Bur. Standards J. Research*, **1**, 635 (1928).

(4) Davis, *Ind. Eng. Chem., Anal. Ed.*, **1**, 61 (1929).

(5) Kistiakowsky, Ruhoff, Smith and Vaughan, THIS JOURNAL, **57**, 876 (1935).

(6) Compare with Todd and Parks, *ibid.*, **58**, 134 (1936).

(7) Forbes and Nelson, *ibid.*, **59**, 693 (1937).

(8) Roper, *Ind. Eng. Chem., Anal. Ed.*, **9**, 414 (1937).

initial treatment previous to storing, the same type of distillation had been performed.

The vapor pressure measurement was then carried out with this freshly distilled material and a small but definite decrease with time was observed. Part A of Fig. 1 shows the data for the first trial, using sample K. Some of the observations appear to be erratic; the only explanation that can be advanced is that possibly the pressure readings were taken too soon (*ca.* fifteen to thirty minutes) after the washing operation on the ice-bath. The ice-bath was replenished at suitable intervals so that 0.000 ± 0.004° was always maintained throughout the duration of the trial; previous to making an individual pressure determination, the ice-bath was brought to within ±0.001° of 0.000° by the washing procedure.[2] ±0.001° is equivalent to ±0.03 mm. in the vapor pressure as determined from the slope of the vapor pressure curve at 0°. At the end of the trial, an attempt was made to free thoroughly the system from polymer, by pumping for a long period.

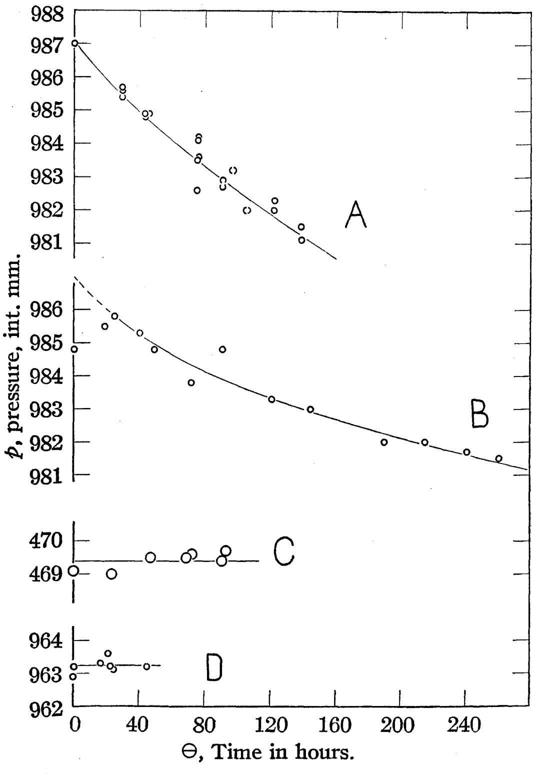

Fig. 1.—Comparison of results. Part A represents the vapor pressure change for isobutene, first trial, part B for the second trial; part C shows the data for the non-saturated vapor of isobutene. Part D gives data obtained for the vapor pressure of 1-butene. The diameters of the circles are 0.2 mm. in parts A, B and D, and 0.3 mm. in part C.

The identical apparatus had been in use for several months previous to this trial and no leaks were apparent. Nevertheless, it appeared necessary to investigate this point and accordingly the pressure was decreased to 470 mm. and readings made on the pressure over a period of time. The varying room temperature gave rise to different pressures of the non-saturated vapor but by means of the average change in p with T, the pressures were corrected to a common temperature. Part C, Fig. 1, presents the results; the data indicate that no leak existed and also that the hydrocarbon is stable in the vapor phase at this temperature.

The vapor pressure trial was then repeated, using a fresh sample of isobutene distilled into the vapor pressure bulb by the −80 to −188° procedure. Part B, Fig. 1, shows the results, which do not exactly parallel those of the first trial but the general behavior is the same. The low values at the commencement are not explainable.

Over a year after the conclusion of the above trials, sample K, which had been stored in glass, was distilled into a new vapor pressure system in the manner outlined. Again a small amount of the high-boiling liquid remained in the container. No attempt was made to study the change in the vapor pressure with time, although it was observed, but four determinations were obtained for the freshly distilled material, averaging 988.6 ± 0.3 int. mm. at 0.000 ± 0.001°.

In distillations after the manner described, of samples D, F and R, a residue of the high-boiling liquid from each has been noted, providing the hydrocarbon sample had been stored for some time in the liquid phase. A second distillation, immediately following the first, reveals no trace of the high-boiling liquid, nor does a distillation on material which has been stored in the gas phase. From sample F 0.25 g. (1.5 weight per cent.) and from sample R 0.40 g. (0.8 weight per cent.) of polymer was secured by collecting the residue remaining in the tube after a −80 to −188° distillation.

Investigation of the High-Boiling Liquid.—A rough freezing point was obtained by means of liquid air and a small pentane thermometer. The ranges −105 to −115° and −100 to −120° were found for the material from samples F and R, respectively. The refractive indices were kindly determined by Dr. J. B. Conn of these Laboratories, and $n^{20}\text{D}$ found to be 1.435 and 1.397 for the material from samples F and R, respectively. The product took up bromine (in carbon tetrachloride solution) first by addition and then shortly thereafter by substitution.

Discussion

With such small amounts of the high-boiling liquid available, purification and accurate boiling and freezing points were not feasible, especially if a mixture is present, for separation by distillation probably would prove to be impossible due to the similarity of the boiling points of the components; the freezing point would be inconclusive if separation were not effected. The physical properties of the two components of di-isobutylene as determined by Tongberg, *et al.*,[1c] are as follows: for 2,4,4-trimethylpentene-1 the freezing point is −93.6°, $n^{20}\text{D}$ 1.408, for 2,4,4-trimethylpentene-2 the freezing point is −106.5° (another form at −108.3°), $n^{20}\text{D}$ 1.416. For triisobutylene, $n^{20}\text{D}$ 1.431;[1c] since there are at least three hydrocarbons present,[9] a freezing point is meaningless, except for the equilibrium mixture. However, a hydrocarbon of the formula $C_{12}H_{24}$ should freeze in the vicinity of $-20°$ ($\pm 20°$). A comparison of the freezing points and refractive indices of the high-boiling liquid with those given above for three possible polymerization products shows that no very definite conclusion can be drawn as to the exact nature of the high-boiling liquid. According to the mechanisms given by McCubbin and Adkins[10] for the addition of isobutene to isobutene, four dimeric products are possible, namely, 2,4,4-trimethylpentene-1, 2,4,4-trimethylpentene-2, 2,5-dimethylhexene-1 and 2,5-dimethylhexene-2.

There does not seem to be any possibility that accidental contamination with some catalytic material can be the cause of this polymerization, since it has been observed with samples from three sources, prepared by two different methods, and under varying conditions. In view of this instability, the properties and reactions of isobutene, to a minor degree, will depend upon its past history.

For the other three butenes, no residue has ever been found in the -80 to $-188°$ distillation and the data obtained on the vapor pressures do not show evidence of change with time. These vapor pressure results were not collected for this particular illustration and it would have been desirable to extend the time of observation; unfortunately, this was not possible. Part D, Fig. 1, shows the results obtained with 1-butene, and gives some idea of the reproducibility of the measuring system. For 1-butene, *trans*-2-butene and *cis*-2-butene vapor pressures at $0.000 \pm 0.001°$, an analysis of the results indicates that the extreme variation is 0.4 mm. or less, the means ± 0.1 mm., measured over forty-five, twenty-nine and twenty hours duration, respectively; these three hydrocarbons were prepared by the collaborators of Professor Kistiakowsky.[5]

Thermodynamic data are available for the polymerization of liquid isobutene to the liquid dimer, trimethylpentene. By utilizing the data of Parks and co-workers,[6,11] the free energy of formation of the liquids may be approximated closely. The value of the equilibrium constant calculated from the free energy for the dimerization reaction is about 10^7 times greater than the value calculated from the weight concentration of high-boiling liquid found, making the assumption that it is trimethylpentene. Two factors could cause such a discrepancy: non-attainment of equilibrium, and a different mechanism than simple dimerization to trimethylpentene. It appears very likely that both factors are operative, although from the observed freezing points and the qualitative observations on the volatility of the high-boiling liquid, not a great quantity of trimer can be present. It is worth noting that the free energy changes for the three possible isomerization reactions of isobutene are all positive values, although rather small, so that isomerization to 1-butene or 2-butene should not occur spontaneously to complicate further the course of this polymerization reaction.

I wish to thank Professor Arthur B. Lamb, under whose direction this work was carried out, for facilities placed at my disposal and for advice in preparing this manuscript. I am grateful to him and to Dr. H. S. Davis, Professor G. S. Forbes, Professor G. B. Kistiakowsky and Dr. J. R. Ruhoff for making available the hydrocarbon samples.

Summary

It has been shown that isobutene in the liquid phase forms a high-boiling liquid, upon standing, which probably is a polymer, with certain evidence pointing to dimerization as the first step. At 0° this reaction causes a lowering of the pressure of the saturated vapor of pure isobutene to the extent of about 0.6%. The other three butenes do not exhibit such behavior.

MALLINCKRODT CHEMICAL LABORATORY
CAMBRIDGE, MASS.
RECEIVED AUGUST 11, 1938

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[9] McCubbin, THIS JOURNAL, **53**, 356 (1931).

[10] McCubbin and Adkins, *ibid.*, **52**, 2547 (1930).

[11] Parks, Todd and Shomate, *ibid.*, **58**, 2505 (1936).

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 657]

The Structure of Ammonium Heptafluozirconate and Potassium Heptafluozirconate and the Configuration of the Heptafluozirconate Group

BY G. C. HAMPSON AND LINUS PAULING

The only work which has been reported so far on the structure of the so-called intercalation compounds of composition M_xAB_7 is that of Hassel and Mark,[1] who carried out an X-ray investigation of the crystals of ammonium heptafluozirconate, $(NH_4)_3ZrF_7$, and ammonium heptafluohafniate, $(NH_4)_3HfF_7$. Both crystals are cubic, the cube edge being 9.35 and 9.40 Å., respectively, and both contain four molecules in the unit cell. From their data Hassel and Mark were unable to deduce the space group absolutely, but they considered that O_h^4 was the most probable and suggested a structure based on this. This structure was built up of NH_4^+ ions, $[ZrF_6]^=$ ions, and F^- ions. It is of considerable interest to know whether odd coördination complexes involving seven atoms surrounding a central atom can or cannot exist, and the work of Hassel and Mark has been quoted[2] as proving the latter contention. It must be remembered, however, that Hassel and Mark's structure was put forward only as a possibility, and it is now clear from our knowledge of atomic and ionic radii that this particular structure is highly improbable.

In the first place, large numbers of ions of the same charge (*e. g.*, six NH_4^+ ions) are grouped together, which is a very unlikely arrangement. Moreover, taking even the most favorable limits of their parameter values it is found that their structure places an ammonium ion only 1.54 Å. from a fluoride ion, whereas the nearest possible distance even assuming hydrogen bond formation is about 2.6 Å. (2.63 Å. is observed in NH_4F[3] and 2.76 Å. in NH_4HF_2[4]).

In view of these facts a reinvestigation of the problem seemed to be justified. We have carried out a study of the structure of ammonium heptafluozirconate and potassium heptafluozirconate, using data obtained from Laue, oscillation, and powder photographs, and have found that the substances do not contain $[ZrF_6]^=$ and F^- ions, but instead contain the complex ion $[ZrF_7]^{\equiv}$, in which zirconium has the coördination number seven. The structure of the crystals is similar to that of $(NH_4)_3AlF_6$, with the $[AlF_6]^{\equiv}$ complexes replaced by $[ZrF_7]^{\equiv}$; the orientation of these complexes is not uniquely determined, however, but shows some randomness, permitting the crystals to assume higher point-group and space-group symmetry than would be possible otherwise.

Crystals of $(NH_4)_3ZrF_7$ and K_3ZrF_7 were grown by dissolving zirconium fluoride in a hot solution containing a large excess of ammonium fluoride or potassium fluoride and allowing the solutions to crystallize slowly.[5] Small transparent optically isotropic octahedra were obtained, with faces which do not show very good reflections; the crystals deteriorate fairly rapidly on exposure to the atmosphere, and were usually protected during the preparation of the X-ray photographs with a thin film of oil or vaseline.

The Structure of $(NH_4)_3ZrF_7$.—Oscillation photographs about [110] (copper Kα radiation), Laue photographs with the X-ray beam parallel to [111], and powder photographs (copper Kα radiation) were prepared of $(NH_4)_3ZrF_7$. No reflections were found to occur from planes with mixed indices (*hkl* part odd and part even). This observation is in disagreement with the results of Hassel and Mark, who reported the presence of reflections of this type. The only such reflections recorded in their tables are (110) and (310). We prepared 5° oscillation photographs permitting reflection from these planes, using long exposure times, and were unable to detect the reflections on our films; there is also no sign of these reflections on our powder photographs, which show more lines than those reported by Hassel and Mark. It seems likely that these investigators were misled by the X-ray continuum, by β lines, or by some other feature of their photographs, and that their report of reflections from planes of mixed indices was due to misinterpretation of their data. Their choice of space group (O_h^4) and their suggested structure were based on

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(1) O. Hassel and H. Mark, *Z. Physik*, **27**, 89 (1924).

(2) For example, by W. G. Penney and J. S. Anderson, *Trans. Faraday Soc.*, **33**, 1363 (1937).

(3) W. H. Zachariasen, *Z. physik. Chem.*, **127**, 218 (1927).

(4) L. Pauling, *Z. Krist.*, **85**, 380 (1933).

(5) C. Marignac, *Ann. chim.*, **60**, 257 (1860); H. Baker, *J. Chem. Soc.*, **35**, 760 (1879).

this presumably erroneous observation, and need not be discussed further.

The absence of any reflections from planes of mixed indices on our oscillation, Laue, and powder photographs makes it highly probable that the crystal lattice is face-centered.

Laue photographs taken with the X-ray beam parallel to [111] of thin crystal sections obtained by grinding octahedra on parallel octahedral faces were found to show a three-fold axis and three planes of symmetry, corresponding to the point groups T_d, O, and O_h. Since the Laue symmetry is of great importance in this investigation, the photographs were very carefully inspected, and were also studied by use of the α-ray integrating microphotometer.[6] Carbon prints were made of the photographs and the intensities of Laue spots due to planes of various holohedral forms were measured with the microphotometer, the intensity measurements being reproducible to within about 5%. No deviation from holohedry was found.

The powder photographic data for $(NH_4)_3ZrF_7$ (Table I) correspond to the value $a_0 = 9.365 \pm 0.010$ Å. for the edge of the unit cube, in good agreement with the value 9.353 Å. given by Hassel and Mark. With $4(NH_4)_3ZrF_7$ in the unit the density is calculated to be 2.32 g./cc.; the directly measured experimental value, 2.20 g./cc. (Hassel and Mark), is slightly smaller.

We have now to locate 4Zr, $12NH_4$, and 28F in the unit. The space groups compatible with the observed holohedral Laue symmetry and based on the face-centered cubic lattice are T_d^2, T_d^5, O^3, O^4, O_h^5, O_h^6, O_h^7, and O_h^8. Of these T_d^5, O^4, O_h^6, O_h^7, and O_h^8 provide no positions for the four zirconium atoms, and are accordingly ruled out of consideration.[7] T_d^2 provides four sets of no-parameter positions (4a, 4b, 4c, 4d) for four equivalent atoms, and sets of positions for 16, 24, 48, and 96 equivalent atoms; with 4Zr, $4(NH_4)_{I}$, $4(NH_4)_{II}$, and $4(NH_4)_{III}$ occupying 4a, 4b, 4c, and 4d, there is no way of placing all of the 28 fluorine atoms, so that this space group is also ruled out. O^3 and O_h^5 are ruled out in the same way; *there is no set of atomic positions for $4(NH_4)_3ZrF_7$ in the unit compatible with the observed holohedral Laue symmetry and face-centered lattice of the crystal.*

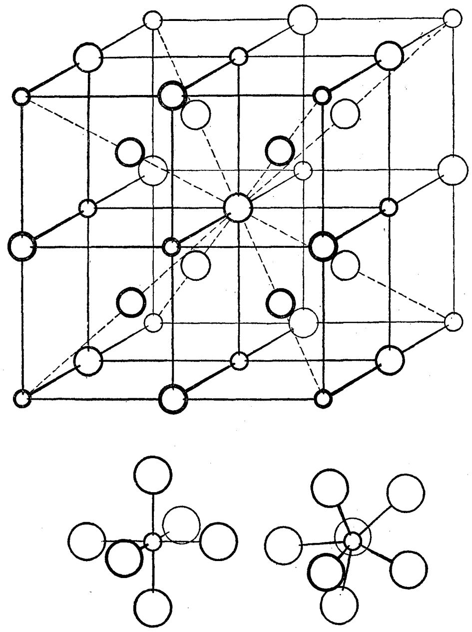

Fig. 1.—In the structure of $(NH_4)_3AlF_6$ each of the aluminum atoms (smallest circles) is surrounded by six fluorine atoms to form the octahedron shown below at the left side. In $(NH_4)_3ZrF_7$ and K_3ZrF_7 the $[AlF_6]^{\equiv}$ complexes are replaced by $[ZrF_7]^{\equiv}$ complexes such as that shown below at the right side.

The resolution of this difficulty might be achieved by assuming that the Laue symmetry is actually hemihedral or that the structure is actually based on a lattice with fewer lattice points than the face-centered lattice of the four-molecule unit, and that the intensities and intensity differences of X-ray reflections differentiating the actual Laue symmetry and lattice from those simulated are so small as to have been overlooked in our careful examination of the photographs. This is rendered improbable, however, by the fact that the crystal does not contain unlike atoms which resemble one another closely enough in stereochemical properties and X-ray reflecting power[8] to permit the simulation of a pseudo-unit in the usual way.

It is probable instead that ammonium heptafluozirconate is to be added to the list of crystals with structures involving some randomness of atomic arrangement, the treatment of which requires variation from the usual methods of application of the theory of space groups. We have found that a reasonable structure involving some randomness in orientation of $[ZrF_7]^{\equiv}$ complexes

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[6] W. T. Astbury, *Proc. Roy. Soc.* (London), **A123**, 575 (1929). We are indebted to Professor J. H. Sturdivant for the use of the microphotometer and to Dr. N. Elliott for assistance with the measurements.

[7] "International Crystal Structure Tables."

[8] As, for example, tetrahedrally coördinated aluminum and silicon atoms in sodalite, $Na_4Al_3Si_3O_{12}Cl$; L. Pauling, *Z. Krist.*, **74**, 213 (1930).

can be formulated which accounts satisfactorily for the X-ray data for $(NH_4)_3ZrF_7$, and that a similar structure can also be assigned to K_3ZrF_7.

The number of possible structures involving randomness of atomic arrangement of one type or another is so great that a straightforward structure determination cannot be carried out; it is necessary instead to apply the method of suggesting reasonable structures and testing them by comparison with the X-ray data. Now the X-ray photographs of $(NH_4)_3ZrF_7$ are closely similar to those of $(NH_4)_3AlF_6$, and it accordingly seems likely that the structure of $(NH_4)_3ZrF_7$ is to be obtained by the introduction of an additional fluorine ion in the $(NH_4)_3AlF_6$ arrangement.[9] This arrangement (Fig. 1) places 12 NH_4 at $^1/_2{}^1/_2{}^1/_2$, $^1/_4\ ^1/_4\ ^1/_4$, $^3/_4\ ^3/_4\ ^3/_4$, etc. (plus the positions obtained by application of the translational operations of the face-centered lattice), and 4 octahedral MF_6 groups at 000, etc. Additional fluorine ions might then be inserted at positions such as *uuu* with $u \cong {}^1/_8$. A fluorine ion here is about 1.9 Å. from three fluorine ions and an ammonium ion. This distance is too small, the minimum distance of approach expected for two fluorine ions (ionic radius 1.36 Å.) being about 2.4 Å. and for a fluorine ion and an ammonium ion about 2.6 Å. It is possible, however, to distort the arrangement of the adjacent ions in such a way, described below, as to give acceptable values to the interionic distances.

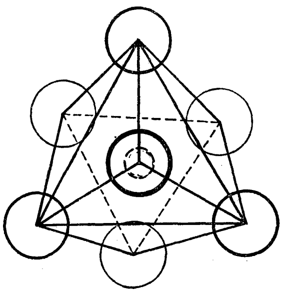
Fig. 2.—The $[ZrF_7]^=$ complex viewed along its three-fold axis.

The distance of the seventh fluorine ion at $^1/_8\ ^1/_8\ ^1/_8$ from the zirconium atom at 000 (1.9 Å.) is about the same as the zirconium–fluorine distance for the other six fluorine atoms—this way of inserting the seventh fluorine ion thus leads to the formation of a $[ZrF_7]^=$ complex. The existence of such a complex is to be expected. The ratio of univalent radii of zirconium and fluorine[10] is 0.80, which corresponds to stability of the coördination polyhedra[11] with coördination numbers 7, 8, or 9.

The distortion of the $[ZrF_6]^=$ octahedron accompanying insertion of the seventh fluoride ion will be such as to make the twelve small F–F distances equal, with the seven Zr–F distances also equal. The resulting polyhedron, shown in Fig. 2, has the angles F_3–Zr–F_7, F_3–Zr–F_6, F_4–Zr–F_6, etc., equal to 77°50′.

The sum of the crystal ionic radii for Zr^{4+} and F^- is 2.16 Å., and the sum of the octahedral covalent radius of zirconium and the covalent radius of fluorine is 2.15 Å. Oxygen and fluorine have nearly equal crystal radii, and the Zr–O distance in ZrP_2O_7 (octahedral coördination) is 2.02 Å.[12] These values suggest about 2.1 Å. for the Zr–F distance in the $[ZrF_7]^=$ complex. With Zr–F = 2.10 Å. the minimum F–F distance in the complex is 2.64 Å., which is only slightly less than twice the ionic radius of fluorine, 2.72 Å.

A reasonable way of orienting the various $[ZrF_7]^=$ groups in a cubic unit can be suggested, based not on the space group O_h^5, as for $(NH_4)_3AlF_6$, but on T^4. With this structure there are sequences of groups $[ZrF_7]^=$, $(NH_4)^+$, $(NH_4)^+$, $(NH_4)^+$, $[ZrF_7]^=$, . . ., along the non-intersecting three-fold axes of T^4. With Zr, $(NH_4)_I$, $(NH_4)_{II}$, and $(NH_4)_{III}$ in the positions 4a ($x,x,x;\ {}^1/_2 + x, {}^1/_2 - x, \bar{x};\ {}^1/_2 - x, \bar{x}, {}^1/_2 + x;\ \bar{x}, {}^1/_2 + x, {}^1/_2 - x$) of this space group and parameter values $x_{Zr} = 0.99$, $x_I = 0.28$, $x_{II} = 0.50$, $x_{III} = 0.72$, and with the $[ZrF_7]^=$ group oriented with F_7 at about $x = 0.12$, the interatomic distances are satisfactory, the minimum NH_4–F distance being 2.6 Å. This structure based on T^4 cannot be accepted, however; it leads to calculated intensity values (deviation from Laue holohedry and from the face-centered lattice) which are incompatible with observation.

If it is assumed that the $[ZrF_7]^=$ complexes have some randomness of orientation, complete agreement with experiment is obtained. Each $[ZrF_7]^=$ group is considered to have its choice of orientation with its three-fold axis parallel to any one of the eight [111] directions, the zirconium

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[9] L. Pauling, This Journal, **46**, 2738 (1924); *Z. Krist.*, **74**, 104 (1930); G. Menzer, *ibid.*, **73**, 113 (1930).

[10] L. Pauling, This Journal, **49**, 765 (1927); **51**, 1010 (1929).

[11] The minimum radius ratio for stability of the seven-cornered polyhedron obtained by inserting a seventh atom at the center of a face of an octahedron (as in $[ZrF_7]^=$) is 0.592; those for stability of the square Archimedean antiprism and of the cube are 0.645 and 0.732, respectively; and that for stability of the nine-cornered polyhedron obtained by introducing three atoms at the centers of the vertical faces of a right triangular prism is 0.732.

Although Penney and Anderson[2] say that Li_4ZrF_8 and Na_3TaF_8 "are undoubtedly not examples of coördination number eight," it is probable that these substances do contain the complexes $[ZrF_8]^{4-}$ and $[TaF_8]^≡$. The radius ratio for tantalum and fluorine, 0.85, is still larger than that for zirconium and fluorine. On the other hand, the radius ratio for silicon and fluorine is only 0.48, and it is accordingly highly probable that the tetragonal crystal $(NH_4)_3SiF_7$ contains $(NH_4)^+$ ions, F^- ions, and octahedral $[SiF_6]^=$ complex ions.

[12] G. R. Levi and G. Peyronel, *Z. Krist.*, **92**, 190 (1935).

atom near 000 assuming one of the corresponding positions uuu, $u\bar{u}\bar{u}$, $\bar{u}u\bar{u}$, $\bar{u}\bar{u}u$, $\bar{u}\bar{u}\bar{u}$, $\bar{u}uu$, $u\bar{u}u$, $uu\bar{u}$, with $u \cong 0.010$. The planes of symmetry of the complex are not preserved in the T^4 structure, the complex being rotated about its three-fold axis by about 10° from the symmetrical orientation relative to the crystal axes. In the random structure this rotation occurs in either the positive or the negative direction. It is thus assumed that there are sixteen orientations accessible to each $[ZrF_7]^{=}$ group. The ammonium ions I and III are similarly considered to be distributed at random among sets of four positions near $^1/_4\ ^1/_4\ ^1/_4$, $^3/_4\ ^3/_4\ ^3/_4$, etc.

It is probable that the randomness is not complete—the immediate environment of each $[ZrF_7]^{=}$ complex is expected to be like that for the T^4 structure. The random structure might be described as involving unit cubes of the T^4 type with different orientations in different small regions of the crystal. In order to account for the non-occurrence of reflections from planes with mixed indices these regions must be smaller than the regions giving coherent X-ray scattering; that is, they are of the maximum order of magnitude of 100 Å. in linear dimensions.

The intensity calculations were made with the usual formula

$$I_{hkl} = C\frac{1 + \cos^2 2\theta}{\sin^2 \theta \cos \theta}\, p\, F^2_{hkl} \qquad (1)$$

in which C is a constant, p is the frequency factor of the form, and F_{hkl} is the structure factor

$$F_{hkl} = \Sigma_j f_j\, e^{2\pi i(hx_j + ky_j + lz_j)} \qquad (2)$$

the summation being over all of the atoms in the unit cell. Screening-constant f-factors[13] were used. The atomic distribution corresponding to the random structure is the following, based on the space group O_h^5:

4 Zr in 32 f: xxx, etc., with $x = 0.99$;
8 N_I, N_{III} in 32 f, with $x_{I,III} = 0.28$;
4 N_{II} in 4b: $^1/_2{}^1/_2{}^1/_2$, etc.;
4 F (F_7) in 32 f, with $x_F = 0.12$;
12 F (F_1, F_2, F_3) in 192 l: xyz, etc., with $x' = 0.20$, $y' = 0.96$, $z' = 0.91$;
12 F (F_4, F_5, F_6) in 192 l, with $x'' = 0.77$, $y'' = 0.94$, $z'' = 0.99$.

In Table I there are given the results of the powder photographic measurements. The indices which are bracketed together are those for planes whose reflections are superimposed on the powder photograph.

TABLE I

POWDER PHOTOGRAPHIC DATA FOR $(NH_4)_3ZrF_7$

Indices	$\theta_{\text{measd.}}$	a_0, Å.	I_{visual}	$I_{\text{calcd.}}$
111	8°7′	9.430	V. v. strong	215
200	9°27′	9.374	Strong	108
220	13°26′	9.367	V. strong	124
311	15°52′	9.335	Weak-medium	24
222	....	....	Absent	0.4
400	19°12′	9.361	Medium-strong	40.7
331	21°1′	9.353	V. weak	9.2
420	21°30′	9.389	Medium	34.7
422	23°45′	9.361	Medium-strong	43.4
511 333	25°14′	9.380	Medium	25.4
440	27°41′	9.367	Weak-medium	22.4
531	29°3′	9.374	Medium	30.4
600 442	29°28′	9.387	Weak-medium	19.0
620	31°20′	9.358	Weak-medium	18.2
533	32°34′	9.374	V. weak	6.1
622	33°10′	9.328	V. weak	9.5
444	34°43′	9.361	V. v. weak	3.6
551 711	35°57′	9.361	Weak	9.4
640	36°23′	9.354	V. weak	7.3
642	37°58′	9.361	Weak-medium	18.2
731 553	39°6′	9.371	Weak	9.3
800	....	....	Absent	1.3
820 644	42°35′	9.376	V. weak	8.7
660 822	44°7′	9.378	V. weak	6.7
751 555	45°16′	9.380	V. v. weak	5.3
840	47°1′	9.406	V. v. weak	3.3
911 753	48°25′	9.371	V. weak	8.2
842	48°49′	9.369	V. weak	8.2
664	50°40′	9.333	V. v. weak	3.9
931	51°37′	9.363	V. v. weak	5.8
844	53°41′	9.356	V. v. weak	4.9
771 755 933	54°56′	9.354	V. weak	8.3
1000 860	55°14′	9.367	V. v. weak	4.8
1020 862	56°48′	9.378	Weak	13.6
951 773	58°10′	9.369	V. weak	7.6
Mean		9.365 Å.		

The agreement between the visually estimated intensity values and the calculated values is satisfactory. It is felt that the parameter values are reliable to within about 0.01 or 0.02; satisfactory agreement was not obtained with the zirconium parameter x equal to 0.00 instead of 0.99, nor with the N_I, N_{III} parameter $x_{I,III}$ equal to 0.25,

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[13] L. Pauling and J. Sherman, *Z. Krist.*, **81**, 1 (1932).

nor with the $[ZrF_7]^{\equiv}$ complex rotated about its three-fold axis through an angle much greater than or less than 10°.[14]

The Structure of K_3ZrF_7.—The powder photographic data for K_3ZrF_7 (Table II) are closely similar to those for $(NH_4)_3ZrF_7$, and indicate a similar structure. The value of a_0, 8.951 ± 0.010 Å., is nearly 5% less than for the ammonium salt. No reflections incompatible with a face-centered lattice were observed. The intensity values calculated for a random structure based on O_h^5 with the same parameter values as for $(NH_4)_3ZrF_7$ agree well with the estimated values. A small improvement is obtained by placing 4 K_{II} in 32 f with $x_{II} = 0.52$ instead of in 4b (corresponding to $x_{II} = 0.500$), and increasing $x_{I,III}$ from 0.28 to 0.29. Values of $I_{calcd.}$ for this arrangement are given in Table II.

TABLE II

POWDER PHOTOGRAPHIC DATA FOR K_3ZrF_7

Indices	$\theta_{measd.}$	a_0, Å.	I_{visual}	$I_{calcd.}$
111	8°35′	8.923	Medium-strong	112.0
200	9°56′	8.916	Medium	45.2
220	14°7′	8.917	V. v. strong	217.6
311	16°35′	8.935	V. weak	7.4
222	....	.....	Absent	1.9
400	20°8′	8.940	Strong	46.7
331	22°5′	8.917	V. weak	6.7
420	22°39′	8.930	Weak	12.9
422	24°54′	8.948	V. strong	86.2
511 333	26°33′	8.939	Medium	19.4
440	29°7′	8.939	Medium-strong	27.2
531	30°31′	8.958	Weak-medium	17.9
600 442	31°1′	8.954	Weak	12.0
620	32°55′	8.952	Medium-strong	24.6
533	34°20′	8.941	V. v. weak	4.0
444	36°31′	8.954	V. weak	5.8
551 711	37°48′	8.960	V. v. weak	6.1
640	38°22′	8.933	Extremely weak	2.2
642	39°56′	8.964	Medium-strong	28.6
731 553	41°10′	8.973	V. weak	7.3
800	43°20′	8.964	V. v. weak	2.4
820 644	44°56′	8.976	V. v. weak	3.9
660 822	46°42′	8.964	Medium	10.1
751 555	48°5′	8.950	V. v. weak	6.5
840	50°14′	8.950	Weak	8.0
911 753	51°31′	8.950	V. weak	7.6
842	51°58′	8.950	V. v. weak	5.7
664	53°46′	8.941	V. v. weak	5.9
931	54°56′	8.962	V. v. weak	5.5
844	57°8′	8.969	V. weak	8.2
771 755 933	58°37′	8.962	V. weak	9.8
1020 862	61°3′	8.962	Medium-strong	20.1
	Mean	8.951 Å.		

Discussion.—The interatomic distances in the crystals, Zr–F = 2.1 Å., F–F ⩾ 2.6 Å., NH_4–F ⩾ 2.6 Å., and K–F ⩾ 2.6 Å., have the magnitudes expected from comparison with other crystals. The parameter values cannot be determined with great accuracy, and the atomic positions are uncertain to about ±0.10 Å.

The existence of discrete MX_7 complexes has not been verified hitherto by structural investigation. It is probable that the configuration found for the $[ZrF_7]^{\equiv}$ ion is possessed also by IF_7 and by other complexes in which seven atoms are coordinated about a central atom. A similar coordination polyhedron is found[15] in the A-modification of La_2O_3 and other rare-earth sesquioxides, in which each rare-earth ion is surrounded by seven oxygen ions; in these crystals the neighboring MO_7 groups share oxygen ions.

It is of interest to note that whereas usually replacement of potassium ion by ammonium ion causes an increase in the dimensions of the crystal unit, a decrease is observed[16] from KHF_2 to NH_4HF_2, presumably as a result of the formation of strong N–H–F hydrogen bonds in the latter crystal. The observation that a_0 is larger for $(NH_4)_3ZrF_7$ than for K_3ZrF_7 indicates that there are not many strong N–H–F hydrogen bonds in the fluozirconate.[17]

Summary

X-Ray photographs of ammonium heptafluozirconate indicate a Laue holohedral face-centered cubic unit of structure with $a_0 = 9.365$ Å., containing 4 $(NH_4)_3ZrF_7$. The theory of space-groups provides no way of placing all of the atoms in definite positions in the unit. A structure involving some randomness of distribution among positions provided by the space group O_h^5

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[14] Satisfactory calculated intensity values were also not obtained with use of the structure factor $\left(\sin \frac{2\pi r_0}{d}\right) \Big/ \frac{2\pi r_0}{d}$ for the fluorine atoms, corresponding to random distribution over the surface of a sphere.

[15] L. Pauling, *Z. Krist.*, **69**, 415 (1929).

[16] L. Pauling, *ibid.*, **85**, 380 (1933).

[17] Weak hydrogen bonds, as in NH_4N_3 [L. K. Frevel, *ibid.*, **94**, 197 (1936)], do not lead to decrease in dimensions of crystals of ammonium compounds relative to the corresponding potassium compounds.

is found to account satisfactorily for the X-ray data. This structure is closely related to that of $(NH_4)_3AlF_6$; the $[AlF_6]^{\equiv}$ complex ions are replaced by $[ZrF_7]^{\equiv}$ complex ions in which zirconium has coördination number seven. Potassium heptafluozirconate is found to have a similar structure, with $a_0 = 8.95$ Å.

PASADENA, CALIF. RECEIVED SEPTEMBER 6, 1938

[CONTRIBUTION FROM THE WILLIAM H. CHANDLER CHEMISTRY LABORATORY OF LEHIGH UNIVERSITY]

The Binary System Cadmium Nitrate–Water: Vapor Pressure–Temperature Relations

BY WARREN W. EWING AND WALTER R. F. GUYER

This article presents the vapor pressure data for the binary system cadmium nitrate–water, and is a continuation of the series of studies being made on the alkaline earth nitrates in this Laboratory. Results for calcium nitrate, magnesium nitrate, and zinc nitrate already have been published. The alkaline earth nitrates are a particularly fruitful group for these investigations for several reasons: the water–nitrate system is quite stable; various hydrates exist, making crystalline mixture studies possible. The salts are very soluble in water, yielding solutions which can be supercooled. Vapor pressures have been obtained for a concentration as high as 86% cadmium nitrate (26 molal).

In addition to the anhydride, three hydrates of cadmium nitrate are mentioned in the literature: the dihydrate, which melts incongruently at 56.8°; the tetrahydrate, which melts congruently at 59.5°; and the enneahydrate which melts incongruently at 3.5°. Although the tetrahydrate was observed as early as 1855, by v. Hauer,[1] the existence of the dihydrate was not satisfactorily demonstrated until the work of G. Malquori[2] was published.

Sieverts and Petzold,[3] in their work on the nitrates of the second group in the periodic system, recently determined the solubility curve of the cadmium nitrate–water system. In the "I. C. T." very fragmentary data of vapor pressure for cadmium nitrate are found.

Preparation of Materials.—C. P. cadmium nitrate tetrahydrate was recrystallized three times as the tetrahydrate. The tetrahydrate was dried by putting it over 55% sulfuric acid in a vacuum desiccator. The single phase solutions were analyzed after the vapor pressure had been determined by ignition in porcelain crucibles to the oxide at 600° for two hours. These solutions had been concentrated almost to dryness in a rapid drier before ignition.

Experimental.—The vapor pressure measurements were made in the modified Smith–Menzies apparatus.[4–6] The dibutyl phthalate trap, having two capillaries, introduced by Ewing and Fisher in their work on zinc nitrate,[7] was used for all of the vapor pressure measurements.

TABLE I

THE VAPOR PRESSURES OF SATURATED SOLUTIONS OF CADMIUM NITRATE (m = metastable)

Temp., °C.	V. p., mm.	Temp., °C.	V. p., mm.
Solid phase: Tetrahydrate		Solid phase: Dihydrate	
0.00	2.93	30.00	5.26m
4.99	4.09	40.03	7.95m
9.97	5.56	49.02	10.59
15.00	7.34	49.93	10.81
19.94	9.81	51.04	11.05
24.88	12.76	52.00	11.26
29.87	16.36	52.42	11.33
35.03	20.68	53.04	11.31
40.18	25.77	54.02	11.48
45.18	30.95	55.03	11.34
50.03	36.09	55.91	11.20
55.06	39.97	56.02	11.00
56.13	40.22	56.60	10.92
57.13	40.14	Solid phase: Anhydride	
58.00	39.39	20.01	1.18m
58.96	32.88	25.00	1.56m
58.00	27.91	30.00	2.13m
57.75	26.10	35.00	2.84m
55.01	18.73	39.98	3.71m
54.86	18.56	50.03	6.45m
49.99	11.58	55.02	8.35m
44.98	7.42m	60.00	10.86
44.62	7.42m	61.43	11.58
39.97	4.80m	61.60	11.70
34.98	3.06m	70.13	17.37

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[1] v. Hauer, *Ber. Wien. Akad.*, **15**, 30 (1855).

[2] Malquori, *Gazz. chim. ital.*, **58**, 206 (1928).

[3] Sieverts and Petzold, *Z. anorg. allgem. Chem.*, **212**, 49 (1933).

[4] Smith and Menzies, THIS JOURNAL, **32**, 1448 (1910).

[5] Ewing, *ibid.*, **49**, 1963 (1927).

[6] Ewing, Klinger and Brandner, *ibid.*, **56**, 1053 (1934).

[7] Ewing and Fisher, *ibid.*, **59**, 1046 (1937).

TABLE II

THE VAPOR PRESSURE OF SOLUTIONS OF CADMIUM NITRATE (m = METASTABLE)

Soln., no.	% $Cd(NO_3)_2$	Molality		Temperature °C.						
				20	30	40	50	60	70	
1	10.900	0.517	P	17.05	31.03	54.01	90.61	146.42		
			P/P_0	0.9727	0.9751	0.9761	0.9772	0.9802		
2	23.358	1.289	P	16.26	29.60	51.56	86.64	139.86		
			P/P_0	0.9283	0.9302	0.9320	0.9365	0.9360		
3	28.908	1.720	P	15.75	28.69	50.00	83.72	135.78		
			P/P_0	0.8981	0.9014	0.9038	0.9050	0.9089		
4	43.935	3.315	P	13.78			73.82	119.92		
			P/P_0	0.7858			0.7979	0.8050		
5	49.615	4.165	P	12.71	23.14	40.62	68.28	111.26		
			P/P_0	0.7248	0.7276	0.7340	0.7382	0.7447		
6	61.701	6.814	P	9.28	17.18	30.39	51.51	84.55		
			P/P_0	0.5287	0.5400	0.5492	0.5569	0.5661		
7	65.357	7.980	P	8.09m	14.98m	26.40	44.88	74.17		
			P/P_0	0.4610	0.4709	0.4774	0.4851	0.4965		
8	69.823	9.786	P		12.02m	21.22m	36.21	60.12		
			P/P_0		0.3777	0.3839	0.3914	0.4025		
9	73.501	11.731	P		9.15m	16.25m	28.04m	47.41	76.29	
			P/P_0		0.2875	0.2938	0.3031	0.3173	0.3265	
10	78.710	15.637	P		5.70m	10.29m	18.14m	30.39	49.56	
			P/P_0		0.1791	0.1859	0.1961	0.2034	0.2121	
11	81.218	18.290	P		4.00m	7.38m	13.20m	22.45	37.25	
			P/P_0		0.1257	0.1336	0.1427	0.1502	0.1596	
12	83.132	20.845	P			6.05m	10.58m	18.23	30.36	
			P/P_0			0.1094	0.1144	0.1221	0.1315	
13	85.176	24.303	P			4.41m	7.90m	13.77	22.91	
			P/P_0			0.0797	0.0855	0.0921	0.0982	
				40	50	55	60	65	70	75
14	86.075	25.886	P	3.88m	6.99m	9.21m	12.13	15.69	20.17	25.85
			P/P_0	0.0701	0.0756	0.0781	0.0812	0.0838	0.0864	0.0894

Vapor pressure measurements were made for the following systems: (1) the metastable anhydride–tetrahydrate mixture of crystals from the eutectic melting point, 33°, to 15° (Table III); (2) the dihydrate–tetrahydrate from the eutectic melting point, 49°, to 20° (Table III); (3) the dihydrate–anhydride from the transition temperature, 56.8°, to 40° (Table III); (4) saturated solutions of the tetrahydrate, the dihydrate and the anhydride in the stable and the metastable regions (Table I); (5) fourteen solutions ranging in concentration from 10 to 86% in various temperature ranges (Table II). Table II also presents the relative humidity, P/P_0 (Babo's constant), for the fourteen solutions.

The data for the saturated solutions (Table I) are the experimental data. The data for the fourteen solutions (Table III) are tabulated for whole degrees, having been extrapolated over a short range, usually less than 0.05°, but occasionally as much as 0.10°, by obtaining the best equation of the form $\ln p = A/T + B$ for the solutions (and this was done for the crystalline

TABLE III

VAPOR PRESSURES OF MIXTURES OF CRYSTALS

Temp., °C.	V. p., mm.
(1) Anhydride–Dihydrate	
40	2.93
45	4.14
50	5.86
55	8.17
(2) Anhydride–Tetrahydrate	
15	0.70
20	1.00
25	1.45
30	1.89
(3) Dihydrate–Tetrahydrate	
20	1.48
25	2.11
30	3.04
35	4.31
40	5.94
45	8.24

mixtures also), and then calculating the change in ln/p for the temperature increment. The data are estimated to be accurate to ±0.03 mm.

Figure 1 is a plot of the complete vapor pressure data for this system over the range covered in this work. Curve AKBC is the saturated tetrahydrate curve; BC is the metastable saturated tetrahydrate curve and is supersaturated with respect to dihydrate. Curve GBH is the saturated dihydrate curve, and GB is supersaturated with respect to tetrahydrate. Curve JHCE is the anhydride saturated curve; curve HC is supersaturated with respect to dihydrate and CE is supersaturated with respect to both tetrahydrate and dihydrate.

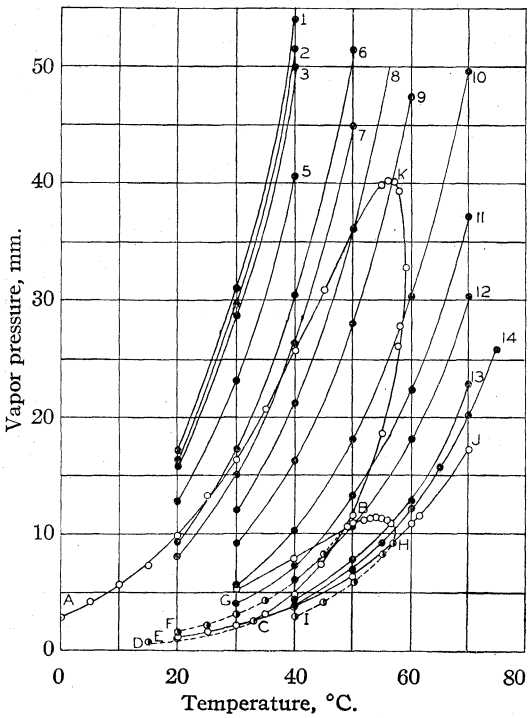

Fig. 1.—●, solution; ◑, crystalline mixture - - -; ○, saturated solution.

The tetrahydrate–dihydrate curve is FB; the anhydride–tetrahydrate, DC; and the dihydrate–anhydride, IH. (In order to avoid confusion in the curves, some of the individual points for these mixtures of crystals are not indicated, but they fall nicely on the curves.)

Solutions are numbered 1 to 14 in accordance with Table II (curve 4 is not plotted because it nearly coincides with curve 3) and are represented in the metastable regions also. The intersections of these solution curves with the saturated solution curves give the freezing points of the solutions of the respective concentrations. The freezing points obtained in this manner are plotted in Fig. 3, along with data of Sieverts and Petzold,[3] for concentrations above 50% $Cd(NO_3)_2$. The vapor pressure method confirms their data obtained by the freezing point method and extends the diagram into the metastable region.

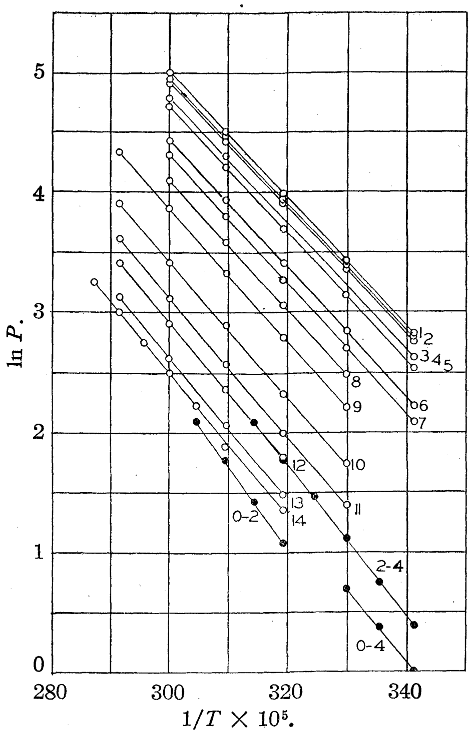

Fig. 2.

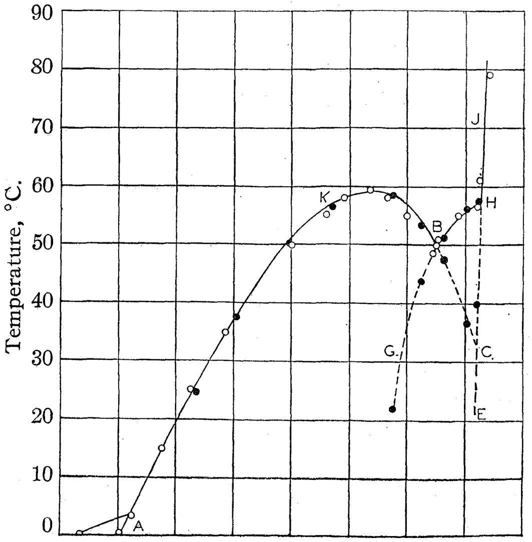

Fig. 3.—○, Sieverts, Petzold; ●, Ewing, Guyer (vapor pressure).

The equation ln $p = A/T + B$ applies to the single phase solutions and to the mixtures of crystals, as is shown in Fig. 2, which is a plot of ln p versus $1/T \times 10^5$ for the fourteen solutions and three crystalline mixtures. Straight lines result in each case.

This equation is applicable to water also in the temperature range 0 to 60° within the error in plotting on ordinary semi-log paper, but above 60° a third term has to be added to the equation. This condition also applies to our dilute solutions. For the more concentrated solutions the two term equation fits the data even more closely than it does the water data, or the dilute solution data.

Discussion

The vapor pressure measurements are considered of sufficient accuracy to study the variation of Babo's constant, P/P_0 (relative humidity), with temperature. In general, the data available up to this paper indicate that this value is constant within the experimental accuracy. Leopold and Johnston[8] stated that there would be a slight increase in relative humidity with increase of temperature for accurate measurements. Table II confirms this statement; there is a definite rise in Babo's constant with rise in temperature. This trend was found for all of the experimental data except the 20° readings for the two most dilute solutions. Duplicate determinations of these two values, however, fell in the general trend. This trend obtained regardless of the order in which the vapor pressure readings were taken for the various temperatures. This same trend has been obtained in general in all of the measurements on the nitrates in this series of studies.

Quite serious errors would arise in measuring the vapor pressure for a solution at one temperature, and then calculating the vapor pressure at another temperature, far removed, by assuming that P/P_0 is constant. For solution 6 [61.70% $Cd(NO_3)_2$], which may be considered typical, determining P/P_0 at 30° (0.5385) and then calculating the vapor pressure at 60° ($P/P_0 = 0.5661$ actually) would cause an error of 4.61%. This is an error of 3.90 mm. for the vapor pressure at this temperature.

Summary

Complete vapor pressure data for the system cadmium nitrate–water are given from 0 to 86% concentration and for the temperature range 20–60°. These vapor pressures are for the unsaturated, saturated, and supersaturated solutions, and for the mixtures of crystals.

Babo's constant (P/P_0) is shown to increase appreciably with temperature for the binary system cadmium nitrate–water.

BETHLEHEM, PENNA. RECEIVED SEPTEMBER 9, 1938

[8] Leopold and Johnston, THIS JOURNAL, **49**, 1974 (1927).

[CONTRIBUTION FROM THE LABORATORY OF PHYSIOLOGY, YALE UNIVERSITY SCHOOL OF MEDICINE]

The Standardization of Hydrogen Ion Determinations. II. A Standardization of the *p*H Scale at 38°

BY DAVID I. HITCHCOCK AND ALICE C. TAYLOR[1]

In a recent paper[2] a revision of the *p*H scale was proposed, as a result of hydrogen electrode measurements made with buffer solutions at 25°, in cells including a stationary liquid junction with saturated potassium chloride solution. This revision involved the use of the thermodynamic dissociation constants of the buffer acids together with an extrapolation based, in part, on the Debye–Hückel theory. A consistent scale was obtained for solutions of about *p*H 4 to 9. Since this range includes that part of the *p*H scale which is of primary importance in physiology and biochemistry, it seemed worth while to extend the work by making similar measurements at 38°, a temperature which is close to that of physiological fluids.

Experimental

The materials, apparatus and technique were practically the same as in the earlier work.[2] The concentrations of the solutions were expressed, as before, in moles per liter of solution at room temperature, 21–23°. The series of buffer solutions was extended by preparing mixtures of hydrochloric acid with sodium or potassium acetate or disodium hydrogen phosphate, in such proportions as to yield 1:1 buffers.

[1] This work was aided by a grant from the Fluid Research Funds of the Yale University School of Medicine.

[2] Hitchcock and Taylor, THIS JOURNAL, **59**, 1812 (1937).

TABLE I

ELECTROMOTIVE FORCE AT 38° OF THE CELL H_2, BUFFER SOLUTION, KCl (SATD.), HCl (0.1 N), H_2 (+)

Dilution factor	Composition of stock solution in moles per liter at 21–23°						
	0.0996 CH_3COOH 0.0990 CH_3COONa	0.0501 CH_3COOH 0.0501 CH_3COONa 0.0501 NaCl	0.0899 CH_3COOH 0.0898 CH_3COOK	0.0501 CH_3COOH 0.0504 CH_3COOK 0.0501 KCl	0.0250 KH_2PO_4 0.0250 Na_2HPO_4	0.0200 NaH_2PO_4 0.0200 Na_2HPO_4 0.0200 NaCl	0.0500 $Na_2B_4O_7$
0.10					0.3682	0.3680	0.4944
.25	0.2231	0.2224	0.2240	0.2232	.3642	.3637	.4936[a]
.50	.2218	.2209	.2230	.2219	.3602	.3592	.4924
.75	.2209	.2197	.2224	.2211	.3573	.3561	.4926
1.00	.2205	.2189	.2220	.2205	.3552	.3537	.4931[b]
E_0	−0.0668	−0.0673	−0.0662	−0.0669	−0.0671	−0.0671	−0.0668

[a] The dilution factor for this borax solution was 0.20 instead of 0.25. [b] Average of seven determinations with different solutions. The figure used in plotting the curve in Fig. 2 was 0.4929.

TABLE II

ELECTROMOTIVE FORCE AT 38° OF THE CELL

H_2, HCl + MCl, KCl(satd.), HCl(0.1 N), H_2 (+)

Dilution factor	Composition of stock solution in moles per liter at 21–23°		
	0.1000 HCl (no salt)	0.0100 HCl 0.0900 NaCl	0.0100 HCl 0.0900 KCl
0.10	0.0602	0.1208	0.1211
.25	.0362	.0969	.0973
.50	.0180	.0787	.0793
.75	.0075	.0680	.0687
1.00	.0000	.0604	.0613
E_0	−0.0657	−0.0668	−0.0665

In addition to the control of temperature given by the water-jacketed electrode vessels, which remained at 38 ± 0.05°, the whole apparatus was placed in an electrically controlled air-bath at 38 ± 0.5°. This served to prevent the deposition of solid potassium chloride in the bridge tubes and the condensation of moisture in the hydrogen train. The purity of the commercial hydrogen was tested in a few experiments by passing it over hot reduced copper; since this purification produced no change in the electromotive force obtained with hydrochloric acid (*p*H 1 or 2) or borax solutions (*p*H 9), it was generally omitted, and the hydrogen was passed only through distilled water at 38°. As before, the experiments consisted in the measurement of the electromotive force of cells of the type

H_2, acid or buffer solution, KCl (satd.), HgCl, Hg (+) (A)

Several different calomel half cells were used at different times, and their constancy and reproducibility were tested by daily measurements against hydrogen electrodes in 0.1 N hydrochloric acid or an acetate buffer. Since the different calomel cells varied, in some cases, by as much as a millivolt, the results were expressed in terms of the following cell, of which the right half served as a constant reference electrode

H_2, acid or buffer solution, KCl (satd.), HCl (0.1 N), H_2 (+) (B)

The values of the electromotive force of this cell are given in Tables I and II.

Method of Calculation and Extrapolation

Tables I and II include also values of E_0, the extrapolated value of the electromotive force which cell B would have if the activity of hydrogen ions in the solution in the left half cell were unity. The values of E_0 were obtained by extrapolation to zero ionic strength of a function E'', obtained from the experimental results by the following equations

Acetate buffers: $$E'' = E - 0.06173\left(4.766 - \log \frac{C_{HA}}{C_A} - 0.520\sqrt{\mu}\right)$$

Phosphate buffers (1:1): $$E'' = E - 0.06173\,(7.190 - 1.560\sqrt{\mu})$$

Borax buffers: $$E'' = E - 0.06173\left(9.143 - \log \frac{C_{HA}}{C_A} - 0.520\sqrt{\mu}\right)$$

Hydrochloric acid solutions: $$E'' = E + 0.06173\,(\log C_H - 0.520\sqrt{\mu})$$

The basis of similar equations was given in the previous paper.[2] Here E is the electromotive force of cell B in volts, 0.06173 is 2.3026 RT/F, 0.520 is the constant of the Debye–Hückel limiting law, μ is the ionic strength of the solution and the numbers 4.766, 7.190 and 9.143 are the negative logarithms of the thermodynamic dissociation constants of the buffer acids, interpolated for 38° from the data of Harned and Ehlers,[3] Nims[4] and Owen,[5] respectively. The ionic strength was calculated on the basis of concentration, in moles per liter at 21–23°, and the same basis was used for C_H of the hydrochloric acid solutions. Strictly this is not consistent with the pK values used, which were obtained on the molal basis. Density determinations showed a maximum discrepancy of 1.2% between the values of C and m for certain solutions at 0.1 ionic strength, but this difference becomes less than 0.25% for very dilute solutions. It was calculated that these differences could not affect the values of E'' and E_0 by more than 0.1 mv., and that the extrapolation therefore yielded

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[3] Harned and Ehlers, THIS JOURNAL, **55**, 652 (1933).

[4] Nims, *ibid.*, **55**, 1946 (1933).

[5] Owen, *ibid.*, **56**, 1695 (1934).

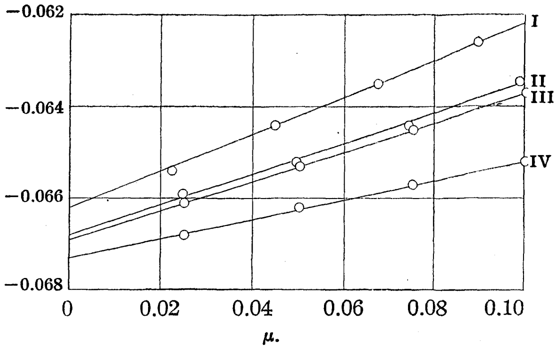

Fig. 1.—Extrapolation of hydrogen electrode data for 1:1 acetate buffers at 38°: I, $CH_3COOH + CH_3COOK$; II, $CH_3COOH + CH_3COONa$; III, $CH_3COOH + CH_3COOK + KCl$; IV, $CH_3COOH + CH_3COONa + NaCl$.

a *p*H scale consistent with thermodynamic dissociation constants expressed in terms of molality. The nature of the extrapolations is illustrated by Figs. 1, 2 and 3.

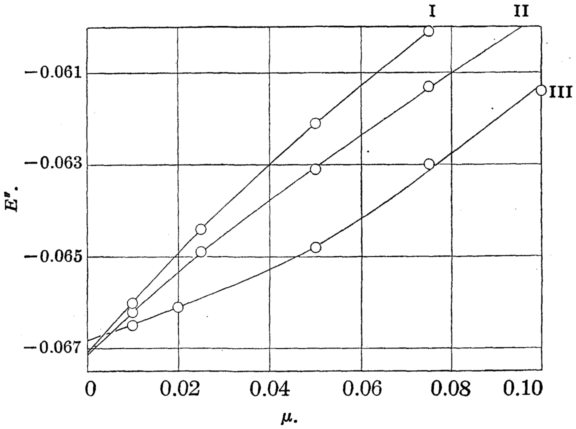

Fig. 2.—Extrapolation of hydrogen electrode data for 1:1 phosphate and borate buffers at 38°: I, $KH_2PO_4 + Na_2HPO_4$; II, $NaH_2PO_4 + Na_2HPO_4 + NaCl$; III, $Na_2B_4O_7$.

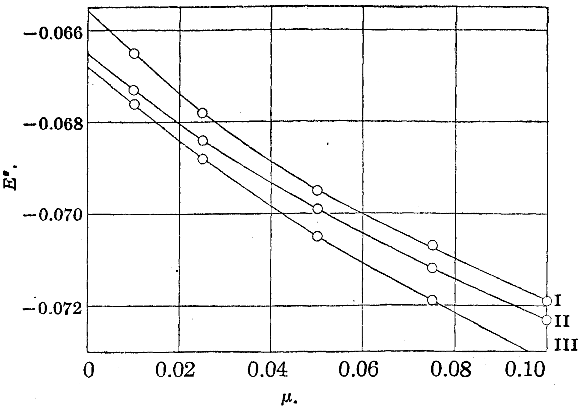

Fig. 3.—Extrapolation of hydrogen electrode data for hydrochloric acid solutions at 38°: I, HCl without salt; II, HCl + KCl (1:9); III, HCl + NaCl (1:9).

Results

The E_0 values for the buffer mixtures at 38°, as given in Tables I and II, are less concordant than those obtained for 25°. There is evidence of a specific effect of different ions, in the order to be expected if the E_0 values include a part of the liquid junction potentials. Solutions containing cations of higher mobility (hydrogen or potassium in place of sodium ions) yielded higher values of E'' and E_0, while those containing anions of higher mobility (chloride in place of acetate or phosphate ions) yielded lower values. If the high figure obtained for the hydrochloric acid solutions without salt is disregarded, as in the previous work[2] at 25°, the mean value of E_0 is −0.0668, with an average deviation of ±0.0002 v. This value, which is identical with that obtained for solutions of hydrochloric acid with sodium chloride (*p*H 2 to 3), acetic acid with sodium acetate (*p*H 4.7), and borax (*p*H 9), was adopted as a basis for a *p*H scale applicable at 38°. The *p*H values were calculated, without correction for liquid junction potentials, by the usual simple equation, which is

$$pH = (E + 0.0668)/0.06173$$

for cell B at 38°.

In Table III are given the *p*H values obtained in this way for a number of standard solutions which may be used for checking electrodes. Values obtained for the same solutions at 25° are included for comparison. Except for 0.1 *N* hydrochloric acid, whose *p*H value is determined by that of E_0 for cell B, the results are reported only to the nearest 0.005 *p*H, which corresponds to 0.3 mv. Since more measurements were made with 0.1 *N* hydrochloric acid and with the 0.1 *N* acetic acid–sodium acetate buffer than with other

TABLE III

STANDARD SOLUTIONS FOR CHECKING ELECTRODES AT 38 AND 25°

Composition in moles per liter at 21–23°	*p*H (38°)	*p*H (25°)
0.1 HCl	1.082	1.085
.1 $KH_3(C_2O_4)_2 \cdot 2H_2O$	1.495	1.480[a]
.01 HCl + 0.09 KCl	2.075	2.075
.05 $KHC_8H_4O_4$	4.025	4.010
.1 CH_3COOH + 0.1 CH_3COONa	4.655	4.645
.025 KH_2PO_4 + 0.025 $Na_2HPO_4 \cdot 2H_2O$	6.835	6.855
.05 $Na_2B_4O_7 \cdot 10H_2O$	9.070	9.180

[a] The *p*H value 1.490, which was published previously[2] for 25°, referred to a tetroxalate solution of lower concentration, 0.0965 *M*.

solutions, their values are particularly recommended as a basis for a *p*H scale applicable at 38°.

Discussion

Table III includes *p*H values for 0.1 *N* hydrochloric acid, although the E_0 values obtained from experiments with this acid alone were not used. This procedure did not invalidate the use of this solution in the reference half cell, since the *p*H scale was determined by the behavior of the various solutions in the left half of cell B. In spite of the discordant E_0 value obtained from data with more dilute hydrochloric acid, it seemed desirable to assign to 0.1 *N* hydrochloric acid, which is a reproducible standard solution, *p*H values consistent with those of the acid–salt mixtures and the buffer solutions.

There is practically no difference between the *p*H values obtained for hydrochloric acid of ionic strength 0.1, either with or without salt, at 25 and 38°. It may be calculated from the data of Harned and Ehlers[6] that the negative logarithm of the mean activity of the ions in 0.1 molal hydrochloric acid is 1.099 at 25° and 1.102 at 38°. Evidently the effect of temperature on these thermodynamic activities is of the same small magnitude as its effect on the non-thermodynamic *p*H values for hydrochloric acid solutions.

The *p*H values given in Table III for the buffer solutions show a somewhat larger variation with temperature, although the effect exceeds 0.02 *p*H in only one case. For the acetate, phosphate and borate solutions the differences, *p*H (25°) − *p*H (38°), are −0.01, +0.02 and +0.11, respectively. The corresponding differences in the *pK* values of the buffer acids at the two temperatures are −0.010, +0.016 and +0.094. Although it is recognized that *p*H values cannot have a strictly thermodynamic significance, it seems worth while to point out that an agreement between these two sets of differences might be deduced from the thermodynamic law of mass action if *p*H were a measure of either the concentration or the activity of hydrogen ions and if the variation with temperature of the activity coefficients of the buffer acids were negligibly small.

The only previous work in which a scale of *p*H values has been based on thermodynamic dissociation constants is that of MacInnes.[7] His experimental data, which have appeared in a paper by MacInnes, Belcher and Shedlovsky,[8] were obtained principally with very dilute acetate buffers, 0.001 to 0.01 in ionic strength, and were extrapolated by a method which gives marked curvature when applied to results for higher concentrations. If their data for 25° are reduced to our reference electrode and plotted by our method, they agree fairly well with ours at 0.01 ionic strength. Below that point, where we have no data, their results approach an E_0 value about 0.5 mv. higher than ours. Hence their *p*H scale should be lower than ours by about 0.008 *p*H. A comparison of their Table VII with Table III of the present paper shows that this is approximately true, except for their 0.1 *N* acetate buffer at 38°. Here they give a *p*H value slightly lower than their value for 25°, while our *p*H value, like that of *pK*, is about 0.01 unit higher for 38 than for 25°. For many purposes a discrepancy of 0.01 *p*H is not significant. It may be concluded that either our scale or theirs gives *p*H values which are reasonably consistent with thermodynamic dissociation constants.

Our work on the standardization of hydrogen ion determinations is being continued by an experimental study of a measure of acidity obtained from cells without liquid junction, according to ideas expressed by Guggenheim[9] and by one of us.[10]

Summary

Measurements of electromotive force at 38° are reported for cells of the type

H_2, buffer or acid solution, KCl (satd.), HCl (0.1 *N*), H_2 (+)

Acetate, phosphate and borax buffers were used, as well as solutions of hydrochloric acid with and without an added chloride. On the basis of the thermodynamic dissociation constants of the buffer acids and a nearly linear extrapolation, a value of E_0 was obtained for the reference electrode: KCl (satd.), HCl (0.1 *N*), H_2. On this basis *p*H values for 38° were assigned to several standard solutions, including 0.1 *N* hydrochloric acid (*p*H 1.082) and 0.1 *N* acetic acid in 0.1 *N*

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[6] Harned and Ehlers, THIS JOURNAL, **55**, 2179 (1933).

[7] MacInnes, *Cold Spring Harbor Symposia on Quantitative Biology*, **1**, 190 (1933). We wish to acknowledge again the courtesy of Dr. MacInnes in supplying us with unpublished data for comparison with our own, and to express our regret over the premature publication of two *p*H values ascribed to him in Table III of our previous paper.[2] These values should be replaced by those given later by MacInnes, Belcher and Shedlovsky.[8]

[8] MacInnes, Belcher and Shedlovsky, THIS JOURNAL, **60**, 1094 (1938).

[9] Guggenheim, *J. Phys. Chem.*, **34**, 1758 (1930).

[10] Hitchcock, THIS JOURNAL, **58**, 855 (1936); **59**, 2753 (1937).

sodium acetate (*p*H 4.655). These *p*H values, without correction for liquid junction potentials, serve to establish a *p*H scale which may be used to obtain the values of thermodynamic dissociation constants at 38°.

New Haven, Conn. Received July 29, 1938

[Contribution from the Chemical Laboratory of the University of Illinois and the Williams Oil-O-Matic Heating Corporation]

Hydrogen Bonds Involving the C–H Link. V. The Solubility of Methylene Chloride in Donor Solvents

By M. J. Copley, G. F. Zellhoefer and C. S. Marvel

Recent publications[1–3] by the authors have shown that hydrogen bonding, involving the C–H link, occurs in solutions of the haloforms in solvents containing the donor atoms, oxygen or nitrogen. In one article[1] data were included on the solubilities of the two dihalogenated methanes, methylene chloride and monofluoromonochloromethane, in three donor solvents (diethylene glycol dimethyl ether, ethyl ether of diethylene glycol acetate and tetraethylene glycol dimethyl ether). Their solubilities were in considerable excess of the values predicted by Raoult's law and almost comparable with the solubilities observed for the haloforms in the same solvents. These results led the authors to suggest that a hydrogen atom of a dihalogenated methane is also capable of forming a hydrogen bond with an oxygen or nitrogen atom having an exposed pair of electrons. Such an activity for hydrogen bonding on the part of the hydrogen atoms, in these very stable compounds, was somewhat unexpected and it seemed important to extend the investigation to include a larger number of types of solvents.

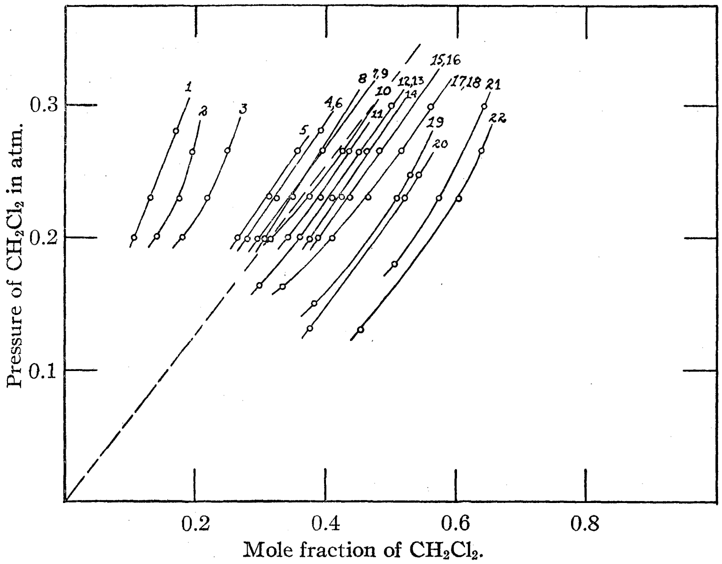

Fig. 1.—The solubility of methylene chloride as a function of pressure in alcohols, ethers, acids, esters, aldehydes, and ketones: 1, phenol; 2, acetic acid; 3, propionic acid; 4, anisole; 5, salicylaldehyde; 6, phenyl vinyl ether; 7, benzaldehyde; 8, Δ^2-cyclohexenone; 9, acetylacetone; 10, paraldehyde; 11, heptaldehyde; 12, ethyl acetoacetate; 13, triphenyl phosphite; 14, cyclohexanone; 15, acetonylacetone; 16, 1,4-dimethoxycyclohexane; 17, ethyl diethylacetoacetate; 18, tri-*o*-cresol phosphate; 19, ethyl ether of diethylene glycol acetate; 20, diethyl ether of diethylene glycol; 21, tri-*n*-butyl phosphate; 22, dimethyl ether of tetraethylene glycol.

The present paper reports the solubilities of methylene chloride in the same group of solvents[3] as was used by the authors in their study of the effect of solvent association on the solubility of haloforms. The remarkable similarity we have observed in the behaviors of dihalogenated methanes and haloforms clearly demonstrates that a hydrogen atom in either type of compound interacts with an unshared pair of electrons on an oxygen or nitrogen atom of a solvent and thus gives rise to the phenomenon called hydrogen bonding.

Experimental

The method[4] used in making the solubility determinations has been described previously in detail. The solvents tested were purified carefully and their boiling or melting points checked. The solubilities were determined over a range of pressure at a temperature of 32.2°. The results of the solubility measurements are plotted in Figs. 1 and 2. To compare the solvents conveniently, the gram per gram and mole fraction solubilities at a partial pressure of methylene chloride corresponding to its vapor pressure at 4.5° are given, re-

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(1) Zellhoefer, Copley and Marvel, This Journal, **60**, 1337 (1938).

(2) Zellhoefer and Copley, *ibid.*, **60**, 1343 (1938).

(3) IV, Copley, Zellhoefer and Marvel, *ibid.*, **60**, 2666 (1938).

(4) G. F. Zellhoefer, *Ind. Eng. Chem.*, **29**, 584 (1937).

spectively, in columns 3 and 4 of Table I. The "ideal" or theoretical mole fraction stated at the top of Table I is calculated using Raoult's law, and it is the ratio of the vapor pressure (0.230 atm.) of methylene chloride at 4.5° to its value (0.739 atm.) at 32.2°. The statement in Table I that the solubility of methylene chloride in each of the two compounds, acetamide and diphenylamine, is *very low* is based on the observation that when these compounds were melted (they are solids at 32.2°) and brought in contact with the vapor of the solute only a minute amount of it dissolved.

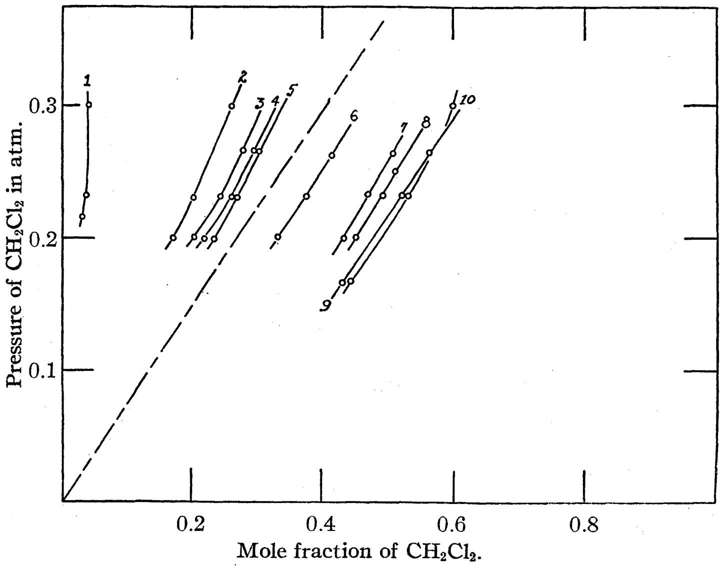

Fig. 2.—The solubility of methylene chloride as a function of pressure in amines, amides, and oximes: 1, formamide; 2, methylformamide; 3, ethyl methyl ketoxime; 4, dimethylformamide; 5, N-methylacetamide; 6, cyclohexylamine; 7, dimethylacetamide; 8, N-methyl-N-cyclohexyl-*n*-butanesulfonamide; 9, N-methyl-N-cyclohexylacetamide; 10, N-ethyl-N-cyclohexylacetamide.

Discussion

A comparison of the solubilities which we have observed for methylene chloride with those reported in a previous communication[3] for monofluorodichloromethane, in the same group of solvents, shows that these two compounds correspond almost exactly in the manner in which their solubilities vary in different types of solvents. In unassociated solvents (ethers, esters, amines and N-disubstituted amides) they both show uniformly high solubilities compared to the values predicted for them by Raoult's law. In solvents which are associated into large polymers (alcohols and amides), by means of the more stable O–H–O and N–H–O bonds, they both show extremely low solubilities compared to the solubilities calculated for them by Raoult's law. In fatty acids, N-monosubstituted amides, and oximes, where the association of the solvent stops at the dimer stage, they have intermediate or almost normal solubilities. It also should be noted that the influence of each of the factors, unsaturation and chelation, is to produce a lowering of solubility in the case of each compound in solvents where these factors are present.

The similar solubilities of methylene chloride and monofluorodichloromethane in widely differ-

TABLE I

SOLUBILITY OF METHYLENE CHLORIDE IN ORGANIC SOLVENTS

(Theoretical or "Ideal" Mole Fraction in Saturated Solution 0.311)

	Formula	Solubility G./g.	Solubility Mole fr.
	Alcohols and Ethers		
Phenol	C_6H_5OH	0.210	0.130
Anisole	$C_6H_5OCH_3$	.385	.328
1,4-Dimethoxycyclohexane	$C_6H_{10}(OCH_3)_2$	.460	.442
Diethyl ether of diethylene glycol	$C_2H_5O(CH_2CH_2O)_2C_2H_5$	.568	.520
Dimethyl ether of tetraethylene glycol	$CH_3O(CH_2CH_2O)_4CH_3$	.580	.602
	Acids and Esters		
Acetic acid	CH_3COOH	0.280	0.174
Propionic acid	C_2H_5COOH	.320	.218
Triethyl phosphate	$(C_2H_5)_3PO_4$	.55	.541
Tri-*n*-propyl phosphate	$(C_3H_7)_3PO_4$	.50	.567
Tri-*n*-butyl phosphate	$(C_4H_9)_3PO_4$	.435	.574
Triphenyl phosphite	$(C_6H_5)_3PO_3$	.192	.412
Tri-*o*-cresol phosphate	$(C_6H_4OCH_3)_3PO_4$	.213	.470
Ethyl ether of diethylene glycol acetate	$C_2H_5O(CH_2CH_2O)_2COCH_3$	.500	.509
Ethyl acetoacetate	$CH_3COCH_2COOC_2H_5$	.454	.410
Ethyl diethylacetoacetate	$CH_3COC(C_2H_5)_2COOC_2H_5$	.403	.468

TABLE I (*Concluded*)

	Formula	Solubility G./g.	Solubility Mole fr.
	Amines, Amides and Oximes		
Cyclohexylamine	$C_6H_{11}NH_2$	0.520	0.377
Diphenylamine	$(C_6H_5)_2NH$	Very low	...
Formamide	$HCONH_2$	0.062	.038
Methylformamide	$HCONHCH_3$	.365	.202
Dimethylformamide	$HCON(CH_3)_2$	.410	.261
Acetamide	CH_3CONH_2	Very low	...
N-Methylacetamide	$CH_3CONHCH_3$	0.427	.269
N,N-Dimethylacetamide	$CH_3CON(CH_3)_2$	.808	.452
N-Methyl-N-cyclohexyl-*n*-butanesulfonamide	$C_4H_9SO_2N(CH_3)C_6H_{11}$	.351	.490
N-Methyl-N-cyclohexylacetamide	$C_6H_{11}N(COCH_3)CH_3$	.600	.521
N-Ethyl-N-cyclohexylacetamide	$C_6H_{11}N(COCH_3)C_2H_5$	.565	.530
Ethyl methyl ketoxime	$C_2H_5(CH_3)C{=}NOH$	.315	.244
	Aldehydes and Ketones		
Benzaldehyde	C_6H_5CHO	0.430	0.349
Salicylaldehyde	*o*-$C_6H_4(OH)CHO$	.320	.315
Heptaldehyde	$CH_3(CH_2)_5CHO$	.473	.388
Paraldehyde	$C_6H_{12}O_3$	.385	.374
Cyclohexanone	$C_6H_{10}O$	.630	.421
Δ^2-Cyclohexenone	C_6H_8O	.473	.349
Acetylacetone	$CH_3COCH_2COCH_3$	.455	.394
Acetonylacetone	$CH_3COCH_2CH_2COCH_3$	.572	.434

ent types of solvents show that the same influence, *viz.*, complex formation by means of hydrogen bonding, is operative in the solutions of each compound.

Summary

The solubilities of methylene chloride have been determined over a range of pressure in several types of organic solvents.

The solubilities are high in esters, ethers, amines and N-disubstituted amides; roughly normal in acids, N-monosubstituted amides and oximes; extremely low in alcohols, and amides.

The remarkable similarity between methylene chloride and monofluorodichloromethane with respect to the way in which their solubilities vary in different types of solvents shows that hydrogen bonding is also present in solutions of methylene chloride in donor solvents.

URBANA AND BLOOMINGTON, ILLINOIS

RECEIVED SEPTEMBER 9, 1938

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF EMORY UNIVERSITY]

A Study of Organic Parachors. I. The Parachors of a Series of Isomeric Esters[1]

BY OSBORNE R. QUAYLE, KATHERINE OWEN AND REIDUS R. ESTES[2]

Of the many attempts to relate physical properties and structure the parachor[3] has been one of the most successful. It has been of value in the determination of semi-polar bonds,[4] chelation,[5] singlet linkages[6] and degree of aromaticity and unsaturation.[7] From his first observations Sugden[3] concluded that the assigned constants held for all series, that the parachor was not influenced by temperature and that the parachors of isomers were identical. The differences between calculated and observed parachors and the differences between isomers were ascribed to experimental error. However, the parachors of branched heptanes[8] and octanes[9] were found to be

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(1) The authors wish to express their appreciation to Prof. E. Emmet Reid for his kindness in supplying the esters measured and for his valuable practical suggestions on the problem.

(2) Abstracted from a thesis by Reidus R. Estes presented to the Graduate Faculty of Emory University in partial fulfilment of the requirements for the degree of Master of Science, June, 1938.

(3) S. Sugden, *J. Chem. Soc.*, **125**, 1177 (1924).

(4) S. Sugden, J. B. Reed and H. J. Wilkins, *ibid.*, **127**, 1525 (1925).

(5) S. Sugden, *ibid.*, 318 (1929).

(6) S. Sugden, *ibid.*, 1173 (1927).

(7) S. Sugden, "The Parachor and Valency," Alfred A. Knopf, New York, N. Y., 1930, pp. 38–40.

(8) G. Edgar and G. Calingaert, THIS JOURNAL, **51**, 1540 (1929).

(9) T. W. Richards, C. L. Speyers and E. K. Carver, *ibid.*, **46**, 1196 (1924).

TABLE I

SURFACE TENSIONS AND MOLECULAR VOLUMES

Ester	Symbol	Surface tension at 26°	35°	50.5°	65°	T'°	Mol. vol. M/D'
Methyl pentadecylate	1–15	29.41	28.38	27.35	26.11	54.4	305.4
Ethyl myristate	2–14	29.16	28.26	26.73	25.19	47.2	304.9
Propyl tridecylate	3–13	28.74	27.89	26.55	25.12	45.2	305.1
Butyl laurate	4–12	28.29	27.47	26.34	25.21	41.8	304.1
Amyl undecylate	5–11	28.22	27.25	26.07	24.94	39.6	303.4
Hexyl decylate	6–10	28.20	27.26	26.00	24.56	38.5	303.4
Heptyl pelargonate	7–9	28.07	27.10	26.25	24.61	27.8	303.1
		26°	35°	50°	65°		
Octyl caprylate	8–8	28.20	27.12	25.88	24.65	37.2	302.9
		25°	35°	50°	65°		
Nonyl heptoate	9–7	28.15	27.51	26.37	25.07	40.8	304.0
Decyl caproate	10–6	28.66	27.61	26.13	24.95	41.7	304.2
Undecyl valerate	11–5	28.39	27.71	26.38	25.26	43.0	304.3
Lauryl butyrate	12–4	28.80	28.18	26.74	25.41	47.2	305.4
Tridecyl propionate	13–3	29.40	28.68	27.35	26.13	55.8	307.4
Tetradecyl acetate	14–2	29.73	28.91	27.47	26.03	55.2	307.0
Pentadecyl formate	15–1	30.40	29.38	28.36	26.54	61.2	307.3

Surface tension = γ = 27 dynes/cm. at T'°; D' = density at T'°.

consistently lower than those of the normal isomers. The parachors of the lower members of the fatty acids series were found to be consistently higher than the calculated while the reverse was true of the higher members of the series.[10] Since many of these variations are greater than experimental error, it has been recognized that the parachor is constitutive as well as additive.[11]

The deviations from calculated parachors have thrown doubt upon the value of this physical constant. Certain regularities in these deviations from the hitherto accepted theoretical values have appeared. Further investigations of these deviations should be made. If the deviations are, in fact, generally or even frequently regular in nature, as a result of constitutive differences, the parachor will become of more rather than of less value once these regularities are determined.

This paper concerns the results of parachor measurements at four temperatures (25, 35, 50, 65°) of fifteen normal isomeric esters of the formula $C_{16}H_{32}O_2$.[12] Desreux[13] questioned the validity of comparing parachors calculated from unequal surface tensions because of the variation of C in Macleod's[14] relation, $\gamma = C(D-d)^4$. Since the comparison of parachors is tantamount to the comparison of molecular volumes at constant surface tension, it should be possible to overcome this objection by calculating molecular volumes from densities taken at temperatures where the surface tensions equal some convenient arbitrarily chosen

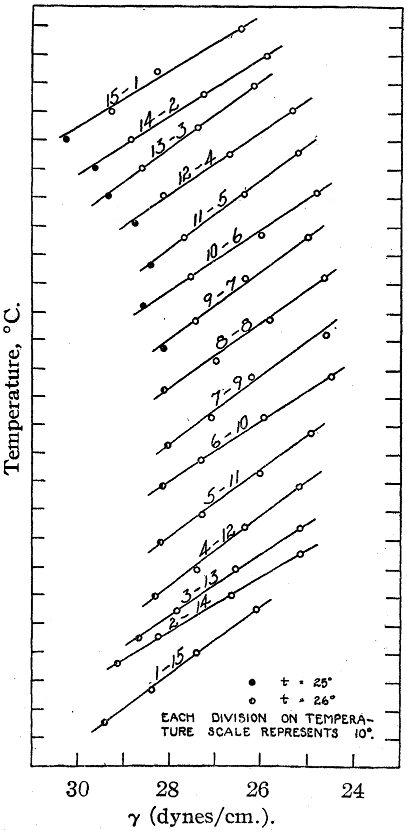

Fig. 1.—Variation of surface tension with temperature.

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(10) K. W. Hunten and G. L. Maas, THIS JOURNAL, **51**, 161 (1929).

(11) S. A. Mumford and J. W. C. Phillips, *J. Chem. Soc.*, 2112–2158 (1929); and others.

(12) The esters were prepared by J. R. Ruhoff and E. Emmet Reid, THIS JOURNAL, **55**, 3825–3828 (1933).

(13) V. Desreux, *Bull. soc. chim. Belg.*, **44**, 249–287 (1935).

(14) Macleod, *Trans. Faraday Soc.*, **19**, 38 (1923).

value (27 dynes/cm.). The surface tension–temperature relation was found to be linear within experimental error (±0.40%) over the 25–65° range studied (Fig. 1). Surface tensions used in calculating parachors were interpolated from graphs of experimental values (Fig. 1).

Densities of the esters were obtained by interpolation from the recorded values.[12] With one exception, the parachor was found to increase with the temperature (typical illustrative curves, Fig. 2), the maximum variation being 10.24 or 1.45%.

TABLE II

PARACHORS AT FOUR TEMPERATURES[15]

Ester	Parachors at 25°	35°	50°	65°
1–15	693.0	694.2	695.7	697.2
2–14	695.3	695.4	695.0	695.1
3–13	694.1	694.9	695.7	696.3
4–12	691.0	692.3	694.2	696.2
5–11	689.9	692.6	692.3	693.6
6–10	689.3	691.1	691.5	692.2
7–9	689.4	690.5	692.1	693.6
8–8	689.9	690.4	690.7	691.0
9–7	690.7	692.1	694.3	696.2
10–6	692.4	693.4	693.8	694.6
11–5	691.1	693.2	694.5	694.8
12–4	693.9	695.0	696.3	697.5
13–3	696.6	697.9	700.0	701.8
14–2	697.6	698.5	699.6	700.5
15–1	699.1	699.5	700.1	700.5

The parachor at all four temperatures measured and molecular volume when $\gamma = 27$ dynes/cm. showed a gradual decrease from either end of the series to a minimum for the central members (Figs. 3 and 4). The parachor values at 25° fall more nearly on a smooth curve than at higher temperatures. The general shape of the curve, however, at all the temperatures measured is unmistakably the same. The parachor variation in the series was found to be 9.67 or 1.38% at 25°, and 13.10 or 1.86% at 65° (Table II) while that for molecular volumes was found to be 4.51 or 1.46% (Table I) (estimated experimental error in parachor, ±0.20%).

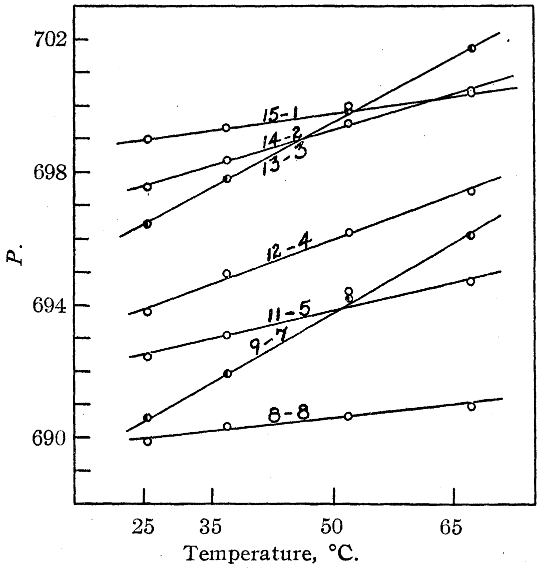

Fig. 2.—Variation of parachor with temperature.

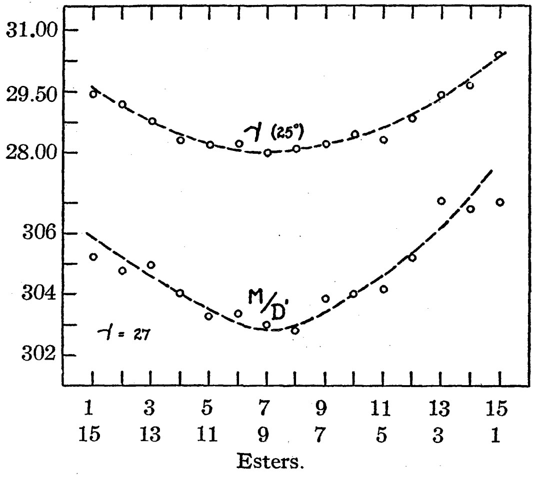

Fig. 3.—Variation of surface tension and molecular volume.

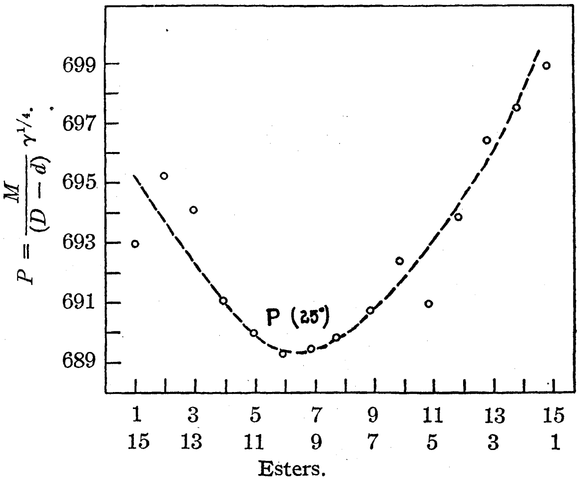

Fig. 4.—Variation of the parachor in the series.

Since unsaturation increases the parachor, it is indicated that the unsaturation of the ester group suffers least reduction by the combination of small and large groups present near the ends. Thus the parachor of methyl pentadecylate is 6.12 units less than that of pentadecyl formate

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[15] The calculated value of the parachor for each of these esters, using the atomic constants of Mumford and Phillips,[11] is 699.0.

because of greater reduction of unsaturation by the methyl group in the former than by the hydrogen in the latter.

Similarly, large values for formates and small values for branched isomers have been observed in eight pairs of esters by Wender[16] in a study of parachors previously determined or calculated from previously recorded surface tensions.

Experimental.—Surface tensions were measured by Sugden's[3] modification of the method of maximum bubble pressure, using *m*-xylene[13] in the manometer and carefully purified benzene as a standard[17] for calibration of the apparatus. To ensure equal hydrostatic pressures, a maximum stable bubble was left on the large capillary while bubble pressures were being measured from the small capillary.[13] The manometer readings were taken with a cathetometer with an accuracy of 0.01 cm. Temperatures were controlled to ±0.08°. After calibration of the bubbler using accepted values of benzene (28.88 dynes/cm. at 20°),[18] readings were taken to check the calibration of CCl_4 and C_6H_5Cl. The observed values of 26.77 and 33.25 (20°) agree with accepted values (26.81 and 33.2).

Summary

1. The surface tensions of 15 normal isomeric esters ($C_{16}H_{32}O_2$) have been measured at 25, 35, 50, and 65° by the method of maximum bubble pressure.

2. The calculated parachors were found to decrease gradually from maxima of 695.3 and 699.1 at the ends of the series to a minimum of 689.3 near the center of the series.

3. Molecular volumes calculated from densities taken at constant surface tension (27 dynes/cm.) varied similarly to parachor.

4. The parachors were found to increase, in general, with the temperature.

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[16] Simon Wender, Emory University thesis, 1935, unpublished.

[17] S. Sugden, *J. Chem. Soc.*, **119**, 1483 (1921).

[18] Richards and Carver, THIS JOURNAL, **43**, 827 (1921).

EMORY UNIV., GA. RECEIVED AUGUST 29, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF OREGON STATE COLLEGE]

Pantothenic Acid. II. Its Concentration and Purification from Liver

BY ROGER J. WILLIAMS, JOHN H. TRUESDAIL, HARRY H. WEINSTOCK, JR., EWALD ROHRMANN, CARL M. LYMAN AND CHAS. H. MCBURNEY

In the first article of this series[1] was announced the discovery of a growth determinant of universal biological occurrence, which was named "pantothenic acid." At the time of this initial report no progress had been made toward the concentration or isolation of the substance and the evidence for the existence of a single effective substance in the various sources was based upon electrolytic, diffusion, hydrogenation, esterification and other experiments in which the behavior of the physiologically active principle was the crucial question.

The concentration of a substance offering the particular difficulties encountered in connection with pantothenic acid had never been accomplished previously and much exploration was required before effective methods could be devised. The difficulties mentioned are based upon the following facts. (1) It is predominantly an acid rather than a basic substance and hence the techniques and precipitants extensively useful with nitrogenous bases cannot be applied except indirectly. (2) The richest convenient source (liver) contains on the order of 40 parts per million, and hence 250 kg. of liver after an extended process yielded only about 3 g. of crude (approximately 40%) material from which the remaining impurities were removed with great difficulty. (3) The substance is highly hydrophilic and we have yet to find any salt or simple derivative which is not highly soluble in water. (4) Due, presumably, to the presence of several types of functional groups, even after purification the substance has failed to crystallize.[2] In this respect it appears to behave somewhat like β-hydroxyglutamic acid, which, according to Dakin,[3] makes up 10% of casein; yet is not available on the market at any price. (5) Pantothenic acid is itself

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[1] Williams, Lyman, Goodyear, Truesdail and Holaday, THIS JOURNAL, **55**, 2912 (1933).

[2] We are indebted to Professor Linus Pauling for X-ray examination of a sample which was suspected of possessing crystalline character. No diffraction pattern was observed and further study confirmed the non-crystalline character of the material.

[3] H. Dakin, *Biochem. J.*, **12**, 290-317 (1918).

unstable and can be handled safely only as a neutral salt. It is readily broken down by acids or bases and is particularly susceptible to destruction by acidic alcohol. (6) Unlike riboflavin and ascorbic acid, pantothenic acid could be tested for by biological tests only, since it has no color, reducing properties or other known outstanding property which can be used as a guide during its isolation. (7) Unlike the amino acids and biotin,[4] pantothenic acid has not been purified successfully by distillation of its ester. Whereas in later studies we have found it possible to esterify it and hydrolyze the ester without great loss, the process is attended by complete destruction unless carefully controlled, and the use of the ester (which seems scarcely more volatile than the acid itself) did not offer promise as a means of purification.

The crucial problem was first to devise some method whereby the acid could be separated from a variety of sugars and other neutral or basic water-soluble material. A solution to this problem was found in converting the acid into its brucine salt (as explained below) and extracting with chloroform, which fails to dissolve the sugars and similar compounds. It was found better to adsorb the acid on charcoal and elute first and later apply the brucine salt conversion. The essential steps in the process as applied to a 9-kg. batch of liver are given below. Sheep liver was used because of its uniformity and convenience. Beef or hog liver can be used. It was necessary, of course, that biological tests be made continuously during the process of concentration. For this purpose "G. M." yeast, the medium previously described[5] and the techniques previously developed[5,6] were used. As a standard material we used first a stable preparation made by the extraction of rice bran with 60% methanol, and assigned to this dry material a "potency" of 1. Other preparations were compared to this *at low dosage levels*. Later in our work a highly concentrated material dissolved in a concentrated sucrose solution was used as a secondary standard, but the ultimate standard remained the rice bran extract tested at a low dosage level. A "unit" of pantothenic acid is that amount which when tested as indicated is equivalent to 1 g. of the dry rice bran extract. The high potency of the material as compared to the low toxicity of brucine for the yeast, allowed us to test brucine salts directly for their effect on yeast growth.

Preparation of Autolysis Extract.—Nine kilograms (20 lb.) of ground sheep liver was mixed thoroughly with 20 liters of water (40°) in a ten-gallon milk can. One liter of benzene was then added and stirred thoroughly into the mixture, which was allowed to autolyze for twenty-four hours at 37°. The vessel was closed to avoid evaporation of benzene.

After twenty-four hours the vessel was placed in a larger barrel or other suitable vessel containing water and the water in the outer jacket was heated as rapidly as possible by means of live steam until its temperature reached 95–100°. In the meantime the liver mixture was stirred frequently in order to heat evenly and prevent local coagulation on the walls of the container. When the liver mixture reached a temperature of 75–80° a coagulum formed. Between 80–86° some frothing took place due to evaporation of benzene. (Inhaling the vapor was avoided.) Finally all the benzene was removed in ten to fifteen minutes at 97° by passing live steam directly into the extract. (For some unknown reason the extract is not consistently obtained in a suitable condition if the amount of benzene originally used is materially decreased.)

While still hot the coagulum was filtered off through muslin with greatest ease, using large funnels. The filtrate was perfectly clear, orange colored and possessed a greenish fluorescence. The "potency" of the extract (19 liters) on a moist basis under most conditions was 0.3 and therefore it contained 5700 "units" of pantothenic acid. Under less favorable conditions (presumably due to the liver) the units obtained might be as low as one-half the above value.

Fuller's Earth Adsorption.—In order to remove organic bases which would interfere with later purification, the solution was treated while still warm with 360 g. of technical fuller's earth (B-K-H). The solution was stirred thoroughly with the earth for fifteen minutes and then filtered. The solution loses substantially no pantothenic acid by this treatment and its appearance remains about the same except for the loss of fluorescence.

Adsorption and Elution from Norite.—Previous to adsorption with Norite the *p*H of the solution was brought approximately to 3.6 after thorough mixing, by the addition of 10–30 ml. of 1–1 sulfuric acid. A flocculent precipitate formed and was filtered off using kieselguhr as a filtering medium.

At this stage the filtrate was cooled (some dilution with ice is permissible) to about 15°, after which about 450 g. (2 g. per 100 cc.) of Norite was added and the mixture kept agitated for two hours. The Norite was then filtered off and the colorless filtrate containing very little pantothenic acid was discarded.

The activated Norite should be eluted immediately after adsorption. It is not necessary, nor desirable, to dry the charcoal before elution. If the charcoal is heated, satisfactory elution becomes impossible. In each of the three elutions, 1500 ml. of 1.6 *N* ammonium hydroxide solution was used. For elution, the mixture was suspended (using a rolling machine) for two hours. The filtration was carried out at the pump on hardened filter paper (S & S 602 h). The combined elutions and rinse

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[4] Kögl and Tönnis, *Z. physiol. Chem.*, **242**, 43 (1936).

[5] Williams and Saunders, *Biochem. J.*, **28**, 1887 (1934).

[6] Williams, McAlister and Roehm, *J. Biol. Chem.*, **83**, 315 1929).

were brought to neutrality (*p*H *ca.* 6.5) by adding a saturated water solution of oxalic acid.

The amount of activity recovered at this stage varied considerably with different batches. In typical cases 85–95% of the active substance was adsorbed by the charcoal and about 60% of that adsorbed was recovered in the eluate. This initial loss of about 50% of the activity was compensated for by the fact that the introduction of the charcoal adsorption step made the material easier to purify later. An average batch of eluate from 9 kilos of liver contained, therefore, about 3000 units.

Brucine Treatment.—To the eluate was added 30 g. of oxalic acid in water solution, then 180 g. of brucine alkaloid in methanol solution, and the *p*H of the resulting solution adjusted to 7. This solution was then evaporated to dryness after adding 225 g. of kieselguhr during the latter part of the evaporation. The evaporation was accomplished by using specially constructed water-jacketed evaporating pans. By use of electric fans the temperature was kept from 50–70°.

During the evaporation, acid production from the liver constituents evidently takes place[7] and it is necessary to add brucine from time to time to keep the solution neutral. Approximately 10 g. of brucine may be required for this purpose. In the end there was obtained from an average batch about 700 g. of dried pulverized material with a "potency" of 3.5 which was dried in a desiccator and ground in a ball mill.

Chloroform Extraction.—The dry kieselguhr residue above was extracted successively three times with 700-ml. portions of chloroform for an hour each. The chloroform solutions were extracted successively with 70, 70 and 35 ml. portions of water and the water solutions combined. Upon partial evaporation (or previously during extracting) some brucine oxalate crystallizes out and can be discarded. The final mixture of dry brucine salts obtained from a sample batch weighed about 20 g. and had a potency of 80. Over-all yields up to this point were in some cases much higher than this, but relatively large losses during the preceding three stages seemed inescapable.

Fractionation of the Brucine Salts.—This step in the process cannot be carried out economically with small batches and hence is described in terms of the material from 250 kg. of liver. The fractionation involved starting with approximately 600 g. of brucine salt mixture and from it obtaining about 9 g. of brucine salts containing over 50% of the activity and therefore about thirty times as concentrated as the original material. Most of the remaining active material was saved in the form of partially concentrated material. The process extended through many months and involved the carrying out of thousands of culture tests. Altogether about 700 fractions were separated besides numerous discards which were not numbered. To give a complete picture of how the fractionation was carried out would be impossible, but we feel that it will be useful to outline briefly the method of attack.

From the standpoint of novelty of operation, probably the most outstanding feature is the fact that we made extractions using quantities of solvents which superficially might seem absurd. For example, if the extraction demanded it we did not hesitate to extract 2 liters of (water-saturated) chloroform with 0.5 ml. of water. Even in such an extreme case the manipulation is not difficult.

When relatively pure brucine pantothenate is shaken with equal volumes of chloroform and water, only about one part in a thousand will remain in the chloroform, *i. e.*, its distribution coefficient is roughly 1000. However, the presence of other salts in crude material alters the characteristics of the solvents so that the distribution coefficient of brucine pantothenate under these conditions may be as low as 70.

The crude mixture of brucine salts obtained from sheep's liver contains about 5% of material with a higher distribution coefficient than brucine pantothenate and about 95% of material with a lower coefficient. The former are termed type *w* salts due to their greater tendency to go into the water layer. The latter are termed type *c* material since they have a greater tendency to go into chloroform solution.

The success of this process depends on taking several fractions in such a manner that the type *w* and type *c* materials can be sorted separately according to potencies, fractionated and discarded independently, at the same time losing but a small amount of activity.

All the crude brucine salt was put through the following first step in batches of about 50 g. The crude material was dissolved in chloroform and shaken with successive small portions of water. The volumes of water taken were small enough so that approximately 20–25% of the original activity would be found in the water layer. (To judge these amounts required extensive experience and many physiological tests.) Under these conditions type *w* material was obtained largely in the first fractions and type *c* material in the later.

The next steps in the process involved combination of type *c* salts (which are large in amount) of similar potency and their refractionation in a manner similar to that described above.

Continued fractionation by dissolving type *c* material in chloroform and extracting with water, would lead to an accumulation of type *w* material and a piling up of the active principle in these fractions. In order to avoid this the extraction procedure was reversed as the process demanded—that is, the material was dissolved in water and extracted with chloroform containing 1% of brucine alkaloid.

Throughout the whole fractionation process very small losses were sustained, but to work up all the material into "high potency" fractions involved an inordinate length of time and hence we were content with a yield of approximately 18,000 units in this form out of about 34,000 units of starting material. Though we were constantly on the lookout for such phenomena, we observed at no time during this fractionation any results which suggested that two or more substances were being concentrated simultaneously.

Conversion to Calcium Salts and their Fractionation.—Brucine salts at any stage of purification were converted readily into calcium salts by treating in solution with an excess of lime water and freeing from brucine by filtration and repeated extraction with chloroform. The purified brucine salts from the fractionation procedure were, therefore, treated in this way and the alkaline solution immediately freed from excess calcium (final *p*H about 7.5) by the

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[7] Kapeller-Adler and Luisada, *Biochem. Z.*, 269–397 (1934).

use of oxalic acid. Solutions containing the calcium salts were then completely decolorized with high-grade blood charcoal and the almost colorless calcium salts were obtained by evaporation, in the form of a varnish. From 9 g. of brucine salts, potency 1600–2300, there was obtained a little over 3 g. of calcium salts, potency about 5000.

We shall not attempt to mention all the devices attempted before we developed the process outlined for the further concentration of pantothenic acid. The procedure adopted for the purification of calcium pantothenate consisted in (a) the precipitation of the active principle from concentrated aqueous solution with absolute alcohol, (b) treatment with mercuric chloride in aqueous and alcoholic solution to remove the presumably basic impurities still present in the concentrate, (c) a thrice repeated fractional precipitation of the calcium salt from an aqueous alcohol solution with isopropyl ether, and finally (d) a fractional precipitation from pyridine with acetone.

Precipitation from Aqueous Solution with Alcohol.—Calcium pantothenate, 431 mg. of "potency" 5700, was dissolved in 3 ml. of water in a 15-ml. centrifuge tube. There was added 10 ml. of absolute ethanol dropwise and with vigorous stirring. A precipitate which was formed was centrifuged from the solution and washed twice with 10 ml. of 95% ethanol. On addition of the washing liquor and 10 ml. additional absolute ethanol to the solution, a further slight precipitate was formed. These low activity fractions weighed 104 mg. and had a potency of 270.

Mercuric Chloride Treatment.—The solution was evaporated almost to dryness in a 15-ml. centrifuge tube, and 3 ml. of ethanol added. An excess (800 mg.) of mercuric chloride was added, the suspension allowed to stand overnight, and the precipitate centrifuged. The precipitate was washed three times with 5-ml. portions of ethanol. The washings were added to the solution, which was then evaporated almost to dryness. On addition of 10 ml. of water, a further precipitate formed, which was centrifuged. The mercuric chloride precipitate retained approximately 3% of the total activity. The solution was saturated with hydrogen sulfide, the mercuric sulfide washed twice with 1-ml. portions of water. The solution and washings were evaporated to half volume to remove the hydrogen sulfide. There was added 500 mg. of silver oxide. This was allowed to stand for two hours, the precipitate being broken up frequently with a stirring rod. On removal of the precipitate of silver chloride and excess silver oxide, the *p*H of the solution was found to be 5.2. It was adjusted to 7.2 with calcium hydroxide solution, and evaporated to dryness.

The above two steps were carried out, in six separate runs, on 3.16 g. of average potency 5000, containing 15,800 units. Ninety-three per cent. of the activity was accounted for, 85% being in the high activity fractions, weight 1.76 g. The potency of these fractions varied from 6500–8900. The remainder of the recoverable activity was found in the low activity fractions and the mercuric chloride precipitate.

Ethanol–Isopropyl Ether Fractionation.—The isopropyl ether used in this fractionation was treated with slightly acid ferrous sulfate solution, sodium carbonate solution, and dried over anhydrous sodium carbonate. Isopropyl ether was used in preference to ethyl ether because of its lower volatility and hygroscopicity. Calcium pantothenate, 216 mg., potency 7600, was dissolved completely in 0.30 ml. of water in a centrifuge tube. There was added 4.0 ml. of absolute ethanol in 0.2-ml. portions. A slight precipitate formed, which was not removed. There was added slowly dropwise, with vigorous stirring, 1.0 ml. of isopropyl ether, to yield fraction A. This was removed by centrifugation. Further addition of 1.2 cc. of isopropyl ether precipitated fraction B. Evaporation of the solution gave fraction C.

Fraction	Weight, mg.	Potency
A	83.5	6250
B	36.9	8250
C	88.9	9100

More of the calcium salt, 485 mg., was treated similarly in three runs, with essentially the same results.

The combined fractions C were again fractionated in the same manner with ethanol and isopropyl ether.

Fraction	Weight, mg.	Potency
D	37.8	9330
E	63.0	10300
F	56.5	10400
G	64.3	8160

A third ethanol–isopropyl ether precipitation of fractions E and F caused no further purification.

Acetone–Pyridine Fractionation.—The pyridine used in these fractionations was dried by allowing to stand over fused potassium hydroxide and distilling from barium oxide. The acetone was distilled from calcium carbonate. Acetone was added slowly dropwise to 95.2 mg. of fractions E and F above, in a solution of 0.15 ml. of water and 2.0 ml. of pyridine. Precipitates were removed at intervals.

Fraction	Weight, mg.	Potency
H	5.6	10,300
I	21.3	10,800
J	55.3	10,250
K	12.6	11,000

These highly active fractions of calcium pantothenate were prepared in the form of a clear, colorless varnish, very difficult to obtain in an entirely anhydrous condition. Pulverization gave a white powder, which was found to be quite hygroscopic. It took up 4–6% moisture under ordinary laboratory conditions.

Fraction J after being pulverized and dried at 56° *in vacuo* was found to have a potency of 11,100. As indicated in succeeding papers this fraction represents nearly pure material. We are able to get a quantitative measure of the amount in a culture solution when only 0.0005 γ per ml., or 5 parts per 10 billion, is introduced.

We desire to acknowledge our indebtedness to Anne King Stout and Ruth Carleton Scott for capable and painstaking help in connection with the concentration and the accompanying physiological tests.

We wish also to express our sincere thanks to those who have supported this work financially. This includes: the local institution; the National

Research Council; Standard Brands Inc. of New York, who have supported the investigation generously for many years; and the Rockefeller Foundation, who have made possible the large scale work by a substantial grant.

Summary

The concentration and purification of pantothenic acid from liver is described. Because of the character of the material this has proved an unusually difficult task. The final preparation (amorphous) has a potency of 11,100 as compared with a standard rice bran extract which was chosen as unity. Further fractionation of this material resulted in no increased purity. For this and other reasons it is thought to be substantially pure. Its presence can be determined quantitatively when only 5 parts is present in 10 billion parts of culture medium (0.0005 γ per ml.).

CORVALLIS, ORE. RECEIVED JUNE 8, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF OREGON STATE COLLEGE]

A Study of Reduction with Hydriodic Acid: Use in Micro Determinations of Hydroxyl Groups

BY HERSCHEL K. MITCHELL AND ROGER J. WILLIAMS

The work described in this paper was undertaken primarily for the purpose of establishment of a new method for the micro determination of hydroxyl groups in amorphous, hydrophilic compounds such as pantothenic acid.[1] It was also desirable to develop a method for the quantitative estimation of a given type of hydroxyl as well as the total number per molecule.

A semi-micro method depending on acetylation with acetic anhydride in pyridine, has been described by Freed and Wynne.[2] Recently the description of a similar micro method has been published by Stodola.[3] A more or less standard procedure for the micro determination of hydroxyl groups in conjunction with other groups containing active hydrogens is that given by H. Roth.[4] This is based upon the Zerewitinoff (Grignard) reaction. A gravimetric method for accomplishing the same purpose, based upon the replacement of hydrogen with deuterium, has been proposed by Williams.[5]

None of the above methods proved suitable for the determination of hydroxyls in highly hygroscopic amorphous materials. In any case the adhering water interferes seriously and in the case of the Zerewitinoff method no solvent (lacking active hydrogen) could be found to dissolve the hygroscopic material.

It was believed probable that the following normal reactions of hydriodic acid with alcohols would be analytically useful

$$\text{(1)}\quad \text{ROH} + \text{HI} \longrightarrow \text{RI} + H_2O$$
$$\text{(2)}\quad \text{RI} + \text{HI} \longrightarrow \text{RH} + I_2$$

Hydroxyl groups, if completely reduced, must pass through both of the steps above. Complete reduction is difficult, however, and the second step may take place only partially. It was assumed that conditions might be found in which at least the first reaction would take place quantitatively.

If the first reaction only, takes place

$$\text{Milliequiv. of OH groups} = \text{Milliequiv. of HI used up}$$

If an additional amount of hydriodic acid is used to complete the second reaction, this amount (which is equivalent to the millimoles of iodine liberated) is subtracted from the total and

$$\text{Milliequiv. of OH} = \text{Milliequiv. HI used up} - \text{Millimoles of } I_2 \text{ liberated}$$

The milliequivalents of OH groups reduced are equal to the millimoles of I_2 liberated and the milliequivalents of OH groups merely replaced are equal to the total hydroxyl groups minus those reduced.

It seemed probable that the stage of completion of reaction (2) above would give information concerning the type of grouping being reacted upon. This was based on the statement[6] given that the reactivity of alkyl halides toward hydrogen iodide is in the decreasing order; tertiary, secondary and primary.

Other Reactive Groups.—There are several types of functional groups that are readily at-

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(1) Williams, Weinstock, Rohrmann, Lyman, Truesdail and McBurney, THIS JOURNAL, **60**, 2719 (1938).

(2) Freed and Wynne, *Ind. Eng. Chem., Anal. Ed.*, **8**, 278 (1936).

(3) Stodola, *Mikrochemie*, **21**, 180 (1937).

(4) F. Pregl, "Quantitative Organic Micro Analysis," Third English Edition, P. Blakiston, Philadelphia, Penna., 1937, pp. 156–166.

(5) Williams, THIS JOURNAL, **58**, 1819 (1936).

(6) Ogg, *ibid.*, **56**, 526 (1934).

tacked by concentrated hydriodic acid. It is well known that HI adds quantitatively to olefin double bonds and various studies of the conditions required have been made.[7] Reduction of halogen compounds also would take place. A quantitative study of a reaction of this type has been made by Shoesmith.[8] Nitroso groups,[9] phenylhydrazine,[10] thiophene or furan derivatives[11] and ethers are reacted upon readily by hydriodic acid. In many of these cases the reaction may be quantitative and hence need not prevent the simultaneous determination of hydroxyl groups.

Experimental Procedure

Samples for analysis (0.5–10 mg. depending on hydroxyl content) are weighed into Pyrex capillary tubes on the micro balance. Forty λ (0.04 cc.) of hydriodic acid (sp. gr. 1.96) is introduced into the sample tubes with a capillary pipet. Extreme care should be taken to prevent droplets of the reagent being deposited near the top of the tubes. Following the introduction of the reagent into a capillary, the pipet is rinsed into a 50-ml. Erlenmeyer flask that has been labeled to correspond to the sample. Each tube is sealed within a few minutes by use of a fine pointed oxygen flame. The sealed tubes are then placed in a bath of constant boiling liquid for five hours (or in some cases for a different period). After the reaction has thus been carried out, each tube is placed in its correspondingly labeled flask and crushed with the end of a glass rod. The solutions are titrated to the usual starch–iodine end-point with sodium thiosulfate (0.015 *N*), followed by titrations of the same solutions to the phenolphthalein end-point with standard sodium hydroxide (0.05–0.15 *N*). Blank tubes containing 40 λ of hydriodic acid alone must accompany each set of determinations. This determines the H^+ and I_2 in the reagent itself.

In carrying out the reactions on esters, the H^+ from the acid produced on hydrolysis introduces a correction in the calculation. A peptide requires no correction since both acidic and basic groups are formed simultaneously on hydrolysis.

The technique in use and the description of the micro pipets used in the procedure given have been published by Kirk.[12] The Pyrex capillary chambers are thin walled, about 4 mm. in diameter and 4 cm. long.

Materials.—The chemicals used were, for the most part, Eastman highest purity products, and were used without further purification. The hydroxybutyric acids used were obtained through the kindness of Professor J. W. E. Glattfeld, of the University of Chicago. Kahlbaum hydriodic acid (sp. gr. 1.96) was used throughout as the reducing agent.

Experimental Data

Table I illustrates the reproducibility of analytical results on a single compound. These were not consecutive analyses but were made over a period of several months. The effect of sample size on the amount of reduction also is shown.

TABLE I

DETERMINATION OF HYDROXYL GROUPS IN MANNITOL AT 100° IN FIVE HOURS

	Mannitol, mmol.	Total OH groups found/mol.	Reduced OH groups found/mol.
1	0.00541	6.0	4.41
2	.00607	5.88	4.56
3	.00616	6.0	4.63
4	.00618	6.2	4.68
5	.00716	6.0	4.68
6	.00723	6.0	4.74
7	.00766	5.64	4.98
8	.00842	5.88	4.86

Table II is a condensation of analytical results obtained on several hydroxy compounds at three temperatures.

Discussion of Results

A careful study of the data leads to the following conclusions of analytical significance.

1. Satisfactory analytical results can be obtained on primary alcohols, poly alcohols, hydroxy acids and negative substituted compounds, but simple secondary and tertiary alcohols, phenols, inositol and threonine fail to give useful results. A variation of from 0 to 4% low is noted on the more reactive types of compounds. These results compare favorably with existing methods for hydroxyl determination.
2. The reactions should be carried out in the range 100–134°.
3. From data not included here it was found that the reaction time of from five to twenty hours was satisfactory. Over the longer periods the thermal decomposition of hydrogen iodide produced a high blank and low results on compounds giving high reduction values. It was observed also that the presence of non-reducing organic compounds decreases thermal decomposition of the reagent.

It becomes evident on a careful consideration of the data that the ease of reduction is not dependent on the type of hydroxyl group as originally assumed, but does depend on the adjacent groupings about the hydroxyl. It may be stated that hydroxyls with what the organic chemists have called "negative groups" on adjacent carbon atoms, are reduced easily by hydriodic acid. The presence of adjacent methyl groups decreases the ease of the reaction. These generalizations

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(7) Kharasch and Hannum, THIS JOURNAL, **56**, 1782–84 (1934).

(8) Shoesmith, *J. Chem. Soc.*, **123**, 2828–30 (1923).

(9) Earl and Kenner, *ibid.*, 2139–45 (1927).

(10) Brewster, *Trans. Kansas Acad. Sci.*, **36**, 111–12 (1933).

(11) Nellensteyer, *Chem. Weekblad*, **24**, 102–5 (1927).

(12) Kirk, *Mikrochemie*, **14**, 1 (1933).

TABLE II

Compound	Detns. at °C.			OH present	OH at 100°		OH at 134°		OH at 163°	
	100	134	163		Red.	Subs.	Red.	Subs.	Red.	Subs.
Mannitol	10	8	2	6	4.70	1.25	4.82	0.69	4.47	0.81
Dulcitol	4	1	1	6	4.72	0.79	4.96	.77	3.22	0.40
Erythritol	2	1	1	4	2.88	1.06	2.86	.86	2.14	1.18
Benzyl alcohol	1	1	1	1	0.71	0.24	0.97[a]	.63[a]	0.69	0
Glucose		1		5			4.74	.21		
Mannose	2	1	1	5	4.07	0.78	4.35	.70	3.05	0.90
Levulose	2	1	1	5	3.60	1.05	3.16	1.49	3.90	.55
Mandelic acid	2	1	1	1	0.95	0	0.94	0.04	0.72	.02
Threonine	2	1	1	1	0	0	0.725	.055	1.91[a]	0
Inositol	2	1	1	6	0	0	1.3	.2	2.51	.01
2-OH-1,4-Me-benzene	1	1	1	1	.10	0.09	0.40	.04	0.54	0
α,β-Di-OH-isobutyric acid	8	3	1	2	1.0	.86	1.81	.23	1.28	0
α,β-Di-OH-butyric acid	2	1		2	0.83	.83	1.25	.75		
β-OH-butyrolactone	2	1	1	2	0.91	.82	0.44	1.38	0.54	.60
Erythronic lactone	8	5	1	3	1.93	.86	1.95	1.02	1.13	.82
α-OH-butyrolactone	2	5	1	2	0.05	.05	0.87	1.09	1.04	.88
Tartaric acid	1	1	2	2	.1	.2	0	0	1.15[a]	1.31[a]
Pentaerythritol	2	2	1	4	.13	.67	.04	3.92	0	2.6
Hexyl alcohol	2	1	1	1	0	.98	0	1.00	0	0.81
Isoamyl alcohol	2	1	1	1	0	.96	0	0.82	0	.64
s-Butyl alcohol	2	1	1	1	.02	.90	0	.87	0	.52
t-Butyl alcohol	1	1	1	1	0	.25	.01	.46	0	.44
t-Amyl alcohol	2	1	1	1	0	.70	0	.61	0	.53
Et acetoacetate	2	2	1	1	.09	.84	.14	.81	0.34	.80
Et benzoate	2	1	2	1	0	1.3[a]	0	2.06[a]	0	1.31[a]
m-OH-benzoic acid	1	1	1	1	0	0	0	0	0	0
				HI used, calcd.	HI at 23°		HI at 100°		HI at 134°	
	23	100	134			subs. or add.		subs. or add.		subs. or add.
Crotonic acid	1		1	1	0	1.0			0	1.0
n-Butyl ether	1	1	1	2	0	0.48	0.1[a]	3.7[a]	0	3.7[a]
β-Alanine		2	1	0	0	0	0	0	0	0

[a] High results are due to reactions with groups other than hydroxyls.

are supported by an observation of the number of reduced hydroxyl groups as listed in Table II. The following comparisons illustrate these facts:

1. Primary alcohols such as hexyl, isoamyl or pentaerythritol substitute completely and do not reduce, while secondary butyl, tertiary butyl and tertiary amyl alcohols show only partial substitution.

2. Poly alcohols such as mannitol or erythritol show high reduction.

3. Benzyl alcohol shows a high reduction value, while an additional negative group, as in mandelic acid, promotes complete reduction.

4. Erythronic lactone and α,β-dihydroxybutyric acid have a tendency to be both substituted and reduced, while in the case of β-hydroxy-γ-butyrolactone and α-hydroxy-γ-butyric lactone less reduction follows the substitution. In the first two compounds the functional groups are all on adjacent carbon atoms, while such is not the case with the latter two substances.

5. α-Hydroxy-γ-butyrolactone reacts with hydriodic acid readily at 134° but not at 100°. Compounds with the hydroxyls adjacent react readily at 100°.

The last three compounds listed in Table II indicate application of the method described to other groups than hydroxyls. These, and others previously mentioned, must be taken into account if present in a compound along with hydroxyl groups. The reaction of butyl ether with hydriodic acid is shown to be of a more complex nature than expected from the textbook reaction

$$ROR + HI \longrightarrow ROH + RI$$

A similar observation has been made by Earl and Kenner.[9]

Summary

1. A new method for the quantitative determination of hydroxyl groups is described and shown to be useful down to quantities of about 1 mg. Satisfactory results were obtained on primary mono alcohols, poly alcohols, hydroxy acids and various negatively substituted hydroxy compounds. The hydroxyl groups in phenols, simple

secondary and tertiary alcohols, inositol, threonine and tartaric acid could not be quantitatively determined by this method.

2. On the basis of experimental data, a generalization is offered for the variation in reactivity of aliphatic hydroxy compounds toward hydriodic acid. The presence of adjacent negative groups increases the reactivity of a hydroxyl while an adjacent methyl group decreases its reactivity.

3. The analytical data give some indication of structural relationships of the functional groups in a compound.

4. It is suggested that the analytical method described might be useful in the determination of any group readily reacted upon by hydriodic acid.

CORVALLIS, OREGON RECEIVED JUNE 8, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

The Kinetics of the Periodate Oxidation of 1,2-Glycols

BY CHARLES C. PRICE AND HARRY KROLL

The cleavage by periodic acid oxidation of the carbon to carbon bond in compounds in which the two carbon atoms each bear an oxygen atom either as a hydroxyl or carbonyl group was first observed by Malaprade.[1]

$$\text{RCHOHCHOHR} + \text{HIO}_4 \longrightarrow 2\text{RCHO} + \text{H}_2\text{O} + \text{HIO}_3$$

$$\text{RCHOHCOR} + \text{HIO}_4 \longrightarrow \text{RCHO} + \text{RCOOH} + \text{H}_2\text{O} + \text{HIO}_3$$

The original investigator, as well as Fleury and Lange,[2] were concerned chiefly with the analytical applications of the reaction. Fleury, Hérissey and Joly[3] made use of the reaction in studying the problem of the ring structure of the sugars, an application which was extensively and successfully investigated by Karrer and Pfaehler and by Jackson and Hudson.[4]

Although Malaprade made the observation that the reaction was much more rapid in acid than in neutral or basic solution, no measurements of the kinetics of the reaction have been made. The purpose of the present investigation was to study the kinetics under various conditions with the object of elucidating the mechanism of this oxidative cleavage in the particular case of 1,2-glycols.

Ethylene glycol and 2,3-butylene glycol consumed the theoretical amount of periodate almost instantaneously in acid solution. Pinacol, however, was found to oxidize at a conveniently measurable rate and was therefore the material used for the kinetic investigation.

Experimental

Standard aqueous solutions of periodic acid or sodium periodate and pinacol were mixed at 25.0° after adjusting the *p*H with 0.5 *N* solutions of sulfuric acid or sodium hydroxide. The course of the reaction was followed by withdrawing samples which were added to acidified potassium iodide solution, the liberated iodine then being titrated with sodium thiosulfate to the disappearance of the iodine color.

The hydrogen ion concentration of the reaction mixture was determined with a Beckmann *p*H meter. It did not vary appreciably during the course of the oxidation.

The Kinetics of the Reaction at Constant *p*H.—The dependence of the rate of the oxidation on the concentrations of the periodate and pinacol was first determined by measurements at a particular hydrogen ion concentration. The reaction was found to follow simple second order kinetics, the rate being directly proportional to the glycol and periodate concentrations as is illustrated by the results of these experiments summarized in Table I. The average deviation for the constants in any of the experiments was less than 5%.

TABLE I

THE RATE CONSTANTS FOR EXPERIMENTS WITH VARIOUS PINACOL AND PERIODATE CONCENTRATIONS AT A CONSTANT *p*H

*p*H, 5.5–5.6; temp., 25.0°

[Periodate][a]	[Pinacol][a]	k[b]
0.00550	0.02327	0.205
.00611	.03116	.207
.00916	.01871	.199
.01221	.01558	.202
.01221	.03513	.197
.01486	.02180	.197
.01960	.05270	.196

[a] Concentrations in moles per liter. [b] $dx/dt = k \times$ [Periodate][Pinacol]; the [Periodate] being the total periodate as determined by titration.

The Effect of Changing *p*H.—It was found that the value of k for the simple second order reaction varied greatly with the *p*H of the reaction mixture. Since this

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[1] Malaprade, *Bull. soc. chim.*, **43**, 683 (1928); *Compt. rend.*, **186**, 382 (1928).

[2] Fleury and Lange, *J. pharm. chim.*, **17**, 196, 313, 409 (1933).

[3] Fleury, Hérissey and Joly, *ibid.*, **20**, 149 (1934).

[4] Karrer and Pfaehler, *Helv. Chim. Acta*, **17**, 766 (1934); Jackson and Hudson, THIS JOURNAL, **59**, 994 (1937).

latter factor remained constant during any one particular experiment, however, the rate constants for each experiment readily were determined. The variation of these constants with the *p*H of the reaction mixture is illustrated in Fig. 1.

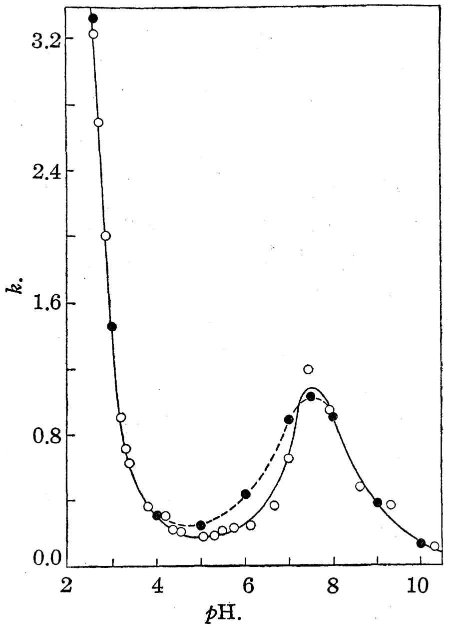

Fig. 1.—The second order rate constants plotted against the *p*H: ○, experimental values; ●, calculated values.

Comparison of Pinacol and Ethylene Glycol.—It has been reported[5] that pinacol and other highly substituted glycols react more readily with lead tetraacetate than those substituted to a lesser degree such as ethylene or 2,3-butylene glycols. This order of reactivity, however, holds for periodate oxidation only in alkaline solution. In acid the relative rates are reversed, since ethylene glycol and 2,3-butylene glycol react much more rapidly than pinacol. The results of experiments demonstrating this fact are summarized in Table II.

TABLE II

COMPARISON OF THE RATE OF OXIDATION OF ETHYLENE GLYCOL AND PINACOL IN ACID AND BASE

	*p*H 4		*p*H 9	
Time, min.	% ethylene glycol oxidized	% pinacol oxidized	% ethylene glycol oxidized	% pinacol oxidized
2	95	20	..	...
5	99	32	26	33
10	100	58	..	...
30	...	86	34	65
240	...	100	51	100

Discussion of Results

It was found that the variation of the simple second order rate constant, *k*, with the *p*H could be accounted for by assuming an uncatalyzed, an acid catalyzed and a base catalyzed reaction between the pinacol and a monovalent periodate ion. The acid reaction was directly proportional to the hydrogen ion concentration while the base reaction was proportional to the square root of the hydroxyl ion concentration.

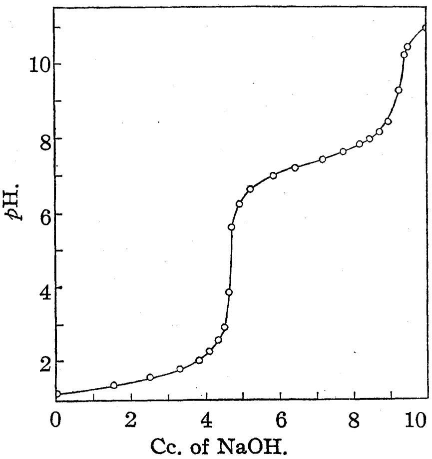

Fig. 2.—The titration of periodic acid (0.1 *N*) with sodium hydroxide (1.0 *N*).

The simple second order rate constant *k*, as calculated from the equation

$$dx/dt = k(A - x)(B - x)$$

where *A* is the total initial periodate concentration, *B* the initial pinacol concentration and *x* the amount of pinacol oxidized (equivalent to the decrease in the periodate titer), is thus a function of the *p*H of the solution which may be expressed as

$$k = k_0 + k_1[H^+] + k_2[OH^-]^{1/2}$$

By substituting the experimentally determined values for *k* at the various values for the *p*H and solving the resultant simultaneous equations, these constants were found to be $k_0 = 0.14$, $k_1 = 1.3 \times 10^3$ and $k_2 = 3.0 \times 10^3$.

The simple rate equation above also must be corrected for the fact that the rate is dependent on the monovalent periodate ion rather than the total periodate concentration. The ratio of these two concentrations as a function of the hydrogen ion concentration may be calculated from the dissociation constants of periodic acid as a mono- and dibasic acid.[6]

$$H_5IO_6 \overset{K_1}{\rightleftharpoons} H^+ + H_4IO_6^- \overset{K_2}{\rightleftharpoons} H^+ + H_3IO_6^=$$

From these equilibria two independent equations

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(5) Criegee, Kraft and Rank, *Ann.*, **507**, 159 (1933).

(6) From the titration curve of periodic acid with sodium hydroxide (Fig. 2) the values for these two constants were determined as $K_1 = 0.11$ and $K_2 = 2.5 \times 10^{-8}$.

for the concentration of the monovalent ion may be derived.

$$[H_4IO_6^-] = K_1[H_5IO_6]/[H^+] \qquad (1)$$
$$[H_4IO_6^-] = [H^+][H_3IO_6^=]/K_2 \qquad (2)$$

Expressing the total periodate concentration as A, that of the monovalent ion as x, and that of the divalent ion as y these equations become

$$x = K_1(A - x - y)/[H^+] \qquad (1')$$
$$x = \frac{[H^+]y}{K_2} \text{ or } y = \frac{K_2x}{[H^+]} \qquad (2')$$

Substitution of (2′) in (1′) leads finally to equation (3) for the ratio of monovalent ion to total periodate as a function of hydrogen ion concentration.

$$x = \frac{K_1\left(A - x - \frac{K_2x}{[H^+]}\right)}{[H^+]}$$
$$[H^+]^2\frac{x}{A} = K_1[H^+] - K_1[H^+]\frac{x}{A} - K_1K_2\frac{x}{A}$$
$$\frac{x}{A} = \frac{K_1[H^+]}{[H^+]^2 + K_1[H^+] + K_1K_2} \qquad (3)$$

Multiplication of the original rate equation by this factor leads to an equation for k as follows

$$k = \frac{(k_0 + k_1[H^+] + k_2[OH^-]^{1/2})K_1[H^+]}{[H^+]^2 + K_1[H^+] + K_1K_2} \qquad (4)$$

Values for k calculated from this expression, using the constants as noted, have been included in Fig. 1 for comparison with those determined experimentally.

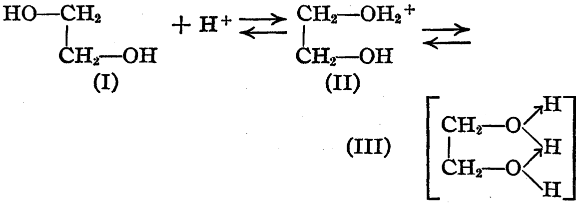
No simple and completely plausible explanation for the dependence of the rate on the square root of the hydroxyl ion concentration seems apparent although it may be accounted for on the basis of some such equilibrium as

$$\underset{\text{metaperiodate ion}}{2IO_4^- + OH^-} \rightleftarrows \underset{\text{dimesoperiodate ion}}{HI_2O_9^=}$$

If now the rate of the reaction were dependent on the square root of such a dimesoperiodate ion value, the kinetics of the reaction would indeed agree with those observed.

The direct dependence of the rate on the hydrogen ion concentration is capable of two simple interpretations: (1) that the rate is dependent not on the periodate ion but on the undissociated periodic acid concentration, the effect of the hydrogen ion being to repress the ionization of the latter; or (2) that the reaction is a hydrogen ion catalyzed reaction between the glycol and periodate ion. The second concept is in better agreement with other observations on the reaction but the first cannot be rigorously excluded.

The reversal of the relative rates of oxidation of ethylene glycol and pinacol on shifting from an acidic to a basic reaction medium, as well as the fact that the order of glycol reactivity toward oxidation in acidic periodate is the reverse of the order with lead tetraacetate, may be due to the effect of hydrogen ion on the relative position of the two hydroxyl groups. In non-aqueous solvents (as for the lead tetraacetate oxidation) or in basic aqueous solution, the glycol probably exists largely as the free molecular species in which the negative character of the two hydroxyl groups may favor a configuration with these two groups on opposite sides of the molecule. On the addition of acid, however, the oxygen of an hydroxyl group may associate with a proton, resulting in a change in the configuration.



It is reasonable to suppose that there is at least considerably more glycol present as (II) or (III) in acid than in base and that (I) should, as an average, tend more toward a *trans* configuration for the hydroxyl groups while in (II) they would tend to be *cis*. Furthermore, the separate or combined effect of dipole moment, electrical charge and hydrogen bonding on promoting or inhibiting the *cis* configuration should be more pronounced the smaller the molecule, *i. e.*, ethylene glycol should tend to be more *trans* in base and *cis* in acid than pinacol in corresponding solutions. On the basis of these premises the experimental facts lead to the conclusion that the *cis* configuration is that more readily oxidized by periodate, a fact which has been experimentally established for lead tetraacetate.[5] Experiments to test the validity of this conclusion by comparison of glycols of known *cis* and *trans* configuration are under way. An alternative interpretation of the experimental facts, however, may be made simply on the basis of the relative base strength of the various glycols. If the acid-catalyzed reaction depends solely on the formation of the complex ion (II), regardless of configuration, then the oxidation of the glycol with the greater base strength (which must be ethylene glycol) would be more effectively catalyzed by acid.

The further experimental work may lead to a decision between these alternatives, although actual measurements of base strength may be required.

Summary

The oxidation of pinacol with aqueous solutions of sodium periodate has been found to obey simple bimolecular reaction kinetics. The variation of the rate with the *p*H of the reaction mixture may be interpreted accurately on the basis of reaction between pinacol and the monovalent periodate ion catalyzed by both acid and base.

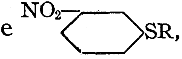
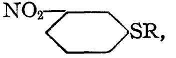
The reversal of the relative rates of oxidation of pinacol and ethylene glycol on shifting from an acidic to a basic reaction medium may be interpreted either on the basis of the configuration of the hydroxyl groups or on the relative base strengths of the two glycols.

URBANA, ILLINOIS RECEIVED AUGUST 13, 1938

[CONTRIBUTION FROM THE GRADUATE SCHOOL OF DUQUESNE UNIVERSITY]

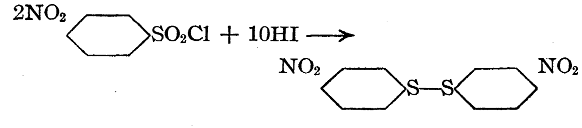
Some Unsymmetrical Aryl Sulfides[1]

BY NOEL E. FOSS,[2] JOHN J. STEHLE, HOWARD M. SHUSETT AND DAVID HADBURG

Zincke and Lenhart[3] and Foss, Dunning and Jenkins[4] have prepared a number of unsymmetrical aryl sulfides of the general type  where R may be various phenolic groups, and NO_2 may be in either the ortho or para position. The present investigation is concerned with the preparation of *m*-nitrophenyl sulfur phenols,  where R may be *p*-hydroxyphenyl, resorcyl, or *β*-hydroxynaphthyl.

The new nitro derivatives were chemically characterized by the preparation of their acetates and bromine substitution products. Two of the series were further identified by the synthesis of their benzyl and benzoyl derivatives, as well as by the reduction of the nitro compounds to the amino compounds.

The general scheme consists in preparing *m,m'*-dinitrodiphenyl disulfide by the following reaction



m-Nitrophenylsulfur chloride was prepared by allowing chlorine to react on the *m,m'*-dinitrodiphenyl disulfide by the method of Zincke and Lenhart[3] and subsequently condensed with the respective phenols. The reactions with phenol are represented by the scheme

$$NO_2C_6H_4SSC_6H_4NO_2 \xrightarrow{Cl_2} 2NO_2C_6H_4SCl$$

$$NO_2C_6H_4SCl + C_6H_5OH \longrightarrow NO_2C_6H_4SC_6H_4OH \xrightarrow{H_2} NH_2C_6H_4SC_6H_4OH$$

Experimental

m,m'-Dinitrodiphenyl disulfide was prepared by a modification of the method of Ekbom.[5] Two moles of the *m*-nitrobenzenesulfonyl chloride were reduced directly by the addition of the calculated amount of 45% hydriodic acid (ten moles). The reaction proceeded smoothly as evidenced by the precipitation of iodine crystals. After refluxing for several hours on the water-bath, the mixture was cooled and sodium bisulfite added until the iodine had been entirely reduced. The crude crystalline material was washed with water and recrystallized from hot acetone. Yellow crystals melting at 81–82° were obtained. The yield of pure product was about 80%.

Condensation of *m*-Nitrophenylsulfur Chloride with Phenols.—*m*-Nitrophenylsulfur chloride was prepared from *m,m'*-dinitrodiphenyl disulfide and condensed with the respective phenol according to the method described by Foss, Dunning and Jenkins.[4] In the case of the resorcinol derivative, 1,3-dihydroxy-2,6-*bis*-(3-nitrophenylthio)-benzene is formed principally unless the resorcinol is kept in excess during the reaction. The crude condensation products were recrystallized from sodium hydroxide and hydrochloric acid. The mononitro derivative also could be recrystallized from hot alcohol. These yellow compounds were insoluble in water, fairly soluble in hot alcohol, and very soluble in acetone and ether.

Acetylation.—The hydroxynitrosulfides and hydroxyaminosulfide were acetylated in the regular manner by refluxing with acetic anhydride and anhydrous sodium acetate. The pale yellow acetyl derivatives were very insoluble in cold water and slightly soluble in hot water,

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(1) Taken in part from theses presented by J. J. Stehle, H. M. Shusett, and D. Hadburg in partial fulfilment of the requirements for the degree of Master of Science in the Graduate School of Duquesne University.

(2) Present address: Burroughs Wellcome & Co. (U. S. A.), Inc., Tuckahoe, New York.

(3) Zincke and Lenhart, *Ann.*, **400**, 1 (1924).

(4) Foss, Dunning and Jenkins, THIS JOURNAL, **56**, 1978 (1934).

(5) Ekbom, *Ber.*, **24**, 335 (1891).

TABLE

Condensation with	Derivative	Formula	M. p., °C.	% Sulfur Found	% Sulfur Calcd.
Phenol		$NO_2C_6H_4SC_6H_4OH$	83.0–83.5	12.88	12.97
	Monoacetyl	$NO_2C_6H_4SC_6H_4(O_2CCH_3)$	66–67	11.04	11.08
	Dibromo	$NO_2C_6H_4SC_6H_2(Br)_2(OH)$	136–137	7.90	7.89
	Monobenzyl	$NO_2C_6H_4SC_6H_4(OCH_2C_6H_5)$	105–106	9.53	9.50
	Monobenzoyl	$NO_2C_6H_4SC_6H_4(O_2CC_6H_5)$	102.0–102.5	9.31	9.13
	Amino	$NH_2C_6H_4SC_6H_4OH$	84.0–84.5	14.69	14.76
Resorcinol		$NO_2C_6H_4SC_6H_3(OH)_2$	150.5–151.5	12.33	12.18
	Diacetyl	$NO_2C_6H_4SC_6H_3(O_2CCH_3)_2$	77–78	9.23	9.23
	Dibromo	$NO_2C_6H_4SC_6H(Br)_2(OH)_2$	128–130	7.90	7.89
β-Naphthol		$NO_2C_6H_4SC_{10}H_6OH$	106	10.76	10.78
	Monoacetyl	$NO_2C_6H_4SC_{10}H_6(O_2CCH_3)$	85.0–85.5	9.25	9.45
	Monobenzyl	$NO_2C_6H_4SC_{10}H_6(OCH_2C_6H_5)$	136–137	8.09	8.28
	Monobenzoyl	$NO_2C_6H_4SC_{10}H_6(O_2CC_6H_5)$	110.0–110.5	7.85	7.99
	Amino	$NH_2C_6H_4SC_{10}H_6OH$	193	11.81	11.99
	Acetylaminoacetyloxy	$(NHCOCH_3)C_6H_4SC_{10}H_6(O_2CCH_3)$	163–164	9.06	9.12
Resorcinol (2 moles:1 mole)		$(NC_2C_6H_4S)_2C_6H_2(OH)_2$	179–180	15.32	15.41
	Diacetyl	$(NO_2C_6H_4S)_2C_6H_2(O_2CCH_3)_2$	109.5–110.5	12.54	12.52
	Monobromo	$(NO_2C_6H_4S)_2C_6H(Br)(OH)_2$	189–190	13.14	12.95

The acetylated hydroxy compounds were easily soluble in the usual organic solvents. The acetylated hydroxyamino compounds were sparingly soluble in alcohol and benzene, and very soluble in chloroform.

Bromination.—The hydroxynitrosulfides were brominated by adding the calculated amount of bromine to a glacial acetic acid solution of the compound. Recrystallization from dilute alcohol yielded canary yellow crystals. The bromo derivatives were insoluble in water, slightly soluble in benzene, and fairly soluble in alcohol.

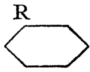
It was found impossible to prepare the bromo substitution product of the β-hydroxynaphthyl derivative by this method. Subsequent analysis and determination of melting point indicated that the compound formed corresponded to the original *m,m'*-dinitrodiphenyl disulfide. No explanation for the phenomenon is attempted.

Benzylation and Benzoylation.—The benzyl and benzoyl derivatives were prepared in the usual manner by the well known Schotten–Baumann reaction. Recrystallization from alcohol yielded canary yellow crystals which were found to be insoluble in water, slightly soluble in alcohol and chloroform, and very soluble in benzene.

Reduction to the Amines.—One part of nitrosulfide dissolved in ten parts of 95% ethyl alcohol was reduced by hydrogen with 0.01 part of Adams[6] platinum black as catalyst. The amino derivatives were insoluble in water, fairly soluble in benzene and alcohol, and very soluble in chloroform.

The accompanying table lists the compounds together with their melting points and analyses.

Summary

Eighteen compounds have been prepared. They are of the general type SR', where R may be NO_2 or NH_2, and R' may be the *p*-hydroxyphenyl, resorcyl, or β-hydroxynaphthyl radical. Some bromo derivatives, acetates, benzoates, and benzyl derivatives have been made.

PITTSBURGH, PA. RECEIVED JULY 21, 1938

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[6] Adams, *Org. Syntheses*, **8**, 92 (1928).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UNIVERSAL OIL PRODUCTS COMPANY]

Reaction of Aliphatic Olefins with Thiophenol[1]

BY V. N. IPATIEFF, HERMAN PINES AND B. S. FRIEDMAN

The alkylation of aromatic hydrocarbons[2] and the C- and O-alkylation of phenols[3] with olefins in the presence of catalysts such as sulfuric or phosphoric acid lead to the formation of compounds having structures which are in accordance with Markownikoff's rule. The mechanism for these reactions has been described[2,3c,4] as involving intermediate ester formation between the acid catalyst and the olefin. Posner,[5] however, reported that the reaction of thiophenol and olefins in the presence of a mixture of sulfuric acid and acetic acid proceeds abnormally, *i. e.*, contrary to Markownikoff's rule.

If Posner's proof of structure, which is open to criticism, is accepted, then one must conclude that either sulfuric acid played no part in the reaction or, what would be less probable, that it formed an intermediate ester of abnormal structure.

Repetition of some of Posner's experiments revealed several errors. The reaction of thiophenol with trimethylethylene in the presence of sulfuric acid yields *t*-amyl- and not *s*-isoamyl phenyl sulfide as reported by him. The compound Posner reported as *t*-amyl phenyl sulfone (m. p. 70°, no analysis) obtained by the metathesis of sodium benzene sulfinate and *t*-amyl bromide was probably benzene sulfinic acid (m. p. after first recrystallization 71°). All attempts to synthesize *t*-alkyl phenyl sulfones by this method led to the isolation only of benzene sulfinic acid and diphenyl disulfide. The disulfide no doubt results from the decomposition of the sulfinic acid by heat in the presence of solvents.[6,7]

Because of the discrepancies in Posner's work further investigation of the reaction of thiophenol with aliphatic olefins was deemed necessary. It was found that in the absence of catalysts thiophenol adds to aliphatic olefins[8] contrary to the mode of addition implied by Markownikoff's rule. Sulfuric acid (diluted with water or acetic acid), however, catalyzes the reaction to yield the normal alkylation product, and not the abnormal product as erroneously reported by Posner. The presence of phosphoric acid scarcely affects the course since the olefins react more readily with thiophenol than with the acid.

The yield of the alkyl phenyl sulfide formed in the absence of any added catalyst depends upon the temperature, contact time and reactivity of the olefin used.

The alkyl phenyl sulfides obtained in these reactions were identified by comparison of their physical properties with those synthesized by the reaction

$$C_6H_5SNa + RBr \longrightarrow C_6H_5—S—R + NaBr \quad (A)$$

and by preparation of solid derivatives (Table II). *t*-Butyl- and *t*-amyl phenyl sulfides could not be prepared by (A) but were obtained for the first time by treating thiophenol with the corresponding *t*-alkyl sulfides according to the method of Lee.[9] All the alkyl phenyl sulfides are water-white liquids possessing a pleasant odor.

It is interesting to note that in the presence of both 75% sulfuric acid, and the sulfuric acid–acetic acid catalyst used by Posner, isopropylethylene underwent isomerization at 0–20° during the alkylation of the thiol group—just as it has been found[10] to do in the presence of 96% sulfuric acid at 0° during the alkylation of benzene—to give a high yield of product containing only the *t*-amyl group.

This study is being extended to investigate the mode of addition to olefins of other compounds containing the thiol group, such as hydrogen sulfide, aliphatic mercaptans and thio acids. The application of these reactions to the problem of identification of olefins is also under investigation.

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[1] Presented before the Organic Division of the American Chemical Society at Milwaukee, Wis., Sept. 5–9, 1938.

[2] Ipatieff and Pines—V. N. Ipatieff, "Catalytic Reactions at High Pressures and Temperatures," The Macmillan Co., New York, N. Y., 1937, p. 656.

[3] (a) Ipatieff, Pines and Schmerling, THIS JOURNAL, **60**, 1161 (1938); (b) Ipatieff, Pines and Friedman, *ibid.*, **60**, 2495 (1938); (c) Niederl and Natelson, *ibid.*, **53**, 273 ,1928 (1931).

[4] Ipatieff, Pines and Corson, *ibid.*, **60**, 577 (1938).

[5] Posner, *Ber.*, **38**, 649 (1905).

[6] Otto and Rössing, *Ber.*, **19**, 1235 (1886).

[7] Smiles and Gibson, *J. Chem. Soc.*, **125**, 176 (1924).

[8] No attempt was made to free the reactants from peroxides or disulfides or to run the reaction in the absence of air. In a private communication Prof. M. S. Kharasch stated that he is investigating the effect of antioxidants on the addition of thiol compounds to olefins. *Cf.* Ashworth and Burkhardt, *J. Chem. Soc.*, 1791 (1928); also *Trans. Faraday Soc.*, **30**, 18 (1934).

[9] Lee, U. S. Patent 2,020,421; *C. A.*, **30**, 489 (1936).

[10] Ipatieff, Pines and Schmerling, THIS JOURNAL, **60**, 353 (1938).

TABLE I

ALKYL PHENYL SULFIDES

PREPARATION AND PROPERTIES

Alkyl	B. p., °C.	Press., mm.	n^{20}_D	d^{20}_4	Yield[b]	Condition of reaction temp.		Method[a]	Analyses, %					
						°C.	Hours		Calcd.			Found		
									C	S	H	C	S	H
n-Propyl	218.5–219.5	750	1.5571	0.9995				A		21.05			20.85	
					72	120	10	B						
					20	60	6	C						
					60	120	8	C						
					15	60	6	B						
Isopropyl	206.5–207.5	750	1.5468	.9855				A	71.05		7.89	71.17		8.00
					16	120	6	D						
n-Butyl[c]	94.5–97	4	1.5463	.9852				A						
					73	100	8	C						
s-Butyl[d]	90–91	4	1.5425	.9789				A						
Isobutyl[c]	107–108	13	1.5430	.9803				A						
	85–87	4			90	33	20	C						
					50	120	5	B						
t-Butyl	73	5	1.5335	.9895	70			E	72.28		8.43	72.34		8.50
n-Amyl	117–118	8	1.5396	.9714				A				73.40		8.72
	93–94	4.5			25	50	12	C						
Isoamyl	100–100.5	6	1.5380	.9681				A	73.33		8.88	73.36		8.96
	87–88	3.5	1.5378		80	55	16	C						
					58	120	8	C						
2-*s*-Amyl	91–92.5	4.5	1.5357	.9642				A				73.43		8.92
3-*s*-Amyl	107–107.5	9	1.5385	.9738				A				73.40		8.82
Active amyl	99–101	4.5	1.5408	.9783				A				73.27		8.94
s-Isoamyl	83.5–86	3.5	1.5393	.9794				A				73.27		8.87
	99–100	5	1.5395		60	Room	168	C[e]						
t-Amyl	91–91.5	6	1.5351	.9679	69			E[f]				73.29		8.81
	88–88.5	3.5	1.5351		15			E[g]						
					88			F[e,g]						

[a] Method
- A, C_6H_5SK + RBr.
- B, C_6H_5SH + Olefin + 90% phosphoric acid.
- C, C_6H_5SH + Olefin.
- D, C_6H_5SH + Alkyl phosphate.
- E, C_6H_5SH + Olefin + 75% H_2SO_4.
- F, C_6H_5SH + Olefin + sulfuric and acetic acids according to directions given by Posner.[5]

[b] Based on mercaptan charged. Method A gave yields ranging from 60 to 85% of the theoretical. [c] Mann and Purdie, *J. Chem. Soc.*, 1549 (1935) report 137–139 (12 mm.) for *n*-butyl phenyl sulfide and 126–127 (12 mm.) for isobutyl phenyl sulfide. [d] Taylor, THIS JOURNAL, **58**, 2649 (1936), reported 104–105 (25 mm.). [e] Trimethylethylene. [f] *t*-Amyl alcohol. [g] Isopropylethylene.

Experimental Part

Preparation of the Alkyl Phenyl Sulfides

Method A.—Two-tenths of a mole each of thiophenol and potassium hydroxide was dissolved in 50 cc. of hot 95% ethanol. To this mixture kept at 60–70°, 0.2 mole of the alkyl bromide was added dropwise (ten minutes); potassium bromide began to separate at once. The reaction mixture was refluxed for fifteen to twenty minutes longer, cooled, diluted with water, and extracted with ether. The ether layer was washed with alkali, then with water, and dried over anhydrous sodium carbonate. After removal of the solvent the product was distilled. The yields ranged from 60 to 85% of the theoretical.

The attempts to prepare *t*-alkyl phenyl sulfides by this method failed. If the reactants were kept at room temperature, potassium bromide was formed, but the thiophenol was recovered unreacted.

Method B.—The method consisted of placing approximately 0.2 mole of thiophenol, 0.15 to 0.2 mole of olefin, and 0.2 mole of 90% phosphoric acid in a glass liner, provided with a capillary closing, and placed in an Ipatieff type rotating bomb. The latter was charged with 30 atm. (at 25°) of nitrogen to keep the reactants inside the liner during the reaction. After being heated at 120° for five to ten hours, the bomb was opened. The product consisted of two layers: the lower of catalyst, and the upper of alkyl phenyl sulfide. The upper layer was washed with water, alkali, and water, then dried over anhydrous sodium carbonate, and distilled.

Method C.—Propene or the butenes and thiophenol were placed in the glass liner of an Ipatieff bomb and left at room temperature or heated overnight in an atmosphere of nitrogen, the initial pressure of which was 20–30 atm. The pentenes in slight excess and thiophenol were placed in sealed glass tubes which were left at room temperature or heated for a number of hours. The products were washed with alkali, water, dried and distilled.

Method D.—An excess of propene was heated with 90% phosphoric acid in the glass liner of an Ipatieff bomb for six hours at 100°. To 40 g. of the isopropyl phosphate so formed was added 23 g. of thiophenol and the mixture heated at 120° for six hours in the bomb charged with nitrogen (initial pressure being 20 atm.). The acid layer of the product weighed 28.5 g. From the upper layer 6 g. of unreacted thiophenol was separated by washing with alkali, leaving 26 g. of alkali insoluble product which was distilled. Much of it appeared to be products of nuclear alkylation of the isopropyl phenyl sulfide, but a few grams of material boiling in the propyl phenyl sulfide range was isolated and shown to consist of the isopropyl thioether.

Method E.—Lee's[9] method for preparing *t*-alkyl sulfides was used with slight modifications for the preparation of (1) *t*-butyl- and (2) *t*-amyl-phenyl sulfides.

One hundred grams of 75% sulfuric acid was placed in a 3-necked, 500-cc. flask which was equipped with a mercury-sealed stirrer, a dropping funnel and an inlet tube at the bottom of the flask. The flask was surrounded by an ice-water bath. To prepare (1), isobutene was bubbled through the rapidly stirred acid until 0.2 mole was absorbed. To prepare (2), isopropylethylene or *t*-amyl alcohol (0.2 mole) was added dropwise from the dropping funnel with stirring. Then 0.1 mole of thiophenol was added dropwise with stirring. When the addition was complete, the ice-water bath was removed to allow the flask to come to room temperature. Stirring was continued for another fifteen minutes. Crushed ice was added to the reaction mixture, after which it was extracted with ether. The ether extract was washed with water, alkali, and water, then dried over anhydrous potassium carbonate, and distilled.

Method F.—Posner's directions were followed in mixing the reactants. However, it is not at all necessary to wait two weeks for the reaction to become complete: the yield at the end of one hour was 80%; at the end of two weeks it was 88%.

Preparation of the Derivatives

Derivative Pd: Palladous Chloride Complexes of Alkyl Phenyl Sulfides.—To an aqueous solution containing a slight excess of palladous chloride was added 0.1 cc. of the alkyl phenyl sulfide, and the mixture shaken for a few minutes. The brown precipitate was separated by filtration and recrystallized by use of *cold* solvents. Usually it was dissolved in acetone; the acetone solution was then filtered and diluted with water until a turbidity just appeared. The yellow or orange needles or prisms which appeared on standing were usually sufficiently pure for a melting point determination. Instead of water, heptane or ligroin may be used with the acetone; alcohol may replace the acetone.

On recrystallization of the *t*-butyl- and *t*-amyl-phenyl sulfides, insoluble brick red powders not melting below 250° were obtained. In the presence of an excess of *t*-butyl- or *t*-amyl-phenyl sulfides, palladous chloride gave soluble yellowish precipitates which after a thorough pressing on a porous plate had fairly satisfactory melting points.

Derivative S: Alkyl Phenyl Sulfones.—Two cc. each of 30% hydrogen peroxide and glacial acetic acid was added to 1 cc. of alkyl phenyl sulfide, and the mixture was heated in a 50-cc. beaker on a water-bath in a hood until the acetic acid and water were evaporated. The beaker was then cooled in dry ice–acetone mixture and scratched with a stirring rod to induce crystallization of the sulfone, which was then recrystallized from hexane or dilute alcohol. Or the crude sulfone was taken directly for nitration to form *m*-nitrophenyl alkyl sulfones.

Derivative NS: *m*-Nitrophenyl Alkyl Sulfones.—To the sulfone (from 1 cc. of sulfide) was added 2 cc. of nitrating mixture (3 parts concentrated sulfuric acid; 1 part

TABLE I.

DERIVATIVES OF ALKYL PHENYL SULFIDES

Alkyl	Method[a] of prepn.	Deriv.[b]	M. p., uncorr.	Form[c]	Solvent[d]	Formula	Analyses, % Calculated C	Calculated H	Calculated N	Calculated Pd	Found C	Found H	Found N	Found Pd[h]
n-Propyl	A, B, C	NS	78.5–79[e]	Prisms										
Isopropyl	A, D	NS	112–113[e]	Rhombic plates										
n-Butyl	A, C	Pd	106–106.5[f]	Orange needles		$C_{20}H_{28}S_2PdCl_2$				20.93				21.39
Isobutyl	A, B, C	Pd	92.5–93.5[f]	Orange prisms										
t-Butyl	E	S	98–99	Bundles of needle-like prisms		$C_{10}H_{14}O_2S$	60.60	7.07			60.64	7.05		
		Pd	84 (>250)[g]	Brick red powder										
n-Amyl	A, C	Pd	75–76	Orange prisms		$C_{22}H_{32}S_2PdCl_2$				19.87				20.19
Isoamyl	A, C	Pd	96–97	Yellow needles		$C_{22}H_{32}S_2PdCl_2$				19.87				20.05
s-Isoamyl	A, C	AS	93–94	Slender prisms	Ether–heptane	$C_{11}H_{17}NO_2S$			6.16				6.21	
t-Amyl	E, F	S	29–30, 72–73 (>250)[g]	Needles	Hexane	$C_{11}H_{16}O_2S$	62.26	7.54			62.22	7.61		

[a] See Footnote (*a*), Table I. [b] Pd = palladous chloride coördination compound; S = sulfone; NS = *m*-nitrophenyl alkyl sulfone; AS = *m*-aminophenyl alkyl sulfone. [c] Colorless unless otherwise stated. [d] See experimental part for directions for recrystallizing palladous chloride complexes; dilute alcohol for all others unless otherwise specified. [e] Baldwin and Robinson, *J. Chem. Soc.*, 1445 (1932), reported 80° for *n*-propyl and 113° for isopropyl. [f] Mann and Purdie, *ibid.*, 1549 (1935) reported 96° for *i*-butyl and 118° for *n*-butyl. Repeated recrystallizations of the latter from various solvents always gave yellow needles melting not higher than 106–106.5°. [g] The low-melting derivatives of the probable formula $(C_6H_5—S—R)_2 \cdot PdCl_2$ were not analyzed. On recrystallization these were always converted to brick red powders which did not melt below 250°. [h] Weighed as metal.

concentrated nitric) and the mixture heated on a water-bath for five minutes, after which it was poured on crushed ice and extracted with ether. The ether solution was washed with water, dried over anhydrous sodium sulfate, and evaporated on a water-bath. The crude nitro compound was recrystallized from dilute alcohol, or used without purification for preparation of the corresponding amine.

Derivative AS: *m*-Aminophenyl *s*-Isoamyl Sulfone.—The reduction of nitrophenyl *s*-isoamyl sulfone was made according to a modified method of Waldron and Reid.[11] The crude nitrophenyl sulfone obtained from 1 cc. of the sulfide was mixed with ten times its weight of iron powder (reduced by hydrogen), 10 cc. of water, and one drop of dilute sulfuric acid. With frequent stirring and adding of water to replace that lost by evaporation and the addition of a drop or two more of the acid, the mixture was heated on a water-bath for one-half to one hour. Sodium bicarbonate was added to the reaction mixture, and the aminosulfone was taken up in ether. The ether extract was treated with dilute hydrochloric acid. The free amine was then isolated by rendering the acid solution basic and extracting with ether. The ether solution was dried over anhydrous potassium carbonate and evaporated on a water-bath. The residue was recrystallized from a mixture of ether and heptane.

Summary

The addition of thiophenol to aliphatic olefins proceeds contrary to Markownikoff's rule. Propene, butene-1, isobutene, pentene-1, isopropylethylene, and trimethylethylene react with thiophenol in the absence of acid catalysts to yield *n*-propyl-, *n*-butyl-, *i*-butyl-, *n*-amyl-, *i*-amyl and *s*-isoamyl phenyl sulfides, respectively. The presence of 90% phosphoric acid scarcely affects the course of the reaction since the olefins react more readily with thiophenol than with the acid.

In the presence of sulfuric acid (diluted with water or acetic acid) the reaction proceeds in accordance with Markownikoff's rule: isobutene and trimethylethylene yield *t*-butyl- and *t*-amyl phenyl sulfides, respectively.

Isomerization occurs during the reaction of isopropylethylene with thiophenol in the presence of sulfuric acid. The product is *t*-amyl phenyl sulfide and not the expected *s*-isoamyl phenyl sulfide.

The physical properties of a number of alkyl phenyl sulfides are described. Several of these were characterized by preparation of solid derivatives.

t-Amyl phenyl sulfone cannot be prepared by the metathesis of *t*-amyl halide and sodium benzene sulfinate, as reported by Posner.

Riverside, Illinois Received June 16, 1938

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[11] Waldron and Reid, This Journal, **45**, 2399 (1923).

[Contribution from the Laboratory of Physiological Chemistry, the Ohio State University]

Studies on the Chemistry of the Fatty Acids. IV. The Purification of Linolenic Acid by Fractional Crystallization of the Fatty Acids of Linseed and Perilla Oils, with Observations on the Properties of this Acid Prepared by Crystallization and by Debromination*

By G. Y. Shinowara and J. B. Brown

Linolenic acid is the principal unsaturated fatty acid of the vegetable drying oils; it occurs in small amounts in some of the semi-drying oils. Although it is rarely, if ever, found in animal lipids, unless the animal has eaten vegetable oils containing it, linolenic acid has been shown to replace linoleic as an essential fatty acid.[1] No new methods for the isolation of linolenic acid have been offered for over twenty-five years. The zinc salt purification proposed by Erdmann and Bedford[2] apparently has not been successful in other hands. The hexabromide reduction method[3] has been the one universally employed. This method has the advantage of starting with a pure solid derivative of the acid and gives a water-white product with an iodine number and molecular weight which are close to the theoretical. As in the case of linoleic acid, the method involves bromination–debromination procedures, which greatly reduce the yield, and the product may or may not be the same as the linolenic acid present in the original oil.

In the present work we have attempted to apply the crystallization procedures described by Brown and Stoner, and Brown and Frankel,

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(*) Presented at the fall meeting of the American Chemical Society Milwaukee, Wis., 1938.

[1] Burr, Burr and Miller, *J. Biol. Chem.*, **97**, 1 (1932).

[2] Erdmann and Bedford, *Ber.*, **42**, 3128 (1909).

[3] Hazura, *J. Soc. Chem. Ind.*, 506 (1888); Hehner and Mitchell, *Analyst*, 313 (1898); Rollett, *Z. physiol. Chem.*, **62**, 410 (1909); **70**, 404 (1910).

which were effective in purifying linoleic acid,[4] to the fatty acids of linseed and perilla oils. Fractional crystallization of the acids of these oils from acetone at −23, −45, −60 and −75° gave a final filtrate which contained 75% linolenic acid. Further crystallization from acetone was effective in raising the purity only slightly but when the 75% acid was crystallized from petroleum ether the precipitate contained 83–88% of the acid, assuming the impurity to be only linoleic acid. Four of the crystallization preparations have been compared with the pure so-called α-acid prepared by debromination.

Specimens of the acid prepared by crystallization gave hexabromide numbers ranging from 72–83. Calculating these to the basis of 100% acid, these values would range from 84.5 to 99. The average value for the four crystallization specimens was 92 as compared to 70–75 for the α-acid. The theoretical is 272. Rollett[3] found the yield of hexabromide to be 23%. From these results and from a comparison of other data it seems likely that the acids prepared by crystallization and by debromination are not identical; they may be different mixtures of isomers, either of the *cis–trans* or double bond position type.

In a previous paper[4b] a method for calculating the amount of linoleic acid in a fatty acid mixture was proposed, the method being based on a comparison of the tetrabromide number of the mixture with the tetrabromide number of pure α-linoleic acid. However, the fact that α-linolenic acid prepared by debromination gives a considerably lower hexabromide number than the acid prepared by crystallization makes us hesitate to apply the same principle to linolenic acid. It is suggested, however, that a similar formula, based on the hexabromide number of a fatty acid mixture in ether, will give much more accurate results than any of the procedures now available for calculating the linolenic acid content. Such a formula is proposed and discussed.

Experimental Part

Raw Materials.—The linseed and perilla oils employed in this work were authentic specimens furnished us through the courtesy of E. E. Ware of the Sherwin–Williams Company. The oils were saponified and the acids liberated from the resultant soaps with hydrochloric acid. The acids were distilled *in vacuo*. The constants of the oils and fatty acids appear in Table I. Iodine numbers were determined by the Wijs method with one hour reaction time. Hexabromide numbers were determined as described by Brown and Frankel for linoleic acid, except that dry ether was used as a solvent. Further, it is important, in view of the results below, to note that not more than 2–2.5-g. samples were used in 35–40 cc. ether. The resultant hexabromides were washed four times with ether cooled to 0° in 50-cc. tared centrifuge tubes.

TABLE I

CONSTANTS OF LINSEED AND PERILLA OILS AND OF THE CONSTITUENT FATTY ACIDS

	Linseed	Perilla
	Original Oils	
Iodine no.	189.2	208.4
Sap. no.	196.2	201.1
	Fatty Acids	
Iodine no.	191.7	214.6
Mean mol. wt.	278.0	277.9
Hexabromide no.	49.7	58.7
Linolenic acid, %[a]	54.0	63.8

[a] Calculated from the hexabromide number, as explained later.

Fractional Crystallization of the Fatty Acids from Acetone. Acetone was added to 500 g. of the acids to a total volume of 6 l. The solution was allowed to stand overnight in a cold room at −20° and was then filtered with suction on a Büchner funnel. The crystals were washed with cold acetone (−20°) and are designated as fraction I. The filtrate was cooled to −45° in a dry-ice–alcohol bath and a second crop of crystals removed (II). The filtrate was further cooled to −60 and −75°, the crystal crops representing fractions III and IV. The acids in the final filtrate constitute fraction V. The solid acids in (I) were recovered by simply drying in air to constant weight. Those in (II) to (V) were recovered by removing the acetone under reduced pressure and distilling the residue at 2 mm. pressure. The analytical data on the fractions are given in Table II.

The iodine numbers of the several fractions progressively increase, indicating a concentration of linolenic acid in the successive filtrates as the temperature was lowered. This bears out our prediction that linolenic acid would be the most soluble acid present. Fraction I with both oils contains most of the saturated acids. The separation into saturated and unsaturated acids is especially efficient in the case of linseed oil. Oleic and linoleic acids in part come out and are removed in the intermediate fractions. The final filtrate acids, fraction V, gave iodine numbers of 252.9 and 249.1, respectively. Assuming these acids to be binary mixtures of linoleic and linolenic acids, and calculating from the iodine numbers, the linolenic acid contents were 77 and 74%, respectively, for linseed and perilla oil acids. Fractions IV of these oils contained 66 and 67%, respectively, of the acid. Values for linolenic acid, thus calculated from the iodine number, are low because small but unknown amounts of oleic acid and traces of saturated acids unavoidably are present in each instance.

In another experiment a similar crystallization was carried out, except that the later fractions were taken off

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[4] (a) Brown and Stoner, THIS JOURNAL, **59**, 3 (1937); (b) Brown and Frankel, *ibid.*, **60**, 54 (1938).

TABLE II

RESULTS OF FRACTIONAL CRYSTALLIZATION OF THE FATTY ACIDS OF LINSEED AND PERILLA OILS

	Linseed				Perilla			
Fraction	Yield, g.	Iod. no.	Mean mol. wt.	Hexabrom. no.	Yield, g.	Iod. no.	Mean mol. wt.	Hexabrom. no.
I (−23°)	65	7.8	...	1.5	40	63.9	...	9.5
II (−45°)	124	165.2	...	35.4	20	142.3	...	30.1
III (−60°)	137	217.6	277.5	56.0	235	220.3	278.4	33.1
IV (−75°)	118	242.1	278.4	66.3	130	242.8	276.0	60.5
V Filtrate	56[a]	252.9	278.3	73.0	65[b]	249.1	277.6	61.5

[a] Yield 11.2% of acids used. [b] Yield 13.0%.

at −55 and −65°. The yields and analytical data appear in Table III.

TABLE III

RESULTS OF FRACTIONATION OF THE FATTY ACIDS OF LINSEED OIL

Fraction		Yield, g.	Iod. no.	Linolenic acid, %	Hexabrom. no.
I	−17°	68	6.8		0
II	−45°	102	162.0		24.8
III	−55°	70	198.0		40.2
IV	−65°	120	225.0	45[a]	52.5
V	Filtrate	140	249.0	73[a]	63.0

[a] Calculated from iodine number.

It is obvious that this procedure has resulted in a much higher yield (28%) of a product of slightly lower purity (73%). Numerous other experiments were conducted in the hope of increasing the yield and the purity. Apparently the degree of success so far as the purity is concerned is limited to the relative solubilities of oleic, linoleic and linolenic acids in acetone.

An attempt to improve the procedure by using petroleum ether as a solvent was unsuccessful, the final filtrate giving an iodine number of only 216. This would indicate that linoleic and linolenic acids are more equally soluble in petroleum ether than in acetone and perhaps explains the success in further purification by recrystallizing the 75% product from petroleum ether described below.

The Further Purification of Linolenic Acid by Crystallization from Petroleum Ether.—Ninety grams of crude linolenic acid (iod. no. 250.4), prepared by crystallization from acetone, was added to 1200 cc. of petroleum ether and cooled to −50°. The acids which crystallized were recovered: yield 66 g.; iodine number 258.1; that of the filtrate was 244.7. This procedure therefore resulted in a considerable improvement in purity (83.5%). The preparation is further described as (1) in Table IV.

Several fractions of iodine number 218–220 were combined and 544 g. of this mixture was made up to 6 liters with acetone. After crystallizing at −60°, the acids in the filtrate (234 g.) were recovered and made up to 3 liters with petroleum ether. Crystal crops were obtained at −55 and −65°; these were combined and distilled. The first 30 g. of distillate (iodine no. 247) was rejected. The next 114 g. was found to have an iodine number of 260 (85%) (see Table IV).

Repeated crystallization from petroleum ether was investigated, starting with 250 g. of acid of iodine number 245 (69%) made up to 4 liters. Six successive crystallizations were made at this volume at −60°, the crystal crop each time being employed. The final yield was 60 g.; iodine number 262; purity 88% (see (3) Table IV).

Still another preparation was made from perilla oil. One kg. of the fatty acids of this oil was made up to 12 liters with acetone and cooled directly to −65°. The precipitate was again dissolved in acetone (8 l.) and cooled to this temperature. The acids of the combined filtrates amounted to 500 g., iodine number 245, purity 69%. This was crystallized five times from petroleum ether at −60°, the crystals each time being used. The product after distilling at low pressure amounted to 130 g., iodine number 259, purity 83% (see (4) Table IV).

Preparation of α-Linolenic Acid by Debromination.—Bromine was added slowly to 2 kg. of the mixed acids of perilla oil in 20% solution in ether, the temperature being kept below 10° with an ice-bath. The resultant bromides were washed very thoroughly seven times with 8 liters of ether, the supernatant wash ether being removed each time by suction. The yield of dried hexabromostearic acid was 640 g., m. p. 179.5–180°.

The hexabromide number as obtained here is only 32, which is much lower than reported above (see Table I). However, when the bromination experiment was repeated starting with 420 g. of the same batch of original acids and making up to only 5% with ether, a much higher yield of insoluble bromides resulted, 256 g. The hexabromide number was 60.9, which is in close agreement with the value obtained under analytical conditions, −58.7. It is apparent from these and other results that the concentration of acids during bromination is an important factor in the yield of bromides obtained.

Six hundred and thirty grams of hexabromostearic acid was suspended in 1500 cc. of hot 95% ethyl alcohol and 630 g. of zinc dust added very slowly in small portions since the reaction is quite vigorous. A few drops of concentrated hydrochloric acid were added occasionally. When all of the zinc had been added, the mixture was refluxed for one hour, the alcohol solution was separated and acidified with hydrochloric acid. About half of the alcohol was removed under reduced pressure. The partly esterified linolenic acid was recovered and distilled and, to remove ethyl ester, it was saponified, the acid recovered and again distilled: yield, 138 g., water-white acid (see (5) Table IV).

Discussion of Results

The analytical data on four crystallization preparations are compared in Table IV with the data on α-linolenic acid. By α-linolenic acid we refer to the debrominated product which may

TABLE IV

ANALYTICAL CONSTANTS OF LINOLENIC ACID PREPARED BY CRYSTALLIZATION AND BY BROMINATION

Specimen and method of prepn.	Purity, %	Mol. wt.	M. p., °C.	n^{20}	Iod. no.	Thiocyanogen no.	Hexabromide no.	Br., %	M. p. bromide, °C.
(1) Crystal.	83.5	279.0		1.4775	258.1	150.1	75.5		
(2) Crystal.	85.1	279.2		1.4775	260.0	152.6	72.0		
(3) Crystal.	88.0	278.9	−11.2–.0	1.4780	262.0	154.1	83.0	63.27	
(4) Crystal.	84.0	278.6	−11.6–.5	1.4795	259.0	151.3	83.2	63.38	180.4– .5
(5) α-Acid	100.0	278.8	−14.5–.4	1.4795	269.5	161.0	70.1[a]	63.13	178.5–9.5
Calcd.	100	278.2			273.7	182.5	272.3	63.32	

[a] This value was slightly higher, *i. e.*, 75, when a large amount of the acid was brominated in 5% solution. Hexabromide numbers reported above were averages of at least two determinations. It is worthy of note that redeterminations of these values eight months later, the specimens having been kept under inert gas at −20°, did not differ appreciably from the above values.

or may not be a mixture of isomeric linolenic acids.

Specimens (1), (2) and (3), described in Table IV, were derived from linseed oil while (4) and (5) originated from perilla oil. With regard to (5), the α-acid, it is assumed that this would be the same acid or mixture of isomeric acids no matter which oil was used in its preparation, since it is derived from ether-insoluble hexabromides. On the other hand, it seems possible that the crystallization acids may be mixtures of isomeric linolenic acids, either of the *cis–trans* or of the double bond position type. Mixtures, resulting from fractional crystallization, may not be identical either as a result of differences in the component linolenic acids of the original oil or as a result of differences in physical properties (solubilities) of these isomers so that certain of the isomers are concentrated by the fractionation. Some of the data support this idea. Specimen (3), 88.0% pure, melted at −11.2°, whereas specimen (4), 84.0% pure, melted at −11.6°. On the other hand, the nearly pure α-acid melted at −14.5°, lower than either. Further, the n^{20} of the 84% acid from perilla oil was actually higher than of the 88% acid from linseed oil and as high as the α-acid. The hexabromide numbers of the 88 and 84% acids were about equal and much higher than that of the α-acid. For these reasons we are inclined to the belief that the crystallization acids prepared from the two oils do not represent identical mixtures of isomeric linolenic acids and, further, with greater emphasis, the crystallization acids as a group are even more different from α-linolenic acid. No evidence for similar differences has been noted in our previous work with linoleic acid. We do not wish at this time to enter into the unanswered question of the occurrence of one or several linolenic acids in the original oils. Nevertheless, we believe that the above evidence seems to favor the multiple nature of "linolenic acid" despite the fact that the melting points of (3), (4) and (5) were quite sharp. The melting point of linolenic acid has not been reported previously.

Three methods have been available previously for the estimation of linolenic acid in fatty acid mixtures: (1) calculation from the iodine number; (2) the thiocyanogen method of Kaufmann[5] which is based on calculation from simultaneous equations using iodine and thiocyanogen numbers; and (3) the hexabromide number. The first of these methods is rarely practical since linolenic acid always occurs with unknown amounts of oleic and linoleic acids which cannot be separated quantitatively by any known procedure. The second method is the best of the three, but fails in being specific since it does not differentiate possible isomeric linolenic acids and also because thiocyanogen does not react quantitatively with two of the double bonds. The thiocyanogen number of the pure α-acid above fails by 21.5 units to approach the theory as expected from reaction with two double bonds. This point has been verified likewise by Kimura.[6] The third method is the oldest of the three and is based on calculation of the amount of linolenic acid present in a mixture from the amount of ether-insoluble hexabromides assuming the formation of such bromides to be quantitative. With one exception, however,[2] no one ever has claimed to have isolated a linolenic acid which would give the theoretical hexabromide number. Both Erdmann's and Rollett's linolenic acids, prepared by debromination, gave yields of hexabromides which were only 23–25% of the theoretical, which agrees well

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(5) Kaufmann and Keller, *Z. angew. Chem.*, **42**, 70, 73 (1929); Kaufmann, *Untersuch. Lebensmittl.*, **51**, 15 (1936).

(6) Kimura, *J. Soc. Chem. Ind.* (*Japan*), **32**, 451 (1929).

with our results for the α-acid. The hexabromide numbers of the five preparations in Table V calculated to the basis of 100% purity are as follows:

Preparation	Purity, %	Hexabrom. no.	Hexabrom. no. calcd. to 100%
(1)	83.5	75.5	91.6
(2)	85.2	72.0	84.5
(3)	88.0	83.0	94.3
(4)	84.0	83.2	99.0
(5)	100.0	70–75	70–75*

In previous work on arachidonic acid[7] an equation was suggested for the determination of the amount of this acid present in fatty acid mixtures based on the polybromide numbers of pure arachidonic acid and of the fatty acid mixture. A similar equation was proposed for linoleic acid, based on tetrabromide numbers.[4b] We hesitate to apply this principle to linolenic acid other than as an approximation, because obviously, from the above data, the hexabromide number is dependent on the concentration of acids being brominated and especially because it varies in different preparations of linolenic acid. The average hexabromide number for the four crystallization specimens, calculated to 100% purity, is 92.3 or in round numbers 92. From this an approximate value for the content of linolenic acid in a mixture could be found from the equation

$$\% \text{ linolenic acid} = \frac{\text{H. N.} \times 100}{92}$$

where H. N. is the hexabromide number of the fatty acid mixture and 92 is the average hexabromide number for crystallization linolenic acid. In calculating the average, the H. N. for the α-acid is omitted for the reason of its obvious difference from the crystallization acids. It also should be pointed out that the hexabromide numbers calculated to 100% are slightly high because the percentage purities were calculated from the iodine numbers as a mixture of linoleic and linolenic acids. In spite of these objections to the method, we believe it to constitute a decided advance over any other now available both in accuracy and in specificity.

Summary

1. Low temperature crystallization procedures for the isolation of linolenic acid have been applied to the fatty acids of linseed and perilla oils.

2. By fractional crystallization of the fatty acids of these oils in acetone, 75% linolenic acid remained in the filtrate at −75°.

3. Crystallization of the 75% acid from petroleum ether resulted in preparations of 83.5 to 88% purity.

4. The constants of the crystallization acids are compared with those of α-linolenic acid, prepared by debromination.

5. The possibility of the multiple nature of linolenic acid is discussed; also the application of the hexabromide number as a method of estimating the amount of linolenic acid present in fatty acid mixtures.

COLUMBUS, OHIO RECEIVED AUGUST 15, 1938

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[7] Ault and Brown, *J. Biol. Chem.*, **107**, 615 (1934).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF CORNELL UNIVERSITY]

The Colloid Chemistry of Leaf and Flower Pigments. I. The Precursors of the Anthocyanins[1]

BY WILDER D. BANCROFT AND JOHN E. RUTZLER, JR.

Introduction

Most of the research work on leaf and flower pigments has been done by organic chemists who were interested primarily in preparing and analyzing pure compounds, or by biologists who were interested primarily in genetics. It has seemed worth while to us to present to some extent the viewpoint of those colloid chemists who are interested especially in the changes of color with changing conditions.

Some points are much simpler when considered as colloid chemistry. Chlorophyll is soluble in benzene; but benzene will take scarcely any chlorophyll out of the green leaf.[2] Tswett[3] has shown that this is due to marked selective adsorption of the pigment of the leaf tissue. The phenomena of co-pigments or intensifying agents, studied by the Robinsons,[4] become more simple when considered as due to adsorption.

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[1] Original manuscript received December 13, 1935.

[2] Willstätter and Hug, *Ann.*, **380**, 177 (1911).

[3] Tswett, *Ber. deutsch. bot. Ges.*, **24**, 318 (1906).

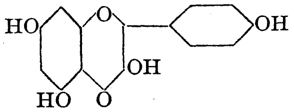
[4] Robinson and Robinson, *Biochem. J.*, **26**, 1663 (1932).

Since chlorophyll is the most important plant pigment and the one best known to the public, it might seem wise to begin with that. We shall get into a more controversial and to us a more interesting field if we start with the red autumn leaves and most of the red and blue flowers. These pigments are known as anthocyanin pigments and there is a wide difference of opinion as to the way they originated. The German chemist, Willstätter, believes that they are formed in the plant by reduction of flavones, while the English chemist, Robinson, believes that they are produced in the plant by hydrolysis and oxidation of what are known as leuco-anthocyanins. In this paper we plan to show how to differentiate between these two diametrically opposed views. Each is right in certain cases and each is wrong in others.

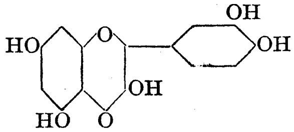
Anthocyanins and Anthocyanidins

In general the anthocyanins vary in color from red or purple through blue and green to yellow as the *p*H of the sap increases. The green is not a pigment color but is due to the combined effect of the yellow and blue. When one starts with a red flower and exposes it to ammonia vapor, the blue is apt not to be permanent in the absence of a stabilizer. If it changes fairly rapidly to yellow one gets no blue but only a green. If it changes very rapidly to yellow one gets neither blue nor green. The red leaves of the poinsettia are a case of this. It seems probable therefore that all blue flowers contain a color-stabilizer, but there apparently has been no systematic study of this point. Sodium chloride, sodium nitrate and alum solutions[5] are said to stabilize the blue in particular cases; but we do not know how general this is or what salts are found in blue flowers. The blue of *Salvia patens* extends over a *p*H range of 4–8.[6] Hirsutin, methyl malvin, is turned blue by a number of co-pigments:[7] tannin, 2-hydroxyxanthone glucoside, rutin, quercetin, vanillin and quinaldine.

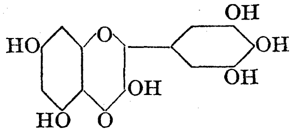
Pedagogically, most anthocyanins and anthocyanidins may be considered as reduction products of one of three flavonols or derivatives of them.[8] The three flavonols are kaempferol, quercetin and myricetin.



Kaempferol

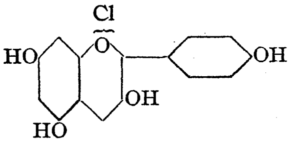


Quercetin

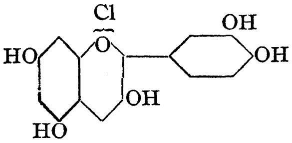


Myricetin

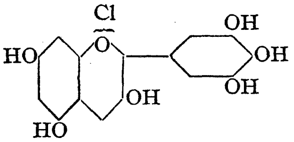
The corresponding anthocyanidin chlorides are pelargonidin chloride, cyanidin chloride and delphinidin chloride



Pelargonidin chloride



Cyanidin chloride



Delphinidin chloride

An anthocyanin differs from an anthocyanidin in having one or more glucose, galactose or rhamnose molecules attached to it. One or more of the hydroxyl groups may be methylated, giving a substituted anthocyanin if there are sugar molecules attached and a substituted anthocyanidin if the molecule is an aglucone.

Willstätter and Mallison[9] showed that cyanidin can be obtained by reduction of quercetin with a metal and an acid. Shibata, Nagai and Kishida[10] got quicker results with magnesium and mercury in acid solution. They consider the mercury as essential to a good result.

At Cornell we have obtained excellent data by

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[5] Willstätter and Everest, *Ann.*, **401**, 189 (1913); Molisch, *Bot. Ztg.*, **47**, 17 (1889); **55**, 49 (1897); Miyoshi, *Botan. Centr.*, **83**, 345 (1900).

[6] Buxton and Darbishire, *J. Genetics*, **21**, 71 (1929).

[7] Robinson and Todd, *J. Chem. Soc.*, 2299 (1932).

[8] Robinson, *Encyclopaedia Britannica*, **2**, 26 (1929).

[9] Willstätter and Mallison, *Ann.*, **408**, 147 (1915); *cf.* Schunck, *Proc. Roy. Soc.* (London), **42**, 187 (1884).

[10] Shibata, Nagai and Kishida, *J. Biol. Chem.*, **28**, 93 (1916–1917).

electrolysis in an acid solution, using a mercury cathode to give high over-voltage. Dr. T. S. Chapman[11] extracted shredded leaves cold with dilute formic acid (2–5%). A pink solution shows the presence of anthocyanins or anthocyanidins. If the pink color appears only after heating, leuco-anthocyanins are present. If a pink, yellowish or colorless solution is shaken with ether and if aqueous ammonia is added to the ether layer, the appearance of a distinctly deeper yellow going practically completely into the water layer indicates the presence of anthoxanthins. Not much deepening of the yellow, with much of the color staying in the ether, indicates the presence of "Tswett's water-soluble yellows."

To carry out the reduction, some of the formic acid extract was poured off the leaves and mixed with an equal volume of approximately molar sulfuric acid solution. Half of the mixture was poured into the reduction cell and half retained for comparison. On electrolysis with a platinum anode and a mercury cathode a change of color was usually noticeable within a few minutes and almost always within fifteen minutes; but it was customary to electrolyze for an hour to ensure a satisfactory reduction. It is wise to keep the solution cold to prevent hydrolysis, which would give a red color if leuco-anthocyanins were present.

Some sixty-five different kinds of leaves containing anthoxanthins were examined by Dr. Chapman and all but five gave satisfactory anthocyanin-like pigments as shown by the red color. The locust, the California privet, the hawthorn and the wayfaring tree yielded reduction products which were rather yellow or orange in comparison with the others. The reduction of the extract from the privet in particular gave a very yellow color to the solution.

There are marked differences in the ease of reduction. The flavones from the forsythia and the jonquil reduce much more readily than those from the sugar maple.

From these and other experiments it is clear that anthocyanins or anthocyanidins can be obtained from flavone or flavonol solutions by chemical or electrolytic reduction; but there is no proof that this happens in the living plant. Willstätter believes that anthocyanins are formed by reduction, but all that has been proved is that they might be so formed.

Many of the English chemists do not agree with Willstätter that anthocyanins and anthocyanidins are produced in the plant by direct reduction of flavones or flavonols. Keeble, Armstrong and Jones[12] came to the conclusion that the decolorization of anthocyanins by alcohol was due to the action of a reducing agent. Unfortunately, this paper was published before the one in which Willstätter showed that decolorization of anthocyanin by alcohol was not due to reduction. That eliminated Keeble's argument.

Robinson is the present leader of the movement in favor of the anthocyanin pigments being produced by oxidation. One reason for believing that flavones are not the immediate precursors of anthocyanins is that in many cases the anthocyanins do not correspond structurally with the flavones existing in the flower. This is not absolutely conclusive, because there might have been two sets of flavones originally and only one was reduced in the plant. Sands, Milner and Sherman[13] say: "We cannot assume that, because a certain flavonol is not found coexisting with its homologous anthocyanidin, the latter was formed independently rather than by way of the flavonol. As mentioned, the particular flavonol in question may have been converted fully into anthocyanidin." This may be true, but it has not yet been proved and we do know that anthocyanins can be made differently in the plant.

Leuco-anthocyanins and Leuco-anthocyanidins

Robinson and Robinson[14] believe that many and perhaps all anthocyanins are derived from leuco-anthocyanins[15] and leuco-anthocyanidins, substances which were not known as such to Willstätter.[16] Laborde found that unripe green or red grapes contain colorless chromogens which are converted into pigment on heating with dilute hydrochloric acid. Malvézin showed that the same chromogen developed color on heating with water at 85°, but only in the presence of air which may have caused oxidation to acid. Dezain, Tswett, Rosenheim, Jonesco and Kozlowski also have showed the formation of pigments of anthocyanin-like nature from colorless or pale yellow chromogens without the use of a reducing agent.

"Rosenheim[17] prepared a white amorphous pow-

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[11] Cornell University, Ph.D. Thesis, 1938.

[12] Keeble, Armstrong and Jones, *Proc. Roy. Soc.* (London), **86B**, 312 (1913).

[13] Sands, Milner and Sherman, *J. Biol. Chem.*, **109**, 203 (1935).

[14] Robinson and Robinson, *J. Chem. Soc.*, 744 (1935).

[15] *Cf.* Staats, *Ber.*, **28**, 2807 (1895).

[16] Willstätter, *Ann.*, **408**, 4 (1915).

[17] Rosenheim, *Biochem. J.*, **14**, 178 (1920).

der of glycosidic nature from the unripe berries of purple grapes or from ripe white grapes and stated that anthocyanidin could be obtained from it by the action of hydrochloric acid in the absence of oxygen. He proposed the expression leuco-anthocyanin for the new group of natural products."

Robinson and Robinson report that leuco-anthocyanins are of widespread occurrence in the vegetable kingdom and that a majority of them yield cyanidin on treatment with hot hydrochloric acid. A 10% sulfuric acid solution is even better because there is no difficulty about volatility. In 1933 Robinson and Robinson[18] said that it is probable that the leuco-anthocyanins and the anthocyanidins formed from them are in the same state of oxidation. In 1937 Mrs. Robinson[19] reported that the gum of *Butea fondosa* contains a substance which cannot be converted into cyanidin chloride by the action of hydrochloric acid alone; preliminary oxidation is necessary.

Robinson and Robinson[20] now consider that the state of oxidation of a leuco-anthocyanidin is that of a dihydroflavylium salt. If this is always true, hydrolysis and oxidation are necessary to produce an anthocyanin pigment from a leuco-anthocyanin. There seems to be nothing to show that an oxidation is always necessary. If Rosenheim is right there must be some cases not involving oxidation. Over-reduction of an anthocyanin or anthocyanidin gives a colorless system which turns red on oxidation,[21] but we do not yet know whether this ever happens in the plant.

Regardless of the question of oxidation it is clear that an anthocyanin pigment can be obtained in the laboratory from a leuco-anthocyanin; but we do not yet know definitely whether this occurs in the plant or, if so, in which plants. One reason for this general uncertainty is that much of the work has been done on flowers where there is usually no change in pigments and one cannot well analyze the flowers for flavones and leuco-anthocyanins before and after the change, though Hugo Fischer[22] says that the first appearance of color in the flower buds is generally two weeks before the time of blooming in the case of red and blue flowers. This is not necessarily true, because cases are known of flowers starting white under suitable conditions and then developing a color.

Variable White Flowers

The flowers of *Hibiscus* L. *mutabilis*[23] and of *Diervilla grandiflora*[24] open white and turn pink or red in the course of the first day. Quite a number of flowers are pale or white when grown in the dark.[25] Among them is the mountain laurel. A low temperature also makes some flowers come white.[25b] With some the reverse is true.[26]

We have not found in the literature any systematic study of the chemistry of these pigments of these variable white flowers. Shibata seems to have shown that the change of color of the white *Diervilla grandiflora* to red is due to a reduction of a flavone-like substance, but in 1916 he of course did not test for the presence of leuco-anthocyanin and consequently there is a possibility of error.

Red Autumn Leaves

If we shift from flowers to green leaves which turn red, it is a simple matter to analyze them before the red color appears. If we take a green leaf, moisten it with dilute sulfuric acid to ensure acidity and electrolyze it with a platinum anode and a mercury cathode, we shall get a red at the cathode if a flavone or flavonol is present because of the reduction and no red, or at most a red at the anode, if a leuco-anthocyanin is present because it does not go red on reduction. Of course precautions must be taken against an error due to hydrolysis. It may not always be easy to see small amounts of red pigment on the mercury; but rinsing it with normal butyl alcohol will concentrate the red color in the alcohol and make it visible. The presence of leuco-anthocyanin can be shown by shredding the green leaf and heating it with approximately 10% sulfuric acid solution until the solution becomes red or pink. Extracting the solution with normal butyl alcohol will make the red color more visible.

We have made tests on the green leaves of the sugar maple and the sumach in August, and on the

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[18] Robinson and Robinson, *Biochem. J.*, **27**, 206 (1933).

[19] Robinson, *J. Chem. Soc.*, 1157 (1937).

[20] Robinson and Robinson, *ibid.*, 747 (1937).

[21] Charlesworth, Chavan and Robinson, *ibid.*, 370 (1932).

[22] Fischer, *Flora*, **38**, 380 (1908).

[23] Kuyper, *Rec. trav. bot. néerl.*, **28**, 1 (1931).

[24] Shibata, Nagai and Kishida, *J. Biol. Chem.*, **28**, 93 (1916).

[25] (a) Hildebrand: "Die Farben der Blüthen," 1879, p. 49; (b) Klebs, *Sitzber. Akad. Wiss. Wien*, **42**, 155 (1905); ref. 22; (c) Sorby, *Proc. Roy. Soc.* (London), **21**, 479 (1873); (d) Kosaka, *Bot. Mag.*, **46**, 551 (1932).

[26] Onslow, "The Anthocyanin Pigments of Plants," 1925, p. 8.

green leaves of the flowering dogwood, the Virginia Creeper (*Parthenocissus quinquefolia*) and the Japanese Creeper (*Ampelopsis*) in September; also on the green skin of a Seckel pear.

The leaves of the sumach, the barberry and the flowering dogwood, contain flavones and no, or practically no, leuco-anthocyanins though there may be a mere trace of leuco-anthocyanin in the leaf of the dogwood. The leaves of the sugar maple and the Virginia Creeper and the skin of the Seckel pear contain leuco-anthocyanin and no, or practically no, flavone, while the leaves of the Japanese Creeper contain both flavone and leuco-anthocyanin. We can, therefore, say definitely that the red autumn leaves of the sumach, the dogwood and the barberry, are due to reduction of flavones, in accord with the view of Willstätter. The red autumn leaves of the sugar maple and of the Virginia Creeper and the red color of the ripened Seckel pear owe their color to the decomposition of leuco-anthocyanin in accord with the view of Robinson, while the red color of the leaves of the Japanese Creeper may be due either to flavones or to leuco-anthocyanins or to both simultaneously. We shall have to devise a new technique for this case or perhaps resort to quantitative analysis. It is now merely a question in most cases of collecting data on other leaves which turn red or which change from red to green.

DeVries[27] says that the leaves of *Drosera rotundifolia* are red when grown in strong light, but otherwise green. There should, therefore, be no difficulty in determining the precursors of the anthocyanins in this plant. Schanz[28] showed that when light less than 400 mμ was cut off by euphos glass, the leaves of red cabbages, young beets and begonias were green and not red. The colors returned in the sunlight. He concluded that the red was developed as a protection against the long ultraviolet. With oak seedlings grown in the open air, the young leaves were a beautiful yellowish-red; under ordinary glass the color was paler; under euphos glass and under red glass the yellow-red did not appear and the leaves were uniformly green.

After the red disappears from the young leaves of the copper beech in summer, leuco-anthocyanins are found to be present. On this statement of facts it seems probable that the red is developed from the leuco-anthocyanins. Abbott[29] has found that leaves of the copper beech are green in the spring when grown in the dark and turn red when exposed to light. He did not analyze these leaves for flavones or leuco-anthocyanins, and consequently one step in the proof is missing.

We do not yet know what factors determine the formation of flavones and leuco-anthocyanins, and consequently we do not know how the relative amounts of these two kinds of substances will vary with changing soil and climatic conditions. In Ithaca the leaves of a certain sugar maple contain flavones and no, or practically no, leuco-anthocyanins in May, and leuco-anthocyanins with practically no flavones in September. It is because of this that we do not yet dare to say definitely that the red of the copper beech is derived from leuco-anthocyanins.

To answer the question whether the conversion of leuco-anthocyanins into anthocyanidins necessarily involves an oxidation we have tried heating equal amounts of the leaves of the sugar maple with sulfuric acid in the presence and in the absence of hydroquinone. There was no marked difference in the amount of red color, and consequently there is no reason to assume that the leuco-anthocyanins must be considered as derivatives of dihydroflavylium salts. Since oxygen is apparently of very little importance in this case, we confirm the observations of Rosenheim. This does not in any way contradict the results obtained by Mrs. Robinson with the gum of *Butea fondosa*. There is no reason as yet why all leuco-anthocyanins should be derivatives of dihydroflavylium salts because some may be.

Enzyme Reactions

Whether in the formation of anthocyanin we are dealing with the reduction of flavone-like substances or with the hydrolysis of leuco-anthocyanins with or without accompanying oxidation, the reaction must apparently be an enzyme reaction because we know of no straight reducing agent that the plant could use which would carry a flavone to an anthocyanin, and because it seems improbable that there would ever be sufficient acidity to produce the hydrolysis of a leuco-anthocyanin without the presence of an enzyme. Miss Wheldale[30] says that "there is little doubt but that the formation of anthocyanin does in-

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(27) DeVries, *Bot. Ztg.*, **44**, 4 (1886).

(28) Schanz, *Pflüger's Arch. Physiol.*, **181**, 229 (1920).

(29) Abbott, *Nature*, **80**, 429 (1909).

(30) Wheldale, *J. Genetics*, **1**, 113 (1911).

volve a series of progressive reactions, each of which is controlled by a certain enzyme."

Enzymes can cause the reduction of sulfates,[31] a reaction which cannot be carried out chemically or electrochemically in the test-tube in the presence of water at ordinary temperatures.

If people can learn how to concentrate the enzymes and to inoculate leaves with them, it should be possible to make the leaves of the Norway maple red. That ought not be a very difficult task, because the stems of the leaves are apt to be red and once in a while one sees an occasional red leaf. When we know more about the enzyme reactions, we shall be able to explain why European forests do not show the brilliant coloring that we get in this country.

In front of the chemistry building at Cornell there is a sugar maple and a copper beech. Both sets of leaves contain leuco-anthocyanin but those in the copper beech do not turn red in the autumn, while those in the sugar maple do. There is no reason to attribute this behavior to differences in climatic or soil conditions and consequently there must be at least one other factor, apparently a genetic one. The green leaves of the Norway maple in Ithaca contain flavones and no leuco-anthocyanins. Since the stems of the leaves are usually red and the leaves only rarely so, there must be some reason why the proper enzyme is found only occasionally in the leaves. Flavones are present in the ginkgo; but we have never seen any red in Ithaca either on stems or leaves. The formic acid extracts of the leaves of the Norway maple and of the ginkgo turn red when electrolyzed with a mercury cathode. The yellowed leaf of the American elm will sometimes develop a little red when bitten by an insect. There is no experimental evidence that the insect causes a preliminary formation of leuco-anthocyanin and we must therefore attribute the red to flavones for the present.

Summary

1. Anthocyanin pigments may be obtained in the laboratory or in the plant by reduction of flavones or by decomposition of leuco-anthocyanins.

2. The red autumn pigments of the sumach, the dogwood and the barberry come from a flavone and those of the sugar maple, the Virginia Creeper and the Seckel pear from a leuco-anthocyanin. The Japanese Creeper contains both flavone and leuco-anthocyanin. We do not yet know which gives rise to the anthocyanin or whether both do.

3. On present data the red of the copper beech comes probably from a leuco-anthocyanin; but this is not yet proved.

4. There is no necessary contradiction between the experiments of Rosenheim and those of Mrs. Robinson. There are apparently some leuco-anthocyanins which require oxygen to develop the full red color and some which do not. On present data the sugar maple belongs in the second class or partly so.

5. The development of anthocyanins is always due to enzymes. If one could inactivate the enzymes without killing the leaves one would prevent the development of red. If one could supply the proper enzyme to the Norway maple, its leaves would turn red in the fall. The stems of the leaves usually turn red in the summer.

6. Since the leaves of the copper beech and of the sugar maple both contain leuco-anthocyanins but behave differently in the autumn, there is apparently a genetic factor to be considered in addition to the effects of soil and climate.

7. A method has been developed which will enable us to distinguish between the views of Willstätter and of Robinson in particular cases.

8. All blue flowers contain a stabilizing agent. A systematic study of this matter will lead to the production of blue roses.

9. There seem to be no satisfactory data on the reds which develop early and temporarily in the tropics.

10. The behavior of the sugar maple suggests the possibility of a flavone being the precursor of a leuco-anthocyanin; but there is no proof of this as yet.

11. There seem to be no data to show whether glucose as a nutrient or a suitable exposure to ultra-violet light will produce anthocyanins more rapidly from leaves containing flavones or from leaves containing leuco-anthocyanins.

Ithaca, N. Y.

Received September 30, 1938

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(31) Pozzi-Escot, *Am. Chem. J.*, **29**, 542 (1903).

The Conductance and Ionization Constants of Propionic and Normal Butyric Acids in Water at 25°

BY DONALD BELCHER

The modern theories of interionic attraction, which are now accepted in the form of limiting laws, are particularly useful in the interpretation of weak electrolytes. It has been shown by several investigators[1–3] that accurate conductance measurements of a weak binary electrolyte should suffice in theory to yield values of the limiting conductance and thermodynamic ionization constant. In media of high dielectric constant, such as water, there is strong evidence for the complete dissociation of the salts of weak acids (or bases) and therefore the limiting conductance of the weak electrolyte may be obtained by use of the additive law of Kohlrausch. But in nonaqueous solvents of low dielectric constant there are no strong electrolytes and hence to determine the limiting conductance it is necessary to apply methods of extrapolation to conductance data on the weak electrolyte alone.

For the additive method it is sufficient to determine the limiting conductance of the sodium salt of the weak acid, since the other necessary data are obtainable from the work of Shedlovsky.[4]

The extrapolation methods are based on a solution of the three simultaneous equations

$$K = \frac{C\theta^2 f_\pm^2}{1-\theta} = K^1 f_\pm^2 \tag{1}$$

where K and K^1 are the thermodynamic and stoichiometric ionization constants, respectively, θ is the degree of dissociation, C is the total concentration of the acid in equivalents per liter, and $f_\pm$ is the mean activity coefficient of the ions. The activity coefficient of the undissociated acid is assumed to be unity.

$$-\log f_\pm = a\sqrt{C\theta} \tag{2}$$

where a is the Debye–Hückel coefficient.

$$\theta = \frac{\lambda}{\lambda_0}\left[\frac{1}{1-\frac{A}{\lambda_0}\sqrt{C\theta}}\right] \tag{3}$$

where λ is the equivalent conductance of the acid at the total concentration C, λ_0 is the limiting conductance of the acid, and A is the Onsager coefficient for uni-univalent ions in water at 25°.

If the right-hand side of (3) is expanded, and terms of order higher than $\sqrt{C}$ discarded, the simple quadratic expression used by Shedlovsky[5]

$$\theta = \frac{\lambda}{\lambda_0}\left[1+\frac{A}{\lambda_0}\sqrt{C\theta}\right] \tag{4}$$

is obtained. A combination of (1), (2), and (4) leads to a simultaneous solution which is much easier to use and, moreover, equation (4) has been shown to fit conductivity data over a much longer range of concentration than the original Onsager expression.

When λ_0 is not known, a trial value is assumed and adjusted until the equations are self-consistent.

With these considerations in mind I have determined accurately the conductance of propionic and normal butyric acids in water at 25°. An examination of this data by the extrapolation method made it clear that data on the salts of these acids were necessary. The determinations of conductances of sodium propionate and sodium butyrate, given later in this paper, were made in collaboration with Dr. Theodore Shedlovsky.

Experimental Assembly and Technique.—The apparatus and technique used follow so closely the practice of Jones and his associates[6,7] and of Shedlovsky[8] that only the briefest description is necessary.

The bridge, of the Jones and Josephs type (with shielding, following the practice of Shedlovsky[8]), was constructed by the Cambridge Instrument Company to order.

A two-stage audio amplifier and telephones of 2000 ohms resistance formed the detector circuit.

A vacuum tube oscillator of the "push-pull" type, constructed as described by Shedlovsky,[8] supplied current to the bridge. The frequency could be varied in steps over a range of 850 to 4000 cycles by a bank of condensers in parallel. The frequency for various condenser settings was determined roughly by audio comparison with a General Radio oscillator which in turn was calibrated by a tuning fork. Several times in each series of measurements the frequency was varied, but since the conductances were found to be independent of frequency an accurate knowledge of the latter was unnecessary.

A shielded decade resistance box, supplied by the Cambridge Instrument Company, permitted direct reading to 11,111 ohms, to the nearest 0.01 ohm. It was calibrated by the National Physical·Laboratory with direct current. None of the coils was thermostated, but the box was enclosed in a lagged wooden case and the temperature was known to the nearest degree.

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[1] Fuoss and Kraus, THIS JOURNAL, **55**, 476 (1933).

[2] Shedlovsky and Uhlig, *J. Gen. Physiol.*, **17**, 549 (1934).

[3] Fuoss, THIS JOURNAL, **57**, 488 (1935).

[4] Shedlovsky, *ibid.*, **54**, 1411 (1932).

[5] Shedlovsky, *J. Franklin Inst.*, **225**, 739 (1938).

[6] Jones and Josephs, THIS JOURNAL, **50**, 1049 (1928).

[7] Jones and Bollinger, *ibid.*, **51**, 2407 (1929); **53**, 411 (1931).

[8] Shedlovsky, *ibid.*, **52**, 1793 (1930); **52**, 1806 (1930).

The thermostat was filled with Mineral Colza Oil and controlled to ± 0.001° by a Thyratron relay.

Two pipet cells of Jena glass were used for the more concentrated solutions. They were calibrated with 0.1 demal potassium chloride, using the recent values of Jones and Bradshaw.[9] The temperature of the thermostat was set to 25 ± 0.005° by using a thermometer recently calibrated by the National Physical Laboratory.

Two flask cells, one of Pyrex and one of clear quartz, were used for the more dilute solutions. The electrodes were lightly platinized. After each run the cells were cleaned with redistilled alcohol and ether, and occasionally with hot chromic acid.

Conductivity water was obtained from a still which followed the general design of Ellis and Kiehl.[10] The boiler was of Pyrex and the condenser of fused silica. Purified nitrogen was passed up the column and out through a water trap. A ball and socket joint connected the Pyrex and silica portions of the still and gave great flexibility and freedom from breakage. The boiler was charged with a good grade of distilled water made 0.025 molar in phosphoric acid. The still yielded one liter per hour of fair conductivity water ($k = 5 \times 10^{-7}$ mhos), and about 400 cc. per hour of the best water ($k = 0.8$ to 2×10^{-7} mhos). For the more dilute solutions the water was distilled directly into the flask cells.

Densities were determined with an ordinary Sprengel pycnometer in a water thermostat.

All solutions were made up by weight. The more accurate weighings were performed on an analytical balance which could be read to 0.1 mg. Water and stock solutions were weighed on a large balance to the nearest 10 mg. Weights were calibrated against a set standardized by the National Physical Laboratory.

Materials.—The propionic and normal butyric acids were Kahlbaum "purest." They were further purified by fractional crystallization and distillation. The freezing point of the recovered portion of propionic acid was −22.4°, which may be compared with −20.8° (Timmermans and Hennaut-Roland[11]) and −22.3° (Broughton[12]). The final portion of butyric acid melted at −5.37°, very close to the value given by Timmermans and Hennaut-Roland.[11] As a check on the purity of the acids they were analyzed by weight titrations against carbon dioxide free sodium hydroxide. By using phenolphthalein and a technique which excluded carbon dioxide it was possible to titrate with a precision of 0.04%. Several titrations gave the purity of the propionic acid as 100.02%, and that of the butyric acid as 99.96%. Accordingly the acids were assumed to be pure within the experimental error. The sodium hydroxide was standardized against a standard brand of benzoic acid.

The molecular weights of the acids were taken from the "International Critical Tables."

Several determinations of the densities of solutions of both acids checked so well with the data of Drucker[13] that the latter's measurements were used to compute concentrations.

Results.—Tables I and II give the data for the two acids. The columns are, respectively, the concentration in equivalents per liter, the equivalent conductance, the degree of dissociation, the mean activity coefficient of the ions; the stoichiometric ionization constant, and the thermodynamic ionization constant. These ta-

TABLE I

EQUIVALENT CONDUCTANCES AND IONIZATION CONSTANTS OF PROPIONIC ACID AT 25°. $\lambda_0 = 385.47$

Concn. $C \times 10^3$	λ	θ	$f_\pm$	$K^1 \times 10^5$	$K \times 10^5$
0.033831	177.94	0.46212	0.9954	1.343	1.331
.035330	174.76	.45377	.9953	1.332	1.320
.072197	134.25	.34880	.9942	1.349	1.333
.16091	96.690	.25136	.9926	1.358	1.338
.24142	81.209	.21116	.9917	1.365	1.342
.26595	77.812	.20234	.9915	1.365	1.342
.35702	68.283	.17761	.9908	1.369	1.344
.37303	66.895	.17400	.9907	1.367	1.342
.56685	55.320	.14395	.9895	1.372	1.343
.72479	49.385	.12853	.9888	1.374	1.343
.87116	45.348	.11805	.9883	1.378	1.345
1.8650	31.657	.082480	.9856	1.383	1.343
2.8788	25.717	.067042	.9839	1.387	1.343
4.8026	20.099	.052440	.9817	1.394	1.343
6.9117	16.852	.043990	.9799	1.399	1.343
6.9880	16.764	.043761	.9798	1.400	1.344
8.8839	14.903	.038920	.9786	1.400	1.341
10.342	13.844	.036164	.9777	1.403	1.341
12.208	12.763	.033351	.9768	1.405	1.340
15.347	11.375	.029738	.9753	1.407	1.338
15.401	11.373	.029732	.9754	1.403	1.335
49.876	6.3628	.016681	.9670	1.411	1.320
75.352	5.1598	.013543	.9635	1.401	1.301
101.64	4.4283	.011633	.9607	1.392	1.285
152.87	3.5375	.0083126	.9544	1.344	1.228
192.95	3.1576	.0064011	.9494	1.279	1.153

TABLE II

EQUIVALENT CONDUCTANCES AND IONIZATION CONSTANTS OF NORMAL BUTYRIC ACID AT 25°. $\lambda_0 = 382.40$

Concn. $C \times 10^3$	λ	θ	$f_\pm$	$K^1 \times 10^5$	$K \times 10^5$
0.029576	193.29	0.50622	0.9955	1.535	1.521
.055746	154.28	.40418	.9945	1.529	1.512
.082109	132.99	.34851	.9938	1.531	1.512
.10606	120.01	.31451	.9933	1.530	1.510
.29695	77.368	.20293	.9910	1.534	1.507
.33908	72.904	.19124	.9907	1.534	1.505
.43277	65.335	.17142	.9901	1.535	1.505
.78715	49.671	.13040	.9883	1.539	1.503
.83817	48.242	.12666	.9881	1.540	1.503
.93748	45.846	.12038	.9877	1.545	1.507
1.0096	44.319	.11638	.9875	1.548	1.509
1.5818	35.848	.094184	.9859	1.549	1.506
2.1506	30.961	.081378	.9848	1.550	1.504
2.1754	30.817	.080999	.9847	1.553	1.506
2.7827	27.394	.072024	.9837	1.556	1.505
2.8099	27.253	.071653	.9837	1.554	1.504
3.6043	24.184	.063609	.9826	1.557	1.504
4.1450	22.610	.059482	.9819	1.559	1.504
5.2881	20.102	.052905	.9808	1.563	1.503
6.4110	18.312	.038209	.9798	1.565	1.503
8.5822	15.893				
17.350	11.247				
99.879	4.6414				
149.96	3.7317				
189.92	3.2776				
240.10	2.8631				
295.42	2.5398				

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[9] Jones and Bradshaw, THIS JOURNAL, **55**, 1780 (1933).

[10] Ellis and Kiehl, *ibid.*, **57**, 2145 (1935).

[11] Timmermans and Hennaut-Roland, *J. chim. phys.*, **27**, 401 (1930).

[12] Broughton, *Trans. Faraday Soc.*, **30**, 367 (1934).

[13] Drucker, *Z. physik. Chem.*, **52**, 641 (1905).

bles are based on λ_0 values obtained from salt conductances by the additive method. Furthermore, the values of $\theta, f_{\pm}$, etc., have been computed by the new and more convenient method due to Shedlovsky.[5] It should be noted that for the present data the various extrapolation methods give identical results in the range of concentration where K is reasonably constant. No water correction has been made in computing the equivalent conductances since the specific conductivity of the water used never exceeded 0.2×10^{-6} mho, and is due largely to the presence of carbon dioxide.

Discussion of Results.—Table I shows that the measured conductances of the four most dilute points are in error. This is undoubtedly due to the use of a Pyrex flask cell. The effect of glass on the conductivity of very dilute solutions of weak acids was noted many years ago by Kraus and Parker.[14] The data of Table II do not show this effect since the butyric acid measurements were made in quartz.

A plot of the logarithm of the stoichiometric ionization constant against the square root of the ionic strength for these two acids gives straight lines for total acid concentrations not exceeding 0.01 normal. These lines have very nearly the Debye–Hückel slope (1.013), and the intercepts give the logarithm of the thermodynamic ionization constant. At higher concentrations log K^1 falls off rapidly with increasing ionic strength, an effect noted by MacInnes and Shedlovsky[15] for acetic acid. Davies[16] showed that this so-called "medium effect" is largely due to viscosity in the case of acetic acid, and I propose to discuss the effect of viscosity in a forthcoming paper.

The extrapolation method yields a thermodynamic ionization constant of 1.343×10^{-5} for propionic acid, in fair agreement with the value 1.332×10^{-5}, obtained by Harned and Ehlers[17] from electromotive force measurements. The latter figure has been reduced from a molar to a concentration basis.

For normal butyric acid extrapolation gives 1.508×10^{-5}, in excellent agreement with the value 1.510×10^{-5}, obtained by Harned and Sutherland[18] from electromotive force measurements.

The Conductance of the Sodium Salts of Propionic and Normal Butyric Acids in Water at 25°

Materials.—Kahlbaum acids were used, but no further purification was attempted since the salt concentrations of stock solutions were known accurately from titrations.

Preparation of Solutions.—A carbonate-free solution of sodium hydroxide was prepared and standardized by weight titrations against Bureau of Standards acid potassium phthalate. The latter was dried before using. Phenolphthalein was used as indicator and nitrogen was passed through the titration vessel for some time before the alkali was added and during the titration. It so happens that the phenolphthalein end-point corresponds very closely to the *p*H of neutralized acid phthalate so that it is possible to titrate to an accuracy of 1 or 2 parts in 10,000. As a check, however, the *p*H of the final solution was determined with the glass electrode and if necessary a small correction applied. The acids were titrated in a similar manner, but since in this case the *p*H of the neutralized solutions does not correspond to the phenolphthalein end-point, the correction was important. By applying the correction it was possible to titrate the acids to a precision of 3 parts in 10,000. This method has the advantage of being much more rapid and convenient than the method of differential electrometric titration of MacInnes and Dole.[19]

When a sufficient number of titrations had established the strength of the acids, stock solutions were made up without indicator. To suppress hydrolysis about 0.5% excess acid was added. The salt concentration was known accurately from the amount of alkali used.

The densities of several solutions of sodium butyrate were measured and it was found that the agreement with sodium acetate solutions was very close in the dilute range. Accordingly it was considered justifiable to use the same density–concentration relationship in the case of sodium propionate.

Table III gives the conductances of sodium propionate and sodium butyrate at 25°.

TABLE III

Sodium Propionate		Sodium Butyrate	
C	λ	C	λ
0.0021779	82.53	0.0012132	80.14
.0041805	81.27	.0025811	78.27
.0078705	79.72	.0071049	76.72
.014272	77.88	.011963	75.21
.025973	75.64	.016858	74.04
		.029336	71.86
		.063417	68.03
		.106195	64.86
$k_{H_2O} = 0.269 \times 10^{-6}$		$k_{H_2O} = 0.467 \times 10^{-6}$	

The specific conductances of the solutions were corrected by 1×10^{-7} mho, that amount of the conductance of the water being estimated as due to salt impurity. The remaining conductance of the water was considered as due to its carbon dioxide content. In the slightly acid solutions

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[14] Kraus and Parker, THIS JOURNAL, **44**, 2429 (1922).

[15] MacInnes and Shedlovsky, *ibid.*, **54**, 1429 (1932).

[16] Davies, *Phil. Mag.*, **4**, 249 (1927); "The Conductivity of Solutions," 1933, p. 141.

[17] Harned and Ehlers, THIS JOURNAL, **55**, 2379 (1933).

[18] Harned and Sutherland, *ibid.*, **56**, 2039 (1934).

[19] MacInnes and Dole, *ibid.*, **51**, 1119 (1929).

the contribution of carbon dioxide would be negligible.

The limiting conductances were determined by using Shedlovsky's[5] method of extrapolation, in which $1/\lambda$ is plotted against $\sqrt{C}$. This gave $\lambda_0 = 85.92$ for sodium propionate, and $\lambda_0 = 82.70$ for sodium butyrate. These values, combined with the limiting conductances for Na^+ and H^+, as determined by MacInnes, Shedlovsky, and Longsworth[20] (corrected to the Jones and Bradshaw basis) give the λ_0 values for the acids which were used in Tables I and II.

The Limitations of the Extrapolation Method

There are now sufficient accurate conductivity data to permit of a critical examination of the validity of the extrapolation method for determining conductances and ionization constants of weak electrolytes. Table IV gives a comparison of λ_0 and K values as obtained (1) from conductance measurements on the weak acid and its alkali salt, and (2) from conductance measurements of the weak acid alone, using the extrapolation method.

TABLE IV

	From acid and salt conductances		From acid conductances alone, by extrapolation	
Acid	λ_0	K	λ_0	K
Carbonic[21]	394.3	4.31×10^{-7}	424	3.65×10^{-7}
Acetic[22]	390.71	1.753×10^{-5}	395.3	1.705×10^{-5}
Propionic[23]	385.47	1.343×10^{-5}	386.34	1.337×10^{-5}
n-Butyric[23]	382.40	1.508×10^{-5}	386.05	1.475×10^{-5}
Monochloroacetic[24]	389.52	1.396×10^{-3}	389.5	1.396×10^{-3}
o-Chlorobenzoic[25]	380.07	1.197×10^{-3}	380.0	1.197×10^{-3}
Benzoic[26]	382.21	6.312×10^{-3}	382.1	6.312×10^{-3}

Table IV shows that the extrapolation method is reliable if the electrolyte is not too weak ($K \geqq 10^{-3}$), but that if the electrolyte is much weaker ($K \leqq 10^{-5}$) the method may give λ_0 and K values that are seriously in error. Therefore, the statement of some authors[1] that the extrapolation method will give a λ_0 value as accurate as the λ values is unjustified. It is obvious why the extrapolation method may fail if the electrolyte is too weak. Even if the limiting laws are obeyed exactly in the concentration range used for the extrapolation, the correct λ_0 will not be found unless the number of experimental points is very large and the distribution of experimental errors is random. Thus, in the worst case of Table IV, *i. e.*, carbonic acid, accurate extrapolation from λ's of the order of 5 to a λ_0 of 394 would require an unobtainable experimental accuracy. However, the extrapolation methods are valid for determining ionization constants if the λ_0's are known accurately.

It follows from the above that in those cases where it is impossible to measure limiting conductances by the additive principle the extrapolation method may not serve if the electrolyte, is too weak.

I wish to thank Dr. D. A. MacInnes and Dr. Theodore Shedlovsky for continued encouragement and invaluable advice during the progress of this work.

Summary

Measurements are reported on the electrical conductance of solutions of propionic acid, sodium propionate, *n*-butyric acid, and sodium butyrate in water at 25°. From these are derived limiting conductances and ionization constants.

The limitations of the extrapolation method for determining limiting conductances and ionization constants of weak electrolytes are discussed.

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(20) MacInnes, Shedlovsky and Longsworth, THIS JOURNAL, **54**, 2758 (1932).

(21) Shedlovsky and MacInnes, *ibid.*, **57**, 1705 (1935).

(22) MacInnes and Shedlovsky, *ibid.*, **54**, 1429 (1932).

(23) Belcher, this communication.

(24) Shedlovsky, Brown and MacInnes, *Trans. Electrochem. Soc.*, **66**, 165 (1935).

(25) Saxton and Meier, THIS JOURNAL, **56**, 1918 (1934).

(26) Brockman and Kilpatrick, *ibid.*, **56**, 1483 (1934).

[CONTRIBUTION FROM THE AMMONIA DEPARTMENT OF E. I. DU PONT DE NEMOURS & COMPANY, INC.]

Optical Crystallographic Studies with the Polarizing Microscope. II. Identification of the Para-bromoanilides of Some Lower Aliphatic Acids[1]

BY W. M. D. BRYANT AND J. MITCHELL, JR.

Para-bromoanilides because of their stability and ease of preparation are excellent derivatives for the identification of organic acids by means of melting point and optical crystallographic properties. Melting points of many fatty acid *p*-bromoanilides are available in the literature[2,3] together with convenient preparative methods, but optical data are limited to those of the acetic and propionic derivatives recently studied in this Laboratory.[1] There was consequently no information available regarding the value of optical crystallographic properties for differentiating between derivatives of structurally isomeric acids. Also, the para-bromoanilides prepared by earlier investigators were confined to the unsubstituted fatty series, so that it was by no means evident that derivatives of substituted acids could be prepared with equal ease.

In the present research para-bromoanilides of nine aliphatic acids were prepared and the optical properties and melting points studied. The group consisted of the two butyric and the four isomeric valeric compounds and in addition the derivatives of methacrylic, methoxyacetic and pyruvic acids, to illustrate the effects of structural isomerism and the substitution of other functional groups for hydrogen. These crystalline derivatives are well suited for optical study. They are easily prepared and quite stable. Interference figures are distinct and usually well centered, thus facilitating the measurement of optical axial angle. This property was particularly useful in the present study because of its sensitivity to changes of composition. The measurement of optic axial angle alone is sometimes sufficient to establish the identity of an unknown acid. Optical character and axial dispersion are valuable properties of this series but are not highly specific of the individual compounds. The refractive indices α, β and γ, however, are useful criteria, and most of the weight of an identification rests upon these constants and optic axial angle. Brief descriptions of crystal habit are included, but as this property is often extremely sensitive to traces of contamination and to minor differences in preparative detail, less reliance is placed upon it and upon the related elongation, as criteria in identification.

Identification of methacrylic and three of the isomeric valeric derivatives is facilitated by the occurrence of metastable phases of considerably different optical properties in crystalline films prepared by fusion. These preparations usually revert to the stable modifications on standing. The metastable methacrylic derivative is stabilized by a trace of impurity. For example, a sample melting 3° lower than the pure substance was definitely dimorphous while under the same conditions the pure material failed to produce a metastable phase. The stable form in the contaminated preparation was scarcely distinguishable by its physical characteristics from the pure material.

It is interesting to note that the Kuehn and McElvain[3] procedure can be used to prepare *p*-bromoanilides of unsaturated acids. It was feared at first that hydrogen chloride, resulting from the action of thionyl chloride on the organic acid, would add at the double bond to form a chloroacyl chloride and give rise to the corresponding *p*-bromoanilide. Analyses of methacrylic *p*-bromoanilide for total halogen, however, have shown that no addition takes place.

Experimental

Materials.—All of the reagents used were from the Eastman Kodak Company with the exception of methacrylic acid, a du Pont product. Some batches of Eastman *p*-bromoaniline contained a purple coloring matter, most of which was removed by one recrystallization from chloroform. It was necessary to subject the *n*-valeric acid used to careful fractionation in order to obtain a sharp melting derivative. All of the remaining chemicals were sufficiently pure as received.

Preparation of the Derivatives.—The *p*-bromoanilides were prepared from the corresponding acids by the method of Robertson[2] as modified by Kuehn and McElvain.[3] Chloroform is a better solvent for the *p*-bromoanilides than benzene and advantageously can replace the latter in preparing derivatives of the lower fatty acids. The methacrylic derivative was analyzed for total halogen by a Parr peroxide bomb method.[4] The analyses showed only

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[1] A further study of para-bromoanilides. For the first paper of this series, see Bryant, THIS JOURNAL, **60**, 1394 (1938).

[2] Robertson, *J. Chem. Soc.*, **115**, 1210 (1919).

[3] Kuehn and McElvain, THIS JOURNAL, **53**, 1173 (1931).

[4] Bulletin No. 113, Parr Instrument Co., Moline, Illinois, p. 8.

the expected amount of halogen, hence contamination by the chloroisobutyryl derivative must have been negligible.

Melting Points.—Where comparisons can be made, the melting points given in Table I are in satisfactory agreement with the literature. Those of the remaining derivatives apparently have not been reported previously. In most cases there is a distinct spread between the melting points of the individual *p*-bromoanilides. Even where this fails, the distinct depression obtained on mixing two different *p*-bromoanilides of similar melting points is sufficient to remove ambiguity. For example, a mixture of equal parts by weight of the isobutyric (m. p. 155.0°) and trimethylacetic (m. p. 155.7°) derivatives melts at 147.6°, representing a depression of 8°. Similarly, a mixture of the isovaleric (m. p. 126.7°) and methylethylacetic (m. p. 122.3°) compounds melts at 112.0°.

TABLE I

MELTING POINTS OF *p*-BROMOANILIDES OF ALIPHATIC ACIDS

Derivative	M. p., °C.[a] (this research)	M. p., °C. (literature)
n-Butyric	112.0	115.0[2]
Isobutyric	155.0	150–151,[3] 128[5]
n-Valeric	107.1	108.0[2]
Isovaleric	126.7	128–129[3]
d,l-Methylethylacetic	122.3	
Trimethylacetic	155.7	
Methacrylic	116.0	
Methoxyacetic	85.3	
Pyruvic	167.8	

[a] Melting points determined by means of a carefully calibrated Dennis melting point bar;[1] average uncertainty ± 0.3°.

Apparatus and Technique.—A Bausch and Lomb LC petrographic microscope was used in this research. The optical equipment and methods of calibration, however, were identical with those used with the LD microscope in an earlier study.[1] The technique of optical examination was essentially the same as that previously described.[1] Both individual crystals mounted in Canada balsam and thin crystalline films prepared by fusion were examined. The pronounced birefringence and good optical quality of the latter facilitated conoscopic examination using an oil immersion system of high numerical aperture (1.25 N.A.). This technique permits direct measurement of the acute optic axial angles regardless of size, and in some cases even the obtuse angles. As previously, the quantity measured is 2H, the optic axial angle relative to cedar oil, from which 2V, the true angle within the crystal, may be calculated by means of appropriate formulas.[1] 2V was calculated from the refractive indices α, β and γ by a graphical method using tables and diagrams developed by F. E. Wright.[6]

Refractive indices were measured by the immersion method as outlined in the first paper of this series.[1] Since, however, the solubility of the present group of *p*-bromoanilides is appreciable in many of the usual organic immersion liquids, the aqueous liquids described in an earlier paper[7] were employed. This series has since been extended to n_D 1.760 in intervals of 0.005, using aqueous solutions of barium mercuric iodide. Above 1.760, the organic series was found satisfactory. The liquids of low refractive index used were standardized at 25° using an Abbe refractometer, while those above 1.650 were determined by the method of minimum deviation using a 30° capillary prism[8] suspended from the crystal adjusting device of a Hutchinson Universal Goniometer.[9] This procedure requires only a drop of the liquid and its precision compares favorably with that of the Abbe refractometer.

Optical Crystallographic Data

Optical constants of the group of nine *p*-bromoanilides of aliphatic acids are given in Table II. Comparison of measurements upon the unheated derivatives with the results obtained with preparations previously subjected to fusion has supplied conclusive evidence of the existence of metastable modifications in three of the four isomeric valeric derivatives and in a slightly contaminated sample of the methacrylic compound. The interference figures observed in the freshly prepared crystalline films were distinctly different from those of the original material as illustrated by the optic axial angle data appearing in Table II. After a few days at room temperature, the metastable crystals reverted to the corresponding stable varieties. Since the conditions suitable for the formation of isolated crystals of the metastable varieties were not known, dependable refractive index measurements could not be made. These metastable modifications are tentatively regarded as true polymorphs. Dynamic isomerism, although less likely, is not excluded.

The optical properties measured may be divided into two classes, those characteristic of the series rather than the individual compound, and exemplified by optical character[10] and axial dispersion, and those of a more specific nature including optic axial angle, the principal refractive indices and the more complex forms of dispersion. Acute bisectrix interference figures are more common than the obtuse in all but the methoxyacetic derivative. The strong inclined dispersion of

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[5] Norton, *Am. Chem. J.*, **7**, 116 (1885).

[6] F. E. Wright, *Am. J. Sci.*, **36**, 509 (1913).

[7] Bryant, THIS JOURNAL, **54**, 3758 (1932).

[8] F. E. Wright, *J. Wash. Acad. Sci.*, **4**, 269 (1914), method 1.

[9] Manufactured by James Swift & Son, Ltd., 81 Tottenham Court Road, London, England.

[10] The optical characters of all of the substances in Table II are positive by the usual test involving the effect of a quartz wedge upon interference figures and also by the approximate test, $\gamma - \beta > \beta - \alpha$. By the exact modification of the latter test described by Wright (*vide supra*, Ref. 6, pp. 529–532) and based on the relation, $1/\beta^2 - 1/\gamma^2 > 1/\alpha^2 - 1/\beta^2$, the *n*-butyric, *n*-valeric and isovaleric derivatives appear negative. However, changes in the refractive indices within the experimental tolerances are sufficient to restore the positive sign in two of the three cases. The optical characters of these three compounds remain in some doubt.

TABLE II

OPTICAL CRYSTALLOGRAPHIC PROPERTIES OF *p*-BROMOANILIDES

Derivative	*n*-Butyric	Isobutyric	*n*-Valeric		Isovaleric		*d,l*-Methylethylacetic	
Polymorph			Stable	Metastable	Stable	Metastable	Stable	Metastable
Elongation Bx_a sections	Inclined 20–40° to α or β	$\parallel\beta$	Inclined 50–75° to α	$\parallel\beta$	Inclined 25–40° to β	Inclined 12° to β	$\perp\beta$	$\parallel\beta$
Bx_0 sections	$\parallel\beta$	$\parallel\beta$	$\parallel\beta$		$\perp\gamma$		$\perp\beta$	
Refractive indices[a] at 25 ± 3° for λ = 5461 Å.	α 1.478	1.520	1.482		1.488		1.578	
	β 1.615	1.588	1.617		1.615		1.602	
	γ 1.783	1.750 ± 0.005	1.773		1.777		1.66 ± 0.01	
Birefringence λ = 5461 Å.	0.305	0.23	0.291	Strong	0.289	Strong	0.08	Strong
Optical character	Positive?	Positive	Positive?	Positive	Positive?	Positive	Positive	Positive
Optic axial angle[b] λ = 5461 Å.	$2H_a$ 95°	77°	92 ± 3°	66.5°	95.5°	71°	64.5°	82°
	$2H_0$	112 ± 2°			103 ± 2°			
	2V $88^{\circ c,d}$	$73^{\circ c,e}$, $71^{\circ d}$	$85^{\circ c}$, $86^{\circ d}$		$88^{\circ c}$, $89^{\circ d}$, $87^{\circ e}$		$61^{\circ c}$, $64–72^{\circ d}$	
Dispersion	r > v, slight	r > v, slight	r > v, slight	Weak indeterminate	r > v, slight	r > v	v > r, strong inclined	r > v, strong inclined
Crystal habit	Long, narrow rectangular crystals from C_2H_5OH	Large rectangular crystals from C_2H_5OH	Fine needles from C_2H_5OH and C_6H_6; rectangular plates from acetone		Small, rectangular plates and prisms from C_2H_5OH; larger plates from acetone		Small rectangular plates from C_2H_5OH, C_6H_6 and acetone	

Derivative		Trimethylacetic	Methacrylic		Methoxyacetic	Pyruvic
Polymorph			Stable	Metastable		
Elongation						
Bx_a sections		$\perp\alpha$	$\perp\alpha$	$\parallel\beta$	$\parallel\beta$	$\perp\alpha$
Bx_0 sections		$\parallel\beta$	$\parallel\beta$		$\parallel\beta$	$\perp\beta$
Refractive indices at 25 ± 3° for λ = 5461 Å.		α 1.570	1.526		1.503	1.535
		β 1.590	1.656		1.620	1.608
		γ 1.708	>1.85		1.83 ± 0.01	>1.85
Birefringence λ = 5461 Å.		0.138	>0.30	Strong	0.33	>0.31
Optical character		Positive	Positive	Positive	Positive	Positive
Optic axial angle	$2H_a$	53°	91°	82.5°	92°	67.5°
λ = 5461 Å.	$2H_0$				102 ± 2°	
	2V	$50^{\circ c}$, $48^{\circ d}$	$81^{\circ c}$		$85^{\circ c,e}$, $83^{\circ d}$	$63^{\circ c}$
Dispersion		r > v	r > v	r > v	r > v	r > v
Crystal habit		Long rectangular plates from C_2H_5OH; needles from acetone	Needles from C_6H_6 and acetone; rectangular plates from C_2H_5OH		Long needle-like crystals from C_2H_5OH and acetone	Rectangular plates from C_2H_5OH; needles from acetone

[a] Precision ±0.003, except where noted. [b] Precision ±1° for 2H, except where noted. [c] Calculated from $2H_a$ and β. [d] Calculated from α, β, γ. [e] Calculated from tangent formula using $2H_a$ and $2H_0$.

both the stable and metastable methylethylacetic modifications is highly specific of this compound.

Acknowledgment.—The authors thank Mr. A. N. Oemler of this Laboratory for his aid in the preparation of the derivatives and for analyses of the methacrylic derivative for halogens.

Summary

1. Optical crystallographic data and melting points of the *p*-bromoanilides of nine lower aliphatic acids have been determined.

2. Metastable crystalline modifications of the *n*-valeric, isovaleric, *d,l*-methylethylacetic, and methacrylic derivatives have been obtained from the molten material.

3. The unsaturated methacrylic derivative was successfully prepared by the regular procedure, without formation of the chloroisobutyric derivative.

WILMINGTON, DELAWARE RECEIVED AUGUST 17, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WISCONSIN]

The Method of Garelli and Racciu for the Preparation of Piperazine: A Criticism

BY DEAN B. ROLLINS AND H. N. CALDERWOOD[1]

With regard to a paper[2] describing a simple and inexpensive dehydration method for obtaining piperazine disulfate by heating monoethanolamine with sulfuric acid, we wish to call attention to the fact that the authors do not prove that the reaction product obtained by them is piperazine disulfate. The solubilities reported and the percentages of nitrogen and sulfate, their only analytical data for the product they designate as piperazine disulfate, hold also for β-aminoethylsulfuric acid. Their only other description, the rhombohedral crystals from dilute ethanol, is characteristic of β-aminoethylsulfuric acid,[3,4] the crystals of piperazine disulfate from dilute ethanol being monoclinic.

The interaction of monoethanolamine and fuming sulfuric acid to form β-aminoethylsulfuric acid was reported in 1918.[4] Believing that Garelli and Racciu might have developed conditions leading to the formation of piperazine disulfate, we attempted to prepare the compound according to the method sketched by them, but in twenty-three experiments, under various time and temperature conditions and with different amounts and concentrations of sulfuric acid, we were unable to obtain even a trace of piperazine, the resulting product in every case being β-aminoethylsulfuric acid.

Our reagents were monoethanolamine, 99.54% purity, from the Carbide and Carbon Chemicals Corporation, and C. P. grade sulfuric acid in concentrations from 88.3 to 20% fuming. Samples of both our crude and recrystallized products analyzed for nitrogen by the semi-micro Dumas method and for sulfur by both wet and dry oxidation gave the results recorded in Table I. These values being valid for both β-aminoethylsulfuric acid and piperazine disulfate, other properties of our purified product were compared with the corresponding properties of an authentic sample of piperazine disulfate.

TABLE I

ANALYSES OF CRUDE AND PURIFIED PRODUCTS

Material		Crude I	Crude II	Purified I	Purified II	Calcd. $C_2H_7NO_4S$
Sample, g.		0.07025	0.07753	0.07117	0.07054	
Nitrogen, %		9.96	9.94	10.13	10.05	9.93
Sample, g.		0.2710	0.2652	0.2745	0.2714	
Sulfur, %	Wet			22.40	22.48	22.68
	Dry	22.34	22.37			

Our product purified by recrystallization from dilute ethanol formed rhombohedral crystals sintering at 230°, as recorded in the literature for β-aminoethylsulfuric acid,[3,4] whereas piperazine disulfate from dilute ethanol gave white monoclinic crystals which began to darken at 325° and charred at 330°. Our purified product gave no precipitate with barium chloride, even after standing at room temperature for ten hours, nor with benzenesulfonyl chloride, whereas piperazine disulfate gave immediately after the addition of barium chloride a copious precipitate of barium sulfate, and with benzenesulfonyl chloride gave a copious white crystalline precipitate melting at 281°.[5] The molecular weight of our purified

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[1] Present address: 3105 Cross Street, Madison, Wisconsin.

[2] Garelli and Racciu, *Atti. accad. sci. Torino*, **69**, 162–165 (1934).

[3] Gabriel, *Ber.*, **21**, 1056 and 2667 (1888).

[4] Frankel and Cornelius, *ibid.*, **51**, 1660 (1918).

[5] Hans T. Clarke, "A Handbook of Organic Analysis," Edward Arnold and Company, London, 4th ed., 1926, p. 207.

product determined by neutralization was 141.2 and 142.5, and by cryoscopy 140.5 and 141.5, values in excellent agreement with the theoretical 141 for β-aminoethylsulfuric acid, whereas piperazine disulfate would have given values at least twice as large.

In case of a remote possibility that β-aminoethylsulfuric acid might under favorable conditions decompose to form piperazine which Garelli and Racciu[6] claim to have isolated from their product, our purified product was treated with an equivalent amount of potassium hydroxide and steam distilled. The pale yellow viscous liquid obtained by evaporating the steam distillate to dryness yielded no piperazine, contained nitrogen but not sulfur, and did not form insoluble derivatives with reagents for either amino or alcohol groups. The use of small and large excesses of potassium and sodium hydroxides failed to yield piperazine or any other definite product. With large excesses of the hydroxides steam distillation was always accompanied by a volatile imine, probably ethyleneimine.[7]

Garelli and Racciu state that they obtained the pure base as a crystalline hydrate, m. p. 44°, to which they assign a formula approximating that of the monohydrate, but incorrect, as printed, for any piperazine hydrate. Since the literature[8] reports that it is piperazine hexahydrate which melts at 44°, this statement of Garelli and Racciu is surprising. Our examination of an authentic sample of piperazine corroborated Berthelot's findings.

It would be interesting to know in detail the method by which Garelli and Racciu isolated the free base from the product which they designate as piperazine disulfate and which had the crystalline form not of piperazine disulfate but of β-aminoethylsulfuric acid, and also in detail the conditions under which they obtained piperazine hydrate, from the base so isolated, by cooling over sulfuric acid the residue obtained by evaporating to dryness on a water-bath the condensate formed in isolating the free base by steam distillation. We found that piperazine hexahydrate when stored at room temperature over sulfuric acid volatilized completely and was absorbed by the acid.

We wish to express our gratitude to Messrs. G. E. Bernard, J. M. Hogrefe, and A. L. Wilson of the Carbide and Carbon Chemicals Corporation for their interest and assistance in this investigation.

Summary

1. The only product that can be isolated from the reaction of monoethanolamine and either concentrated or fuming sulfuric acid by the method of Garelli and Racciu is β-aminoethylsulfuric acid.[9]

2. β-Aminoethylsulfuric acid does not form an insoluble derivative with benzenesulfonyl chloride.

3. Both piperazine disulfate and piperazine hexahydrate form the same insoluble derivative with benzenesulfonyl chloride.

4. From dilute ethanol piperazine disulfate forms monoclinic crystals which begin to darken at 325° and char at 330°. This crystalline form and its behavior upon heating are reported for the first time here.

MADISON, WISCONSIN RECEIVED MARCH 28, 1938

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[6] Ref. 2, p. 164.

[7] Wenker, THIS JOURNAL, **57**, 2328 (1935).

[8] Berthelot, *Compt. rend.*, **129**, 688 (1899), and *Ann. chim. phys.*, [7] **20**, 471 (1900).

[9] We have just received a letter written on August 5, 1938, by Prof. G. Bruni, lifelong friend of Prof. Garelli, who allows us to quote him as authority for the fact that after the departure of Dr. Racciu from his Institute, Professor Garelli had occasion to repeat his preparation, recognized the product as β-aminoethylsulfuric acid and was planning a short paper rectifying the mistake, when illness and death overtook him.

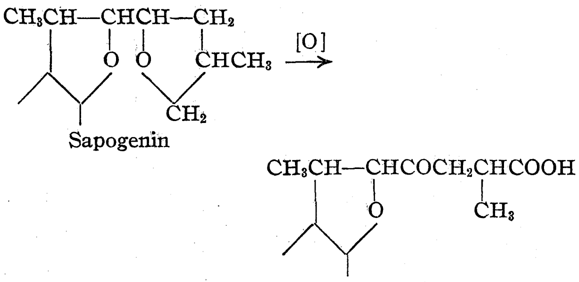
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Sarsasapogenin. II. Sarsasapogenoic Acid

BY LOUIS F. FIESER AND ROBERT P. JACOBSEN[1]

The observations reported in this paper are concerned with a study of sarsasapogenoic acid, a C_{27}-acid obtained as described in Part I[2] by the oxidation of sarsasapogenin acetate with chromic acid at 60–65° and subsequent gentle saponification of the acidic fraction. Under the conditions found most favorable for the isolation of this acid, the neutral fraction contains a small amount of the acetate of the hydroxy lactone $C_{22}H_{34}O_3$, together with a substance previously regarded[2] as unchanged sarsasapogenin acetate but now recognized as consisting in large part of an isomorphous substance of higher oxygen content, possibly the acetate of a hydroxysarsasapogenin. Sarsasapogenoic acid, which probably is a stereoisomer of Tschesche and Hagedorn's[3] tigogenoic acid ($C_{27}H_{42}O_5$), displays a number of interesting if perplexing properties, and a further study of the substance was undertaken with the idea that it might hold the key to the structure of the sapogenin side chain. The extent of experimentation has been somewhat limited by the low yield of this oxidation product of the rather difficultly accessible genin, the average yield being about 5 g. of acid from 20 g. of sarsasapogenin acetate, representing the material from some 20 lb. (9 kg.) of root.[4] Farmer and Kon[5] did not encounter the acid in the mixture obtained on conducting the oxidation at the temperature of the steam-bath with a larger amount of chromic acid, and oxidation at 32–33° by the procedure found by McMillan and Noller[6] to give a good yield of chlorogenoic acid diacetate proved to be unsatisfactory for the sapogenin under consideration. A slight difference in one part of a steroid molecule often alters considerably the susceptibility to attack by chromic acid at some other site.

Tschesche and Hagedorn[3] tentatively suggested that tigogenoic acid may be a γ-keto acid arising from the opening of one of the postulated five-membered oxide rings. They were not able, however, to demonstrate the presence of a carbonyl group, the ethyl ester forming no oxime or semicarbazone under the usual conditions, and absorbing no hydrogen on attempted hydrogenation. Sarsasapogenoic acid is similarly inert to carbonyl reagents, the methyl ester, for example, being recovered unchanged after attempted oximation in boiling alcohol, and the acid yielding no semicarbazone under the usual conditions. McMillan and Noller[6] made a similar observation concerning chlorogenoic acid diacetate. On treating sarsasapogenoic acid or ester with carbonyl reagents under forcing conditions we were able to bring about reactions, but these all proved to be more profound than a simple condensation or addition involving only a carbonyl group. Thus the acid and its ester both react with two molecules of hydroxylamine at 130° and give products which appear to be unrelated but which contain two atoms of nitrogen (see chart). Paralleling the experience of Tschesche and Hagedorn, we found sarsasapogenoic acid to be very resistant to hydrogenation, but under certain conditions we were able in at least some experiments to effect a slow hydrogenation. On the above formulation one would expect to obtain a hydroxy acid or its lactone, but the substance isolated proved to be a free acid corresponding to the introduction of two or four hydrogen atoms and the loss of a molecule of water; the compound evidently is an anhydrohydro acid and not a lactone. This loss of water in some way other than by lactonization is surprising; it cannot be attributed to the presence of water of crystallization in the starting material (m. p. 193°) for this gives a normal ester, acetate and methyl ester benzoate.



(Formulation of Tschesche and Hagedorn)

The elimination of a molecule of water was observed also in a curious reaction of sarsasa-

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[1] Du Pont Research Fellow.

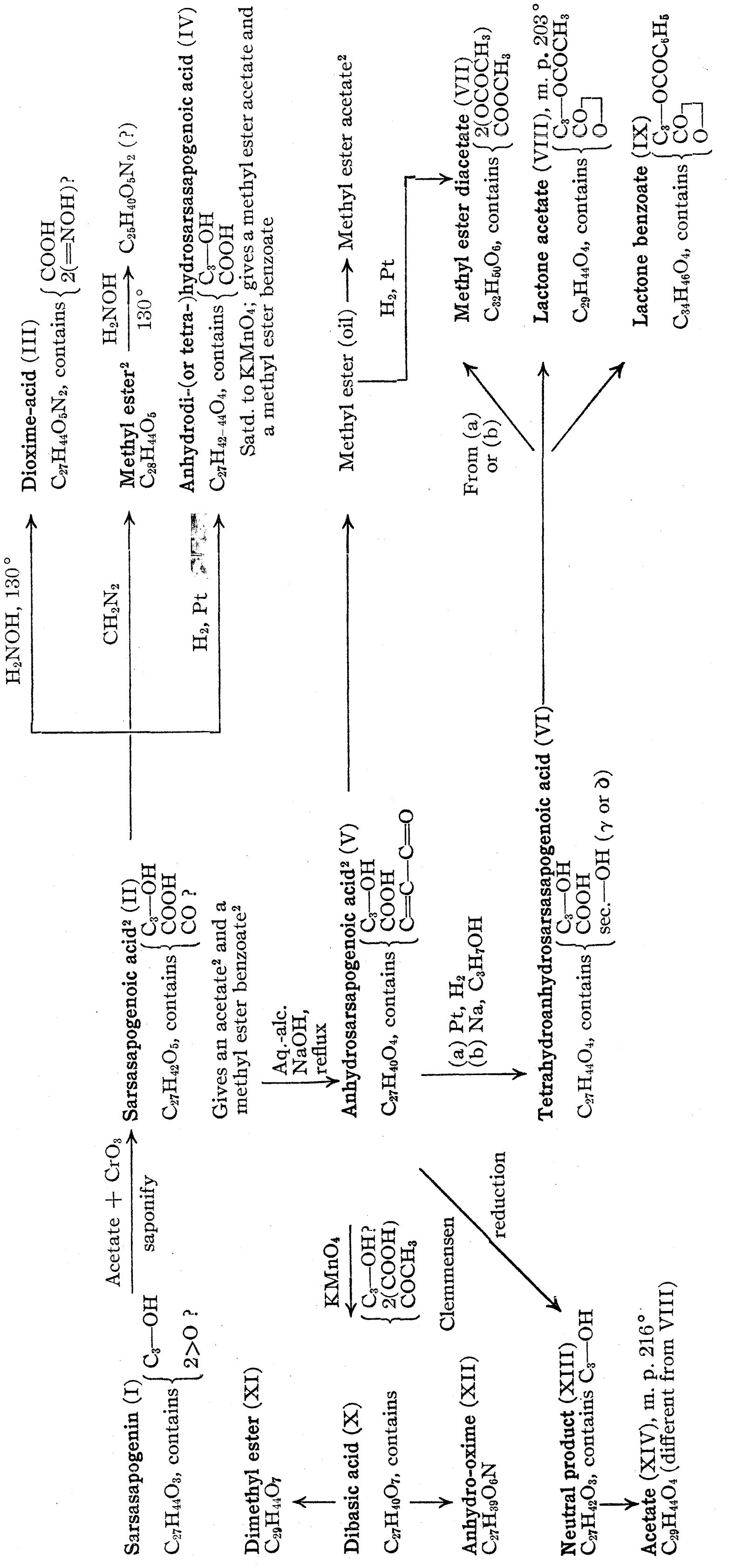
[2] Fieser and Jacobsen, THIS JOURNAL, **60**, 28 (1938).

[3] Tschesche and Hagedorn, *Ber.*, **68**, 1412, 2247 (1935).

[4] We are greatly indebted to E. R. Squibb and Sons for generous supplies of sirupy glycoside extracted from Mexican (sarsaparilla) root under the supervision of Dr. J. M. Ort.

[5] Farmer and Kon, *J. Chem. Soc.*, 414 (1937).

[6] McMillan and Noller, THIS JOURNAL, **60**, 1630 (1938).



pogenoic acid with alkali.² When heated with dilute aqueous alcoholic alkali for two hours, the sapogenoic acid ($C_{27}H_{42}O_5$) is converted into a higher melting acid $C_{27}H_{40}O_4$, designated anhydrosarsasapogenoic acid. This substance is quite reactive and, as indicated in the chart, has been converted into a number of transformation products. The presence of a carboxyl group and of the original C_3-hydroxyl group was established by the preparation of a crystalline methyl ester acetate. The anhydro acid rapidly absorbs two moles of hydrogen in the presence of platinum oxide catalyst giving a tetrahydro acid, and the same compound (VI) was obtained by reduction with sodium and *n*-propyl alcohol. The latter reaction suggested the presence of a conjugated system, and this inference was fully confirmed by a determination of the absorption spectrum kindly carried out for us by Dr. T. J. Webb at the Merck Research Laboratories. The absorption maximum at 243 mμ (Fig. 1) clearly indicates that the substance is an α,β-unsaturated ketone. The four oxygen atoms are therefore present as a hydroxyl, carboxyl, and conjugated carbonyl group, and it is clear that both of the original oxide rings of the sapogenin have been severed. A further significant inference can be drawn from the behavior of tetrahydroanhydrosarsasapogenoic acid (VI). On esterification with diazomethane followed by acetylation, this gave a crystalline methyl ester diacetate (VII), as shown by the analysis and saponification equivalent. The same substance (VII) was also obtained from the anhydro acid (V) in a different sequence: esterification, hydrogenation, and acetylation. The free acid group is thus characterized, one of the acetylated hydroxyls must be that originally present in the nucleus at C_3, and the other is a new secondary alcoholic group arising from the addition of hydrogen to the carbonyl group of the anhydro acid. When the tetrahydroanhydro acid was acetylated without prior esterification it yielded, in place of a diacetate, a lactone acetate (VIII); a lactone benzoate (IX) was similarly obtained on benzoylation. The new hydroxyl group formed in the reduction of the anhydro acid must, therefore, be in a position with respect to the carboxyl group favorable for lactone formation, and it is concluded that the carbonyl group of anhydrosarsasapogenoic acid is γ or δ to the carboxyl group.

From its composition, anhydrosarsasapogenoic acid must contain either one isolated double bond, in addition to that conjugated with the carbonyl group, or a newly formed carbon ring. The fact that the tetrahydro acid resists further hydrogenation and is saturated to permanganate points to the presence of a new ring.

The anhydro acid was altered on attempted oximation at 130° but gave a non-crystalline product, and the methyl ester acetate was attacked only slowly by chromic acid at 95° and afforded no crystalline material. The free acid, however, is oxidized smoothly and rapidly by alkaline permanganate and gives in good yield a nicely crystalline dibasic acid (X), m. p. 207°, of the composition $C_{27}H_{40}O_7$. The reaction

$$C_{27}H_{40}O_4 + 3[O] \longrightarrow C_{27}H_{40}O_7$$

involving the production of a new carboxyl group, can only be interpreted as follows

$$\left\{\begin{array}{l} -CH \\ \;\,\| \\ -C- \end{array}\right. \longrightarrow \left\{\begin{array}{l} -COOH \\ \\ >CO \end{array}\right.$$

One of the unsaturated carbon atoms carries a hydrogen atom and the other is joined to two carbon residues, and since no loss of carbon atoms occurs on severing the ethylenic linkage it is evident that the double bond is inserted in a carbon chain which is joined to the main body of the molecule on both sides of the point of unsaturation. This is perhaps a further indication of the presence of a fifth ring in the anhydro acid. For further characterization the dibasic acid X was heated with hypoiodite in dioxane–alkali, according to the haloform test of Fuson and Tullock,[7] and it yielded iodoform. The carbonyl group generated in the oxidation therefore is present in the form of an acetyl group, and the knowledge of the oxidation can be elaborated thus

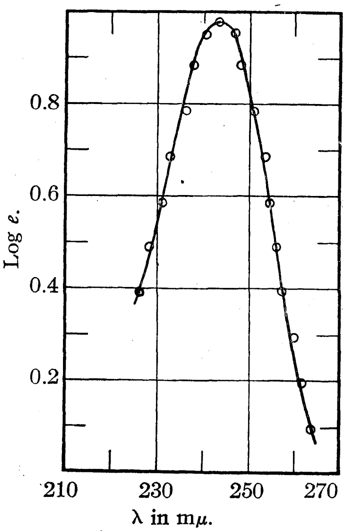


Fig. 1.—Anhydrosarsasapogenoic acid (V) in absolute alcohol.

$$\left\{\begin{array}{l} -CH \\ \;\,\| \\ -CCH_3 \end{array}\right. \longrightarrow \left\{\begin{array}{l} -COOH \\ \\ -COCH_3 \end{array}\right.$$

The conjugated carbonyl group of anhydrosarsasapogenoic acid may be attached to either of the two unsaturated carbon atoms. A further requirement is that this group must be placed γ (or δ) to the carboxyl group, and from the evidence of the absorption spectrum it appears that the carboxyl group is not conjugated with the 1,4-system. The anhydro acid, therefore, must contain one of the groupings

$$\underbrace{-C(CH_3){=}CHCO\overset{\cdot}{\underset{\cdot}{C}}\overset{\cdot}{\underset{\cdot}{C}}}COOH \text{ or}$$

$$\underbrace{-CH{=}C(CH_3)CO\overset{\cdot}{\underset{\cdot}{C}}\overset{\cdot}{\underset{\cdot}{C}}}COOH$$

Only the first of these groupings can be accommodated to the cholesterol side chain, and it remains only to place the carbon bridge connecting the residues on the two sides of the double bond. Inspection of the possible structures shows that the choice lies between the six-ring structure indicated in the partial formula and a seven- or eight-ring structure; the six-ring formula is the more likely both from the point of view of ring size and because ring closure in this case would involve an activated position α- to the carbonyl group.

It is inferred that the anhydro acid probably has the structure shown and that it contains a new

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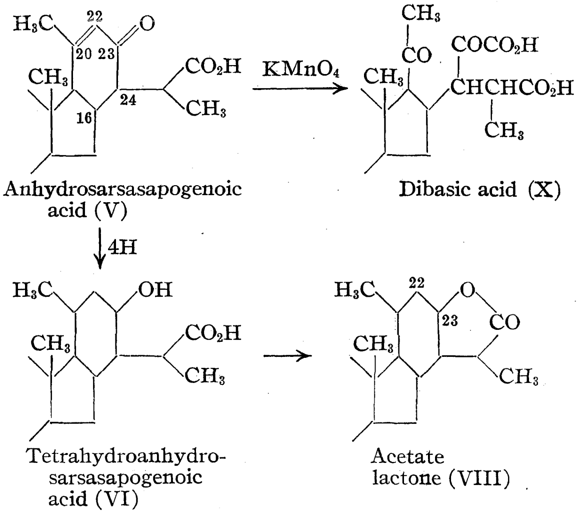
[7] Fuson and Tullock, THIS JOURNAL, **56**, 1638 (1934).

ring formed by condensation between the C_{24}-position of the side chain and position 16 of Ring D. According to this formulation the dibasic acid produced on permanganate oxidation has two carbonyl groups, but since they are both subject to considerable hindrance the formula is perhaps not inconsistent with the observation that the dimethyl ester does not react with hydroxylamine at 130°. The free acid does react under these conditions and yields an anhydro-oxime. It is known only that the substance is not a β,γ-unsaturated enol lactone (negative Legal test), but with so many functional groups present any formulation, such as that shown, is purely conjectural. Uncertain also is the structure of a nicely crystalline product obtained in one small-scale hypohalite oxidation of the dibasic acid. Preliminary analyses indicate that probably two carbon atoms are lost in the oxidation and that the composition is $C_{25}H_{38}O_7$ or possibly $C_{25}H_{36}O_7$. Since a titration with a small sample (in the cold) pointed to a dibasic acid, the second structure shown is the more probable.

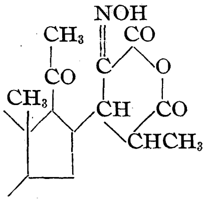


Anhydrosarsasapogenoic acid (V)

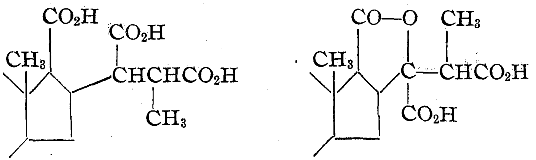
Dibasic acid (X)

Tetrahydroanhydrosarsasapogenoic acid (VI)

Acetate lactone (VIII)



Anhydro-oxime XII (?)

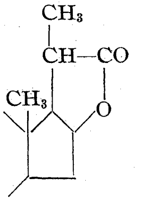


$C_{25}H_{38}O_7$ $C_{25}H_{36}O_7$

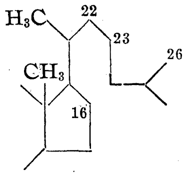
Hypohalite oxidation product (?)

While the nature of these little studied transformations is still highly uncertain, the formulation given above for tetrahydroanhydrosarsasapogenoic acid is reasonably secure; all of the functional groups have been characterized adequately, particularly by conversion to the lactone acetate and benzoate. As shown on the reaction chart, anhydrosarsasapogenoic acid was also converted in poor yield by Clemmensen reduction into a neutral product giving an acetate of the same composition as the acetate lactone VIII. The substances melt at not greatly different temperatures but show a distinct depression when mixed. The acetate resulting from the Clemmensen reduction product may be a δ-lactone with the oxygen attached at the 22-position, or, considering the opportunity for the migration of the double bond in the acid mixture, it may be a stereoisomeric γ-lactone different from VIII in the configuration at C_{23}.

With the knowledge gained of the nature of anhydrosarsasapogenoic acid, the next step is to attempt to trace the manner of its formation and the structure of this part of the sapogenin molecule. The carbonyl group at C_{23} and the terminal carboxyl group must have arisen by the rupturing of one of the original oxide linkages at C_{23} and C_{26} in the chromic acid oxidation, and the degradative experiments of Farmer and Kon[5] have established the attachment of an oxide bridge at C_{16}. The presence of a double bond in the anhydro acid between positions C_{20} and C_{22} is understandable only on the assumption that an oxide ring originally extended to one of these positions. The former position is eliminated by the observation that derivatives of the sapogenin can be oxidized to saturated C_{22}-lactones in which the carbon atom in question is not hydroxylated.[8,5] The evidence therefore indicates that the oxidic linkages of the sapogenin are joined at positions 16, 22, 23, and 26. The only structures for the



C_{22}-Saturated lactone



Position of oxide linkages

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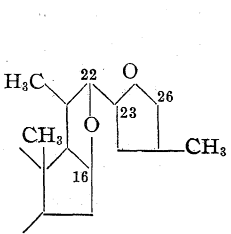
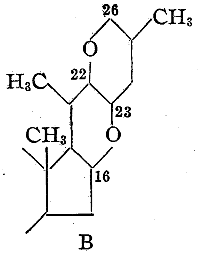
[8] Simpson and Jacobs, *J. Biol. Chem.*, **110**, 565 (1935).

sapogenin admissible on this basis are those shown in Formulas A and B, and only the first of these accounts for the appearance of a carbonyl group



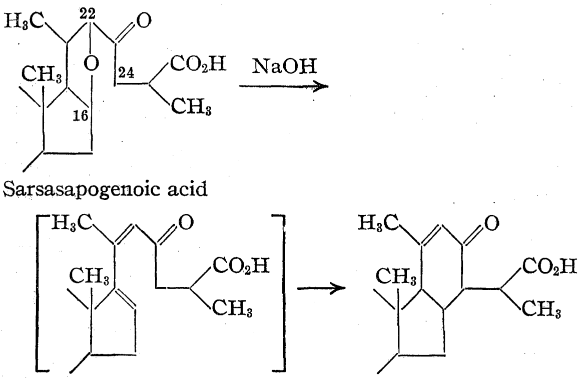
A



B

at C_{23} and a terminal carboxyl group in the oxidation, as demonstrated in the characterization of the anhydro acid. The structure A, which is the formulation tentatively suggested by Tschesche and Hagedorn,[3] thus accords best with the observations reported.

Sarsasapogenoic acid is then a γ-keto acid, corresponding also to the formulation of Tschesche and Hagedorn. The remarkable transformation brought about by the action of alkali involves elimination of the oxide bridge and a condensation between positions 16 and 24. Position 16 is a point of attachment of the oxygen atom, and the methylene group at position 24 is adjacent to an activating carbonyl group, which may account for the disposition to cyclize under the influence of alkali. The ready cleavage of the oxygen bridge may also be attributable to the activating influence of the carbonyl group adjacent to C_{22}, and the reaction possibly involves the intermediate formation of a dienone.

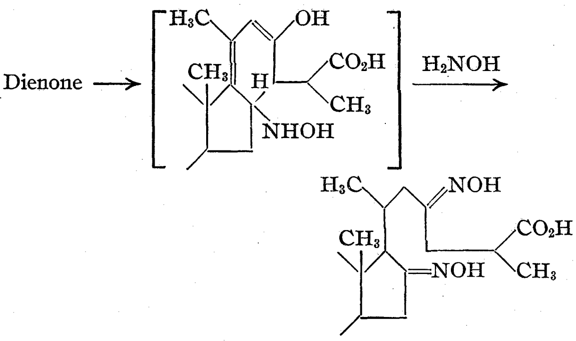


Sarsasapogenoic acid

Dienone

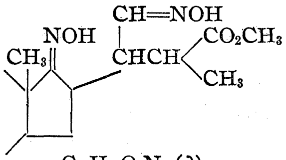
Anhydro acid

This hypothetical dienone may be an intermediate in other reactions of the sapogenoic acid, cleavage of the oxide ring occurring under the forcing conditions required to overcome the resistance of the carbonyl to additions. The inert character of this group may be associated with a hindrance arising from a special steric arrangement, although this does not seem very plausible, or to a tendency for the substance to exist in the lactol form. If the reaction with hydroxylamine at 130° involves cleavage of the oxide ring, one molecule of the reagent may add to the ends of the conjugated system of the dienone or dienone oxime giving, by a succession of ketonizations, the saturated dioxime-acid of the formula shown.



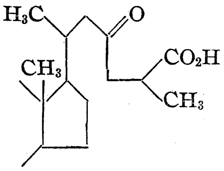
Dioxime-acid (III)

The reaction of the sapogenoic methyl ester with hydroxylamine at 130° seems to result in the loss of three carbon atoms and may follow some other course; a purely speculative formulation satisfying the present analytical data is as follows.



$C_{25}H_{40}O_5N_2$ (?)

The product obtained from sarsasapogenoic acid in some experiments in a slow hydrogenation may be either a di- or a tetrahydride; the analytical data do not distinguish between the two possibilities but agree slightly better with the tetrahydride formula. Possibly the activated oxide ring is eliminated by hydrogenolysis, or the dienone is slowly formed and saturated with hydrogen, giving in either case a saturated γ-keto acid. The substance may also be a saturated dihydride with a linkage between C_{16} and C_{24}, as in the anhydro acid.



Anhydrotetrahydrosarsa-
sapogenoic acid, $C_{27}H_{44}O_4$ (?)

While many of the new compounds described need to be characterized much more fully in order to establish the structures, the evidence regarding the structure of the anhydrosapogenoic acid is now secure and the only formulation of the sapogenin side chain consistent with this structure is that suggested by Tschesche and Hagedorn.[3]

Experimental Part[9]

Extraction of the Genin.—In working further batches of the sirupy extract from Mexican (sarsaparilla) root we followed a suggestion kindly made by Dr. J. C. E. Simpson and simplified the process by omitting the initial extraction with ligroin. The gum was defatted during the precipitation of the crude glycoside by running a 3.5-kg. portion in a thin stream into 10 l. of vigorously stirred ether. The resulting viscous gum was then processed as before,[2] centrifuging the aqueous solution of the gum prior to hydrolysis, when clarification was necessary. One batch of 18.2 kg. of crude sirup yielded 195 g. of pure sarsasapogenin, which is about the amount previously reported;[2] another lot of 20.0 kg. processed in the same way gave only 67 g. of genin. We were not able to determine the variable factor involved.

Notes on the Preparation and Characterization of Sarsasapogenoic Acid.—In studying further the oxidation of sarsasapogenin acetate,[2] material (3.8 g.), m. p. 141–145°, recovered from the neutral fraction and previously designated as "unchanged sarsasapogenin acetate" was crystallized repeatedly from acetone–chloroform to yield 2 g. of flat needles melting constantly at 165–167°. This material resembles sarsasapogenin acetate in crystalline form but melts about 20° higher. On saponification with alcoholic potassium hydroxide this gave a product crystallizing from acetone–chloroform in elongated plates, m. p. 216–218° (av. of three analyses: C, 76.09; H, 10.06). The crystals are similar in appearance to those of sarsasapogenin but the m. p. is distinctly higher. This substance on reacetylation and crystallization as above gave material, m. p. 158–160°, apparently identical with the original acetate (no depression). This was analyzed with the following results.

Anal. Calcd. for $C_{29}H_{46}O_5$: C, 73.38; H, 9.76; sapon. equiv., 475. Found: C, 73.20, 73.21; H, 9.71, 9.93; sapon. equiv., 487.

These analyses suggest that the substance is the acetate of a hydroxysarsasapogenin, but the carbon content of the saponified material is about 1% higher than that required for the normal desacetyl compound. All that can be said is that the substance recovered from the neutral fraction is definitely not pure sarsasapogenin acetate and probably is an oxidation product, or contains such a substance.

Among other attempts to improve the yield of sarsasapogenoic acid, sarsasapogenin acetate (4 g.) was oxidized by the exact procedure worked out by McMillan and Noller[6] for the conversion of chlorogenin diacetate into the sapogenoic acid diacetate in good yield (32–33°), and the precipitated material was extracted with aqueous sodium carbonate from ether. Acidification of the extract gave 2 g. of solid, but no crystalline product could be obtained from this material. After gentle saponification, as in our original procedure,[2] and crystallization from dilute acetone 0.4 g. of crude sarsasapogenoic acid was obtained, m. p. 188–190°. The neutral fraction yielded (from aqueous acetone) 0.32 g. of needles, m. p. 162–166°. On conducting the oxidation (4 g. of acetate, 6 g. chromic anhydride) initially at 35–37° and then at 45°, no crystalline sapogenoic acid could be isolated.

Trials were made of the action of chromic anhydride on sarsasapogenoic acid acetate (0.85 g.) at 60–65° and at 90–95°, but in each instance the only crystalline product isolated from the acidic fraction after saponification was unchanged sarsasapogenoic acid (0.2 g.) and there was no appreciable neutral fraction, indicating the absence of the acetate lactone $C_{24}H_{36}O_4$.

An attempted Clemmensen reduction of sarsasapogenoic acid (0.5 g.), using 20 cc. of benzene, 70 cc. of alcohol, and 20 cc. of 6 *N* hydrochloric acid with fresh additions of concentrated acid (ten hours) gave a resin which formed dense clusters of fine needles (0.3 g.) from ether–hexane, but satisfactory crystals could not be obtained free from gum. Reduction with sodium and *n*-propyl alcohol gave an even less promising product.

Heated with semicarbazide acetate in alcohol for two hours, sarsasapogenoic acid gave only non-crystalline material. When treated with hydroxylamine under similar conditions, the methyl ester was recovered unchanged. Oximation of the methyl ester at 130° for three hours gave in a poor yield a substance crystallizing from dilute methanol in fine needles, m. p. 169–171° (Found: C, 66.96, 67.21; H, 8.68, 9.30; N, 6.41, 6.49. $C_{25}H_{40}O_5N_2$ requires C, 66.92; H, 8.99; N, 6.25). Because of the very low yield, the substance was not studied further.

Dioxime-Acid (III) from Sarsasapogenoic Acid.—A mixture of 500 mg. of sarsasapogenoic acid, 0.33 g. of hydroxylamine hydrochloride, and 0.5 g. of potassium acetate in 35 cc. of absolute methanol was heated in a sealed tube at 130° for three hours. The solution was concentrated and diluted with water and the finely divided solid which separated was collected, dried, and crystallized by dissolving it in about 150 cc. of alcohol and concentrating the solution to a volume of 35 cc. The product then separated in small leaves, and after a second crystallization there was obtained 350 mg. of pure material which, when dried in vacuum at 80° over phosphorus pentoxide, melted with decomposition at 247° in a bath preheated to 235°.

Anal. Calcd. for $C_{27}H_{44}O_5N_2$: C, 68.03; H, 9.31; N, 5.76; neut. equiv., 477. Found: C, 67.86, 67.88; H, 9.18, 9.16; N, 5.89, 5.98; neut. equiv., 461.

It seems necessary to adhere strictly to the conditions specified in order to obtain the pure dioxime in satisfactory yield, for non-crystalline products were obtained when the oximation was conducted at a slightly higher temperature or for a longer time, or on varying the proportion of the reagents. Attempted hydrolysis of the dioxime acid with methyl alcoholic hydrochloric acid gave no crystalline product.

Anhydrodi-(or tetra)-hydrosarsasapogenoic Acid (IV).—One-half gram of carefully purified sarsasapogenoic acid (from aqueous acetone, m. p. 190–191°) in 40 cc. of pure

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[9] All melting points are corrected. Analyses by Mrs. Verna R. Keevil, Dr. C. Fitz, and the Arlington Laboratories.

acetic acid was shaken with hydrogen at atmospheric pressure in the presence of 0.1 g. of Adams catalyst. Absorption of hydrogen continued slowly for fifteen to twenty hours; the apparent consumption was about 1 mole of hydrogen, but this could not be determined accurately. The solvent was partially removed in vacuum, and after dilution with water a solid product was obtained. The dried material when crystallized from 90% acetone yielded 380 mg. of short needles, m. p. 171–178°. This material was apparently nearly pure; after four more crystallizations from the same solvent the melting point range was 174–184°.

Anal. Calcd. for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83. Calcd. for $C_{27}H_{44}O_4$: C, 74.96; H, 10.25. Found: C, 75.01, 74.97; H, 10.18, 10.06. Earlier analyses of a less highly purified sample gave the results: C, 75.59, 75.15; H, 9.92, 10.25.

The reduced acid is markedly less soluble in acetone than sarsasapogenoic acid. It is soluble in alkali but does not decolorize permanganate.

Although the absorption of hydrogen proceeded steadily if slowly in the above experiment, hydrogenation subsequently was accomplished only in a few of several trials with various preparations of catalyst. Even so it usually was necessary to continue shaking for a prolonged period, work up the mixture, separate a small amount of the less soluble reduced acid, and submit the recovered starting material to further hydrogenation. No reduction was observed with Raney nickel in absolute alcohol at 80° and 2000 lb. (133 atm.) pressure of hydrogen. Using Adams catalyst and glacial acetic acid, 1 g. of acid shaken with hydrogen at 90–100° and 500 lb. (33 atm.) pressure for six hours yielded 30 mg. of the acid IV, m. p. 173–183°.

Methyl Ester Acetate of IV.—Treated with diazomethane, the reduced acid IV gave an oily methyl ester mobile at −15°. On acetylation with acetic anhydride and potassium acetate this yielded a product which became crystalline on being moistened with methanol. Crystallization from aqueous methanol gave leaves melting at 64–66° with evolution of gas. After repeated crystallization from the same solvent the substance formed glistening hexagonal plates, m. p. 64–66°, dec. For analysis the sample was dried at room temperature over phosphorus pentoxide.

Anal. Calcd. for $C_{30}H_{46}O_5 \cdot {}^1/_2CH_3OH \cdot {}^1/_2H_2O$: C, 71.59; H, 9.65; solvent of crystallization, 4.89. Calcd. for $C_{30}H_{48}O_5 \cdot {}^1/_2CH_3OH \cdot {}^1/_2H_2O$: C, 71.31; H, 10.01; solvent of crystallization, 4.87. Found: C, 71.57, 71.50; H, 10.06, 9.93; loss in weight at 110° and 5 mm., 4.99, 4.97.

Methyl Ester Benzoate of IV.—The liquid methyl ester from 0.3 g. of the acid IV was heated with 1 cc. of benzoyl chloride in 4 cc. of dry pyridine for thirty minutes, and the mixture was diluted with water and extracted with ether. After washing with acid and alkali and evaporating the ether, the residue was crystallized from methanol. This gave silvery leaves, m. p. 136.5–139°, and after repeated crystallization the substance melted, when dried at 100° and 15 mm., at 138.5–140.5°.

Anal. Calcd. for $C_{35}H_{48}O_5$: C, 76.64; H, 8.87. Calcd. for $C_{35}H_{50}O_5$: C, 76.32; H, 9.15. Found: C, 76.37, 76.35; H, 9.06, 8.83.

Tetrahydroanhydrosarsasapogenoic Acid (VI). (a) **By Catalytic Hydrogenation of V.**—One-half gram of the anhydro acid (m. p. 244–246°, dec.) in 50 cc. of absolute alcohol with 0.1 g. of Adams catalyst was shaken with hydrogen at atmospheric pressure. The reaction proceeded at a regular rate and stopped with the absorption of 2 moles of gas in four to five hours. When concentrated and diluted with water the solution deposited 480 mg. of flat needles which effervesce on melting at 182°. Further crystallization from aqueous alcohol, ether–hexane, or benzene–acetone did not greatly change the decomposition point. Other preparations melted with effervescence at temperatures ranging from 179 to 188°. The product is soluble in alkali but does not decolorize permanganate.

Anal. Calcd. for $C_{27}H_{44}O_4$: C, 74.96; H, 10.25. Found: C, 74.99; H, 10.57.

(b) **With Sodium and Alcohol.**—A solution of 0.5 g. of the anhydro acid V in 20 cc. of *n*-propyl alcohol was refluxed for one hour while adding 2 g. of sodium in small portions. The solution was diluted with a large volume of water, acidified with dilute sulfuric acid, and the chalky precipitate was collected and crystallized from aqueous methanol. Needles were obtained (300 mg.) melting with effervescence at 170°. Further crystallization from aqueous methanol and from ether–hexane gave material melting at 181° with decomposition and showing no depression when mixed with the sample prepared by catalytic hydrogenation.

Methyl Ester Diacetate VII. (a) **From Tetrahydroanhydrosarsasapogenoic Acid.**—On treating 0.46 g. of the tetrahydro compound VI (prepared by catalytic hydrogenation) with diazomethane in ether there was obtained a non-crystalline residue. This was taken up in acetic anhydride (10 cc.) and heated with potassium acetate (0.1 g.). Treatment with water afforded a solid product and on crystallization from methanol this gave 380 mg. of lustrous leaves, m. p. 158–160°. Further crystallization from methanol and from ether–hexane raised the melting point (of the well-dried material) to 159.5–161°.

Anal. Calcd. for $C_{32}H_{50}O_6$: C, 72.41; H, 9.50; sapon. equiv., 177. Found: C, 72.58, 72.40; H, 9.33, 9.29; sapon. equiv., 181.

The same compound was obtained from a sample of VI prepared by reduction with sodium and alcohol; the purified substance melted at 160–162° and the mixed m. p. was 160–161.5°.

(b) **From the Methyl Ester of Anhydrosarsasapogenoic Acid.**—The oily ester prepared from V with diazomethane was hydrogenated as in (a) and the crude reaction product treated with acetic anhydride and potassium acetate. This gave material which crystallized from methanol as glistening leaves, m. p. 159–161°, and there was no depression when mixed with the first sample of diacetate described above.

Lactone Acetate VIII.—A solution of 200 mg. of tetrahydroanhydrosarsasapogenoic acid and 50 mg. of potassium acetate in 3 cc. of acetic anhydride was heated slowly to boiling during forty-five minutes; treatment with water gave 180 mg. of solid material. This crystallized from 80% methanol in flat needles, m. p. 200–203° (dried in vacuum at 80°).

Anal. Calcd. for $C_{29}H_{44}O_4$: C, 76.27; H, 9.71; sapon. equiv., 228. Found: C, 76.58, 76.11; H, 9.77, 9.51; sapon. equiv., 233.

The compound is insoluble in cold alkali, saturated to permanganate and tetranitromethane, and does not react with diazomethane.

Lactone Benzoate IX.—The tetrahydro acid VI (100 mg.) was heated at 50–55° for one hour with benzoyl chloride (1 cc.) in pyridine (3 cc.). After decomposing the excess benzoyl chloride the mixture was extracted with ether and the ether layer was washed with acid and sodium bicarbonate solution, dried and evaporated. When the oily residue was moistened with petroleum ether and allowed to stand in the cold room for several days, 50 mg. of a fine powder separated, m. p. 218–223°, dec. Repeated crystallization from acetone–hexane gave flat, bluntly tapering needles melting gradually with slight yellowing at 225–235° (well dried).

Anal. Calcd. for $C_{34}H_{46}O_4$: C, 78.72; H, 8.94. Found: C, 78.54; H, 8.86.

The benzoate is insoluble in cold alkali and does not react with diazomethane.

Clemmensen Reduction of Anhydrosarsasapogenoic Acid: Neutral Product XIII.—A mixture of 500 mg. of the acid, 20 cc. of alcohol, 2 g. of amalgamated zinc, and 5 cc. of concentrated hydrochloric acid was refluxed for five and one-half hours, with the further addition during this period of two 5-cc. portions of acid. The solution was poured into water and the finely divided solid collected and taken into ether. After washing with water the solution was extracted with sodium hydroxide solution, the alkaline extract depositing 20 mg. of solid when acidified. The ethereal solution of the neutral fraction was evaporated, and the residue yielded a crystalline product (100 mg.), m. p. 212–219°, from ether–hexane. Twice recrystallized from ether–hexane, the substance was obtained as rectangular plates (75 mg.), m. p. 226–229° (dried in vacuum).

Anal. Calcd. for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21. Found: C, 78.11; H, 10.39.

Acetylation of the Neutral Product: Acetate XIV.—After heating 50 mg. of the product XIII with acetic anhydride and potassium acetate, treatment with water gave a solid. This crystallized from aqueous methanol as long, flat needles, m. p. 212.5–214°. Repeated crystallization from the same solvent brought the m. p. of well dried material to 214–216°.

Anal. Calcd. for $C_{29}H_{44}O_4$: C, 76.27; H, 9.71. Found: C, 76.32; H, 9.44.

This acetate is different from the lactone acetate VIII from tetrahydroanhydrosarsasapogenoic acid, for a mixture of the two samples began to melt somewhat below 185°.

Oxidation of Anhydrosarsasapogenoic Acid: Dibasic Acid X.—One-half gram of the anhydro acid V was suspended in 20 cc. of water and neutralized with sodium hydroxide. The solution was cooled to 0° and a 2% solution of potassium permanganate was dropped in with stirring until the color was no longer discharged, the end-point being very apparent. The solution was filtered through a thin layer of Norite to remove manganese dioxide and the nearly colorless filtrate was acidified with dilute sulfuric acid. The precipitate was dried at room temperature in vacuum over sulfuric acid and crystallized from ether–hexane, giving 350 mg. of prisms, m. p. 193–203°, dec. After two crystallizations from ether–acetone–hexane, it melted at 206–207°, dec.

Anal. Calcd. for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46; neut. equiv., 238. Found: C, 68.20; H, 8.84; neut. equiv., 232.

Attempted Clemmensen reduction of the acid gave a non-crystalline product. Gas is evolved at the melting point of the dibasic acid, and this is not carbon dioxide. When heated at 235° under nitrogen the acid was converted into a brittle glass which was separated with bicarbonate into neutral and acidic fractions, but neither yielded crystals.

Dimethyl Ester XI.—The dibasic acid X (200 mg.) with excess diazomethane in ether gave a solid ester which crystallized from ether–hexane in fine, silky needles, m. p. 163.5–165°, and on recrystallization melted at 164.5–165° after thorough drying.

Anal. Calcd. for $C_{29}H_{44}O_7$: C, 69.02; H, 8.79. Found: C, 69.26, 69.01; H, 8.84, 9.12.

The ester was recovered unchanged on attempted oximation in refluxing alcohol for three hours and in methanol at 130° for two hours.

Anhydro-oxime XII from the Dibasic Acid.—The acid X (200 mg.) was heated at 135° for three hours with an excess of hydroxylamine acetate in absolute methanol. The solvent was partially evaporated and the residue treated with water. The white solid was dried and taken into ether–acetone; on long standing there was obtained 0.2 g. of crystalline material, m. p. 263–266°, dec. (effervesces and becomes dark brown). Further crystallization from methanol–acetone gave glistening microneedles (95 mg.), m. p. 268°, dec. The substance gives a negative Legal test.

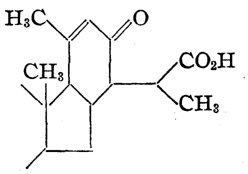
Anal. Calcd. for $C_{27}H_{39}O_6N$: C, 68.47; H, 8.30; N, 2.96. Found: C, 68.32; H, 8.88; N, 3.33.

Haloform Oxidation of the Dibasic Acid X.—A solution of 0.6 g. (m. p. 204–206°, dec.) of the dibasic acid in 15 cc. of dioxane and 6 cc. of 10% sodium hydroxide was treated at 60° with iodine–potassium iodide until the color persisted for two minutes.[7] No iodoform separated on dilution with water, but a halogen-containing acid was obtained on acidification. This was redissolved in 5% alkali and warmed with iodine–potassium iodide solution on the steam-bath, and after three minutes yellow crystals of iodoform (odor) separated, m. p. 117–122°. The alkaline solution was chilled and acidified, and the dried precipitate after two crystallizations from dilute acetone yielded 50 mg. of glistening, small leaves, m. p. 212–213°, dec. (gas evolution). Preliminary analyses gave the results: C, 66.82, 67.00; H, 8.75, 8.97; neut. equiv., 233; $C_{25}H_{36}O_7$ requires: C, 66.93; H, 8.09; $C_{25}H_{38}O_7$ requires: C, 66.63; H, 8.50. On attempting to recover the material used in determining the neutralization equivalent it was found that the substance had undergone alteration (isomerization?).

Summary

From a study of a number of transformation products of sarsasapogenoic acid and anhydro-

sarsasapogenoic acid it is concluded that the latter substance is an unsaturated γ-keto acid containing the grouping shown. The sapogenin and the sapogenoic acid very probably are correctly represented by the formulas of Tschesche and Hagedorn.



CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASSACHUSETTS RECEIVED AUGUST 18, 1938

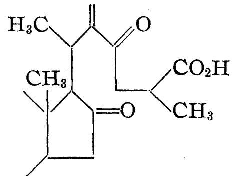
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Sarsasapogenin. III. Concerning Desoxysarsasapogenin and the Degradation of the C_{22}-Hydroxy Lactone

BY LOUIS F. FIESER AND ROBERT P. JACOBSEN[1]

Simpson and Jacobs[2] prepared desoxysarsasapogenin by reduction of the sapogenyl chloride with sodium and amyl alcohol, but the over-all yield from the sapogenin was only about 14% and the method was employed only after other possible methods of removing the hydroxyl group had been considered and abandoned as unsatisfactory. Attempted reduction of sarsasapogenone by the Wolff–Kishner method was unsuccessful, and Clemmensen reduction of the ketone was considered unsuitable because of the known sensitivity of the side chain to acids.[3] In our experiments on the acid cleavage of the side chain,[4] we had observed that this sensitivity is manifested particularly when acetic acid is employed as the solvent but that cleavage occurs much less readily in alcoholic solution. It therefore seemed possible that with this solvent reduction of the ketone might be accomplished at an acidity below that at which cleavage occurs. It was also thought that the addition of an immiscible solvent, as in Martin's[5] procedure, might provide added protection for the sensitive steroid. These hopes were realized, for on refluxing sarsasapogenone for five days with amalgamated zinc in a two-phase medium of alcohol, benzene, and 6 *N* hydrochloric acid, pure desoxysarsasapogenin was obtained in an over-all yield of 43.5% from sarsasapogenin.

The comparatively simple new method of preparing the desoxysapogenin may have other applications, and this consideration has prompted us to report the observation at the termination of the fellowship work of the junior author, even though the investigation of the desoxy compound has not yet reached a very advanced stage. In connection with our work on the oxidation of sarsasapogenin acetate,[4,6] we hoped to extend a brief observation of Simpson and Jacobs[2] and gain further information concerning the acidic substances resulting from the oxidation of desoxysarsasapogenin with chromic acid. Simpson and Jacobs were interested chiefly in the lactone $C_{22}H_{34}O_2$, which they obtained in 15–18% yield on conducting the reaction at 75°, but they investigated incidentally the acidic material encountered as a by-product. Neither the acidic product nor the material obtained from it on esterification yielded homogeneous crystals, but the oily ester on reaction with semicarbazide acetate gave in very small yield a pure substance having the composition of the disemicarbazone methyl ester of an acid characterized by the analyses as either $C_{27}H_{40}O_5$ or $C_{27}H_{42}O_5$. Simpson and Jacobs were inclined to accept the first formula and to regard the oxidation product as a triketo acid with one inert carbonyl group, as in I. A similar oxidation product of sarsasapogenin acetate was isolated by Farmer and Kon[7] as the methyl ester acetate, apparently of the acid $C_{27}H_{40}O_6$. We conducted the oxidation at the



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[1] Du Pont Research Fellow.

[2] Simpson and Jacobs, *J. Biol. Chem.*, **110**, 565 (1935).

[3] Jacobs and Simpson, *ibid.*, **105**, 501 (1934).

[4] Fieser and Jacobsen, THIS JOURNAL, **60**, 28 (1938).

[5] Martin, *ibid.*, **58**, 1438 (1936).

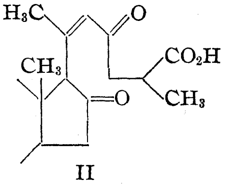
[6] Fieser and Jacobsen, *ibid.*, **60**, 2753 (1938).

[7] Farmer and Kon, *J. Chem. Soc.*, 414 (1937).

lower temperature of 60–65° and from the neutral fraction isolated the desoxy lactone $C_{22}H_{34}O_2$[8] in 13% yield. The acidic fraction afforded two crystalline products. One of these was obtained in amounts too small for thorough purification but corresponded approximately in composition to a desoxysarsasapogenoic acid ($C_{27}H_{42}O_4$).

The other substance, isolated in 20% yield as flat needles, m. p. 111°, is a monobasic acid of the formula $C_{27}H_{42}O_5$. The composition is that of a hydroxydiketo acid, and this formula was recognized by Simpson and Jacobs as an alternative possibility for the substance which they characterized as the methyl ester disemicarbazone. It is doubtful, however, that our acid is the substance which they characterized, for the behavior toward carbonyl reagents is quite different. Our acid with diazomethane gave a crystalline anhydro ester, a molecule of water being eliminated in the process, and the pure ester gave no crystalline product on prolonged refluxing with semicarbazide acetate in methanol, in contrast to the behavior of the crude ester investigated by Simpson and Jacobs. The anhydro ester liberates approximately one mole of methane in the Zerewitinoff test. Our acid was found to react with hydroxylamine at 100°, but the product proved to be an anhydro-monoxime.

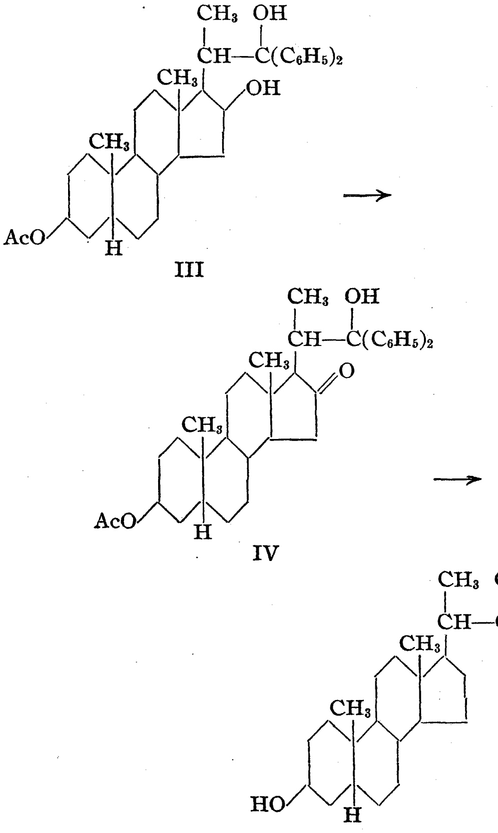
The interesting oxidation product gave no crystalline material on attempted acetylation, and was recovered unchanged after being heated with acetic–hydrochloric acid or with *o*-phenylenediamine. It decolorizes permanganate on warming, but not in the cold. The formation of an anhydro ester and an anhydro oxime may mean that the substance contains an easily eliminated hydroxyl group, but it seems unlikely that dehydration of an alcoholic group should occur on treatment with diazomethane in ether but not on refluxing with an acetic–hydrochloric acid mixture. The low-melting acid more probably is a hydrate, possibly of the unsaturated diketo acid II.



II

The behavior of the anhydro ester in the Zerewitinoff test would then be attributable to enolization, and some analogy for the failure of a carbonyl group at C_{16} to exhibit normal response to typical reagents is furnished by the results of the following series of experiments.

A Grignard degradation of the hydroxy lactone $C_{22}H_{34}O_3$ was carried in Part I[4] to the stage of a diphenylcarbinol monoacetate of the probable structure III (position of the substituent in Ring A still uncertain), only the less hindered secondary hydroxyl group at C_3 being acetylated in pyridine solution. Under controlled conditions (20–25°) it has been possible to oxidize this compound to a monoketone (IV) in good yield.



III

IV

V

This substance failed to form an oxime or semicarbazone under the usual conditions. Clemmensen reduction gave a desoxy diphenyl carbinol of the probable formula V, but the yield was so low that the degradation could not be carried further with the amount of material available.

Experimental Part[9]

Desoxysarsasapogenin.—The crude sarsasapogenone prepared from 15 g. of sarsasapogenin by the method of

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[8] The formula was incorrectly written as $C_{22}H_{32}O_3$ in Part I,[4] p. 31.

[9] All melting points are corrected. Analyses by Mrs. G. M. Wellwood, Mrs. Verna R. Keevil, the Arlington Laboratories, and Lyon Southworth.

Simpson and Jacobs[10] was dissolved in 150 cc. of benzene and refluxed for seventy hours with 75 g. of zinc (amalgamated with 7.5 g. of mercuric chloride), 50 cc. of 6 *N* hydrochloric acid, and 50 cc. of alcohol, with the addition at five- to ten-hour intervals of 5-cc. portions of concentrated hydrochloric acid. The benzene layer was separated and combined with benzene extracts of the aqueous layer. After washing the benzene solution with water and concentrating it to a volume of about 150 cc., the reduction was continued, using 25 g. of amalgamated zinc to supplement the unused metal from the first treatment and adding fresh concentrated acid. After refluxing for fifty hours more, the benzene layer was washed and concentrated. On adding alcohol to the concentrated benzene solution, there was obtained 7.4 g. of crude desoxysarsasapogenin in the form of diamond-shaped plates, m. p. 209–216°. The mother liquors yielded only a sticky gum readily soluble in alcohol. One further crystallization of the solid product from benzene–alcohol gave 6.3 g. of material, m. p. 214–217°; yield from sarsasapogenin, 43.5%. Simpson and Jacobs[2] report the melting point 216–217°.

Anal. Calcd. for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.64; H, 10.76.

Oxidation of Desoxysarsasapogenin.—A suspension of 5.1 g. of the desoxysapogenin in 400 cc. of glacial acetic acid was stirred mechanically and treated with a solution of 4.3 g. of chromic anhydride in 75 cc. of 80% acetic acid, keeping the temperature at 60–65°. The addition was completed in one-half hour, and stirring was continued for one and one-quarter hours longer. The mixture was poured into water, and after standing overnight the gummy solid which separated was taken into ether. The ethereal solution was washed thoroughly with water and extracted with dilute sodium hydroxide solution. The alkaline extract was washed once with ether and acidified, and the precipitated solid was dried over sulfuric acid in vacuum. Crystallized from dilute acetone, this yielded 1.2 g. of small leaves of acidic material, m. p. 103–106°. When treated with cold methanol, a very small amount of amorphous solid remained undissolved. (When purified partially by crystallization from dilute acetone, this material, m. p. 218–220°, corresponded most nearly in composition to desoxysarsasapogenoic acid, calcd. for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83. Found: C, 75.87; H, 9.02.) The solution was concentrated and a few drops of water added, and on cooling, the pure **desoxy acid** separated in the form of flat needles (1.15 g.), m. p. (well dried) 108–111°. There was no change in melting point after two further crystallizations from aqueous methanol. The sample for analysis was dried at 80° (18 mm.) over phosphorus pentoxide.

Anal. Calcd. for $C_{27}H_{42}O_5$: C, 72.61; H, 9.48; neut. equiv., 447. Found: C, 72.49, 72.23; H, 9.80, 9.56; neut. equiv., 447.

The acid is saturated to alkaline permanganate in the cold but rapidly decolorizes the reagent on warming. Attempted acetylation gave a gummy product. The substance was recovered unchanged after heating with *o*-phenylenediamine in alcoholic solution and also after being refluxed with acetic acid (10 cc.) and concentrated hydrochloric acid (2 cc.). It does not reduce Tollens' reagent.

The ethereal solution containing the neutral fraction was evaporated and the residue crystallized from benzene–alcohol. The first material separating was crude desoxysarsasapogenin, amounting to 0.75 g., and after this had been removed the residue from the mother liquor was dissolved in hot aqueous methyl alcoholic sodium hydroxide and heated for twenty minutes on the steam-bath. The alkaline solution was diluted with water, filtered hot through a thin layer of Norite, cooled, and acidified. The precipitated solid on crystallization from aqueous methanol gave 0.55 g. (13%) of flat needles, m. p. 125.5–127.5°, and a further crystallization raised the melting point to 127–129°. This gave no depression when mixed with the sample of the **desoxy lactone $C_{22}H_{34}O_2$**, m. p. 129.3–130.5°, prepared in our earlier work.[4]

Anhydro-methyl Ester of the Desoxy Acid.—The acid (200 mg.) was treated with excess diazomethane in ether and the crude product left on evaporation of the solvent melted at 74–76°. Crystallized from dilute methanol, this was obtained in the form of thin, glistening leaves, m. p. 78.5–79.5°.

Anal. Calcd. for $C_{28}H_{42}O_4$: C, 75.97; H, 9.57. Found: C, 75.97, 75.79; H, 9.96, 9.91.

The ester was recovered unchanged after short heating with acetic anhydride and potassium acetate. In a Zerewitinoff determination it liberated 0.63 mole of methane. In an attempt to prepare a semicarbazone the ester was heated on the steam-bath for seventeen hours with semicarbazide acetate in methanol, but no crystalline product was obtained.

Anhydro-oxime from the Desoxy Acid.—This was obtained by heating 200 mg. of the acid with hydroxylamine acetate in absolute methanol in a sealed tube at 100° for two hours. The gummy solid separating on dilution with water was dried and taken up in ether; on standing there separated 60 mg. of crystalline solid, m. p. 177–178°, dec. This material, which is very sparingly soluble in ether, was crystallized repeatedly from acetone and gave in poor yield small leaves melting with decomposition at 193–195° in a bath preheated to 188°. On rapid heating, starting with a cold bath, the substance began to turn brown at about 178° and melted at 189–191°, dec.

Anal. Calcd. for $C_{27}H_{41}O_4N$: C, 73.10; H, 9.32; N, 3.16. Found: C, 72.58; H, 9.72; N, 3.76.

Oxidation of the Monoacetate of the Diphenyl Carbinol $C_{34}H_{46}O_3$: Ketone Acetate IV.—A solution of 650 mg. of the previously described[4] monoacetate (III, m. p. 189–190°) in 50 cc. of glacial acetic acid was stirred at 20–25° and treated with 100 mg. of chromic anhydride in 10 cc. of 90% acetic acid, added in ten minutes. After ten minutes more the mixture was poured into cold water and the collected solid was washed, dried, and crystallized from ether–petroleum ether, giving 500 mg. of silky needles, m. p. 156–159°. After a further crystallization from ether–hexane the **ketone acetate** melted at 157–159° (well dried).

Anal. Calcd. for $C_{36}H_{46}O_4$: C, 79.67; H, 8.54. Found: C, 79.56; H, 8.90.

Attempts to prepare an oxime or semicarbazone were

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[10] Simpson and Jacobs, *J. Biol. Chem.*, **109**, 573 (1935).

unsuccessful. Reduction with hydrazine according to Staudinger[11] was tried without success.

Clemmensen Reduction of the Ketone Acetate: Desoxy Diphenyl Carbinol V.—The above ketone acetate (390 mg.) was refluxed for seven hours with 1.2 g. of amalgamated zinc in 25 cc. of alcohol and 7 cc. of 8 *N* hydrochloric acid. The solid material obtained on diluting the filtered solution with water yielded no crystals and was refluxed for one-half hour with alcoholic alkali for saponification. The solid which precipitated on dilution was dried and crystallized from ether–hexane, the solution depositing glistening prisms mixed with slightly gummy, fine, felt-like needles. The prisms were separated mechanically (m. p. 224–226°) and recrystallized repeatedly from ether–hexane, giving 20 mg. of satisfactory material, m. p. 226–228° (well dried). The composition is approximately that of the desired **desoxy diphenyl carbinol.**

Anal. Calcd. for $C_{34}H_{46}O_2$: C, 83.90; H, 9.53. Found: C, 84.26; H, 9.04.

The slightly gummy needles (180 mg.) could not be freed completely from the above material by repeated crystallization from ether–hexane. Acetylation gave a resin and this on saponification gave an intractable mixture separating from methanol in clusters of small needles and soft wax-like nodules.

Summary

Conditions have been found for the reduction of sarsasapogenone to desoxysarsasapogenin in good yield by the Clemmensen method without alteration of the side chain. A preliminary account is given of a new C_{27}-acid obtained by the oxidation of desoxysarsasapogenin with chromic acid, and further observations are reported on the degradation of the hydroxy lactone $C_{22}H_{34}O_3$.

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[11] Staudinger, *Ber.*, **44**, 2204 (1911).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY]

Heats of Organic Reactions. VII. Addition of Halogens to Olefins

BY JOHN B. CONN, G. B. KISTIAKOWSKY AND ELGENE A. SMITH

It has been shown in the earlier papers of this series[1] that the heats of addition of hydrogen to the olefinic bond vary in a regular manner with the constitutional make-up of the rest of the molecule. It seemed highly desirable to investigate whether these variations are specific for hydrogenations or are characteristic generally of addition reactions opening the ethylenic bond. The reaction with halogens was selected to test the question because of its convenience and the lack of accurate combustion data on dihalides. Another reaction considered, the addition of hydrogen halides, had to be discarded because we were unsuccessful in creating catalytic conditions under which this reaction occurs rapidly in the gas phase at temperatures below *ca.* 150°, the upper limit of usefulness of the present calorimeter. The results to be presented here unfortunately are neither as reliable nor as extensive as those on the heats of hydrogenation; nevertheless, even allowing for all possible errors, they are many times more accurate than the available combustion data.

Method and Compounds

The calorimeter itself and the general procedure were the same as described in the first paper of this series and only changes need to be recorded.

To avoid premature reaction, bromine or chlorine was carried to the calorimeter through a separate conduit in a stream of inert gas and mixed with excess hydrocarbon in the catalyst chamber within the calorimeter. Upon reaction and heat exchange the gases passed through a valve which directed the stream either to a cold trap for collection of a sample and tests for completeness and cleanliness of the reaction (in the fore- and after-periods), or, during the calorimetric run, to a jet where the gases were burned in excess oxygen and the halogens determined as such and as hydrogen halides.

The halogens were contained in an efficient spiral bubbler, kept at constant temperature (ice for bromine, Dry-Ice and alcohol for chlorine), through which passed a metered stream of inert gas (carbon dioxide with bromine, argon with chlorine).[2] Frequently additional inert gas was by-passed around the bubbler and added to the main gas stream to dilute the reaction mixture and so avoid the condensation of the product in the calorimeter. The hydrocarbon vapor also was metered, so that a condition of constant gas flow prevailed in the calorimeter during a run.

Several substances have been tried for their catalytic effect on the halogenation reaction, the choice being finally calcium bromide and calcium chloride for the bromination and the chlorination, respectively. Glass wool, asbestos, platinized asbestos, ferric halides, bismuth halides and activated charcoal were also experimented with but discarded either because of insufficient activity at the temperatures in question (around 100°) or because substitution reactions took place with the hydrocarbons used. The catalysts were made by evaporating a solution of cal-

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[1] THIS JOURNAL, **57**, 65 (1935); **57**, 876 (1935); **58**, 137 (1936); **58**, 146 (1936); **59**, 831 (1937); **60**, 440 (1938).

[2] Nitrogen had to be avoided since nitrogen oxides are formed in the free flame used in the analytical system, and disturb the analysis.

cium halides (30%) with cleaned asbestos fibers (70%) and drying above 100°.

The conditions in the calorimeter were maintained such that a complete reaction of the halogen occurred, the exit gases being a mixture of the inert gas, the excess hydrocarbon and the dihalide. Because of this, a determination of the total halogen content of the gases sufficed to find the amount reacted. Figure 1 shows semi-schematically the analytical setup. After leaving the control valve the reacted gases entered a quartz jet and burned there in an excess of oxygen; some hydrogen was added to the combustible gases to ensure a healthier flame. The ignition was started by a spark-coil, the current being turned on a few seconds before turning the valve. Immediately surmounting the flame vessel was a quartz tube in a furnace maintained at bright red heat; this tube was filled with chips of porcelain, which ensured the combustion of the organic material and completed the conversion of the halogens to the free state or to the form of hydrogen halides. From the furnace the gases passed a trap in a Dry-Ice or ice-bath, surmounting which was a tower filled with glass beads and solid potassium iodide. Finally there was a bubbler filled with a potassium iodide solution which acted, however, merely as an indicator that absorption of halogens was complete. After the run the furnace was flushed with nitrogen and the connecting tubing flamed to distil the condensed water into the trap. The contents of the tower were then washed into the trap with potassium iodide solution and water, and the whole was made up to a liter. Aliquot parts were titrated with thiosulfate solution; the sample was then brought to boiling, cooled and potassium iodate added; a second titration with thiosulfate followed. In case of bromine the fraction present as hydrogen bromide was usually quite small (about 5%), but with chlorine the acid constituted the bulk of the product (*ca.* 95%).

Ordinarily two titrations were made on each run, but in the few cases when they disagreed by more than 0.1%, repeated titrations ensured the reliability of the result to better than that figure.

The thiosulfate solution was standardized with potassium bromate according to accepted procedure,[3] the results of repeated determinations agreeing to within 0.05%.

Before the calorimetric work was started, various tests of the analytical setup with weighed samples of pure organic halides showed that results correct to nearly 0.1% could be expected. Thereupon other preliminary work and calorimetric runs were undertaken, which occupied the fall and winter of 1937–1938. When the series of brominations was completed, the tests with weighed samples were done again, but to our considerable dismay it was discovered that losses of halogen to the extent of 0.5 to 1.0% occurred somewhere. Extensive search for sources of this error traced it finally to a coating of platinum on the porcelain chips in the furnace, which was present there from the work on hydrogenations. It is very difficult to explain why the same furnace gave satisfactory results a year earlier, the only possibility being that its temperature may have changed in the meantime. The mechanism by which the halogens are removed from the gas stream is also puzzling since the small amount of a solid distillate from the furnace was always flamed after the run to ensure its decomposition, the remainder appearing to be metallic platinum.

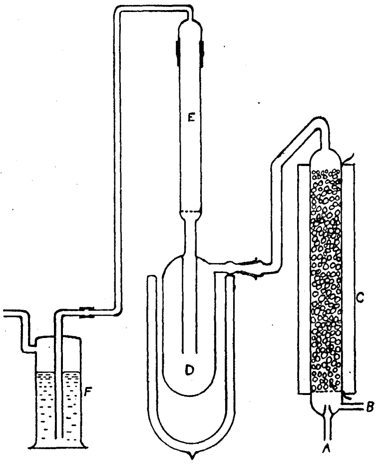

Fig. 1.—A, gas inlet; B, oxygen inlet; C, porcelain filled quartz furnace; D, cold trap; E, moist potassium iodide-glass pearl filled absorption tower; F, bubbler of 10% potassium iodide solution.

Nonetheless, whatever the precise cause of the failure of the original furnace, its repacking with clean porcelain remedied the situation, as shown in Table I, which presents the data on runs with weighed samples of organic halides and of molecular bromine. These samples were contained in sealed thin-walled glass ampoules placed in the gas stream instead of the calorimeter, and were broken after the flame was started, the rest of the procedure and the composition of the gases (except for the halogen, of course) being essentially the same as in ordinary calorimetric runs. Table I contains all runs made with sealed samples, none being discarded for "inconsistency" of the result. The runs with molecular bromine give the best agreement, then follow runs with ethylene dibromide which are also good; small losses of chlorine are noted in runs with ethylene dichloride but these, we believe, are within experimental uncertainties of the method. How-

TABLE I

Sample	Sample, g.	Moles of halogen recovered, $\times 10^3$	Error of analysis, %
Br_2	0.9794	6.137	−0.07
Br_2[a]	1.5556	9.753	+0.20
$C_2H_4Br_2$	1.6994	9.034	−0.15
	1.4568	7.760	+0.06
$C_4H_8Br_2$	1.0496	4.836	−0.51
	1.4040	6.472	−0.47
	1.6234	7.481	−0.51
$C_2H_4Cl_2$	0.7826	7.873	−0.43
	0.6857	6.918	−0.26
	1.3767	13.883	−0.21

[a] Ethylene present in the gas stream.

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[3] Treadwell and Hall, "Quantitative Analyses," John Wiley and Sons, Inc., New York, N. Y., 1928, Vol. II, p. 554.

TABLE II

HEATS OF HALOGENATION REACTIONS

Hydrocarbon	Expts. made	Preliminary $-\Delta H_{355^\circ}$	n^{20}_D product measured	Literature	Final $-\Delta H_{355^\circ}$ $\frac{\text{cal}}{\text{mole}}$
			A. Bromination		
C_2H_4	13	29,231 ± 100	1.5380 ± 0.0001	1.5379	29,058 ± 300
C_3H_6	5	29,585 ± 29	1.5199 ± .0001	1.5203	29,412 ± 200
C_4H_8-1	3	29,758 ± 3	1.5150 ± .0001	1.5150[4]	29,585 ± 200
trans-C_4H_8-2	1	29,148	1.5113	1.5116[4]	29,075 ± 200
cis-C_4H_8-2	3	30,350 ± 23	1.5149 ± .0001	1.5147[4]	30,177 ± 200
Trimethylethylene	2	30,577 ± 2	1.5054 ± .0003		30,398 ± 200
			B. Chlorination		
C_2H_4	3	43,653 ± 27	1.4443 ± .0003	1.44432	43,653 ± 150

ever, the very constant shortage of bromine in dibromobutane is outside the analytical errors and must be due to a slight impurity of the compound used for analysis (redistilled dibromide prepared for this work). This is best demonstrated by a run in which molecular bromine in the sealed ampoule and ethylene in the gas stream were used. Before the gases reached the analytical unit, the conversion of bromine to ethylene bromide was nearly complete and yet no shortage of bromine developed.

At the time of the discovery of the analytical errors, the still available quantities of pure hydrocarbons were so limited that a repetition of the entire series of brominations would have required new preparations of several of the olefins. To avoid this we have chosen to sacrifice somewhat the final accuracy of the data, making only one run on each of the olefins with the corrected combustion furnace. The average difference between the new runs and the old averages was used to correct the latter. This presumes that the furnace was misbehaving in the same manner during the entire series of brominations and thus introduces a not excessively large but nevertheless a considerable additional uncertainty.

Chlorination runs were made after the refilling of the furnace and therefore no analytical uncertainty impairs these results.

Bromine used for the reaction was Mallinckrodt analytical grade; iodimetric titration gave the correct molecular weight but no further tests or purification were undertaken.

Chlorine was distilled into the spiral bubbler directly from a used tank.

Excepting ethylene and propylene the hydrocarbons used were samples remaining from the work on hydrogenations; their description is superfluous.

Ethylene and propylene were generously presented to us by the Linde Air Products Company and were subjected by them to fractional distillations; the former is rated as 99.88% pure, the latter as 99.89% pure.

It is to be noted that in contrast to our work on hydrogenations, the method of analysis here devised is such that small amounts of saturated hydrocarbons in the material used have no effect on the results. Even the presence of minor olefinic impurities is of very small import because the heats of bromination, as will be seen presently, change only slightly with the nature of the olefin.

Results

The two important chemical sources of error in the measurement of brominations and chlorinations by the method here outlined are the incompleteness of the reaction and the occurrence of substitution. Fortunately, both are readily detected, one by introducing into the stream of exit gases a Congo Red paper, the other by introducing a paper moistened with starch–potassium iodide solution. Both these tests were applied before and after each run and were so sensitive that 0.1% of the original halogen present as such or as hydrogen halide, could have been detected readily. Only runs in which both tests were negative are reported in the following. Samples of the dihalides were collected and their refractive indices taken, but no freezing curves studied.

Table II presents a summary of the results obtained in the brominations and chlorinations. The literature values for the refractive indices are from "I. C. T." except where otherwise stated. Where more than one experiment was performed on a compound, both the rate of flow of the gases through the calorimeter and the bromine:olefin ratio were varied, but no systematic trends in the heats were observed. The deviations from the given heats of halogenation in the column of "preliminary values" represent the average deviations from the mean values; the deviations from the final values are estimated total probable errors. Deviations of the measured refractive indices from the given figures are maximum deviations of individual samples from the mean.

The experiments with ethylene extended during a period of over four months, many adjustments and minor changes of technique being made between successive runs. Undoubtedly the earlier mentioned losses of bromine did not remain quite constant, which accounts for the rather large

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(4) Dillon, Young and Lucas, THIS JOURNAL, **52**, 1953 (1930).

deviations from the mean. It is preferable, however, to use all these runs in forming the average since no safe clue is available for a rejection of some runs.

In experiments with propylene and higher hydrocarbons a Dry-Ice trap was placed in the gas stream before it reached the Congo Red paper, since otherwise a hydrolysis of the bromide caused a change in color of the test paper. In experiments with trimethylethylene difficulty was experienced in freeing the sample of the dibromide from the unreacted olefin and the product turned purple on standing in the air, presumably due to a loss of hydrogen bromide and rearrangement to a ketone caused by the moisture of the air.

Cyclohexene and isobutene could not be brominated because in both cases substitution took place. With the latter hydrocarbon much methallyl bromide was recovered.

Propylene and higher hydrocarbons could not be chlorinated successfully because substitution took place to an extensive and variable degree. No catalyst could be found to promote the quantitative chlorination of *cis*- and *trans*-dichloroethylenes at the temperature of the calorimeter.

Table III presents the results obtained in the bromination reaction with the repacked furnace and shows the deviations of the new results from the averages of the "preliminary" column of Table II. The deviations are not very constant, but an estimation on the basis of all available data suggests that they are not outside the limits of possible accidental errors. This is demonstrated best by a comparison of the propylene and the butene-1 reactions, the products of which surely will undergo combustion in much the same manner. These two series of runs followed one another and thus the furnace should have behaved also quite similarly. And yet the variations between the earlier and the new experiments with the two compounds differ appreciably. It is therefore preferable to interpret all variations in the fourth column of Table III as accidental and take their average for the correction of the third column of Table II. The so calculated values are given in the last column of Table II.

TABLE III

BROMINATION WITH THE CORRECTED ANALYTICAL PROCEDURE

Hydrocarbon	Expts. made	$-\Delta H_{355°}$ cal./mole	Diff. from the mean of Table II cal./mole
C_2H_4	1	29,126	−105
C_3H_6	1	29,277	−308
C_4H_8-1	1	29,682	− 76
trans-C_4H_8-2	1	28,945	−203
			Mean −173

It may be noted that no more trimethylethylene and *cis*-butene-2 were available at the time of the repeat runs and therefore the average from the other hydrocarbons in Table III was used to correct the data of Table II.

Discussion of the Results

Since the heat of addition of chlorine to ethylene was measured after the alteration of the analytical furnace, no significant systematic error should be involved in the results and the error of the average is of the same order of magnitude as the mean deviation and not more than 0.3%.

The same is not true for brominations: first, the individual values show greater scattering, due no doubt to the somewhat irreproducible losses of bromine in the platinum coated furnace; second, a semi-systematic error is introduced in correcting for bromine losses. The uncertainty from the first cause can be estimated as 0.3% (except for ethylene, where a slightly larger value is used), that from the second, as not more than 0.7%; altogether, then, somewhat less than 1%.

These imperfections, fortunately, do not disfigure the results to an extent large enough to void any of the following deductions; they leave the new data decidedly superior in accuracy to values which can be derived from combustion heats. A perusal of the standard reference works reveals that extremely little has been done on combustion of dihalides derivable from olefins by addition of halogens. In fact, the only available data are on ethylene dihalides, which have been summarized by Bichowsky and Rossini.[5] Using their values, the heats of the gaseous additions are found readily

$$C_2H_4 + Cl_2 = C_2H_4Cl_2 - 40.3 \text{ kcal.}$$
$$C_2H_4 + Br_2 = C_2H_4Cr_2 - 29.2 \text{ kcal.}$$

The agreement of these values with those here reported is as good as could be expected.

The series of olefins investigated in the bromine reaction is not very extensive but it includes those essential compounds, the study of which previously led to the establishment of the regularities of the heats of hydrogenation. It is possible, therefore, to draw a rather interesting conclusion that

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(5) Bichowsky and Rossini, "Thermochemistry of Chemical Substances," Reinhold Publishing Corp., New York, N. Y., 1936.

the trend of the heats of the two reactions is in the opposite direction when the substitution on the ethylenic group is changed; with increasing substitution the heats of hydrogenation show a very decided decrease, the heats of bromination, on the other hand, show a less pronounced increase. This is brought out very clearly in Fig. 2.

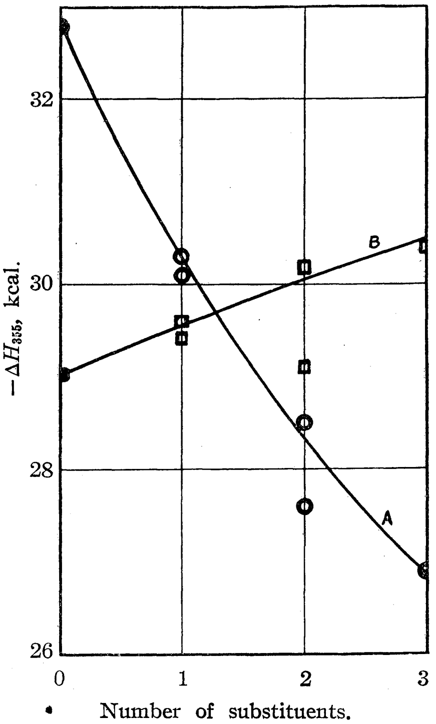

Fig. 2.—The effect of substituents on the heats of reactions: curve A, hydrogenations; curve B, brominations.

Some time ago it was suggested that the heats of iodination of olefins follow the same trend[6] as the heats of hydrogenation. This conclusion was reached, however, on the basis of rather limited and not too accurate experimental material and must be revised in view of the present findings on the heats of brominations. The iodination of butene-1 is in reality probably more exothermic than that of ethylene. This conclusion can be reconciled with the experimental data presented in the cited work; consequently the entropy changes in the two reactions are significantly different.

The opposite trends in the hydrogenation and halogenation reactions suggest that the changes themselves are due not so much to variations in the strength of the ethylenic bond as to variable bond strengths of the addenda; they must be subject to constitutional influences from the groups attached to the ethylenic system. These effects may be termed for short steric, although a naïve interpretation based on the volume requirements of the different atoms and radicals involved leads to completely wrong conclusions. Indeed, a replacement of the small hydrogen atoms by the more bulky methyl radicals in ethylene, reduces the heat of addition of the small hydrogen atoms but enhances that of the larger bromines. A qualitatively correct interpretation is offered by considerations of electrostatic induction effects. The replacement of an electropositive hydrogen atom by a more electronegative methyl radical should make the ethylenic carbon atom more electropositive and therefore favor the addition of bromine, making the addition of hydrogen less exothermic. It is very doubtful, however, whether such effects are strong enough to account for some 6 kcal./mole change in the reaction heats and, besides, another effect must be included, the direct electrostatic attraction or repulsion of the atomic groups in ethylene on the addenda. Evidently this action will cause opposite trends in the reaction heats from those just deduced and the over-all effect is in doubt.

Whatever may be the correct atomistic interpretation of the results here described, they serve admirably to explain on a thermodynamic basis the so-called Markownikoff rule, which states that normally the addition of hydrogen halides to olefins occurs so that the halogen adds to a more highly substituted carbon atom. To give this interpretation a quantitative character, it is necessary to formulate a rule which may be stated as follows. The heat of addition to the ethylenic linkage is the sum of two nearly independent terms, the heats of addition to each of the two ethylenic carbon atoms. The heats of hydrogenation provide a sound basis for this rule; they show that, except for effects of conjugation, only atoms or radicals once removed in the molecule have significant effects upon one another. Upon addition to the ethylenic bond, however, the addenda are twice removed from each other and therefore only minor interaction should be expected between them.

The lowering of the heat of hydrogenation in going from ethylene to propylene means therefore that less heat is evolved on adding hydrogen in a secondary position, the lowering being equal to the

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[6] Cline and Kistiakowsky, *J. Chem. Phys.*, **5**, 990 (1937).

difference in observed reaction heats. On the contrary, an increase of the heat of bromination means that the addition of bromine in a secondary position is accompanied by more heat evolution than that in the primary one.

Reasoning in this manner it is possible to account for all our previous observations to about 1 kcal. accuracy, which is therefore to be considered as the accuracy of the enunciated rule.

If the rule is generally correct, then the heat of addition of hydrogen halide must be an average of the heats of addition of hydrogen and halogen, corrected by the heat of formation of the hydrogen halide. Using combustion data this comparison may be made and is shown in Table IV. The values of the first column of heat data were all derived from figures given by Bichowsky and Rossini;[5] the figures in the last column are averages of the observed heats of hydrogenation and halogenation, the heat of iodination being derived from equilibrium measurements[7] and therefore subject to a larger uncertainty. These data were converted to 25° by deducting 0.2 kcal. and corrected by the heat of formation of the hydrogen halide. The agreement of the two columns is well within the combined experimental errors, which shows that even a profound change of one of the addenda leaves unaltered the heat of addition of the other one.

TABLE IV

HEATS OF ADDITION OF HALOGEN ACIDS TO ETHYLENE

	From heats of combustion: ΔH, kcal./mole	Calculated ΔH in kcal./mole
$C_2H_4 + HCl = C_2H_5Cl$	−14.6	−15.9
$C_2H_4 + HBr = C_2H_5Br$	−17.9	−18.3
$C_2H_4 + HI = C_2H_5I$	−17.9 (?)	−21.4 (±1)

A further interesting case, which tests the rule, is the addition of hydrogen bromide to isobutene to form the tertiary bromide. The heat of this reaction has been calculated from the equilibrium measurements[8] and the value, 18.9 kcal./mole, is fairly accurate (±0.9 kcal.). The heat of addition of bromine to isobutene has not been measured but by analogy with hydrogenations it may be taken to be identical with the heat of bromination of *cis*-butene-2, *i. e.*, 30.0 kcal. at room temperature. The difference of this value from that found for ethylene (28.9) will be attributed to the addition on the tertiary carbon atom. Hence for this reaction we can write: isobutene + $^1/_2$ Br_2 (in tertiary position) = 30.0 − $^1/_2$(28.9) = 15.5 kcal. Hydrogen addition occurs in the primary position and therefore one half of the heat of hydrogenation of ethylene (16.3 kcal.) applies to this reaction. Together 31.8, and when this figure is corrected for the heat of formation of hydrogen bromide (Bichowsky and Rossini;[7] −12.4 kcal. from the gaseous elements), the result is 19.4 kcal. in excellent agreement with the directly measured figure.

The heats of addition of hydrogen chloride and hydrogen iodide to isobutene are 17.1[8] and 19.1[9] kcal., respectively. It is thus evident by comparison with Table IV that addition of chlorine or iodine in tertiary position is accompanied by an increased heat evolution similar to that discussed above for bromine.

Under normal conditions in the liquid reaction and certainly in the gas phase, the tertiary bromide is formed in preference to isobutyl bromide; this is according to the Markownikoff rule and, as we can now show, means that in the reaction the thermodynamically more stable compound results. Indeed, the heat of formation of isobutyl bromide, according to the enunciated rule, is made up of 14.4 kcal. for the addition of bromine in the primary position (as in ethylene) and 28.2 − $^1/_2$(32.6) = 11.9 for hydrogen (heat of hydrogenation of isobutene less one half the heat of hydrogenation of ethylene). Together 26.3 kcal., which, when corrected by the heat of formation of hydrogen bromide, gives 13.9 kcal. and shows that isobutyl bromide is considerably less stable than the tertiary compound, since its entropy cannot be so much larger as to overcome the exothermicity of the reaction to form the tertiary compound. In the cited work it was found that the equilibrium constant in the reaction isobutyl chloride–tertiary butyl chloride was somewhat larger than 10 at 270°. Assuming zero entropy change in the reaction between the bromides at 270°, an equilibrium constant of 10^2 is calculated in close agreement with the above value for the chlorides.[10]

On the whole it appears then that the Markownikoff rule, although it deals with the essentially kinetic problem of the relative rates of two competing reactions, can be correlated with the thermodynamic stability of the preferentially formed

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(7) Cuthbertson and Kistiakowsky, *J. Chem. Phys.*, **3**, 631 (1935).

(8) Kistiakowsky and Stauffer, THIS JOURNAL, **59**, 165 (1937).

(9) Jones and Ogg, *ibid.*, **59**, 1943 (1937).

(10) Similar conclusions can be drawn from the work of Brouwer and Wibaut [*Rec. trav. chim.*, **53**, 1001 (1934)] on the formation of and equilibrium between the primary and secondary propyl bromides and chlorides. See also Schjånberg, *Z. physik. Chem.*, **A172**, 197 (1935).

compound. It is obviously incorrect to postulate a close proportionality between the free energy decrease in a reaction and the rate at which it occurs, since too many exceptions to such a correlation can be cited. Nevertheless, in a series of homologous reactions a correlation of this type must frequently exist. Some cases have been discussed earlier.[11] Also in the field of catalytic reactions two instances may be cited; in the series of hydrogenations from ethylene to tetramethylethylene, studied calorimetrically, the heats of the addition decrease markedly; simultaneously the speed of the reaction on a given catalyst decreases also; thus the copper catalyst used could hydrogenate ethylene instantaneously even at 0°, but with tetramethylethylene it was ineffective even at 80° and the intermediate compounds fell in between these limits. On the other hand, the heats of bromination rise with increasing substitution; in parallel to this an increasing activity of the calcium bromide catalyst was observed.

Kharasch and others have cited instances when the Markownikoff rule breaks down, the condition apparently being that the reaction be catalyzed by oxygen or a peroxide. This effect is not noted in the gas phase reaction[8,9] and is undoubtedly due to the promotion of a chain reaction, in the course of which the peroxide or some other intermediate adds temporarily to one end of the double bond. This is then blocked for the addition of one of the atoms in the hydrogen halide and the reaction is forced to take the unnatural course.

Another instance where the rates of reaction seem to change parallel to the heat content changes in a series of analogous reactions, is the substitution of bromine in hydrocarbons. Since the reaction may be looked upon formally as a dehydrogenation, followed by addition of hydrogen bromide, the calculations discussed on the previous pages may be again employed. It is thus readily found that the substitution of bromine in a primary position is accompanied by 10.5 kcal. heat evolution, substitution in the secondary one by 13.6 and that in the tertiary one by 16.0 kcal. The increasing heat evolution in this order is wholly paralleled by the well-known kinetic tendency of bromine to replace hydrogen on the most highly substituted carbon atom of a hydrocarbon molecule.

The opposite trends of the heats of hydrogenation and bromination, so prominent in the ethylenic series, must be limited to those molecules where the changes of the reaction heats are conditioned by the interactions of the addenda with the neighboring groups. In particular, a decrease in the heat of hydrogenation due to the existence of conjugation in a diene or some other conjugated system, must be paralleled by a similar decrease of the heat of bromination, unless the now accepted theory of conjugation is incorrect and the phenomenon is not a stabilization of the double bond system by mutual interaction. There is thus offered, in the comparative study of the hydrogenation and the bromination heats, a more reliable and accurate method for a differentiation between conjugation energies and "steric" effects, than is possible from the analysis of the hydrogenation data alone; it is hoped to put this idea into practical form in the near future.

The failure to measure the heat of bromination of isobutene merits a brief comment. It has been known for some time[12] that upon addition of halogens to isobutene there is a tendency to form methallyl halide and free halogen acid. Under the conditions of bromination in the calorimeter this last reaction is thermodynamically possible, which conclusion is arrived at by comparison with the equilibrium between isobutene, hydrogen bromide and *t*-butyl bromide.[8] The noteworthy point is, however, that neither propylene nor trimethylethylene gives rise to such a reaction when brominated under *identical* conditions, although in at least one of these cases the equilibrium must be as favorable for decomposition of the dibromide as with isobutene. Thus purely kinetic factors of undetermined but highly specific nature must make the decomposition of the dibromide of isobutene occur exceptionally rapidly.

In concluding this discussion it may be pointed out that the difference of the heats of bromination of the *cis*- and *trans*-butenes-2 is quite close to the difference in their heats of hydrogenation. In the latter of these reactions the same end product is obtained, but the bromination of *cis*-butene-2 leads to the *dl*-mixture, while *trans* gives the *meso* form of the dibromide.[4] It is therefore evident that the heat content difference of these two compounds is quite small, if not zero.

Acknowledgment.—The late Professor E. P. Kohler has given us, as usual, much helpful ad-

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(11) Ogg and Polanyi, *Trans. Faraday Soc.*, **31**, 482 (1935); Gershinowitz, *J. Chem. Phys.*, **4**, 363 (1936).

(12) Pogorshelski, *J. Russ. Phys.-Chem. Soc.*, **36**, 1129, 1486 (1905); Linnemann and Zotta, *Ann.*, **162**, 36 (1872).

vice and we are also grateful to Dr. J. B. Conant for his valuable suggestions. Dr. W. E. Vaughan and Dr. Ralph D. Thompson have taken part in the early stages of this work.

Summary

Certain brominations and chlorinations have been studied calorimetrically, the following being the results

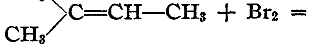
$$C_2H_4 + Br_2 = C_2H_4Br_2 - 29{,}058 \pm 300 \text{ cal.}$$

$$C_3H_6 + Br_2 = C_3H_6Br_2 - 29{,}412 \pm 200 \text{ cal.}$$

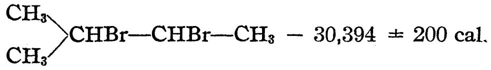
$$H_2C{=}CH{-}C_2H_5 + Br_2 = CH_2Br{-}CH_2Br{-}C_2H_5 - 29{,}585 \pm 200 \text{ cal.}$$

$$trans\text{-}H_3C{-}CH{=}CH{-}CH_3 + Br_2 = i\text{-}CH_3{-}CHBr{-}CHBr{-}CH_3 - 29{,}075 \pm 200 \text{ cal.}$$

$$cis\text{-}H_3C{-}CH{=}CH{-}CH_3 + Br_2 = dl\text{-}CH_3{-}CHBr{-}CHBr{-}CH_3 - 30{,}177 \pm 200 \text{ cal.}$$



$$(CH_3)_2C{=}CH{-}CH_3 + Br_2 =$$



$$(CH_3)_2CBr{-}CHBr{-}CH_3 - 30{,}394 \pm 200 \text{ cal.}$$

$$C_2H_4 + Cl_2 = C_2H_4Cl_2 - 43{,}653 \pm 120 \text{ cal.}$$

All heats of reaction refer to 355°K. and gases at one atmosphere total pressure.

The most notable conclusion to be drawn from these data is that substitution on the ethylenic group results in increased heat evolution on addition of bromine, while previously it was found to decrease the heat of hydrogenation.

It is pointed out that the observed trends give a thermodynamic basis to the so-called Markownikoff rule and to the trend of bromine to replace hydrogen on the most substituted carbon atom of a saturated hydrocarbon. A rule is formulated which makes possible a calculation of quite accurate heats of addition of hydrogen halides and of substitution of bromine.

CAMBRIDGE, MASS. RECEIVED AUGUST 5, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WILLIAMS COLLEGE]

The Solubility of Carbon Dioxide in Deuterium Oxide at 25°[1]

BY JAMES CURRY AND C. L. HAZELTON

In the course of measuring the first ionization constant of deuterio-carbonic acid, it was found necessary to determine the solubility of carbon dioxide in deuterium oxide. This measurement is of interest in itself since, up until the present, no values for the solubility of gases in deuterium oxide have appeared in the literature.

Experimental

Apparatus.—The apparatus used was of the Ostwald type[2] and the measurements were carried out by means of the "dry method." The buret, which was surrounded by a water jacket, had a volume of 10 cc. and was graduated in 0.05 cc. The absorption vessel had a volume of approximately 7 cc. The buret and the absorption vessel were connected by a flexible piece of copper tubing 1.5 meters long and 1 mm. internal diameter. In order to fasten the copper tubing to the glass, short pieces of 7-mm. glass tubing were sealed to the three-way capillary stopcocks which were at the top of the buret and the absorption vessel. The copper tubing was inserted to a depth of about 3 cm. into the glass tubing and the joints were then made fast with picein. In order to minimize breakage the copper tubing was held by a brass clamp at a point near the picein joint at the buret stopcock. This clamp in turn was fastened to the ringstand which held the buret. Another type of brass clamp, acting as a splint, strengthened the other copper–picein–glass joint at the absorption vessel. This mode of connection permitted a vigorous shaking of the absorption vessel but when necessary it was very simple to disconnect the latter.

Materials.—The carbon dioxide came from a commercial tank. It was analyzed by absorption in a potassium hydroxide solution and was found to be 99.8% pure.

The deuterium oxide was from a commercial source and at the beginning of the measurements was 99.9% D_2O. It was purified by distillation from alkaline permanganate, then from phosphoric anhydride and finally carried through a distillation without any reagents in a still especially reserved for this purpose. Before use the deuterium oxide was refluxed in order to remove any dissolved gases. During this operation it was protected from the atmosphere by means of a soda lime–calcium chloride tube. After the solubility measurements were completed the deuterium oxide was used for ionization constant determinations and when these were finished the analysis was 99.1% D_2O.

Measurements.—These were carried out in the usual manner except that a few slight modifications were necessary because the quantities of deuterium oxide used were relatively small and deuterium oxide is hygroscopic. During a measurement the absorption vessel was shaken in a thermostat adjusted to 25.00 ± 0.01°. The absorption vessel contained a short piece of 1-mm. copper wire which moved about during the shaking and thus aided in

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[1] Based on a thesis presented by C. L. Hazelton to Williams College in 1938, in partial fulfilment of the requirements for the degree of Master of Arts.

[2] Just, *Z. physik. Chem.*, **37**, 342 (1901).

lessening the time required to reach equilibrium. The amount of water in the absorption vessel was obtained from the weight of the dry vessel and the weight of the vessel plus contents at the end of the measurements, allowance being made for the weight of the carbon dioxide present.

Equilibrium was established in about ten minutes. The vessel was then allowed to stand for fifty minutes in contact with the carbon dioxide and was then shaken for a few minutes. No additional absorption was ever noted.

Results

In order to test the apparatus, measurements were also made on the solubility of carbon dioxide in ordinary water. The experiments were carried out in exactly the same way except that H_2O was used in place of D_2O. Thus if any errors were present while one kind of water was being used they also would be present during the measurements with the other kind of water. The experimental data and the calculated results are given in the table.

SOLUBILITY OF CARBON DIOXIDE IN H_2O AND D_2O AT 25°

The total volume of the absorption vessel was 6.811 cc. except in the first experiment with H_2O, where it was 8.868 cc.

Atm. pres., mm.	Buret t, °C.	Buret Change in vol., cc.	Abs. vessel Par. pres. of CO_2 mm.	Abs. vessel Wt. of water, g.	Ostwald coef. λ	
			H_2O			
749.4	21.6	7.64	722.9	4.7374	0.816	
754.0	21.2	6.12	728.2	2.2735	.822	
747.5	21.8	6.12	721.5	2.4543	.834	
735.5	21.3	5.90	709.3	3.3496	.813	
				Av.	0.821	± 0.007
			D_2O			
741.2	20.8	6.11	718.6	2.6003	0.817	
743.7	21.0	5.90	720.4	3.9476	.818	
749.9	21.4	5.92	726.6	3.8461	.817	
732.8	21.2	6.00	709.7	3.5729	.831	
735.9	23.0	5.94	712.6	4.0429	.823	
754.5	21.3	5.88	731.2	3.9585	.810	
				Av.	0.819	± 0.005

There is no general agreement as to the best method for expressing the solubility of gases in liquids. We have chosen the Ostwald coefficient, λ, *i. e.*, the volume of gas (measured at experimental conditions) absorbed by unit volume of liquid, because it is often used in theoretical discussions.

In order to determine the partial pressure of the carbon dioxide in the absorbing vessel it was necessary to know the vapor pressures of the two waters at 25°. For deuterium oxide the value 20.7 mm. was used.[3]

As mentioned previously, the composition of the deuterium oxide changed slightly during the experiment. The average composition was taken as 99.8% D_2O. Thus in calculating the above results $d^{25}{}_4$ was taken as 1.1042. In the calculations correction was made for the slight amount of impurities in the carbon dioxide.

Discussion

Shedlovsky and MacInnes[4] have made the most recent determination of the solubility of carbon dioxide in H_2O. The value they obtained was 0.03372 mole per liter per atmosphere. In terms of the Ostwald coefficient this corresponds to $\lambda = 0.825$. Our value agrees with theirs well within our experimental error, which is less than 1%, so we can conclude that our results are fairly reliable. It should be pointed out that the precision obtainable in solubility measurements is largely determined by the quantities of water used. With the present high cost of D_2O it is necessary to make some sacrifice in precision.

Thus, from our data, it is apparent that the values for the Ostwald coefficient for carbon dioxide in H_2O and D_2O are the same within less than 1%. Consequently on a molal basis (moles/1000 g. of water) carbon dioxide is less soluble in D_2O than in H_2O, the respective solubilities being 0.0304 and 0.0337 molal when the partial pressure of carbon dioxide is one atmosphere.

This result is about what one would expect from theory. It has been known for a long time that there usually is at least a qualitative relationship between solubility of a gas and surface tension of the solvent. Uhlig[5] has been one of the latest to attempt a quantitative expression. Early workers reported a difference of about 7% in the surface tension of the two kinds of waters but this result has not been substantiated. Jones and Ray[6] found that the surface tensions were the same within 0.054%. Thus one would expect no great difference in the solubility of a gas, such as carbon dioxide, in the two waters, particularly since, in addition, the values for the dielectric constants are the same within 1%.[7]

We are indebted to the Class of 1900 Fund for a

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(3) Wahl and Urey, *J. Chem. Phys.*, **3**, 411 (1935).

(4) Shedlovsky and MacInnes, THIS JOURNAL, **57**, 1708 (1935). For a summary of the literature see Morgan and Pyne, *J. Phys. Chem.*, **34**, 1578 (1930).

(5) Uhlig, *J. Phys. Chem.*, **41**, 1215 (1937).

(6) Jones and Ray, *J. Chem. Phys.*, **5**, 505 (1937). See also Lachs and Minkow, *Nature*, **136**, 186 (1935).

(7) Lewis, Olsen and Maroney, THIS JOURNAL, **55**, 4731 (1933).

grant which enabled us to purchase the deuterium oxide used in this work.

Summary

The solubility of carbon dioxide in 99.8% D_2O at 25° has been measured relative to its solubility in H_2O at the same temperature. In terms of the Ostwald coefficient the solubilities are the same within less than 1%. On a molal basis this means that carbon dioxide is 0.902 times as soluble in D_2O as in H_2O.

WILLIAMSTOWN, MASS. RECEIVED JUNE 10, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WILLIAMS COLLEGE]

The First Thermodynamic Ionization Constant of Deuterio-carbonic Acid at 25°[1]

BY JAMES CURRY AND C. L. HAZELTON

Introduction

Since carbon dioxide plays an important role in many physiological processes and the effect of deuterium oxide on living matter has been studied extensively, it is of importance to determine the strength of deuterio-carbonic acid. From the standpoint of chemical theory the strength of this acid is also of interest.

The method used in this work followed that of Korman and La Mer[2] very closely. In this paper it was shown that heavy water studies could be made using a quinhydrone electrode in cells without transference of the type developed by Harned and Ehlers.[3] On account of the cost of deuterium oxide the measurements were limited to a relative determination of the first thermodynamic ionization constants of proto- and deuterio-carbonic acid in dilute solutions. No extrapolation to infinite dilution was attempted.

Measurements were made using the following cells

$$\text{Pt, Q, QH}_2\text{, H}_2\text{CO}_3\text{, KHCO}_3\text{, KCl, AgCl, Ag} \qquad \text{(I)}$$

$$\text{Pt, Q, QD}_2\text{, D}_2\text{CO}_3\text{, KDCO}_3\text{, KCl, AgCl, Ag} \qquad \text{(II)}$$

As is well known, the potential of cell I is given by

$$E = E_0 - \frac{RT}{F} \ln m_{\mathrm{H}} m_{\mathrm{Cl}} - \frac{RT}{F} \ln f_{\mathrm{H}} f_{\mathrm{Cl}} \qquad (1)$$

where the E_0 term includes the standard electrode potential for the quinhydrone and the silver–silver chloride electrodes in H_2O, m is the concentration in molal terms and f is the activity coefficient of the quantities indicated by the subscripts.

The primary dissociation of proto-carbonic acid may be written in the following manner

$$CO_2 + H_2O \rightleftarrows H_2CO_3 \rightleftarrows H^+ + HCO_3^-$$

The first thermodynamic ionization constant for proto-carbonic acid is accordingly

$$K_{\mathrm{H}} = \frac{m_{\mathrm{H}}\, m_{\mathrm{HCO_3}}}{m_{\mathrm{CO_2}}} \cdot \frac{f_{\mathrm{H}}\, f_{\mathrm{HCO_3}}}{f_{\mathrm{CO_2}}} \qquad (2)$$

where $m_{\mathrm{CO_2}}$ represents the total concentration ($CO_2 + H_2CO_3$) of dissolved carbon dioxide in molal terms.[4] A similar expression would hold for the thermodynamic ionization constant of deuterio-carbonic acid, K_{D}.

Replacing m_{H} in (1) by its value from (2) we obtain for the e. m. f. of cell I

$$E = E_0 - \frac{RT}{F} \ln \frac{m_{\mathrm{Cl}}\, m_{\mathrm{CO_2}}}{m_{\mathrm{HCO_3}}} - \frac{RT}{F} \ln K_{\mathrm{H}} - \frac{RT}{F} \ln \frac{f_{\mathrm{Cl}}\, f_{\mathrm{CO_2}}}{f_{\mathrm{HCO_3}}} \qquad (3)$$

In order to determine K_{H} this expression may be put into a somewhat more convenient form. In an aqueous solution, in the region of a partial pressure of 760 mm., carbon dioxide obeys Henry's law so we may say that $m_{\mathrm{CO_2}} = hp_{\mathrm{CO_2}}$ where h is a constant. Using this expression and rearranging (3) we obtain

$$\log K_{\mathrm{H}} = \frac{E_0 - E}{0.0591} - \log \frac{m_{\mathrm{Cl}}}{m_{\mathrm{HCO_3}}} - \log h - \log p_{\mathrm{CO_2}} - \log \frac{f_{\mathrm{Cl}}\, f_{\mathrm{CO_2}}}{f_{\mathrm{HCO_3}}} \qquad (4)$$

The similar expression which holds for cell II is

$$\log K_{\mathrm{D}} = \frac{E_0' - E}{0.0591} - \log \frac{m_{\mathrm{Cl}}'}{m_{\mathrm{DCO_3}}'} - \log d - \log p_{\mathrm{CO_2}} - \log \frac{f_{\mathrm{Cl}}'\, f_{\mathrm{CO_2}}'}{f'_{\mathrm{DCO_3}}} \qquad (5)$$

The prime terms refer to the values for D_2O and d corresponds to h except that it refers to the solubility of carbon dioxide in D_2O.

Since carbon dioxide is a neutral molecule its activity will be unaffected by ions in dilute solutions so we may put $f_{\mathrm{CO_2}} = f_{\mathrm{CO_2}}' = 1$.[5] If the

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[1] Based on a thesis presented by C. L. Hazelton to Williams College in 1938, in partial fulfilment of the requirements for the degree of Master of Arts.

[2] Korman and La Mer, THIS JOURNAL, **58**, 1396 (1936).

[3] Harned and Ehlers, *ibid.*, **54**, 1350 (1932).

[4] For a discussion of this expression see MacInnes and Belcher, *ibid.*, **55**, 2630 (1933).

[5] This statement is not absolutely true due to the salting-out effect of the electrolytes on the carbon dioxide. The influence of this factor will be considered later.

molal concentration of potassium chloride is about the same as that of potassium bicarbonate, then in dilute solutions, since they are both uni-univalent electrolytes, their respective activity coefficients will be practically equal, so in (4) and (5) the last logarithmic term on the right-hand side will be almost zero and consequently may be neglected. This will be true for both the H_2O and D_2O solutions. Even if these terms do not vanish completely they should be the same in H_2O and D_2O solutions of the same molal concentrations since the dielectric constant of H_2O is nearly identical with that of D_2O. Therefore, in order to determine the ratio of ionization constants it is only necessary to determine K_H and K_D at one and the same ionic strength. The measurements should be carried out in dilute solutions which have been made up so that m_{Cl} and m_{HCO_3} (or m'_{Cl} and m'_{DCO_3}) are about equal. A discussion of the remaining quantities in equations (4) and (5) will be given later.

Experimental

Materials.—The carbon dioxide was obtained from a commercial tank and was 99.8% pure. The deuterium oxide was purified as previously described[6] and at the end of the measurements was 99.1% D_2O. Eastman Kodak Co. quinhydrone was used without further purification. The potassium bicarbonate was purified by the method of MacInnes and Belcher[4] (p. 2633) and the potassium chloride was recrystallized twice from distilled water and dried at 120°. A semi-micro balance was used in making up the D_2O solutions.

Electrodes.—The silver–silver chloride electrodes were prepared by the method of Brown.[7] Pairs showing a potential difference of not more than 0.05 mv. were used in each experiment. The platinum electrodes were of the spiral type and were kept in cleaning solution when not in use. They agreed with each other better than 0.05 mv. Before insertion into the cells, both types of electrodes were well rinsed with the appropriate solution. This required about 1.6 cc. per electrode.

Cells.—Two identical cells (A and B) were used and all measurements were carried out in duplicate. Each cell was shaped like the letter H. The two side arms had an inside diameter of 8 mm. and a length of 8 cm. and were of course closed at the bottom. The top of each arm was widened out so that it would take a no. 2 rubber stopper. The two side arms of a cell were connected by means of a stopcock which had a 1.5-mm. bore. The connection tubes were sealed in just where the side arms started to widen out and the stopcocks were greased only at the top and bottom. Each rubber stopper carried an electrode, an inlet tube for the introduction of carbon dioxide and an outlet tube. The total amount of solution needed for each cell was about 6 cc. The cells were immersed in a thermostat adjusted to 25.00 ± 0.01°.

Before the carbon dioxide entered the cell it was saturated with water vapor by allowing it to bubble through a trap immersed in the thermostat and filled with the appropriate water. After bubbling through the cell solution the carbon dioxide escaped into the air through a tube which dipped just under the surface of some paraffin oil.[8] Thus the pressure of carbon dioxide over the solution was essentially equal to the atmospheric pressure minus the vapor pressure of water in the cell. The gas connections were arranged so that the pressure was the same in all four compartments. It should be pointed out that carbon dioxide was bubbled through both the quinhydrone and the silver–silver chloride electrode compartments. This was done in order to eliminate the possibility of any liquid junction potential.

Experimental Procedure.—Measurements were made with a Leeds and Northrup type K potentiometer and a type R galvanometer. The standard cell was checked against one calibrated by the Bureau of Standards. Measurements were made first with H_2O and then with D_2O. Reproducible results were obtained without resorting to a vacuum technique to remove oxygen. In making measurements the appropriate solution was first saturated with carbon dioxide and then part of it was put in cell A and part in cell B. Quinhydrone was then added, the stoppers inserted tightly and carbon dioxide bubbled through the cells with the stopcocks closed. A gentle flow of gas was maintained except when e. m. f. measurements were actually being made. Equilibrium was established in about thirty minutes and the potential of any one cell remained constant within 0.2 mv. for a period of two to three hours. After equilibrium was established the e. m. f. values were the same whether or not the stopcocks were open.

Results and Discussions

In order to test the method, apparatus and materials the thermodynamic ionization constant for acetic acid in H_2O was determined using the above method except that acetic acid and potassium acetate were used instead of carbon dioxide and potassium bicarbonate. At an ionic strength of 0.06132 the ionization constant was found to be 1.75×10^{-5}, which is in good agreement with the value in the literature.[9]

Table I lists our experimental data and the calculated results.

Several of the quantities in equations (4) and (5) require further discussion. E_0 was obtained from Harned and Wright's[10] data for the quin-

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(6) Curry and Hazelton, THIS JOURNAL, **60**, 2771 (1938).

(7) A. S. Brown, *ibid.*, **56**, 646 (1934).

(8) With this technique it is conceivable that the cell solution became supersaturated with carbon dioxide. If such an effect did occur it must have been small because, as will be pointed out later, our value for K_H agrees well with careful measurements made by other workers. Even if supersaturation did occur it should be practically the same in H_2O and D_2O and accordingly have no appreciable effect on K_H/K_D.

(9) See for example reference (3), page 1355.

(10) Harned and Wright, *ibid.*, **55**, 4849 (1933).

TABLE I

FIRST THERMODYNAMIC IONIZATION CONSTANTS OF PROTO- AND DEUTERIO-CARBONIC ACID AT 25°

$E_0 = -0.4775$, $\log h = -4.3533$; $E_0 = -0.5119$, $\log d = -4.3987$

p_{CO_2}, mm	Molality		E			pK	$K \times 10^7$
	KCl	Bicarbonate	Cell A	Cell B	Av.		
			H_2O				
711.8	0.02580	0.02122	0.0182	0.0176	0.0179	6.354	4.43
719.7	.02612	.02224	.0183	.0182	.01825	6.338	4.59
719.3	.02546	.01229	.0323	.0318	.03205	6.351	4.46
718.3	.03054	.02351	.0202	.0203	.02025	6.347	4.50
							4.50 ± 0.05
			>99.1% D_2O				
716.4	.02608	.02530	.0206	.0206	.0206	6.775	1.68
725.0	.03161	.02431	.0265	.0263	.0264	6.783	1.63
718.5	.02393	.01959	.0256	.0255	.02555	6.766	1.72
							1.68 ± 0.02

$K_H/K_D = 2.68$

hydrone electrode and the silver–silver chloride electrode. The term E_0' is made up of the standard electrode potential of quinhydrone in D_2O and the standard electrode potential for the silver–silver chloride electrode in D_2O. The quinhydrone potential was obtained from the work of La Mer and Korman,[11] and is equal to -0.7341 v. The standard electrode potential of the silver–silver chloride electrode should be the same in D_2O as in H_2O since there is no theoretical reason for thinking that f_{Cl} and f'_{Cl} differ, provided the molal concentrations of the chloride ions are the same in the two kinds of water.

The terms h and d are the Henry's law constants for the molal solubility of carbon dioxide in H_2O and D_2O when the partial pressure of this gas is expressed in mm., and these, or rather their logarithms, have been calculated from some previous work done by us.[6] In very exact work the salting out effect of the electrolytes on the carbon dioxide should be considered but this often is neglected. At the ionic strengths we used, if this correction were made the values of K_H and K_D recorded above would have to be increased by about 0.7%. This correction would certainly be practically the same for both kinds of water and accordingly would not affect the K_H/K_D ratio given above.

No account has been taken of the secondary dissociation of carbonic acid. This is allowable since it is very small ($K_{II} = 7 \times 10^{-11}$) compared to the first dissociation. It also should be pointed out that the solution actually used for cell II was made up using $KHCO_3$ but exchange must take place very rapidly and at the concentrations used the equilibrium point should be far over on the $KDCO_3$ side.

In order to establish the reliability of our measurements it is necessary to compare our values for K_H with those recorded in the literature. Up until a few years ago it was thought that K_H was equal to 3.5×10^{-7} at 25°. Recently, however, MacInnes and associates redetermined K_H using two methods; with a glass electrode[4] they found K_H equaled 4.5×10^{-7}, and by conductivity methods[12] to be 4.3×10^{-7}.

Our value of 4.5×10^{-7} agrees very well with that of MacInnes and Belcher at the same ionic strength. Of course we used a potentiometric method also but ours differed considerably from theirs in respect to details.

The heavy water used in determining the above K_H/K_D ratio was at least 99.1% D_2O. To a first approximation the curve $K_H/K_D - N_{D_2O}$ is linear and this would mean that for 100% D_2O the ratio would be greater but certainly not more than 1% higher. Since this is less than the precision of our measurements this correction will not be applied.

It is of interest to compare our results with those of other workers. Rule and La Mer,[13] making very careful measurements on five acids, found that the K_H/K_D ratio increases as the strength of the acid decreases. This is in accordance with the prediction of Lewis and Schutz and the theory of Halpern.[14] From the Rule–La Mer data one might expect for carbonic acid a ratio of 3.6.

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(11) La Mer and Korman, THIS JOURNAL, **57**, 1511 (1935). See also ref. (2).

(12) Shedlovsky and MacInnes, *ibid.*, **57**, 1705 (1935).

(13) Rule and La Mer, *ibid.*, **60**, 1974 (1938).

(14) Lewis and Schutz, *ibid.*, **56**, 1913 (1934); Halpern, *J. Chem. Phys.*, **3**, 456 (1935).

Our value, 2.68, is 25% smaller, and this difference is much greater than our experimental error which is about 2%. However, it should be remembered that carbonic acid is a peculiar acid in that the proton (or deuteron) must come exclusively from the water. Thus the hydration equilibrium plays an important role and it probably will not be the same in H_2O and D_2O. This factor may account for the difference mentioned above.

We are indebted to the Class of 1900 Fund for a grant which enabled us to purchase the deuterium oxide used in this work.

Summary

The ratio of the first thermodynamic ionization constants of proto- and deuterio-carbonic acid has been determined potentiometrically using a cell without transference in which the electrodes were quinhydrone and silver–silver chloride. Using 99.1% D_2O the ratio, K_H/K_D, has been found to be 2.68 at 25°.

WILLIAMSTOWN, MASS. RECEIVED JUNE 10, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY]

Conductivities of Concentrated Mixtures of the Nitrates of Some Uni-, Di-, and Trivalent Cations in Aqueous Solution

BY PIERRE VAN RYSSELBERGHE AND GOON LEE

As a further step in our investigation of the conductivity of concentrated mixtures of strong electrolytes[1] we have studied a number of nitrates of uni-, di-, and trivalent cations at different total concentrations ranging from 1 to 5 *N*. All possible types of binary mixtures have been included: two univalent cations, one uni- and one divalent cation, two divalent cations, one uni- and one trivalent cation, one di- and one trivalent cation, two trivalent cations. The method was essentially the same as in our previous work. The conductivities of the pure salts were found to be in close agreement with the existing standard data (I. C. T.; L. B. R.), except in three cases [$LiNO_3$, $Mg(NO_3)_2$, $Cr(NO_3)_3$] for which the standard data seem to be somewhat in error. Moreover, some conductivities of pure salts are reported here for the first time. Others have been obtained for the first time at 25°. The results are recorded in Table I in which we give the conductivities of twenty types of mixtures arranged in series corresponding to the same total equivalent concentration. We represent by x and $1-x$ the fractions of the total equivalent concentration corresponding to salts 1 and 2, salt 1 being the first in the title of the series. For each solution we give the specific and the equivalent conductivity and the difference $\Delta\Lambda$ between the measured conductivity and that calculated from the simple, uncorrected mixture rule:

$$\Lambda = x\Lambda_1 + (1 - x)\Lambda_2$$

Two series of mixtures (19 and 20) contain nitric acid as one of the components, the maximum amount of nitric acid present being in both cases half the total normality.

TABLE I

CONDUCTIVITIES OF CONCENTRATED MIXTURES AT 25°

Composition x	$1-x$	Specific conductivity	Equivalent conductivity Measured	Equivalent conductivity Calculated	$-\Delta\Lambda$
	1.1	1 *N* mixtures of $KNO_3 + NaNO_3$			
1	0	0.09254	92.54		
$^3/_4$	$^1/_4$	.08798	87.98	88.37	0.39
$^1/_2$	$^1/_2$	.08324	83.24	84.19	.85
$^1/_4$	$^3/_4$	.07973	79.73	80.02	.29
0	1	.07585	75.85		
	1.2	2 *N* mixtures of $KNO_3 + NaNO_3$			
1	0	0.15848	79.24		
$^3/_4$	$^1/_4$	.14993	74.97	75.20	0.23
$^1/_2$	$^1/_2$	.14104	70.52	71.17	.65
$^1/_4$	$^3/_4$	.13383	66.92	67.12	.20
0	1	.12617	63.09		
	1.3	3 *N* mixtures of $KNO_3 + NaNO_3$			
1	0	0.21042	70.16		
$^3/_4$	$^1/_4$	.19996	65.99	66.00	0.01
$^1/_2$	$^1/_2$	.18413	61.38	61.85	.48
$^1/_4$	$^3/_4$	.17222	57.41	57.72	.31
0	1	.16075	53.58		
	2	5 *N* mixtures of $NaNO_3 + LiNO_3$			
1	0	0.19815	39.65		
$^3/_4$	$^1/_4$	.18944	37.89	38.28	0.39
$^1/_2$	$^1/_2$	.18167	36.42	36.72	.30
$^1/_4$	$^3/_4$	.17511	35.02	35.27	.25
0	1	.16910	33.82		

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[1] Van Rysselberghe and Nutting, THIS JOURNAL, **56**, 1435 (1934); **59**, 333 (1937); Van Rysselberghe, Grinnell and Carlson, *ibid.*, **59**, 336 (1937).

TABLE I (*Continued*)

Composition x	$1-x$	Specific conductivity	Equivalent conductivity Measured	Equivalent conductivity Calculated	$-\Delta\Lambda$
3.1 1 *N* mixtures of $KNO_3 + Cd(NO_3)_2$					
1	0	0.09236	92.36		
$^3/_4$	$^1/_4$	.08392	83.92	84.84	0.92
$^1/_2$	$^1/_2$	.07522	75.22	77.33	2.11
$^1/_4$	$^3/_4$	.06894	68.94	69.81	0.87
0	1	.06230	62.30		
3.2 2 *N* mixtures of $KNO_3 + Cd(NO_3)_2$					
1	0	0.15912	79.56		
$^3/_4$	$^1/_4$	.13947	69.78	71.53	1.75
$^1/_2$	$^1/_2$	.12313	61.56	63.50	1.94
$^1/_4$	$^3/_4$	.10778	53.89	55.47	1.58
0	1	.09487	47.44		
3.3 3 *N* mixtures of $KNO_3 + Cd(NO_3)_2$					
1	0	0.21009	70.03		
$^3/_4$	$^1/_4$	.18015	60.05	61.58	1.53
$^1/_2$	$^1/_2$	.15243	50.81	53.13	2.32
$^1/_4$	$^3/_4$	.12895	42.98	44.68	1.70
0	1	.10868	36.23		
4 3 *N* mixtures of $KNO_3 + Zn(NO_3)_2$					
1	0	0.21019	70.06		
$^3/_4$	$^1/_4$	.18973	63.24	63.75	0.51
$^1/_2$	$^1/_2$	.17035	56.78	57.44	.66
$^1/_4$	$^3/_4$	.14966	49.89	51.13	.24
0	1	.13446	44.82		
5.1 2 *N* mixtures of $KNO_3 + Cu(NO_3)_2$					
1	0	0.15928	79.64		
$^3/_4$	$^1/_4$	.14380	71.90	73.06	1.16
$^1/_2$	$^1/_2$	.13002	65.01	66.48	1.47
$^1/_4$	$^3/_4$	.11746	58.73	59.90	1.17
0	1	.10664	53.32		
5.2 3 *N* mixtures of $KNO_3 + Cu(NO_3)_2$					
1	0	0.21000	70.00		
$^3/_4$	$^1/_4$	.18482	61.61	62.98	1.37
$^1/_2$	$^1/_2$	.16200	54.00	55.92	1.95
$^1/_4$	$^3/_4$	.14368	47.89	48.93	1.04
0	1	.12570	41.90		
6.1 3 *N* mixtures of $LiNO_3 + Cd(NO_3)_2$					
1	0	0.14494	48.31		
$^3/_4$	$^1/_4$	.13504	45.01	45.29	0.28
$^1/_2$	$^1/_2$	.12613	42.04	42.29	.25
$^1/_4$	$^3/_4$	.11741	39.13	39.28	.15
0	1	.10881	36.27		
6.2 5 *N* mixtures of $LiNO_3 + Cd(NO_3)_2$					
1	0	0.16910	33.82		
$^3/_4$	$^1/_4$	.14894	29.78	30.57	0.79
$^1/_2$	$^1/_2$	.13345	26.69	27.34	.65
$^1/_4$	$^3/_4$	.11797	23.59	24.10	.51
0	1	.10432	20.86		
7 4 *N* mixtures of $LiNO_3 + Zn(NO_3)_2$					
1	0	0.16168	40.42		
$^3/_4$	$^1/_4$	.15711	39.27	39.33	0.06
$^1/_2$	$^1/_2$	.15277	38.19	38.26	.07
$^1/_4$	$^3/_4$	.14842	37.10	37.18	.08
0	1	.14440	36.10		
8 3 *N* mixtures of $LiNO_3 + Mg(NO_3)_2$					
1	0	0.14409	48.03		
$^3/_4$	$^1/_4$	.14032	46.77	46.87	0.10
$^1/_2$	$^1/_2$	.13679	45.59	45.72	.13
$^1/_4$	$^3/_4$	.13323	44.41	44.56	.15
0	1	.13120	43.40		
9.1 2 *N* mixtures of $Cu(NO_3)_2 + Cd(NO_3)_2$					
1	0	0.10664	53.32		
$^3/_4$	$^1/_4$	.10369	51.85	51.91	0.06
$^1/_2$	$^1/_2$	.10083	50.42	50.50	.08
$^1/_4$	$^3/_4$	.09805	49.03	49.08	.05
0	1	.09534	47.67		
9.2 3 *N* mixtures of $Cu(NO_3)_2 + Cd(NO_3)_2$					
1	0	0.12570	41.90		
$^3/_4$	$^1/_4$	.12146	40.49	40.51	0.02
$^1/_2$	$^1/_2$	.11728	39.09	39.11	.02
$^1/_4$	$^3/_4$	.11303	37.68	37.72	.04
0	1	.10896	36.32		
10.1 3 *N* mixtures of $Mg(NO_3)_2 + Cd(NO_3)_2$					
1	0	0.13120	43.40		
$^3/_4$	$^1/_4$	.12420	41.40	41.62	0.22
$^1/_2$	$^1/_2$	.11875	39.58	39.84	.26
$^1/_4$	$^3/_4$	.11373	37.91	38.05	.14
0	1	.10882	36.27		
10.2 5 *N* mixtures of $Mg(NO_3)_2 + Cd(NO_3)_2$					
1	0	0.14555	29.11		
$^3/_4$	$^1/_4$	.13102	26.20	27.05	0.75
$^1/_2$	$^1/_2$	.12119	24.24	24.99	.75
$^1/_4$	$^3/_4$	.11000	22.00	22.92	.92
0	1	.10432	20.86		
11 4 *N* mixtures of $Zn(NO_3)_2 + Cd(NO_3)_2$					
1	0	0.14440	36.10		
$^3/_4$	$^1/_4$	.13549	33.87	33.99	0.12
$^1/_2$	$^1/_2$	.12683	31.71	31.88	.17
$^1/_4$	$^3/_4$	.11808	29.52	29.77	.25
0	1	.11068	27.67		
12 3 *N* mixtures of $KNO_3 + Al(NO_3)_3$					
1	0	0.21019	70.06		
$^3/_4$	$^1/_4$	.19026	60.09	61.75	1.66
$^1/_2$	$^1/_2$	.15467	51.56	53.44	1.88
$^1/_4$	$^3/_4$	.12971	43.24	45.13	1.89
0	1	.11045	36.82		
13 4 *N* mixtures of $LiNO_3 + Al(NO_3)_3$					
1	0	0.16168	40.42		
$^3/_4$	$^1/_4$	.14832	37.08	37.36	0.28
$^1/_2$	$^1/_2$	.13567	33.92	34.30	.38
$^1/_4$	$^3/_4$	.12339	30.85	31.25	.40
0	1	.11276	28.19		
14 2 *N* mixtures of $KNO_3 + Cr(NO_3)_3$					
1	0	0.15857	79.29		
$^3/_4$	$^1/_4$	.13537	67.69	68.46	0.77
$^1/_2$	$^1/_2$	.11395	56.98	57.64	.66
$^1/_4$	$^3/_4$	.08986	44.93	46.81	1.88
0	1	.07198	35.99		
15 3 *N* mixtures of $Zn(NO_3)_2 + Al(NO_3)_3$					
1	0	0.13446	44.82		
$^3/_4$	$^1/_4$	.12701	42.34	42.82	0.48

TABLE I (*Concluded*)

Composition x	$1-x$	Specific conductivity	Equivalent conductivity Measured	Equivalent conductivity Calculated	$-\Delta\Lambda$
$^1/_2$	$^1/_2$	.12116	40.39	40.82	.43
$^1/_4$	$^3/_4$	.11334	37.78	38.82	1.04
0	1	.11045	36.82		
16 4 N mixtures of $Cd(NO_3)_2 + Al(NO_3)_3$					
1	0	0.11068	27.67		
$^3/_4$	$^1/_4$	.11120	27.80	27.80	0.00
$^1/_2$	$^1/_2$	.11144	27.86	27.93	.07
$^1/_4$	$^3/_4$	.11186	27.97	28.06	.09
0	1	.11276	28.19		
17.1 2 N mixtures of $Cd(NO_3)_2 + Cr(NO_3)_3$					
1	0	0.09562	47.81		
$^3/_4$	$^1/_4$	.09034	45.17	44.76	−0.41
$^1/_2$	$^1/_2$	.08498	42.49	41.71	− .78
$^1/_4$	$^3/_4$	.07752	38.76	38.65	− .11
0	1	.07119	35.60		
17.2 4 N mixtures of $Cd(NO_3)_2 + Cr(NO_3)_3$					
1	0	0.11040	27.60		
$^3/_4$	$^1/_4$	.11170	27.92	27.25	−0.67
$^1/_2$	$^1/_2$	.11181	27.95	26.89	−1.06
$^1/_4$	$^3/_4$	.10963	27.43	26.54	−0.89
0	1	.10471	26.18		
18.1 1 N mixtures of $Al(NO_3)_3 + Cr(NO_3)_3$					
1	0	0.06264	62.64		
$^3/_4$	$^1/_4$	.05797	57.97	57.63	−0.34
$^1/_2$	$^1/_2$	.05349	53.49	52.62	− .77
$^1/_4$	$^3/_4$	.04828	48.28	47.61	− .67
0	1	.04260	42.60		
18.2 2 N mixtures of $Al(NO_3)_3 + Cr(NO_3)_3$					
1	0	0.09647	48.24		
$^3/_4$	$^1/_4$	.09207	46.04	45.08	−0.96
$^1/_2$	$^1/_2$	.08617	43.09	41.96	−1.13
$^1/_4$	$^3/_4$	.07997	39.99	38.82	−1.17
0	1	.07136	35.68		
18.3 4 N mixtures of $Al(NO_3)_3 + Cr(NO_3)_3$					
1	0	0.11232	28.08		
$^3/_4$	$^1/_4$	.11380	28.45	27.54	−0.91
$^1/_2$	$^1/_2$	.11413	28.53	26.99	−1.54
$^1/_4$	$^3/_4$	.11010	27.52	26.45	−1.07
0	1	.10361	25.90		
19 2 N mixtures of $HNO_3 + KNO_3$					
1	0		(289.80)		
$^1/_2$	$^1/_2$	0.36682	183.42	184.59	1.17
$^2/_5$	$^3/_5$	.31319	156.59	163.54	6.95
$^1/_4$	$^3/_4$	.25680	128.40	131.97	3.57
$^1/_5$	$^4/_5$	.23726	118.63	121.44	2.81
0	1	.15879	79.37		
20 2 N mixtures of $HNO_3 + Cd(NO_3)_2$					
1	0		(289.80)		
$^1/_2$	$^1/_2$	0.32599	163.00	168.83	5.83
$^2/_5$	$^3/_5$	.27131	135.66	144.63	8.97
$^1/_4$	$^3/_4$	.20242	101.21	108.30	7.09
$^1/_5$	$^4/_5$	.18164	90.82	96.24	5.42
0	1	.09572	47.86		

Discussion

In all the mixtures, except those of chromium nitrate with cadmium nitrate and of chromium nitrate with aluminum nitrate, the conductivity calculated according to the mixture rule is larger than the measured conductivity. As previously observed with other types of mixtures, the maximum difference between measured and calculated conductivities in a series of given total equivalent concentration follows the same trend as the difference between the conductivities of the pure salts. This is shown in Table II where the various groups of mixtures are classified according to the value of the difference λ between the conductivities of the pure salts, $\Delta\Lambda$ being the largest departure from the mixture rule in the series. If one excludes the mixtures of chromium nitrate with cadmium and aluminum nitrates and those containing nitric acid, Table II could be combined with the corresponding tables of our previous papers. We note, however, that $\Delta\Lambda$ for 1 N mixtures of $KNO_3 + NaNO_3$ is larger than for the 1 molal mixtures previously studied.

TABLE II

N	Mixtures	λ	$-\Delta\Lambda$
2	$HNO_3 + Cd(NO_3)_2$	241.94	8.97
2	$HNO_3 + KNO_3$	210.43	6.95
2	$KNO_3 + Cr(NO_3)_3$	43.30	1.88
3	$KNO_3 + Cd(NO_3)_2$	33.80	2.32
3	$KNO_3 + Al(NO_3)_3$	33.24	1.89
2	$KNO_3 + Cd(NO_3)_2$	32.12	1.94
1	$KNO_3 + Cd(NO_3)_2$	30.06	2.11
3	$KNO_3 + Cu(NO_3)_2$	28.10	1.95
2	$KNO_3 + Cu(NO_3)_2$	26.32	1.47
3	$KNO_3 + Zn(NO_3)_2$	25.24	0.66
1	$Al(NO_3)_3 + Cr(NO_3)_3$	20.04	− .77
1	$KNO_3 + NaNO_3$	16.69	.85
3	$KNO_3 + NaNO_3$	16.58	.48
2	$KNO_3 + NaNO_3$	16.15	.65
5	$LiNO_3 + Cd(NO_3)_2$	12.96	.79
2	$Al(NO_3)_3 + Cr(NO_3)_3$	12.56	−1.17
4	$LiNO_3 + Al(NO_3)_3$	12.23	0.40
2	$Cd(NO_3)_2 + Cr(NO_3)_3$	12.21	− .78
3	$LiNO_3 + Cd(NO_3)_2$	12.04	.28
4	$Zn(NO_3)_2 + Cd(NO_3)_2$	8.43	.25
5	$Mg(NO_3)_2 + Cd(NO_3)_2$	8.25	.92
3	$Zn(NO_3)_2 + Al(NO_3)_3$	8.00	1.04
3	$Mg(NO_3)_2 + Cd(NO_3)_2$	7.13	0.26
5	$NaNO_3 + LiNO_3$	5.83	.39
2	$Cu(NO_3)_2 + Cd(NO_3)_2$	5.65	.08
3	$Cu(NO_3)_2 + Cd(NO_3)_2$	5.58	.04
3	$LiNO_3 + Mg(NO_3)_2$	4.63	.15
4	$LiNO_3 + Zn(NO_3)_2$	4.32	.08
4	$Al(NO_3)_3 + Cr(NO_3)_3$	2.18	−1.54
4	$Cd(NO_3)_2 + Cr(NO_3)_3$	1.42	−1.06
4	$Cd(NO_3)_2 + Al(NO_3)_3$	0.52	0.09

The behavior of the $Cr(NO_3)_3 + Cd(NO_3)_2$ and $Cr(NO_3)_3 + Al(NO_3)_3$ mixtures seems abnormal, particularly in 4 N solutions where some mixtures exhibit larger conductivities than those of the two pure salts. We have noticed that the slope of the conductivity curve of $Cr(NO_3)_3$ is, at least in the range of concentrations here studied, appreciably smaller than the slopes for the other nitrates, these being all nearly equal. When the conductivities of $Cr(NO_3)_3$ and of the other salt in the mixture are nearly equal, there is a positive $\Delta\Lambda$ due to this difference in the slopes. When the conductivities are quite different, as in the 2 N mixtures with KNO_3, $\Delta\Lambda$ is negative because the effect of this difference is larger than that of the difference in the slopes.

On account of the very large difference between the conductivity of pure nitric acid and that of KNO_3 or $Cd(NO_3)_2$ we would expect $-\Delta\Lambda$ to be much larger than is observed. We found in our previous work that, with salts, a difference of 100 in Λ corresponds to a $\Delta\Lambda$ of 14 to 16. The abnormal behavior of mixtures containing acids was pointed out in one of our papers and is evidently connected with the peculiar mechanism of proton conductivity. A common ion effect on the degree of ionization of nitric acid would tend to increase the lowering of the conductivity with respect to the mixture rule. Such an effect is to be expected, whether we accept Rao's[2] claim that nitric acid, alone among all nitrates, is incompletely dissociated, or whether we make the less drastic and more reasonable assumption that, at these high concentrations, nitric acid is less completely dissociated than the salts. The corresponding effect on the conductivity of mixtures containing nitric acid apparently is overshadowed to a certain extent by an effect in the opposite direction due to the adjustment of mobilities.

Strong evidence for the incomplete dissociation of nitrates is provided by Davies'[3a] recent analysis of Van Rysselberghe and Nutting's data[3b] on the conductivity of mixtures of KNO_3 with NaCl and of $NaNO_3$ with KCl. Davies gives a striking explanation for the fact that the calculated Λ's are smaller than the experimental values in the former group of mixtures, and larger in the latter. On the basis of dissociation constants previously obtained for KNO_3 and $NaNO_3$ he is able to calculate $\Delta\Lambda$ values in excellent agreement with the experimental ones.

Summary

1. Conductivities of twenty groups of binary mixtures of nitrates of uni-, di-, and trivalent cations have been measured at total equivalent concentrations ranging from 1 to 5 N.
2. All mixtures studied, except those of chromium nitrate with cadmium and aluminum nitrates, exhibit conductivities lower than the values calculated from the simple mixture rule. The departure from the mixture rule is the larger the larger the difference of the conductivities of the pure salts.
3. The behavior of mixtures containing chromium nitrate and of those containing nitric acid is briefly discussed.

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[2] Rao, *Proc. Roy. Soc.* (London), **A127**, 279 (1930).

[3] (a) Davies, *J. Chem. Soc.*, 448 (1938); (b) Van Rysselberghe and Nutting, This Journal, **59**, 333 (1937).

[CONTRIBUTION FROM THE LABORATORIES OF CHEMISTRY AND PHYSICS OF UNION COLLEGE]

Heats of Solution and Heats of Reaction in Liquid Ammonia. V.[1] The Alkali and Alkaline Earth Metals

BY FREDERIC C. SCHMIDT, FRANK J. STUDER AND JOSEPH SOTTYSIAK

In earlier papers in this series a liquid ammonia calorimeter has been described and results of measurements of heats of solution and reaction in liquid ammonia have been published.[2] In the present work, the heats of solution of the alkali and alkaline earth metals have been studied over a fairly wide range of concentrations. Kraus and Schmidt previously measured the heat of solution of metallic sodium in this solvent[2] and found it to have a negative heat of 1385 cal. Metallic lithium also has been studied, but only at quite low concentrations. In this paper the results of the heats of solution of lithium at higher concentrations are reported, as well as those of calcium, barium and strontium, and they show a markedly large change in the atomic heat effect with a change in concentration. Atomic heats of solution of the metals, potassium, rubidium and cesium have also been measured.

Experimental Details

A new calorimeter made of "Nonex" glass was used in these experiments. This instrument was the same in all details as the one described by Kraus and Schmidt.[2] The calorimeter constant was determined experimentally by introducing a known amount of heat into water in the calorimeter and noting the difference in the heat introduced and that taken up by the water at 20°. Allowing for the change in the specific heat of the glass with the temperature, this reduces to 9.16 cal. per degree at the boiling point of liquid ammonia. Uncertainties in this value do not affect the precision of the results, as the temperature changes are, for the most part, very small. The radiation constant of the calorimeter was determined and found to be 0.10 cal. per degree per minute. This correction was generally insignificant, due to the short duration of the determinations. The amount of ammonia used in all the determinations was 29.80 g., which was corrected for the ammonia vaporized due to the heat evolved. The following constants were employed: specific heat of ammonia at the boiling point 1.067 cal./deg.,[3] heat of vaporization 327.7 cal./g.[4] In the case of the metals potassium, rubidium and cesium, whose heat effects were zero, the current in the battery circuit of the Queen potentiometer was diminished by means of a resistance so as to spread out the scale readings and catch any small temperature change that might have occurred. The temperature change in all of these measurements was zero to an accuracy of 0.005°.

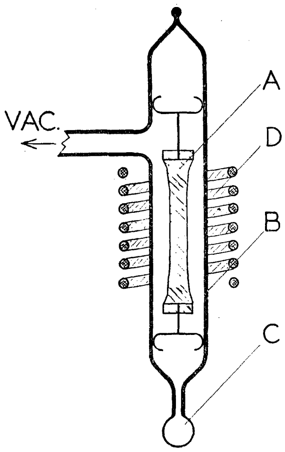

Fig. 1.

Preparation of the Metals.—The metals rubidium and cesium were reduced from their respective chlorides by granulated metallic calcium in the apparatus shown in Fig. 1. Twenty-five grams of the chloride was quickly and thoroughly mixed in an atmosphere of dry air with approximately 5% more than an equivalent of the calcium and put into a pure nickel tube (A), the ends of which were folded over. The charged tube was introduced into the apparatus at (B) and supported by nickel wire springs. The apparatus was then sealed off at the top and immediately evacuated. The glass was heated with a hand torch during the evacuation so as to degas the interior as thoroughly as possible. Coil (D) from an induction furnace was used to heat the nickel tube to red heat in order to initiate the reaction. Sufficient heat was maintained by the reaction to carry the reduction to completion. Both rubidium and cesium distilled and exuded from the seams of the nickel tube, free from unreacted salts and calcium chloride, and ran down into the fragile bulb (C) which was then sealed off. The metals were then redistilled into weighed fragile bulbs to be used for the heat measurements. Yields ranging from 35 to 45% were obtained in the case of both metals. Chemical examination of these metals showed no impurities. The potassium used was twice distilled. The lithium and the alkaline earth metals were better than 99.5% pure. In an atmosphere of dry hydrogen, these metals were cut into as large pieces as were permitted by the size of the capillary tubes on the fragile bulbs. The metals were free of their respective nitrides and oxides.

Experimental Results

The heats of solution of lithium, potassium, rubidium and cesium are presented in Table I, and those of the alkaline earth metals, calcium, barium and strontium, in Table II.

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(1) This present investigation was made possible by a Grant-in-Aid from the Society of the Sigma Xi and the Warren Fund of the American Academy of Arts and Sciences.

(2) C. A. Kraus and J. A. Ridderhof, THIS JOURNAL, **56**, 79 (1934); Kraus and Prescott, *ibid.*, **56**, 86 (1934); Kraus and Schmidt, *ibid.*, **56**, 2297 (1934); Schmidt, Sottysiak and Kluge, *ibid.*, **58**, 2509 (1936).

(3) Osborne and Van Dusen, Bureau of Standards, Scientific Paper No. 313, issued Dec. 13, 1917; THIS JOURNAL, **40**, 1 (1918).

(4) Roy Overstreet and W. F. Giaugue, *ibid.*, **59**, 254 (1937).

TABLE I

ATOMIC HEATS OF SOLUTION OF METALLIC LITHIUM, POTASSIUM, RUBIDIUM AND CESIUM

Wt., g.	Moles NH_3 per atom	Obsd. ht. effect, cal.	Atomic heat effect, cal.
	(A) Lithium		
0.1056	102.8	120.9	7961
.1769	67.6	202.9	7962
.2953	39.7	346.6	8144
.4100	28.2	487.9	8260
.4822	23.6	585.1	8421
.5448	20.9	646.4	8380
	(B) Potassium		
1.2918	52.9	0.00	0.0
1.7200	39.8	.00	.0
	(C) Rubidium		
0.4837	309.6	0.00	0.0
.6375	233.7	.00	.0
1.0689	139.6	.00	.0
	(D) Cesium		
1.0800	215.2	0.00	0.0
3.3963	68.4	.00	.0

TABLE II

ATOMIC HEATS OF SOLUTION OF CALCIUM, BARIUM AND STRONTIUM

Sample	Moles NH_3 per atom	Observed ht. effect, cal.	Atomic ht. of soln., cal.
	(A) Calcium		
0.1907	366.0	46.47	9,764
.2470	282.0	62.36	10,116
.2779	251.0	74.77	10,780
	(B) Barium		
0.3850	621.0	30.90	11,024
.5477	435.0	50.03	12,547
.7469	319.0	77.53	14,258
.9011	262.0	93.80	14,298
1.3658	173.0	160.32	16,124
	(C) Strontium		
0.3000	507.0	59.40	17,351
.3831	397.0	78.44	17,940
.6606	248.0	125.98	18,200
.9720	155.0	214.90	19,380

Discussion

As will be noted upon examination of Figs. 2 and 3, the atomic heats of solution of lithium and the alkaline earth metals vary regularly over the range of concentrations measured, decreasing with a decrease in concentration. The high heats of solution of these metals are due, in part, to a heat of reaction to form an ammoniated metal ion. The other metals measured, potassium, rubidium and cesium, do not form solvated ions. The atomic heats of solution of lithium and calcium in liquid ammonia were calculated by Kraus from vapor pressure measurements and found to be 8698 and 10,230 cal., respectively, for their saturated solutions at 0°.[5] Our measurements of these metals were made at the boiling point of the solvent and in the concentrated region agree very well in magnitude with the calculated values at the higher temperatures.

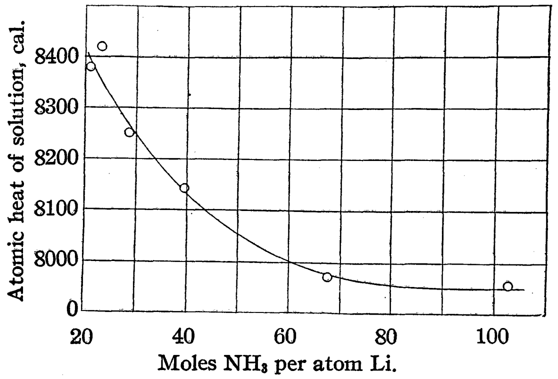

Fig. 2.—Atomic heats of solution of lithium in anhydrous liquid ammonia.

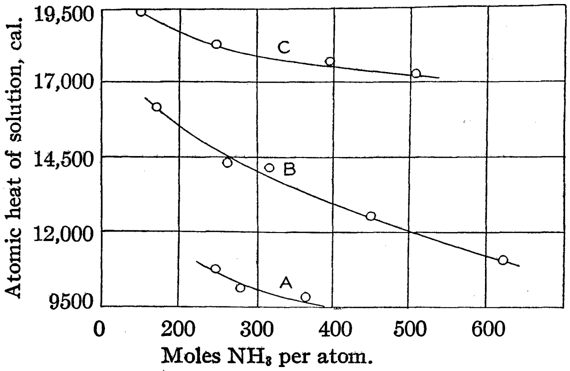

Fig. 3.—Atomic heats of solution of calcium, barium, and strontium.

In the case of the solution of metallic calcium in anhydrous liquid ammonia two phases are formed, one of which is quite dilute and one of which is quite concentrated.[5] There are no data regarding such happening in the case of the metals barium and strontium, but in all probability similar two phase systems are formed. It would seem that such a phenomenon would show as a break in the atomic heat of solution–concentration curves of these metals. Examination of these curves in Fig. 3 shows that apparently such is not the case in the region of the concentrations studied.

Summary

A method is described for the extraction of pure rubidium and cesium from their respective halides in good yields.

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(5) C. A. Kraus, THIS JOURNAL, **30**, 653 (1908).

The atomic heats of solution of potassium, rubidium and cesium have been measured over a fairly wide range of concentrations and found to be zero.

The atomic heats of solution of metallic lithium, calcium, barium and strontium have been measured over a range of concentrations and have been found to have a negative heat of dilution.

SCHENECTADY, N. Y. RECEIVED SEPTEMBER 29, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

The Kinetics and Mechanism of α-Aminoisobutyronitrile Formation

BY T. D. STEWART AND CHOH-HAO LI

Introduction

The α-amino nitriles are generally obtained by the reaction of equimolecular proportions of an alkali cyanide and an amine salt with an aldehyde or ketone in aqueous or aqueous alcoholic solution,[1] or by the reaction between equimolecular proportions of a cyanohydrin and an amine.[2] The main reaction is

$$R_2C(OH)CH + R_2NH \rightleftharpoons R_2C(NR_2)CN + H_2O \quad (1)$$

This equation implies that the oxygen is removed from the cyanohydrin and is replaced by the amino group directly; but in view of the following argument this path is extremely unlikely.

When a cyanohydrin is placed in an alkaline medium, such as a solution of an amine, the following equilibria are rapidly established

$$R_2C(OH)CN \rightleftharpoons R_2CO + HCN \quad (2)$$

$$HCN + R_2NH \rightleftharpoons R_2NH_2CN \rightleftharpoons R_2NH_2^+ + CN^- \quad (3)$$

The rapid appearance of cyanide ion demonstrates an apparent high reactivity of the carbon–cyanide bond in the cyanohydrin and shows the improbability of the hydroxyl group being dissociated or exchanged in alkaline solution. Ultee[3] showed that this reactivity was not a property of the cyanohydrin as such, because in acidic medium prussic acid was not formed.

The mechanism[4] of the dissociation in alkali can be expressed

$$R_2C(CN)OH + OH^- \rightleftharpoons R_2C(CN)O^- + H_2O \quad (4)$$

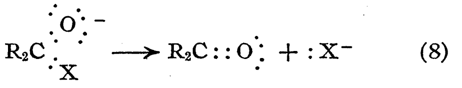
$$R_2C(CN)O^- \rightleftharpoons R_2CO + CN^- \quad (5)$$

in which both reactions are rapid and reversible. Equations (4) and (5) are of particular interest inasmuch as a similar effect of alkali has been noted in other cases, namely, aldehyde bisulfite and formocholine dissociations.

$$C_6H_5CH(SO_3)OH^- \xrightleftharpoons{-OH^-} C_6H_5CH(SO_3)O^= \longrightarrow C_6H_5CHO + SO_3^= + H_2O \quad (6)$$

$$(CH_3)_3\overset{+}{N}CH_2OH \xrightleftharpoons{-H^+} CH_3)_3\overset{+}{N}CH_2O^- \longrightarrow (CH_3)_3N + CH_2O \quad (7)$$

In each case[5] the rate of appearance of cyanide ion, sulfite ion or trimethylamine, respectively, is proportional to the hydroxide ion concentration which in turn governs the concentration of the intermediate ion. In each case the intermediate takes the form



$$R_2C\overset{:\ddot{O}:^-}{\underset{\cdot X}{:}} \longrightarrow R_2C::\ddot{O}: + :X^- \quad (8)$$

in which the electron pair bonding the radical X is replaced by an unshared electron pair of the charged oxygen; the dissociation is therefore a substitution reaction and not an ionization in the ordinary sense, and as such would be a relatively rapid reaction.[6] The alkaline catalysis of sugar mutarotation as well as alkaline catalysis of diacetone alcohol dissociation[7] may be represented similarly. It is clear that in an acidic medium the concentration of the intermediate ion would be reduced and hence the rate of dissociation inhibited; in alkali neither the cyanohydrin as such nor the intermediate ion could be expected to dissociate hydroxyl or react to replace it by the amine group.

A clue as to the path by which the oxygen (Eq. 1) is removed is given by the known reactions of the α-amino alcohols and their ethers. Lapworth and his co-workers[8] have pointed out

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[1] "Organic Syntheses," John Wiley and Sons, Inc., New York, 1931, Vol. XI, p. 4.

[2] Zelinski and Stadnikoff, *Ber.*, **39**, 1722 (1906).

[3] A. J. Ultee, *Rec. trav. chim.*, **28**, 248 (1909).

[4] A. Lapworth, *J. Chem. Soc.*, **85**, 1206 (1904).

[5] (a) T. D. Stewart and L. H. Donnally, THIS JOURNAL, **54**, 2333 (1932); (b) T. D. Stewart and H. P. Kung, *ibid.*, **55**, 4813 (1933).

[6] A. R. Olson, *J. Chem. Phys.*, **1**, 418 (1933).

[7] F. H. Westheimer and H. Cohen, THIS JOURNAL, **60**, 90 (1938).

[8] (a) W. Cocker, A. Lapworth and A. Walton, *J. Chem. Soc.*, **111**, 449 (1930). (b) T. D. Stewart and W. E. Bradley, THIS JOURNAL, **54**, 4172 (1932).

the capacity of the hydroxyl and alkoxyl groups in these substances to dissociate

$$R_2C(NR_2)OH + H^+ \rightleftharpoons R_2C{=}N^+R_2 + H_2O \quad (9)$$

The reaction conforms to the generalized intramolecular substitution reaction presented in Equation 8, and, unlike the cyanohydrin case, both the oxygen and nitrogen systems are susceptible to dissociation. It is evident that in the α-amino alcohols a means is to be found by which the oxygen of a ketone may be removed readily. We may therefore superimpose upon the system represented in Equations 2 and 3 the further reactions

$$R_2C{=}O + R_2NH \rightleftharpoons R_2C(OH)NR_2 \quad (10)$$

$$R_2C(OH)NR_2 + HCN \rightleftharpoons R_2C(CN)NR_2 + H_2O \quad (11)$$

$$R_2C(OH)NR_2 + R_2C(OH)CN \rightleftharpoons R_2C(CN)NR_2 + R_2C(OH)_2 \quad (12)$$

showing how the hydroxyl of the cyanohydrin is formally replaced by the amine group. Evidence favoring this viewpoint is presented below.

Experimental Results

The Rate Law in Acetone as a Solvent.—The rate of the reaction

$$(CH_3)_2C(OH)CN + (C_2H_5)_2NH \longrightarrow (CH_3)_2C(CN)N(C_2H_5)_2 + H_2O$$

was determined to be proportional to the concentration of each of the reactants in acetone solution. Tables I and II present typical data; *a* and *b* represent the concentration of acetonecyanohydrin and diethylamine, respectively, and k'' is the specific reaction rate constant as normally calculated for a second order reaction. In Table II the rate constant was calculated for each interval of time and shows no trend up to 65% of the total reaction, showing that the equilibrium lies far to the right in this solvent.

TABLE I

RATE OF REACTION USING DIFFERENT INITIAL CONCENTRATIONS AT 25°

a g. mole/l.	*b* g. mole/l.	Time sec. × 10^{-3}	% of *b* reacted	$k'' \times 10^5$ g. mole/l./sec.
0.1277	0.1277	86.4	11.95	1.225
.2554	.1277	43.2	11.80	1.174
.1277	.2554	43.2	6.05	1.211
.0487	.4756	22.2	1.25	1.233

TABLE II

RATE OF REACTION BETWEEN DIETHYLAMINE AND ACETONECYANOHYDRIN AT 25°; $a = b = 0.1277$

Time sec. × 10^{-3}	Per cent. reacted	$k'' \times 10^5$ g. mole/l./sec.
0.0	0.0	
86.4	11.95	1.225
175.2	21.62	1.276
262.8	29.20	1.218
376.8	37.38	1.266
585.0	48.26	1.248
1196.4	65.40	1.225
	Av.	1.243

Catalysis by Tertiary Amines.—When triethylamine or tri-*n*-propylamine is added to the reacting mixture of acetonecyanohydrin and diethylamine in acetone, the rate of the reaction is increased in proportion to the concentration of tertiary amine present, as shown in Fig. 1. If k''_t is the over-all bimolecular specific reaction rate constant we may write

$$k'' = k'' + mk''_c$$

where *m* is the molarity of the tertiary amine, k''_c the specific reaction rate constant of the catalyzed reaction, and k'' that of the uncatalyzed reaction. The rate law becomes

$$\text{Rate} = k''(a)\,(b) + k''_c(a)\,(b)\,(m)$$

as an expression of two independent rate determining steps. The data are summarized in Table III.

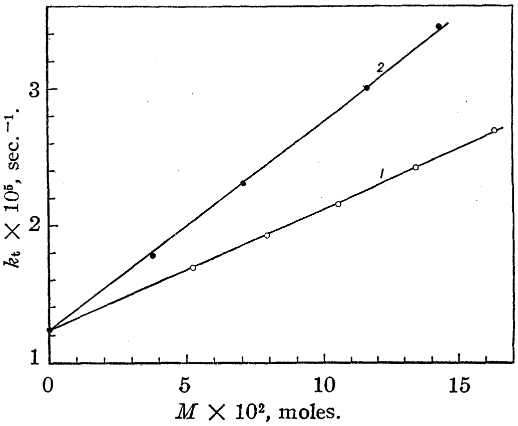

Fig. 1.—The catalytic effect of tertiary amines: 1, tri-*n*-propylamine; 2, triethylamine.

TABLE III

CATALYTIC EFFECT OF TERTIARY AMINES AT 25°

Triethylamine $k'' = 1.539 \times 10^{-4}$ 100*m*	$k''_t \times 10^5$	Tri-*n*-propylamine $k''_c = 8.890 \times 10^{-5}$ 100*m*	$k''_t \times 10^5$
0.000	1.240	0.000	1.240
3.799	1.783	5.245	1.690
7.078	2.355	7.940	1.930
11.620	3.037	10.560	2.162
14.300	3.457	13.430	2.428
		16.360	2.698

Catalysis by Alcohols.—Figure 2 and Table IV show the change in specific reaction rate when varying portions of ethanol are added to the ace-

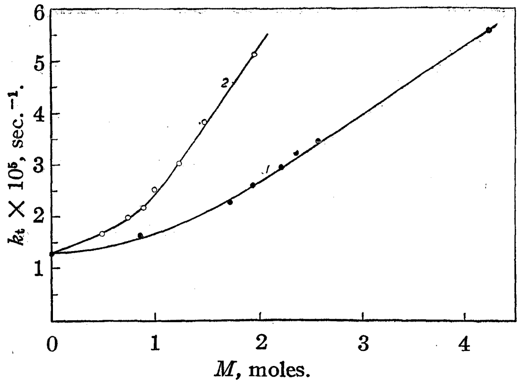

Fig. 2.—The catalytic effect of alcohols: 1, ethanol; 2, methanol.

tone solution. No correction was necessary for initial dissociation of the cyanohydrin (Eqs. 2 and 3) for the calculation of the rate constant, since the dissociation was negligible due to the high acetone concentration. In these solvents equilibrium is reached when the reaction has proceeded about 60%, so that for each solvent the equilibrium was determined and used in the calculation of the rate constant. Table V presents typical data in which k_t has been calculated, using the equation

$$dx/dt = k_t(a - x)(b - x) - k_2x^2$$

where k_t and k_2 are specific velocity constants of the forward and reverse reactions, respectively.

TABLE IV

CATALYTIC EFFECT OF ETHANOL AT 25°

Molality of ethanol	$k_t \times 10^5$
0.000	1.240
.855	1.618
1.352	1.948
1.712	2.260
1.931	2.588
2.205	2.942
2.372	3.207
2.570	3.450
4.240	5.579

TABLE V

TYPICAL KINETIC DATA IN ETHANOL-ACETONE MIXTURE AT 25°

Molality of ethanol: 4.240; equilibrium constant, K, 1.872; $a = 0.0925\ M$; $b = 0.925\ M$.

Time (sec. × 10^{-3})	X ($M \times 10^3$)	$k_t \times 10^5$ (g. mole/l./sec.)
00.0	0.00	
12.9	6.08	5.44
31.5	13.62	5.45
45.0	18.69	5.58
85.8	29.38	5.42
118.2	37.10	5.79
167.1	44.08	5.82
212.1	48.25	5.58

Methanol also shows the same effect on the rate as ethanol as shown numerically in Table VI and graphically in Fig. 2 (curve II). Addition of *t*-butyl alcohol does not affect the rate up to 3 *M* alcohol; dioxane up to 2 *M* has no effect upon the reaction rate in acetone.

TABLE VI

CATALYTIC EFFECT OF METHANOL AT 25°

Molality of methanol	$k_t \times 10^5$
0.000	1.240
.491	1.657
.734	1.972
.884	2.170
.983	2.525
1.225	3.003
1.475	3.820
1.950	5.115

The Rate Law in Alcohol. Catalysis by Acetone.—It is found in alcohol containing up to 1.4 *M* acetone that the rate constant calculated from the bimolecular rate law decreases as the initial concentration of the reactants increases. The rate of the reaction is actually independent of acetonecyanohydrin and at constant acetone concentration is proportional to the concentration of diethylamine as shown in Figs. 3 and 4. Since the acetone concentration is high,[9] the dissociation of cyanohydrin is small and may be considered to be constant over the small portion of the total reaction studied. The data are shown graphically in Figs. 3 and 4 where the logarithm of the diethylamine concentration is plotted against the time. The velocity constants, summarized in Table VII, were evaluated by multi-

TABLE VII

INITIAL CONCENTRATIONS AND REACTION RATES IN ALCOHOL SOLUTION. RATE DATA PLOTTED IN FIGS. 3, 4 AND 5

Run	a(Cyanohydrin) m./l.	b(Diethylamine) m./l.	c(Acetone) m./l.	$k'_t \times 10^6$
E_7	0.1058	0.1058	0.4160	3.38
E_{22}	.1062	.2124	.4170	....
E_{13}	.2155	.2155	.440	....
E_5	.1033	.1033	.1541	....
E_6	.2106	.2106	.1551	1.44
E_9	.2166	.2166	.1710	....
E_{17}	.2157	.2157	.6910	....
E_{23}	.1050	.1050	.6793	5.12
E_{18}	.2159	.1079	.6920	....
E_{19}	.2166	.2166	1.3680	9.67
E_{24}	.1059	.1059	1.3545	....
E_{16}	.2147	.2147	0.073(x.)	0.928
E_{20}	.2160	.1080	1.3500	....

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[9] In Expt. E16 no acetone was added; that present was due to dissociation of the cyanohydrin. The initial reaction rate only was calculated, as the acetone concentration was not constant in this case.

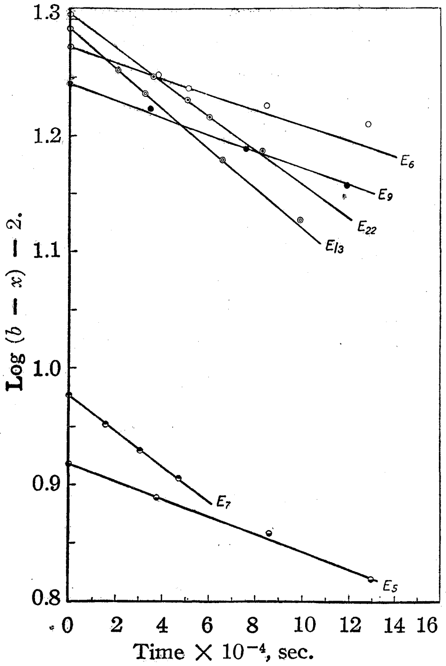


Fig. 3.—The reaction rate in ethanol.

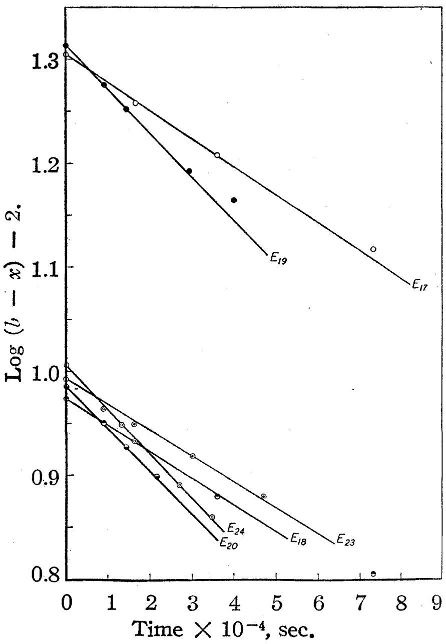


Fig. 4.—The reaction rate in ethanol.

plying the negative slopes of the straight lines by 2.303. In Fig. 5 the acetone concentration is plotted against the unimolecular rate constants of Table VII. The result indicates a reaction rate proportional to the acetone concentration.

Discussion of Results

Empirical rate laws have been obtained in solutions using acetone as solvent with varying amounts of alcohol present, and in solutions using alcohol as solvent with varying acetone content. For the first series the rate law found is

$$d(P)/dt = k''(\text{amine})(\text{cyanohydrin}) \qquad (A)$$

where P is the product of the reaction.

In ethanol as solvent a different rate law has been found

$$d(P)/dt = k'(\text{acetone})(\text{amine}) \qquad (B)$$

It is improbable that these rate laws should involve two fundamentally different mechanisms, and an attempt will be made to derive them from a simple mechanism.

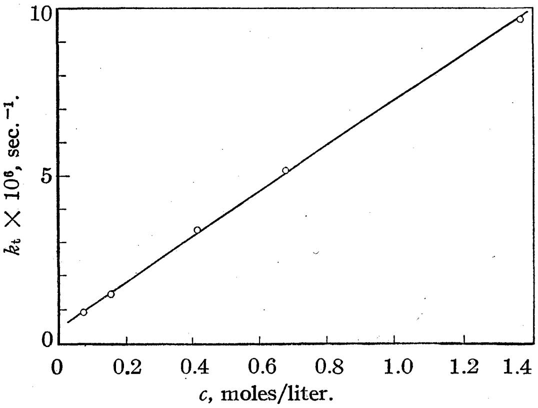


Fig. 5.—Effect of acetone concentration upon the specific reaction rate in alcohol.

The Reaction Mechanism.—Assume the existence of the reaction

$$R_2C{=}O + R_2NH \underset{k_2}{\overset{k_1}{\rightleftharpoons}} R_2C(OH)NR_2 \qquad (13)$$

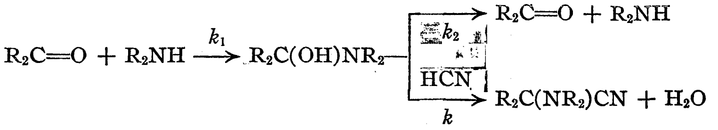
where k_1 is the specific rate of amino alcohol formation and k_2 its specific dissociation rate. We also assume that the mechanism of aminonitrile formation may be expressed

$$d(P)/dt = k(\text{amino alcohol})(\text{HCN}) \qquad (C)$$

The concentration of the hydrocyanic acid is determined by the equilibrium

$$R_2C(OH)CN \rightleftharpoons R_2C{=}O + HCN \qquad (14)$$

From these considerations the empirical rate laws above (Eqs. A and B) may be derived upon the additional assumptions that in acetone as a solvent the equilibrium between the amino alcohol, acetone and amine (Eq. 13) is maintained as the reaction proceeds, whereas in alcohol as a solvent the amino alcohol is no longer at its equilibrium concentration but a low steady state value. This value is determined largely by the acetone concentration. A low acetone concentration permits a higher hydrocyanic acid concentration (Eq. 14) and thereby decreases the probability that any amino alcohol formed will dissociate into its original constituents.



$$R_2C{=}O + R_2NH \xrightarrow{k_1} R_2C(OH)NR_2 - \begin{cases} \xrightarrow{k_2} R_2C{=}O + R_2NH \\ \xrightarrow[k]{HCN} R_2C(NR_2)CN + H_2O \end{cases}$$

The rates of appearance and disappearance of amino alcohol may be expressed

$$\mathrm{d(amino\ alcohol)}/\mathrm{d}t = k_1\mathrm{(acetone)(amine)}$$
$$-\mathrm{d(amino\ alcohol)}/\mathrm{d}t = k_2\mathrm{(amino\ alcohol)} + k\mathrm{(amino\ alcohol)\ (HCN)}$$

When the steady state is established, these rates are equal and

$$\mathrm{(amino\ alcohol)} = \frac{k_1\mathrm{(acetone)\ (amine)}}{k\mathrm{(HCN)} + k_2}$$

Therefore

$$\mathrm{d(P)}/\mathrm{d}t = \frac{k_1\mathrm{(acetone)\ (amine)\ (HCN)}}{k\mathrm{(HCN)} + k_2} \qquad \mathrm{(D)}$$

If k_2 is small and negligible in comparison with the factor k(HCN), Equation (D) becomes

$$\mathrm{d(P)}/\mathrm{d}t = k'\mathrm{(acetone)(amine)} \qquad \mathrm{(B)}$$

which is the empirically determined rate law, and implies that the major rate determining step is the rate of amino alcohol formation.

In acetone as the solvent, where the amino alcohol is maintained at or near its equilibrium concentration[10]

$$\mathrm{(amino\ alcohol)} = k_1/k_2\mathrm{(acetone)(amine)}$$

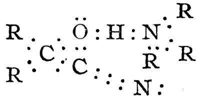
and from Equations C and 14

$$\mathrm{d(P)}/\mathrm{d}t = kk_1k_2\mathrm{(acetone)(amine)(HCN)} \qquad \mathrm{(E)}$$
$$= k''\mathrm{(amine)(cyanohydrin)} \qquad \mathrm{(A)}$$

It is thus possible to use a single reaction mechanism (Eq. C) involving amino alcohol and hydrocyanic acid over the whole range of mixed solvents, and yet account in a simple way for the observed change in the rate law from an apparent bimolecular form in pure acetone, to a pseudo-monomolecular law in alcohol as a solvent.

The Catalytic Effect of Tertiary Amines and Alcohols.—The factor described as (HCN) in the rate determining steps (Eq. C) was evaluated from Eq. 14 as the ratio: (cyanohydrin)/(acetone). An equally valid evaluation would be the ratio: (amine cyanide salt)/(amine). Actually, hydrocyanic acid is present not only as such, but in various solvated forms; the cyanohydrin itself as well as a tertiary amine salt could be considered as belonging to the solvated hydrocyanic acid species of molecule, and as such enter the rate law. Each such variation of hydrocyanic acid would contribute to the total reaction rate in a specific and characteristic way. From the slopes of the curves in Figs. 1 and 2 the catalytic constants in acetone for the alcohols and amines appear in the order: ethanol, 4.0; methanol, 8.0; tri-*n*-propylamine, 89; and triethylamine, 154.

It is striking that there is no evidence of the secondary amine (one of the reactants) taking the place of the tertiary amine (a catalyst) and thereby entering the rate law to the second power. A ten-fold excess of diethylamine was used to test this, and any adequate hypothesis of this catalytic action should consider it. It is obvious that as bases, the tertiary and secondary amines are nearly equivalent, but in one respect their complexes with acetone cyanohydrin are very different.



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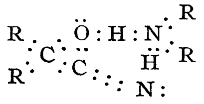
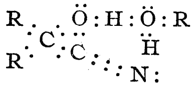


II



III

Formulas II and III present chelated complexes between the cyanohydrin and secondary amine and alcohol. In these cases, the presence of the protons from the secondary amine and alcohol, respectively, offers opportunity for completion of a ring structure through hydrogen bond formation between the cyanide group and the nitrogen or oxygen atoms. The corresponding tertiary amine structure is not chelated, and, as discussed in the Introduction, its formation would increase the reactivity of the cyanide residue and thereby increase the availability of cyanide for replacement of the hydroxyl group of the amino alcohol (Eqs. 11 and 12). Chelation in II would both stabilize the complex, and in case of rupture of the carbon–cyanide bond, effectively reduce the activity of the cyanide ion by its association with the amine residue. The alcohol complex, on the other hand,

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[10] The fact that pure acetone and diethylamine react only slightly to form the amino alcohol is indicated by the properties of their binary solution. Results of this study will appear in a separate communication.

is intermediate in its reactivity; as a chelated structure it might be reasonably stable and less reactive than the tertiary amine derivative; as an oxonium rather than an ammonium derivative it would offer a source of hydrocyanic acid far more reactive than the secondary amine complex. It is interesting that *t*-butyl alcohol and dioxane do not participate in this catalysis, a result which clearly indicates that these substances are no better proton acceptors than acetone, and very much poorer than the primary alcohols.[11]

The Reaction in Alcohol.—The pseudo first order reaction found in alcohol as a solvent is well supported. Doubling cyanohydrin concentration produces very little difference in the rate of the reaction, as measured by the slopes of the curves in Figs. 3 and 4. On the other hand, doubling the amine concentration doubles the actual rate but not the specific rate. Moreover, tertiary amines do not catalyze the reaction in alcohol, that is, under conditions where the rate determining step is primarily amino alcohol formation. Since the reaction probably comes to an equilibrium at close to 60% completion in alcohol, the measurements have been carried to but 25% in any one experiment. In Fig. 3, Curve E_{22}, there is evidence of a slower reaction than would be predicted from Curves E_7 and E_{13}, and this may be ascribed to the fact that amine is in excess in this experiment, with consequent increase in the steady state value of the amino alcohol concentration. The fact that in Fig. 5 where the specific reaction rate constant is plotted against the acetone concentration, the straight line does not pass through the origin, indicates that the steady state value of the amino alcohol concentration is not zero, but decreases relatively with decreasing acetone concentration. At any one acetone concentration k_2 is small compared to k_2 (HCN) as discussed above, and no interference arises with the apparent first order law. The accuracy of the data does not warrant an attempt to calculate specific values for k_1, k_2 and k_3 which would be required for a complete analysis.

Experimental

Materials.—The preparation of acetonecyanohydrin has been described already.[11] All amines were fractionated after standing over fused potassium hydroxide for at least one week. The fractions used distilled as follows: $(C_2H_5)_2NH$, 55.46° (corr.); $(C_2H_5)_3N$, 89.23° (corr.); and $(CH_3CH_2CH_2)_3N$, 156.47° (corr.). Acetone was refluxed for several days with solid potassium permanganate, distilled, dried over calcium chloride and fractionated in a 1-meter column of the Podbielniak type. The central fraction had a constant boiling point of 56.20° (corr.). Alcohols were treated as previously described.[11]

Experimental Procedure.—The diethylamine was dissolved in the dried solvent, pure acetone or acetone–alcohol mixtures, in known concentrations, and added to weighed portions of cyanohydrin in a thermostat. Aliquot parts of this solution were transferred at known time intervals to known volumes of 0.020 *M* silver nitrate in 0.20 *M* nitric acid solution and the mixture allowed to stand for an hour to complete the precipitation of silver cyanide. The latter was then filtered off, washed with water, and the filtrate titrated with standard thiocyanate using ferric alum as indicator. Accuracy in the end-point depends upon having an appreciable excess of silver nitrate in the filtrate and thorough removal of the precipitated silver cyanide.

The above analytical method for the determination of the amount of aminonitrile formed depends upon several factors. In the presence of appreciable acetone the cyanohydrin does not dissociate hydrocyanic acid, even in the presence of amines. In the solvents low in acetone allowance was made for such dissociation. Neither does the cyanohydrin lose cyanide ion to acidified silver nitrate. The rate at which aminonitrile loses cyanide ion depends upon the acidity. When the excess nitric acid is 0.05 *M*, half of a given amount of aminonitrile reacts in three minutes; when the excess acid is 0.13 *M* the half-life is about six and one-half minutes; no appreciable reaction occurs in 1 *M* nitric acid. It is important that no local concentration of alkali exist during the mixing of the alkaline reaction mixture and the acidified silver nitrate. To avoid this, vigorous stirring is employed and a concentration of acid greater than the concentration of amine is required.

Summary

The specific reaction rates of the reaction

$$(CH_3)_2C(CN)OH + (C_2H_5)_2NH \longrightarrow (CH_3)_2C(CN)N(C_2H_5)_2 + H_2O$$

have been measured in acetone and in alcohol as solvents, and the corresponding rate laws deduced. The two rate laws are, for the alcohol and acetone solvents, respectively

$$d(P)/dt = k'(\text{acetone})(\text{amine})$$
$$d(P)/dt = k''(\text{amine})(\text{cyanohydrin})$$

These have been shown to be related through a common reaction mechanism, and this in turn has been discussed from the general standpoint of the reactions of carbonyl systems.

BERKELEY, CALIF.

RECEIVED JULY 22, 1938

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[11] C. H. Li and T. D. Stewart, THIS JOURNAL, 59, 2596 (1937).

[Contribution from the School of Chemistry and Physics of the Pennsylvania State College]

The Reducing Action of Primary Grignard Reagents with Trimethylacetyl Chloride

By Frank C. Whitmore, R. E. Meyer, G. W. Pedlow, Jr., and A. H. Popkin

Recent studies have been made of the reducing action of Grignard compounds on acid chlorides.[1]

In the present work, the preparation of a series of secondary carbinols, for use in subsequent rearrangement studies, involved the addition of trimethylacetyl chloride to various primary Grignard reagents. The results, tabulated below, are in accord with previous reduction studies in this Laboratory.

Grignard reagent	% Yield of reduction products $(CH_3)_3CCH_2OH$	$(CH_3)_3CHOHR$
Ethyl[2]	None	69
n-Propyl	20	76
Isopropyl	23	53
n-Butyl[3]	28	71
Isobutyl	61	26
n-Amyl	20	75
Isoamyl[4]	15	71

The reduction of trimethylacetyl chloride to trimethylcarbinol by each of the Grignard reagents except ethyl is in sharp contrast to the failure to reduce *t*-butylacetyl chloride to neopentylcarbinol even by a tertiary Grignard reagent.[1] The obvious explanation that the reduction depends on the attachment of a tertiary group directly to the COCl group is unsound since *n*- and isobutyryl chlorides are reduced to the primary alcohols in 20 and 9% yields by *t*-butylmagnesium chloride.[1]

In these reactions, trimethylacetyl chloride was added to an excess of Grignard reagent. It has since been found that the reverse addition of a primary Grignard reagent to an excess of trimethylacetyl chloride produces carbinols in the form of the corresponding esters, with a marked change in the yield of reduction products. This is being investigated further.

Grignard solutions used in this study were filtered.

Experimental

The columns used were of the total condensation variable take-off type packed with single-turn glass helices. The dimensions (cm.) are of the packed portions: Column I, 45 × 0.9; II, 35 × 1.1; III, 43 × 0.5; IV, 67 × 1.3; V, 75 × 1.2.

Addition of Trimethylacetyl Chloride to Ethylmagnesium Bromide.—The ethylmagnesium bromide was prepared from 545 g. (5 moles) of ethyl bromide, b. p. 36° at 730 mm., $n^{20}D$ 1.4240, 121.5 g. (5 moles) magnesium and 900 cc. of dry ether. Addition of 181.5 g. (1.5 moles) of trimethylacetyl chloride, b. p. 57.6° at 150 mm., $n^{20}D$ 1.4125, prepared in 84% yield from thionyl chloride and trimethylacetic acid, required two and one-half hours for completion. The complex was then decomposed with ice, extracted with ether, and after removal of ether through column IV was fractionated through column I to give fractions: 1–3, 31.9 g. ether, b. p. 34–35° at 732 mm., $n^{20}D$ 1.3532; 4–5, 12.4 g., 50–130.5°, 1.4026–1.4205; 6, 14.6 g., 130.5–133°, 1.4218; 7–11, ethyl-*t*-butylcarbinol, 75.4 g., 133–134° at 732 mm., 1.4223–1.4225; 12, 9.8 g., 85–114° at 150 mm., 1.4292; 13–15, diethyl-*t*-butylcarbinol, 43.5 g., 114.5° at 150 mm., 1.4424–1.4427; residue 10 g.

Cut 4 on refractionation through column III gave: 16, 0.5 g., b. p. 33.5–60° at 735 mm., $n^{20}D$ 1.3696; 17, 1.5 g., 60–75°, 1.4057; 18, 1.1 g., 75–110°, 1.3825; 19, 0.6 g., 110°, 1.4142; residue 0.8 g. No indication of neopentyl alcohol could be found. The identity of fractions 6–13 was proved by m. p. and mixed m. p. of 109–110° for the α-naphthylurethan of ethyl-*t*-butylcarbinol. Fractions 13–15 were diethyl-*t*-butylcarbinol, b. p. 114.5° at 150 mm., $n^{20}D$ 1.4424, d^{20}_4 0.8524, in agreement with the constants given by Nasarow.[5]

Fraction 17 contained ethyl alcohol as shown by the m. p. and mixed m. p. of the 3,5-dinitrobenzoate, 93–94°.

Addition of Trimethylacetyl Chloride to *n*-Propylmagnesium Bromide.—The addition of 181.5 g. (1.5 moles) of trimethylacetyl chloride to 4.5 moles of *n*-propylmagnesium bromide in 1900 cc. of dry ether was completed in eighty minutes. The complex was decomposed with ice, extracted with ether, and the solvent removed through column IV. The product was then fractionated through column I to give: fractions 1–4, 59.8 g. ether, b. p. 32.5–42.0° at 739 mm., $n^{20}D$ 1.3529–1.3531; 5–7, 8.9 g., 45.0–107°, 1.3821–1.3953; 8, 3.2 g., 107–110°, 1.4010; 9–12, 24.1 g., 66.5–104° at 150 mm., m. p. 50°; 13–15, 19.0 g., 104–105.5° at 150 mm., 1.4245–1.4260; 16–20, 114.0 g., 105.5–106.5° at 150 mm., 1.4270–1.4276; residue 6.4 g.

Fractions 5–7 contained *n*-propyl alcohol as identified by the 3,5-dinitrobenzoate, m. p. and mixed m. p. 73–74°.

Fractions 8–12 were neopentyl alcohol, phenylurethan, m. p. and mixed m. p. 113–114°.

Fractions 13–20 were *n*-propyl-*t*-butylcarbinol, phenylurethan, m. p. and mixed m. p. 70.5–71.5°.

Addition of Trimethylacetyl Chloride to Isopropylmagnesium Bromide.—The addition of 181.5 g. (1.5 moles) of trimethylacetyl chloride to 4.5 moles of isopropylmagnesium bromide in 900 cc. of dry ether required three

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[1] Greenwood, Whitmore and Crooks, This Journal, **60**, 2028 (1938); Whitmore and co-workers, *ibid.*, **60**, 2030, 2458, 2462 (1938).

[2] A 20% yield of diethyl-*t*-butylcarbinol was formed as the high boiling fraction.

[3] Yields in this reaction checked with those previously reported.[1]

[4] 7% of olefin, corresponding to the dehydrated tertiary carbinol was also found.

[5] Nasarow, *Ber.*, **69**, 21–24 (1936).

hours. The product was decomposed and extracted in the usual manner and fractionated through column V to give: fractions 1, ether, b. p. 35–36° at 743 mm., $n^{20}\text{D}$ 1.3535; 2–7, 9.6 g., 43–99°, 1.3574–1.3840; 8–12, 30.3 g., 111° at 743 mm. and 73–75° at 150 mm., m. p. 50°; 13–14, 5.9 g., 81–96° at 150 mm., 1.4108–1.4212; 15–16, 11.6 g., 98–100° at 150 mm., 1.4277–1.4285; 17–25, 93.5 g., 100° at 150 mm., 1.4290–1.4295; residue 8.2 g.

Fractions 4–6 contained isopropyl alcohol as identified by the phenylurethan, m. p. and mixed m. p. 89–90°.

Fractions 8–12 were neopentyl alcohol, phenylurethan, m. p. and mixed m. p. 113–114°.

Fractions 15–25 were isopropyl-*t*-butylcarbinol, phenylurethan, m. p. and mixed m. p. 86–86.5°.

Addition of Trimethylacetyl Chloride to Isobutylmagnesium Bromide.—Addition of 181.5 g. (1.5 moles) of trimethylacetyl chloride to 4.5 moles of isobutylmagnesium bromide was completed in three hours. The complex was decomposed and extracted in the usual manner and fractionated through column V to give: fractions 1, ether, b. p. 34–35° at 735 mm., $n^{20}\text{D}$ 1.3535; 2–9, 13.3 g., 52–104°, 1.3574–1.3952; 9–18, 81.4 g., 106–111 and 76° at 150 mm., m. p. 50°; 19–20, 3.2 g., b. p. 100–109° at 150 mm., 1.4131–1.4212; 21–22, 12.2 g., 110–111° at 150 mm., 1.4270–1.4293; 23–27, 43.2 g., 111–112° at 150 mm., 1.4299–1.4302; residue 5.8 g.

Fractions 5–8, 7.8 g., contained isobutyl alcohol, phenylurethan, m. p. and mixed m. p. 83–84°.

Fractions 9–18 were neopentyl alcohol, phenylurethan, m. p. and mixed m. p. 113–114°.

Fractions 21–27 were isobutyl-*t*-butylcarbinol, phenylurethan, m. p. and mixed m. p. 112–112.5°, α-naphthylurethan, m. p. and mixed m. p. 103.5–104.5°.

Addition of Trimethylacetyl Chloride to *n*-Amylmagnesium Bromide.—The addition of 181.5 g. (1.5 moles) of trimethylacetyl chloride to 4.5 moles of *n*-amylmagnesium bromide in 1900 cc., of dry ether was completed in two hours. The complex obtained was decomposed with ice, extracted with ether, the solvent being removed through column IV and the product on fractionation through column II gave: fraction 1–2, 17.5 g. ether, b. p. 32–55.0° at 741 mm., $n^{20}\text{D}$ 1.3535–1.3545; 3–5, 26.9 g., 55–127.0°, solid; 6, 9.6 g., 127.0–176.5°, 1.4171; 7, 4.7 g., 39–61.5° at 18 mm., 1.4340–1.4342; 8–13, 22.1 g., 61.5–86.0° at 18 mm., 1.4176–1.4332; 14–17, 77.7 g., *n*-amyl-*t*-butylcarbinol, 86.0–88.0° at 18 mm., 1.4340–1.4342; 18–19, 62.3 g., b. p. 85–89° at 17 mm., 1.4345–1.4346; 20–23, 10.2 g., 85.0–134.0° at 14 mm., 1.4360–1.4484; residue 6.8 g.

Fractions 3–5 were neopentyl alcohol, identified by the phenylurethan, m. p. and mixed m. p. 113–114°.

Fractions 6–7 failed to produce any evidence of *n*-amyl alcohol. This fraction is probably a mixture of neopentyl alcohol, *n*-amyl alcohol, and the secondary alcohol (*n*-amyl-*t*-butylcarbinol).

Fractions 8–13 and 18–23 on refractionation through column I gave: fractions 24–25, 13.1 g., b. p. 42–67.8° at 7 mm., $n^{20}\text{D}$ 1.4199–1.4294; 26–30, 56.4 g., 67.8–72.5° at 7 mm., 1.4336–1.4348; residue 4.4 g.

Fractions 14–17 and 26–30 were *n*-amyl-*t*-butylcarbinol: *MR* found 49.80, calcd. 49.92.

Addition of Trimethylacetyl Chloride to Isoamylmagnesium Bromide.—The addition of 181.5 g. (1.5 moles) of trimethylacetyl chloride to 4.5 moles of isoamylmagnesium bromide required two hours. The complex was decomposed and extracted in the usual manner and fractionated through column I, to give: fractions 1–3, 25.3 g., ether, b. p. 34–35° at 742 mm., $n^{20}\text{D}$ 1.3535; 4–7, 26.8 g., 84–113° and 62–81.5° (150 mm.), 1.4000–1.4047; 8–12, 31.6 g., 81.5–128° at 150 mm., 1.4060–1.4130; 13–15, 50 g., 128–133.2° at 150 mm., 1.4284–1.4319; 16–18, isoamyl-*t*-butylcarbinol, 80.3 g., 133.2–133.5° at 150 mm., 1.4320–1.4323; 19–20, 31.9 g., 133.5–134° at 150 mm., 1.4325; 21–22, 24.4 g., 99–108° at 18 mm., 1.4407–1.4410; residue 1.6 g.

Fractions 4–7 were refractionated through column III to give: fractions 23–27, 3.4 g., b. p. 33–107° at 735 mm., $n^{20}\text{D}$ 1.3540–1.4080; 28–29, 20.5 g., 107–126°, solid; residue 2.2 g.

Fractions 8–12 were refractionated through column III to give: fractions 30–32, 8.4 g., b. p. 73–101 at 150 mm., $n^{20}\text{D}$ 1.4072–1.4080; 33–37, 14.2 g., 101–105.5° at 150 mm., 1.4098–1.4100; residue 1.7 g.

Fractions 30–32 contained isoamyl alcohol, phenylurethan, m. p. and mixed m. p. 54°.

Fractions 28–29 were neopentyl alcohol, phenylurethan, m. p. and mixed m. p. 113–114°.

Fractions 33–37 were olefins formed by the dehydration of isoamyl-*t*-butylcarbinol, d^{20}_4 0.7278; *MR* calcd. 47.43; found 47.37.

Fractions 13–20 were isoamyl-*t*-butylcarbinol d^{20}_4 0.8236; *MR* calcd. 49.92, found 49.74.

Fractions 21–22 were olefins from the dehydration of diisoamyl-*t*-butylcarbinol, d^{20}_4 0.7772; *MR* calcd. 71.03, found 71.34.

Summary

1. The reducing action of Grignard reagents with acid chlorides has been studied further by the addition of trimethylacetyl chloride to the Grignard reagents of ethyl, *n*- and isopropyl, *n*- and isobutyl and *n*- and isoamyl.

2. Neopentyl alcohol was obtained with all except the ethylmagnesium bromide. Even the latter gave reduction as represented by a 68% yield of ethyl-*t*-butylcarbinol.

State College, Penna.
Received August 23, 1938

[Contribution from the School of Chemistry and Physics of The Pennsylvania State College]

The Action of Primary Grignard Reagents with *t*-Butylacetyl Chloride. II[1]

By Frank C. Whitmore, J. S. Whitaker, K. F. Mattil and A. H. Popkin

This is a continuation of the studies in this Laboratory on the reducing action of Grignard reagents.[2]

In the first paper of this title[1] the acid chloride was added to excess of Grignard solutions. The chief products isolated were tertiary alcohols of the type $(CH_3)_3CCH_2C(OH)R_2$ in which R was ethyl, *n*-propyl, *n*-butyl, or *n*-amyl, and the corresponding olefins $(CH_3)_3CCH{=}CR_2$ and their isomers. The other products were secondary carbinols of the type $(CH_3)_3CCH_2CHOHR$, in which R was *n*-propyl, *n*-butyl, or *n*-amyl. No reduction product of this type was found when ethylmagnesium bromide was used.

In the present study each of the four Grignard solutions was added to a slight excess of *t*-butylacetyl chloride in anhydrous ether.

Ethylmagnesium bromide gave the largest amount of the primary product, the ketone of the type $(CH_3)_3CCH_2COR$, giving about 51% of neopentyl ethyl ketone. The *n*-propyl, *n*-butyl, and *n*-amyl Grignard reagents gave 37, 34, and 29%, respectively, of the corresponding ketones.

Reduction by means of the Grignard reagent would convert these ketones to secondary carbinols $(CH_3)_3CCH_2CHOHR$. These would appear as the *t*-butylacetates. About 7% of such reduction took place with the ethyl Grignard solution. This is in contrast to the result of adding the acid chloride to the ethyl Grignard solution which gave no reduction.[1] The other three Grignard solutions gave about 20, 23, and 21% of the corresponding secondary alcohols as the *t*-butylacetates.

It is significant that these yields are nearly the same as those obtained by adding the acid chloride to an excess of the Grignard reagents.[1] As in the earlier experiments no trace of neopentylcarbinol or its ester was found even by extended searches. This is in contrast to the action of trimethylacetyl chloride which gives neopentyl alcohol in about 20% yields with *n*-propyl, *n*-butyl, and *n*-amyl Grignard reagents.[2]

A small amount of ethyl *t*-butylacetate was found in each of the four reactions. This was due apparently to interaction of the acid chloride with the solvent ether.

The Grignard solutions used were filtered from free magnesium under nitrogen pressure.

Experimental

The *t*-butylacetyl chloride, b. p. 76–77° at 140 mm., n^{20}_D 1.4212, used in these reactions was prepared, in 86% yield, from *t*-butylacetic acid and thionyl chloride.

The Grignard compounds were prepared from the corresponding alkyl bromides, magnesium, and dry ether in the usual way. They were filtered and titrated.

Addition of Ethylmagnesium Bromide to *t*-Butylacetyl Chloride.—Ethylmagnesium bromide (1.84 moles in 1 liter of ether) was added to 250 g. (1.86 moles) of *t*-butylacetyl chloride in 1200 cc. of ether, during fifty minutes. After standing overnight, the complex was decomposed with ice, extracted with ether, and the products after removing most of the solvent using column XII[3] were fractionated through column XI, using a solid carbon dioxide trap, to give: nos. 1–5, 71.4 g., b. p. 98–100° at 200 mm., n^{20}_D 1.4150–1.4163; residue 130 g.; trap contents 68 g. All fractions contained water, indicating dehydration.

The trap contents with nos. 1–5 were refractionated through column XI to give: 6, 27.5 g., 35° at 736 mm., 1.3580; 7, 1.4 g., 133°, 1.4060; 8–12, 46.5 g., 143°, 1.4150–1.4160. The main residue was added and fractionation continued to give: 13–22, 101.2 g., 62–110° at 23–74 mm., 1.4120–1.4163; 23–24, 14.5 g., 118° at 23 mm., 1.4253–1.4263; 25–27, 15.7 g., 118–135° at 23 mm., 1.4323–1.4500; residue 5 g.

Fractions 6–22, 25–27, and the residue were again refractionated, by parts, through column XI to give: 28–37, 123.2 g., 92° at 150 mm., 1.4130–1.4160; 38, 4.2 g., 105–134° at 150 mm., 1.4175; 39, 7.0 g., 134° at 150 mm., 1.4130; 40–43, 20.0 g., 124–166° at 90 mm., 1.4152–1.4500; residue 6.2 g.

Fraction 7, ethyl *t*-butylacetate, was saponified by aqueous potassium hydroxide to give ethyl alcohol, 3,5-dinitrobenzoate, m. p. and mixed m. p. 92°; and *t*-butylacetic acid, anilide, m. p. and mixed m. p. 130–131°.

Fractions 23, 24, and part of 25 represented a 7% yield of neopentylethylcarbinyl *t*-butylacetate. Alcoholic saponification gave neopentylethylcarbinol, previously reported,[1] b. p. 96° at 150 mm., n^{20}_D 1.4248, 3,5-dinitrobenzoate, m. p. and mixed m. p. 81–82°; and *t*-butylacetic acid, anilide m. p. and mixed m. p. 130–131°.

Fractions 28–37 represented a 51% yield of ethyl neopentyl ketone, m. p. and mixed m. p. of the dinitrophenylhydrazone 135–136°.

The high index of fraction 38 appeared to be due to the

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[1] No. I, Whitmore, Popkin, Whitaker, Mattil and Zech, This Journal, **60**, 2462 (1938).

[2] Whitmore and co-workers, *ibid.*, **60**, 2028, 2030, 2458, 2462, 2788 (1938).

[3] The fractionating columns used have been described: Whitmore, Popkin, Whitaker, Mattil and Zech, *ibid.*, **60**, 2459 (1938).

presence of diethylneopentylcarbinol or the corresponding olefins.[1]

Fraction 39 contained *t*-butylacetic acid, m. p. and mixed m. p. of the anilide 130–131°.

All attempts to find neopentylcarbinol and neopentylcarbinyl *t*-butylacetate failed.

Addition of *n*-Propylmagnesium Bromide to *t*-Butylacetyl Chloride.—The addition of 1.85 moles of *n*-propylmagnesium bromide, in 1 liter of ether, to 260 g. (1.94 moles) of *t*-butylacetyl chloride in 600 cc. of ether, was completed in forty-five minutes. The complex stood overnight and the products were isolated as above to give: 1–18, 166.3 g., b. p. 20–98° at 11 mm., $n^{20}D$ 1.4078–1.4250–1.4147; 19–22, 45 g., 111–112° at 13 mm., 1.4272–1.4181; 23–25, 7.5 g., 121–128° at 13 mm., 1.4340–1.4442; residue 3.8 g.; trap contents 37 g.

The trap contents on removal of the ether yielded 5.7 g. of oil, $n^{20}D$ 1.3985. This oil together with 1–18 was fractionated by parts through column X to give: 26–29, 14.9 g., 95–102° at 150 mm., 1.4032–1.4085; 30, 5.9 g., 107° at 150 mm., 1.4100; 31–32, 13.1 g., 109.5°, 1.4132–1.4140; 33, 4.8 g., 99–108°, 1.4105; 34–44, 83.5 g., 108–110°, 1.4132–1.4153; 45–47, 15.2 g., 51–58° at 7 mm., 1.4161–1.4273; 48–49, 7.9 g., 64–74° at 7 mm., 1.4315–1.4228; 50–51, 16.7 g., 78°, 1.4135–1.4122; residue 1 g.

Fractions 26–29 were identified as ethyl *t*-butylacetate. Aqueous saponification gave ethyl alcohol, 3,5-dinitrobenzoate m. p. and mixed m. p. 92°; and *t*-butylacetic acid, anilide m. p. and mixed m. p. 130–131°.

Fractions 31–32 and 34–44 were identified as neopentyl *n*-propyl ketone, semicarbazone m. p. and mixed m. p.[4] 93–94°, yield 36.7%.

Fractions 47–49 contained dodecenes, as previously reported,[1] obtained by dehydration of the tertiary alcohol.

Fractions 50–51 were *t*-butylacetic acid, anilide m. p. and mixed m. p. 130–131°.

Fractions 19–22 represented a 20% yield of neopentyl-*n*-propylcarbinyl *t*-butylacetate. Alcoholic saponification gave neopentyl-*n*-propylcarbinol,[1] b. p. 120–121° at 150 mm., $n^{20}D$ 1.4270, m. p. and mixed m. p. of phenylurethan 80–82°; and *t*-butylacetic acid, m. p. and mixed m. p. of anilide 130–131°.

All attempts to find neopentylcarbinol and neopentylcarbinyl *t*-butylacetate failed.

Addition of *n*-Butylmagnesium Bromide to *t*-Butylacetyl Chloride.—The addition of 2.01 moles of *n*-butylmagnesium bromide, in 1 l. of dry ether, to 292 g. (2.18 moles) of *t*-butylacetyl chloride, in 600 cc. of ether, was completed in eighty minutes. After standing overnight the products were isolated to give: 1–18, 173.6 g., b. p. 34° at 742 mm. to 59° at 4 mm., $n^{20}D$ 1.4070–1.4195; 19–23, 27.6 g., 68–95° at 4 mm., 1.4232–1.4415–1.4365; 24–29, 55.2 g., 98–99° at 4 mm., 1.4300–1.4315; 30, 6.1 g., 109° at 4 mm., 1.4430; residue 5.1 g.; trap contents 18.6 g.

The trap contents, on removal of ether, yielded 8.9 g. of oil. This and 1–18 were fractionated by parts through column X to give: 31–32, 2.7 g., 48–52° at 150 mm., 1.4332–1.4300; 33–38, 22.6 g., 63–102°, 1.4030–1.4098; 39–43, 38.6 g., 127°, 1.4192–1.4195; 44–49, 55.0 g., 126–127°, 1.4182–1.4178; 50–53, 39.6 g., 130–134°, 1.4170–1.4150; 54–55, 8.0 g., 134–155° at 150 mm., 1.4270–1.4400; residue 2.0 g.

Fractions 33–38 were ethyl *t*-butylacetate.

Fractions 39–52 were identified as a mixture of neopentyl *n*-butyl ketone, m. p. and mixed m. p.[5] of semicarbazone 82–84°, and *t*-butylacetic acid, anilide m. p. and mixed m. p. 130–131°; which contained 105.2 g. of the ketone and 28.0 g. of the acid, as determined from a composition—index of refraction curve. This represented a 34% yield of neopentyl *n*-butyl ketone.

The index of refraction of 20–23 corresponded to tetradecenes.[1]

Fractions 24–29 with part of fraction 23 represented a 23% yield of neopentyl-*n*-butylcarbinyl *t*-butylacetate. Alcoholic saponification gave neopentyl-*n*-butylcarbinol,[1] b. p. 92° at 100 mm., $n^{20}D$ 1.4295–1.4305, phenylurethan m. p. and mixed m. p. 84–85°; and *t*-butylacetic acid, anilide m. p. and mixed m. p. 130–131°.

All attempts to identify neopentylcarbinol and its *t*-butylacetate failed.

Addition of *n*-Amylmagnesium Bromide to *t*-Butylacetyl Chloride.—Addition of 1.9 moles of *n*-amyl Grignard solution to 271 g. (2 moles) of *t*-butylacetyl chloride in fifty minutes as above gave: 1–16, 161.7 g., 67–145° at 150 mm., $n^{20}D$ 1.4240–1.4090–1.4235; 17–18, 21.8 g., 128–132° at 20 mm., 1.4342–1.4450; 19–22, 42.3 g., 133–144°, 1.4450; 23–27, 54.1 g., 146–147°, 1.4332–1.4350; 28, 7.1 g., 147°, 1.4412; residue 3 g.; trap contents 91 g.

The trap contents with fractions 1–17 gave: 29–30, 9.8 g., 65–90° at 150 mm., 1.4370–1.4210; 31–34, 45.1 g., 90–103°, 1.4060–1.4080; 35–42, 44.6 g., 103–134°, 1.4160–1.4140; 43–52, 76.3 g., 122–138°, 1.4212–1.4280; residue 1 g.

Fractions 31–34 were identified as ethyl *t*-butylacetate.

Fractions 35–42 were largely *t*-butylacetic acid, anilide m. p. and mixed m. p. 130–131°. The other component was identified as neopentyl *n*-amyl ketone, semicarbazone m. p. and mixed m. p. 99–102°.[1]

Fractions 43–52 were largely neopentyl *n*-amyl ketone. This together with an estimate from fractions 35–42 represented a 29% yield of this ketone.

Fractions 19–22 were hexadecenes.[1]

Fractions 23–27 represented a 21% yield of neopentyl-*n*-amylcarbinyl *t*-butylacetate. Alcoholic saponification of 26–27 gave neopentyl-*n*-amylcarbinol,[1] b. p. 132° at 100 mm., $n^{20}D$ 1.4340–1.4347, phenylurethan m. p. and mixed m. p. 62–63°; and *t*-butylacetic acid, anilide m. p. and mixed m. p. 130–131°.

All attempts to identify neopentylcarbinol and its *t*-butylacetate failed.

Preparation of Neopentylcarbinyl *t*-Butylacetate.—A solution of 0.8 mole of neopentylmagnesium chloride was prepared from neopentyl chloride, b. p. 82° at 740 mm., $n^{20}D$ 1.4042. An excess of dry formaldehyde, generated by heating dry paraformaldehyde, was passed into the solution during four hours. The complex was decomposed with ice and 30% H_2SO_4 and fractionated through column X to give 48 g. (0.47 mole) of neopentylcarbinol, b. p. 140–146° at 739 mm., $n^{20}D$ 1.4120–1.4034.

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(4) This ketone and the semicarbazone prepared by H. C. Crafton, Jr., of this Laboratory.

(5) Unpublished work of E. Rohrmann, this Laboratory.

Heating 22.2 g. (0.22 mole) of the above carbinol for two hours with 29 g. (0.2 mole) of *t*-butylacetyl chloride, b. p. 79° at 150 mm., $n^{20}D$ 1.4215, and fractionation through column X gave: 1–2, 7.7 g., b. p. 78–140° at 150 mm., $n^{20}D$ 1.4050–1.4190; 3–5, 22.2 g., 104° at 26 mm., 1.4198–1.4202; residue 4.8 g.

Fractions 3–5 represented a 57% yield of neopentylcarbinyl *t*-butylacetate. Saponification of 16.0 g. of this ester with alcoholic potassium hydroxide gave neopentylcarbinol, α-naphthylurethan m. p. and mixed m. p. 81–82°; and *t*-butylacetic acid, anilide m. p. and mixed m. p. 130–130.5°.

Preparation of Ethyl *t*-Butylacetate.—A mixture of 57.5 g. (0.54 mole) of *t*-butylacetic acid, $n^{20}D$ 1.4096, 125 cc. of absolute ethyl alcohol, and 25 cc. of concd. sulfuric acid was refluxed fifteen hours. The mixture was dissolved in ether, washed with water and dilute potassium carbonate solution, dried over magnesium sulfate, and fractionated through column X to give 60.1 g. or a 77% yield of ester of b. p. 102° at 740 mm., $n^{20}D$ 1.4032–1.4040.

Summary

1. Ethyl, *n*-propyl, *n*-butyl, and *n*-amyl Grignard solutions, when added to a slight excess of *t*-butylacetyl chloride, gave ketones of the type $(CH_3)_3CCH_2COR$ in about 51, 37, 34, and 29% yields, respectively. They also gave esters of the type $(CH_3)_3CCH_2CHROCOCH_2C(CH_3)_3$. The latter were obtained in about 7, 20, 23, and 21% yields, respectively, from the four Grignard solutions.

2. Ethyl *t*-butylacetate and neopentylcarbinyl *t*-butylacetate have been prepared.

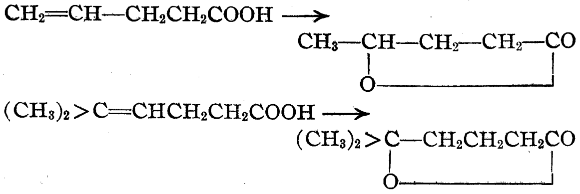
STATE COLLEGE, PENNA. RECEIVED AUGUST 24, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Lactone Formation in the Addition Product of Maleic Anhydride and Bicyclohexenyl

BY ROGER ADAMS AND E. E. GRUBER[1]

The addition of maleic anhydride to bicyclohexenyl takes place readily with the formation of $\Delta^{4a,5a}$ - dodecahydrophenanthrene - 9,10 - dicarboxylic acid anhydride (I).[2] During the course of the study of this compound, several reactions were noted which have a general bearing upon lactone formation of γ,δ-unsaturated acids. Linstead has demonstrated[3] that the ease and direction of lactonization of aliphatic γ,δ-olefinic acids depend on the substituents on the δ-carbon. The formation of a γ-lactone is favored if hydrogens, a δ-lactone if alkyl groups, are present. Lactonization is promoted by mineral acids and in some cases merely by heating the olefinic acids.



$$CH_2{=}CH{-}CH_2CH_2COOH \longrightarrow \begin{array}{l} CH_3{-}CH{-}CH_2{-}CH_2{-}CO \\ \qquad\;\; \lfloor O \rule[0.5ex]{6em}{0.4pt} \rfloor \end{array}$$

$$(CH_3)_2{>}C{=}CHCH_2CH_2COOH \longrightarrow \begin{array}{l} (CH_3)_2{>}C{-}CH_2CH_2CH_2CO \\ \qquad\quad\;\; \lfloor O \rule[0.5ex]{6em}{0.4pt} \rfloor \end{array}$$

When I or its anhydride (V) is esterified with absolute ethanol and hydrogen chloride, a monoethyl ester lactone (II) is obtained. Saponification of this compound gives a sodium salt of an hydroxy acid (III) which on acidification results not in the hydroxy dibasic acid but in a lactone acid (IV). By the action of heat or acetic anhydride, I forms the anhydride (V) which upon treatment with cold sodium ethylate leads to an ester acid (VI). Hot sodium ethylate, however, results in a complicated reaction, the character of which was not determined. The ester acid (VI) can be hydrolyzed by boiling with dilute alkali to the dibasic acid (I). Heating I alone gives a mixture of anhydride (V) and lactone (IV).

Of significance is the fact that the action of bromine in carbon tetrachloride differentiates between the dibasic acid derivatives and the lactone acid derivatives. Thus, compounds I, V and VI absorb bromine while compounds II and IV do not.

As lactonization of one of the carboxyls results when I or V is esterified and no diethyl ester may be isolated, it is obvious that lactonization of the second carboxyl is the more rapid of the competing reactions. Lactonization also takes place merely by heating the acid (I) in acetone solution in presence of hydrochloric acid; lactone (IV) is formed.

The structures of the lactones obviously may be either those given in II and IV or the isomeric γ-lactones. Stereochemically the γ- or δ-lac-

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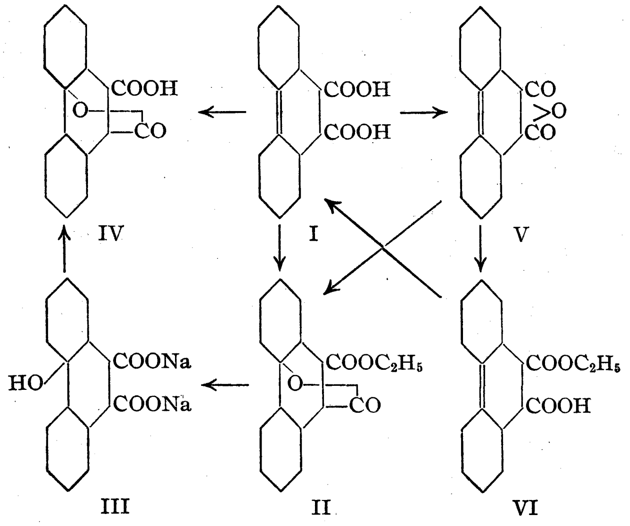
[1] Portion of a thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in chemistry.

[2] Gruber and Adams, THIS JOURNAL, **57**, 2555 (1935).

[3] Linstead and others, *J. Chem. Soc.*, 115 (1932); *ibid.*, 557, 561, 568, 577, 580 (1933).



tones might form with equal ease. It seems likely, in view of Linstead's work, that the factors which lead to δ-lactone formation are probably more influential than those which lead to the γ-lactone.

Unfortunately, all of the reactions described are accompanied by side-products of an oily character which exclude quantitative studies.

Experimental

$\Delta^{4a,5a}$-Dodecahydrophenanthrene-9,10-dicarboxylic Acid.—The preparation of this product and its lactone was described previously.[2] The anhydride is also conveniently formed from the acid by the action of acetic anhydride.

$\Delta^{4a,5a}$-Dodecahydrophenanthrene-9,10-dicarboxylic Acid Anhydride.—A solution of 2 g. of dibasic acid in 20 cc. of acetic anhydride was refluxed for five hours. The acetic anhydride and acetic acid were removed by distillation *in vacuo* and the residue extracted with 125 cc. of hot ligroin (b. p. 60–110°). Upon filtering and evaporating to 75 cc., a tan precipitate separated on cooling. Purification from cyclohexane gave colorless crystals of m. p. 121°. The yield was low.

Monoethyl Ester of Hydroxytetradecahydrophenanthrene-9,10-dicarboxylic Acid Lactone (II).—Dry hydrogen chloride was bubbled through a solution of 11 g. of $\Delta^{4a,5a}$-dodecahydrophenanthrene-9,10-dicarboxylic acid in 150 cc. of absolute ethanol for one and one-half hours and the mixture was then refluxed on a steam cone for one hour. About 50 cc. of ethanol was distilled off and the residue poured into 200 cc. of ice water. The oil was extracted with benzene, the solution washed with dilute aqueous sodium carbonate and 10% sulfuric acid, then evaporated and the oil distilled *in vacuo*, b. p. 225–250° at 13 mm.; yield 8.2 g. (68%). After standing in a desiccator for several days, it solidified and was recrystallized from cyclohexane; white microcrystals, m. p. 109–110°.

Anal. Calcd. for $C_{18}H_{26}O_4$: C, 70.54; H, 8.56. Found: C, 70.29; H, 8.61.

The product is insoluble in cold or warm 10% aqueous sodium hydroxide but goes into solution on prolonged boiling.

A second procedure using the anhydride follows: dry hydrogen chloride was bubbled for three-quarters of an hour through a solution of 2 g. of dodecahydrophenanthrene-9,10-dicarboxylic acid anhydride in 30 cc. of absolute ethanol. After refluxing for about twenty-four hours on a steam cone, the alcohol was evaporated by means of a stream of warm air and the residue poured into water. Extraction with benzene and purification as described above gave the same product.

Tetradecahydrophenanthrene-9,10-dicarboxylic Acid Lactone (IV). Compound III as Intermediate.—A solution of 1.5 g. of the ethyl ester of the lactone in 10 cc. of 5% sodium hydroxide was refluxed for a few hours until all the solid had dissolved. Upon cooling, a solid precipitated. This proved to be a disodium salt.

Anal. Calcd. for $C_{16}H_{22}O_5Na_2$: Na, 13.51. Found: Na, 13.81.

The sodium salt, as well as the filtrate from the sodium salt, on acidification gave a precipitate, which still contained sodium. If, however, it was warmed with hydrochloric acid, a crystalline product separated on cooling. After purification from dilute acetone, it formed long blunt prisms, m. p. 246–247°.

Anal. Calcd. for $C_{16}H_{22}O_4$: C, 69.02; H, 7.97; neut. equiv., 278. Found: C, 69.14; H, 8.09; neut. equiv., 278.

Monoethyl-$\Delta^{4a,5a}$-dodecahydrophenanthrene-9,10-dicarboxylate (VI).—To a cold solution of 0.2 g. of sodium in 20 cc. of absolute ethanol was added 3 g. of $\Delta^{4a,5a}$-dodecahydrophenanthrene-9,10-dicarboxylic acid anhydride. After standing a day at room temperature, the alcohol was evaporated by means of a stream of air. The solid residue was dissolved in 35 cc. of water and acidified with dilute hydrochloric acid. The clumpy precipitate was allowed to dry and any material that gradually separated from the acidified solution added to it. Crystallization from cyclohexane, followed by several crystallizations from dilute acetone, gave small white plates, m. p. 127–128°.

Anal. Calcd. for $C_{18}H_{26}O_4$: C, 70.54; H, 8.56; neut. equiv., 306. Found: C, 70.71; H, 8.52; neut. equiv., 323.

Effect of Heat upon $\Delta^{4a,5a}$-Dodecahydrophenanthrene-9,10-dicarboxylic Acid.—A sample of 0.9 g. of acid was heated in a test-tube at 200–210° for fifteen minutes. Upon cooling, 30 cc. of cyclohexane was added and the mixture heated to boiling. Insoluble material was filtered from the hot solution. This solid product was crystallized from dilute acetone and prisms were obtained which proved to be lactone acid (IV).

Heating the acid (I) above its melting point, and direct extraction of the reaction mass with petroleum ether gave a small amount of crystalline material, m. p. 123–123.5°, which proved to be anhydride.

Conversion of $\Delta^{4a,5a}$-Dodecahydrophenanthrene-9,10-dicarboxylic Acid to Tetradecahydrophenanthrene-9,10-dicarboxylic Acid Lactone (IV).—To a solution of 2 g. of dicarboxylic acid in 50 cc. of acetone was added 10 cc. of concentrated hydrochloric acid. After refluxing for four to five hours the solution was poured into ice water and filtered. The filtrate upon evaporation left a brown crystalline residue which was recrystallized from dilute acetone; m. p. 213°.

Since the neutral equivalent determination indicated that the material was probably impure lactone acid, it was recovered and subjected to three more recrystallizations. This treatment yielded long blunt prisms, m. p. 242–244°, which proved to be the lactone acid by mixed melting point.

Summary

$\Delta^{4a,5a}$ - Dodecahydrophenanthrene - 9,10 - dicarboxylic acid and its anhydride are converted into a lactone ester and not into a diester upon esterification. Saponification of this lactone ester with alkali gives the alkali salt of an hydroxy dibasic acid which on acidification gives a monobasic acid monolactone. It is assumed by analogy to previous results on the study of γ,δ-olefinic acids that in these molecules a δ-lactone probably has formed.

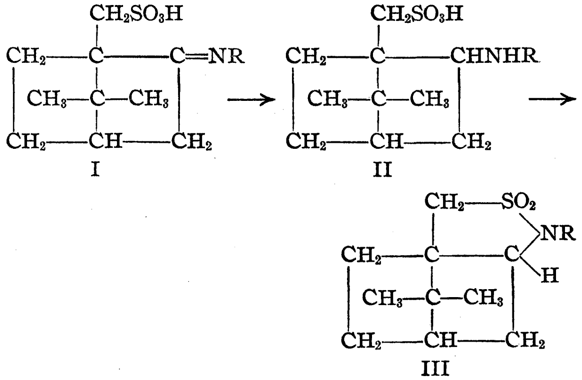
URBANA, ILLINOIS RECEIVED SEPTEMBER 30, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Anomalous Mutarotation of Salts of Reychler's Acid. VI. Synthesis and Structure of the Sultam of 2-(N-Methylamino)-*d*-camphane-10-sulfonic Acid

BY R. L. SHRINER, JAMES A. SHOTTON AND HARRY SUTHERLAND

One of the reactions used to establish the ketimine structure (I) of the dehydration products of primary amine salts of Reychler's acid[1] was reduction to the substituted amino sulfonic acid (II). The two forms of the latter underwent dehydration, producing compounds whose analyses and properties indicated the sultam structure,[1c] (III).

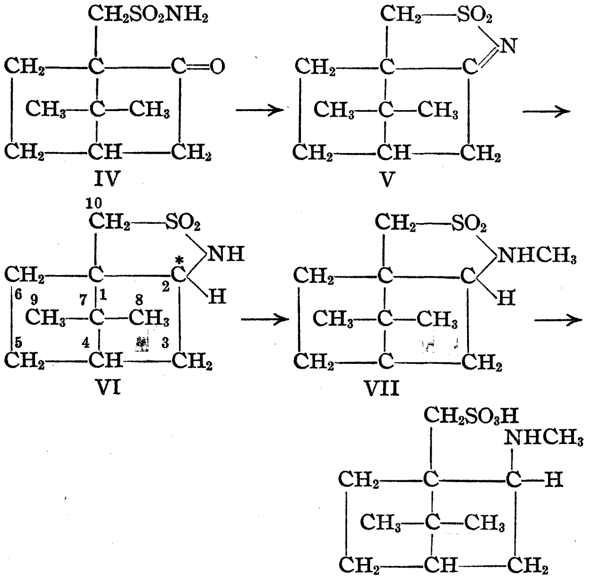

I

II

III

The purpose of the present investigation was to synthesize one of these sultams by an independent method in order to establish this structure.

Accordingly, use was made of an observation by Reychler[2] that *d*-camphor-10-sulfonamide (IV) underwent dehydration to an anhydro compound to which Armstrong and Lowry[3] had assigned the structure shown in formula V. In the present work this anhydramide was reduced catalytically with hydrogen and Raney nickel to the sultam, VI. Although the latter may exist in two diastereoisomeric forms, since carbon atom 2 is now asymmetric (*), only one form actually was produced. The sodium salt of this sultam was treated with methyl iodide and the N-methyl sultam, VII, obtained. Hydrolysis by means of concentrated hydrochloric acid opened the heterocyclic ring and produced the α-form of 2-(N-methylamino)-*d*-camphane-10-sulfonic acid (VIII). Although Reychler's acid and its amide are dextrorotatory, all the derivatives V, VI, VII and VIII were levorotatory; the specific rotations being −32, −33, −59 and −98°, respectively.


IV

V

VI

VII

VIII

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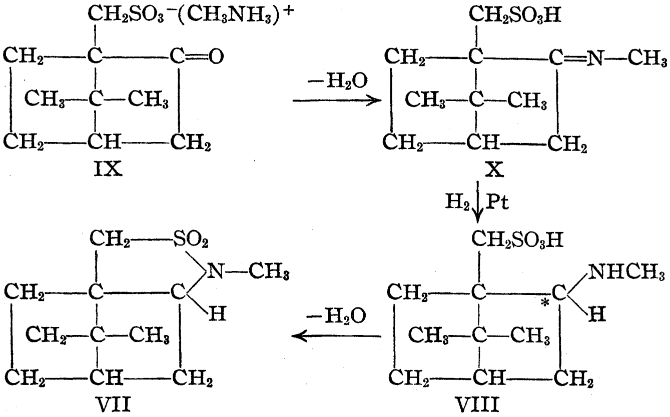
[1] (a) Schreiber and Shriner, THIS JOURNAL, **57**, 1306 (1935); (b) *ibid.*, **57**, 1445 (1935); (c) *ibid.*, **57**, 1869 (1935); Sutherland and Shriner, *ibid.*, **58**, 62 (1936); *ibid.*, **60**, 1314 (1938).

[2] Reychler, *Bull. soc. chim.*, **19**, 127 (1898).

[3] Armstrong and Lowry, *J. Chem. Soc.*, **81**, 1448 (1902); Lowry and Desch, *ibid.*, **95**, 1340 (1909); Richards and Lowry, *ibid.*, **127**, 1503 (1925).

Samples of the N-methyl sultam (VII) and its hydrolytic product (VIII) were next prepared from the methylamine salt of Reychler's acid (IX) which was dehydrated to the ketimine (X).



Catalytic reduction produced the two diastereoisomeric forms of 2-(N-methylamino)-*d*-camphane-10-sulfonic acid (VIII). These isomers were separated by fractional crystallization and the α-form possessed the same decomposition point and specific rotation as the sample of compound VIII obtained by the first series of reactions. By refluxing this α-form with acetic anhydride the N-methyl sultam (VII) was obtained which was identical in melting point with the N-methyl sultam described above.

These two series of reactions not only establish the structure of these sultams but also serve to confirm Lowry and Armstrong's formula for *d*-camphor-10-sulfonanhydramide.

Experimental

***d*-Camphor-10-sulfonanhydramide** (V).—A mixture of 25 g. of *d*-camphor-10-sulfonic acid and 5 cc. of thionyl chloride was warmed on the steam-bath until the reaction started and then another 30 cc. of thionyl chloride was added slowly. The mixture was heated on the steam-bath for four hours, cooled and poured slowly into a mixture of 100 cc. of concentrated ammonium hydroxide and 400 g. of cracked ice. The crude anhydramide was filtered and recrystallized from 95% ethanol. The aqueous mother liquor deposited additional crops of crystals of the anhydramide after standing overnight. Concentration of the ethanol mother liquor above yielded a product which melted at 126°, being an impure form of *d*-camphor-10-sulfonamide. When this material is warmed for ten minutes with concentrated hydrochloric acid, it is converted into the anhydramide. By working up all these fractions there resulted a total yield of 19.1 g. (90%) of colorless crystals of *d*-camphor-10-sulfonanhydramide which melted at 224° (corr.) and possessed a specific rotation[4] of −32° in chloroform (*c*, 5). These values check closely those given by Armstrong and Lowry.[3]

Sultam of 2-Amino-*d*-camphane-10-sulfonic Acid (VI).—A mixture of 10 g. of the anhydramide, 10 g. of Raney nickel catalyst and 150 cc. of warm 95% ethanol was shaken with hydrogen under 45 lb. (3 atm.) pressure. The anhydramide was only partially in solution at the start but dissolved as the reduction proceeded. The reduction was complete in one and one-half hours after which time the catalyst was removed by filtration and the filtrate concentrated. The sultam which separated melted at 181–182°. It was subjected to fractional crystallization but all the fractions melted at 181–182°, showing that only one form had been produced. The sultam was soluble in dilute aqueous sodium hydroxide and was precipitated upon acidification. It had a specific rotation in chloroform (*c*, 5) of −33.0°.

Anal. Calcd. for $C_{10}H_{17}O_2NS$: N, 6.51; S, 14.88. Found: N, 6.62; S, 14.83.

Sultam of 2-(N-Methylamino)-*d*-camphane-10-sulfonic Acid (VII).—A solution of 0.5 g. of sodium in 10 cc. of absolute ethanol was added to a solution of 5 g. of the above sultam (VI) in 25 cc. of absolute ethanol. To this solution was added 2.5 cc. of methyl iodide and the mixture refluxed for two hours. It was then poured into 50 cc. of water and acidified with hydrochloric acid. An oil separated which solidified on stirring and rubbing. The solid was removed by filtration and the filtrate concentrated to obtain an additional crop of crystals. The crude N-methyl sultam was recrystallized from hot water. A total yield of 4.5 g. (89%) of colorless crystals was obtained which melted at 80° and possessed a specific rotation in chloroform (*c*, 5) of −59.6°.

Anal. Calcd. for $C_{11}H_{19}O_2NS$: N, 6.11; S, 13.96. Found: N, 6.07; S, 14.10.

Hydrolysis of the N-Methyl Sultam (VII).—Three grams of the above N-methyl sultam was refluxed with 50 cc. of concentrated hydrochloric acid for twenty-four hours. The mixture was evaporated to dryness and the residue recrystallized from absolute ethanol. An 83% yield of the α-form of 2-(N-methylamino)-*d*-camphane-10-sulfonic acid was obtained which decomposed at 325–326° on the Maquenne block. Its specific rotation in ethanol (*c*, 1) was −98.0°.

Anal. Calcd. for $C_{11}H_{21}O_3NS$: N, 5.66; S, 12.95. Found: N, 5.43; S, 13.10.

2-(N-Methylimino)-*d*-camphane-10-sulfonic Acid (X).—One sample of this ketimine was prepared according to the method previously described.[1b] Fifty grams of Reychler's acid was added to an ethanol solution of 9.2 g. of methylamine and the salt obtained by evaporation to dryness. Dehydration was effected by heating the salt for six hours at 184° *in vacuo*. Four recrystallizations from absolute ethanol with the use of Norite were necessary in order to obtain a pure product.

A modified procedure proved simpler and yielded a product more easily purified. To a solution of 6.8 g. of methylamine in 100 cc. of ethanol were added 30 g. of Reychler's acid and 150 g. of ethylene glycol. The mixture was dis-

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[4] All rotations were taken at 25° with sodium D light. The concentration in grams per 100 cc. of solution is denoted by *c*.

tilled until the volume of the residue was about 50 cc. This residual solution was cooled and the ketimine filtered and washed with cold ethanol. Recrystallization from absolute ethanol gave 12.8 g. of colorless crystals which melted at 312–313° (Maquenne block) and possessed a specific rotation of −137.6° in ethanol (*c*, 1). These constants checked with those previously obtained.[1b]

2-(N-Methylamino)-*d*-camphane-10-sulfonic Acid (XI).—2-(N-Methylimino)-*d*-camphane-10-sulfonic acid (18.8 g.) was dissolved in 150 cc. of absolute ethanol and catalytically reduced with hydrogen and platinum-oxide platinum black. It was necessary to use two successive portions of 0.5 g. of catalyst in order to secure complete reduction, which required about twenty-four hours. The catalyst was removed by filtration and the filtrate concentrated. The crude product was fractionated by a series of systematic crystallizations from 95% ethanol. The two diastereoisomers were isolated as colorless crystals.

α-Form.—This form had a decomposition point of 320° and a specific rotation in ethanol (*c*, 1) of −98.6°. *Anal.* Calcd. for $C_{11}H_{21}O_3NS$: C, 53.41; H, 8.56; N, 5.66. Found: C, 53.51; H, 8.54; N, 5.54.

β-Form.—This isomer decomposed at 338–343° and had a specific rotation in ethanol (*c*, 1) of +38.8°. *Anal.* Calcd. for $C_{11}H_{21}O_3NS$: C, 53.41; H, 8.56; N, 5.66. Found: C, 53.52; H, 8.49; N, 5.65.

The α-form was identical with the compound obtained by hydrolysis of the N-methyl sultam (VII).

Conversion of the α-Form of 2-(N-methylamino)-*d*-camphane-10-sulfonic Acid to the Sultam (VII).—One-tenth of a gram of the α-form of 2-(N-methylamino)-*d*-camphane-10-sulfonic acid was heated with 3 cc. of acetic anhydride for eighteen hours. The mixture was then poured into 5 cc. of water and evaporated to dryness. Three cubic centimeters of acetic anhydride was added and the mixture again heated to the boiling point. The mixture was cooled and then 3 cc. of water was added. This mixture was then evaporated to dryness. Two cubic centimeters of water was added and the white crystals collected on a filter. The substance melted at 79°. The mixed melting point with the methyl sultam (VII) was 79–80°.

Summary

The sultam of 2-(N-methylamino)-*d*-camphane-10-sulfonic acid was synthesized by alkylation of the sultam of 2-amino-*d*-camphane-10-sulfonic acid which was obtained by catalytic reduction of *d*-camphor-10-sulfonanhydramide. The sultam was hydrolyzed to 2-(N-methylamino)-*d*-camphane-10-sulfonic acid. The latter was shown to be identical with the α-form obtained by catalytic reduction of 2-(N-methylimino)-*d*-camphane-10-sulfonic acid. This α-form was converted to the N-methyl sultam by acetic anhydride.

URBANA, ILLINOIS RECEIVED SEPTEMBER 6, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WISCONSIN]

The Determination of Dissolved Oxygen by Means of the Dropping Mercury Electrode, with Applications in Biology

BY HAROLD G. PETERING AND FARRINGTON DANIELS

The measurement of respiration constitutes but one of the many demands for an accurate and rapid method for the quantitative determination of oxygen. The differential pressure manometer such as the Warburg–Barcroft manometer is widely used for this purpose. The Winkler process is another standard method. The results of this investigation show that for many purposes the concentration of dissolved oxygen can be determined with great simplicity, accuracy, and rapidity by means of the dropping mercury electrode.

The method described here is a modification of the polarographic method, shown by Vitek[1] to be applicable to the determination of oxygen. The recording features of the polarograph are dispensed with and the apparatus is constructed from ordinary laboratory materials in such a way that readings of oxygen concentration in water or other conducting solvents can be made in a few seconds. It is especially useful for studying systems which involve a changing oxygen concentration.

This method may be regarded merely as an empirical analytical procedure which has been checked against chemical standards. On the other hand, theoretical interpretations of the polarographic method have been proposed.

Theory

The use of the dropping mercury electrode for analytical purposes depends on the fact that solutes (electrolytes or non-electrolytes) are reduced (or oxidized) when a current is passed through the solution at voltages above the decomposition potential. The current flowing de-

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(1) Vitek, *Chimie et Industrie*, **29**, 215 (1933); *Coll. Czech. Chem. Comm.*, **7**, 537 (1935).

pends on the rate of diffusion of the material to the electrode, and this in turn depends on the concentration. The dropping mercury electrode gives reproducible results because a fresh surface of the electrode is being exposed continuously. At low voltages a small residual current flows, and then as the voltage is increased above the decomposition potential the current depends directly on the voltage in accordance with Ohm's law. As the voltage is still further increased, a point is reached after which the current is limited by the rate of diffusion of the reducible substance into the surface of the dropping mercury cathode. The current–voltage curve then becomes flat in the ideal case, and the current remains constant and independent of the voltage until the voltage becomes high enough to produce some other chemical reaction at the electrode.

The dropping mercury electrode was originally used by Kucera[2] to measure the interfacial tension of polarized mercury. Heyrovsky[3] is responsible for its extensive use in analytical chemistry. He devised the sensitive, self-recording polarograph which enables one to obtain easily and accurately the current–voltage curves of any dissolved reducible (or oxidizable) material—electrolyte or non-electrolyte. The decomposition potentials corresponding to breaks in the curve are used for qualitative analysis and the magnitude of the current at the "waves" is used for quantitative analysis.

There are several complications in the quantitative determination of a solute by this method. Other materials which have decomposition potentials in the same voltage range as oxygen will also give diffusion currents. As in any analytical procedure, these materials must be eliminated or corrected for. In this case, the readings are calibrated with a chemical method which is specific for oxygen, or these extraneous materials are determined when oxygen is removed by bubbling hydrogen through the cell. Again, these materials do no harm if only differences in oxygen concentration are being determined. When electrolytes are being determined the migration current of the ions affects the observed galvanometer readings, but this difficulty is removed by adding an excess of an indifferent electrolyte[4] such as potassium chloride (about 0.1 mole per liter). In the case of oxygen, which is a non-electrolyte, this migration current is not a factor.

Another complication is due to the (electrostatic) adsorption of reducible molecules on the surface of the mercury, which then causes a current to flow which is greater than the limiting current set by the diffusion rate. This phenomenon is evident in the maximum shown in the dotted line of Fig. 1A. These maxima are reproducible, but they may not be proportional to the reducible matter in solution, and it becomes necessary to eliminate them by the addition of small amounts of adsorbable material which are not reduced at the given potentials. Materials used to suppress these maxima are colloids such as proteins and carbohydrates, polymers, soaps, dyes, and alkaloids.[5] The adsorption of these materials tends to prevent the adsorption of the reducible material, and it does not affect the readings because they have a different decomposition potential than the material in question. It has been found in this investigation that for the analysis of oxygen there is sufficient material of this type in most biological samples and even in water which has been passed through filter paper to eliminate or greatly suppress the adsorption maximum of oxygen. The elimination of the objectionable maximum by the addition of algal cells is shown in Fig. 1B, while

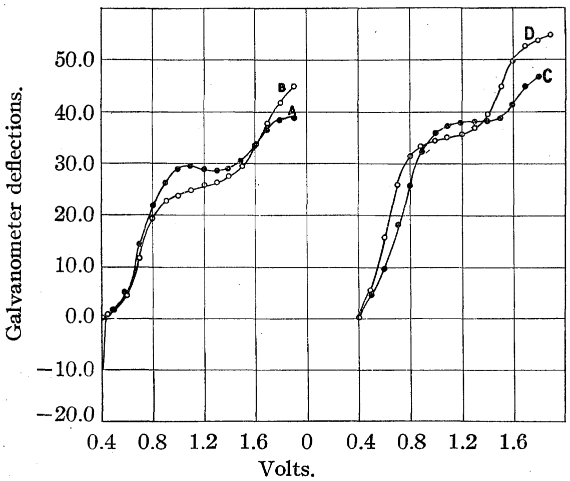

Fig. 1.

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(2) Kucera, *Ann. Physik*, **11**, 529 and 698 (1905).

(3) Heyrovsky, *Phil. Mag.*, **45**, 303 (1923); *Trans. Faraday Soc.*, **19**, 692 (1923).

(4) For a discussion of the migration current, *cf.* Ilkovic, *Coll. Czech. Chem. Comm.*, **6**, 498 (1934).

(5) This subject is fully treated by Heyrovsky in "Actualités scientifiques et industrielles," No. 90, Hermann et Cie, Paris, 1934. It has been found in this work on dissolved oxygen that the alkaloids do not lead to the same diffusion current as the colloids do when the maximum is suppressed. Gelatin and ethyl cellulose are good agents for suppressing the maximum.

the dotted line A for a smaller concentration of algal cells shows that the maximum has been only partially suppressed.

As already stated, oxygen was determined with a polarograph by Vitek.[1] He showed that the absorption coefficients of oxygen in water, ethanol, and methanol, were proportional to the wave heights (*i. e.*, diffusion currents corresponding to the flat parts on the polarographic records) for oxygen in these three solvents. He gave the precision of the method as 4% and the range of dissolved gas capable of being measured as 0.04 mg. per liter up to saturation, but he did not report quantitative measurements on the absolute concentrations of oxygen. No further application of the method seems to have been published since that time.[6]

The object of the present research has been to simplify the method and to show how it can be used to advantage in a number of problems, particularly to those of biology. The simplification consists in dispensing with the recording features of the polarograph and in determining the current only at two voltages which have been determined previously by experiment.

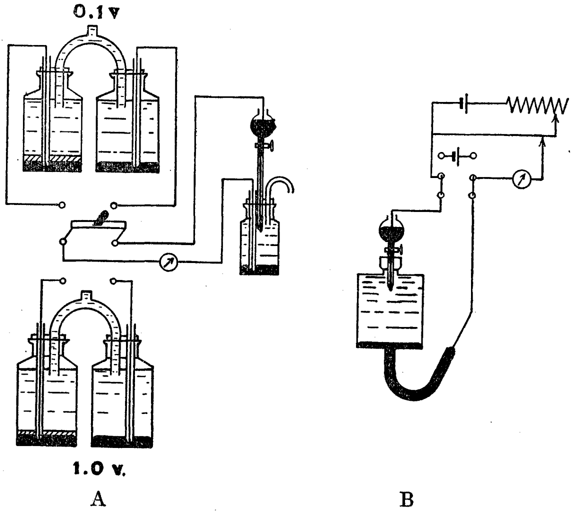

Fig. 2.

According to present practice, quantitative analysis by means of the dropping mercury electrode involves the determination of the whole current–voltage curve either by graphic or by automatic recording as in the polarograph. In some cases the difference in currents between two adjacent flat parts of the curve is taken as a measure of the concentration of the material whose decomposition potential falls in this range. In another method, parallel tangents are drawn at a definite angle above and below the region of the diffusion current, and the difference in current between the points of tangency is taken as the significant diffusion current which is proportional to the concentration.[7] The interpretation of the polarograms is fully discussed by Hohn.[8] It is much simpler, however, to determine the current at a predetermined voltage slightly less than the decomposition voltage of the electrode reactants, and again at a second voltage above the decomposition potential in the region of the diffusion current but below the decomposition voltage of a second electrode reaction. The difference between the currents flowing at these two voltages is proportional to the concentration of the substance (oxygen) taking part in the first electrode reaction. The results of this investigation show that this procedure is adequate, provided that the voltages are predetermined by experiment and the calibration curve is shown to be reproducible. The experimental apparatus then becomes extremely simple.

Apparatus

The apparatus, shown in Fig. 2B, consists merely of a stream of mercury dropping from a capillary tube into a solution in a closed bottle. The mercury stream is made the cathode and the pool of mercury the anode in a circuit which contains a storage battery, adjustable resistance and a galvanometer. The potential is varied by means of the resistance and measured with a simple potentiometer. The galvanometer need not be of the most expensive type, a sensitivity of 5×10^{-7} amp. per scale division being sufficient. A portable box type with a light and scale will do if the scale is long enough (6–10 cm.).

Since a study of the whole current–voltage curve showed that only two voltages are necessary for the analysis, it is evident that even the potentiometer may be dispensed with and two large capacity standard cells substituted for it as shown in Fig. 2A. The standard cells are made from two eight-ounce square bottles taped together, closed with rubber stoppers, and connected with a salt bridge. Connections are made with the mercury or amalgams, at the bottom of the bottles, by means of platinum wire fused to copper wire and sealed into glass tubes fitting into the stoppers. In the 1.0-v. Weston cell one bottle contains 100 g. of 13% cadmium–mercury amalgam. (The cadmium dissolves more quickly if its surface is in-

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(6) After this manuscript was completed it was learned that Baumberger and O. H. Müller reported an application of the polarographic method to respiration measurements at the meeting of the Western Society of Naturalists in 1935.

(7) Borcherdt, Adkins and Meloche, THIS JOURNAL, **59**, 2171 (1937).

(8) Hohn, "Chemische Analysen mit dem Polarographen," Verlag von Julius Springer, Berlin, 1937.

creased by cautiously pouring the molten metal into water.) The other bottle contains about the same amount of pure mercury covered with a paste of mercurous sulfate in 2 molar cadmium sulfate. Both bottles are then filled to the top of the bridge with approximately 2 molar cadmium sulfate and the opening at the top of the bridge is closed. Such a cell maintains a constant potential of about 1.04 v. over long periods of time and is unaffected by ordinary currents during continued usage.

The 0.1-v. cell is a cadmium–lead cell[9] in a similar double-bottle. One electrode contains 10% lead in 90% mercury over which stands a solution of about 1 molar cadmium iodide saturated with lead iodide. The other electrode contains 11% lead, 9% cadmium and 80% mercury in a solution of about 1 molar cadmium iodide.

As shown in Fig. 2A a double pole-double throw switch is used for throwing in first the 1.0-v. cell and then the 0.1-v. cell. The difference in galvanometer readings with the two cells gives the desired measurement which is proportional to the concentration of dissolved oxygen.

The dropping mercury cathode must be adjusted carefully to give maximum galvanometer deflections with minimum oscillation and without clogging of the capillary tube. A separatory funnel is connected with a capillary tube from a broken thermometer through a minimum length of pure gum rubber tubing or rubber which has been boiled with sodium hydroxide to remove sulfur. The rubber tube is wired on and reinforced if necessary with a wrapping of tape. A 50-cm. head of mercury is satisfactory and the tip is so made that the mercury drops off at the rate of about one drop every one or one-half seconds.

Several different types of cells were used in this work. The cells are completely filled with the liquid, leaving no gas space. In one type (Fig. 2A) the solution overflows as the mercury flows in. In another type (Fig. 2B) the mercury pool at the bottom is kept at a constant level, by allowing the mercury to overflow. In still another type the anode was a calomel electrode connected through a bridge of potassium chloride (1.0 *N*) solution. In the photochemical work the sides of the cell were made of polished glass and care was taken to place the mercury cathode in the center of the cell.

Calibration

In using the dropping mercury electrode it is necessary to calibrate the galvanometer readings directly against the concentration of the substance being analyzed under the same conditions, and in the simple method proposed here it is necessary first to determine empirically at what voltage the galvanometer readings should be taken in order to give a straight line when the concentration is plotted against deflections. Using the same tip and the same apparatus, then the concentration of an unknown solution is obtained readily by interpolation on this straight line or by simply multiplying the galvanometer readings by a constant, *i. e.*, by the slope of the calibration line.

In Fig. 3 are shown current–voltage curves at 18° for various concentrations of oxygen in a solution containing some suspended algae. The full curve is shown at a concentration of 3.00×10^{-4} mole per liter while for the other concentrations the range only from 0.7 to 1.0 v. is shown. When the currents at 0.7, 0.8, 0.9, 1.0 v. are plotted against the concentration of oxygen, only the points at 1.0 v., marked with double circles, give a straight line, as shown in A of Fig. 4. It is clear from an inspection of Fig. 3 that if a straight line is produced at 1.0 v., a straight line cannot be produced at the other voltages.

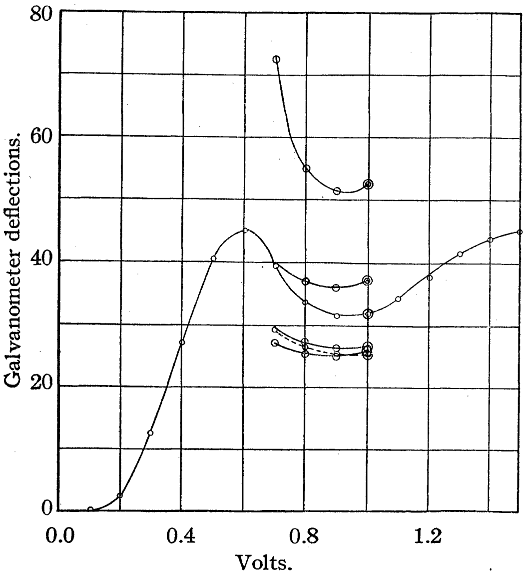

Fig. 3.

In these calibrations the oxygen concentration was determined by titration with sodium thiosulfate using the standard Winkler method[10] with manganous sulfate and potassium iodide. The oxygen concentration was controlled by equilibrating the nutrient solution in which the chlorella were suspended (or just the salt solution, for example 0.1 *N* potassium chloride) with air at the specified temperature, and then passing through this solution oxygen, or nitrogen, or gases containing some oxygen. The closed vessel, containing the solution with dissolved oxygen, was fitted with a siphon, and the samples were withdrawn quickly for chemical analysis and for analysis with the dropping mercury electrode under conditions giving a minimum of change in the oxygen concentration.

Four different calibration curves (A, B, C, and D) obtained by the first method are shown in Fig. 4. These curves illustrate the necessity for separate calibrations for each tip and for each temperature as well as for each galvanometer and electrical circuit. Calibrations A, B, and C were all made with the same dropping mercury cathode tip, but at different temperatures—namely, 18, 22, and 28°, respectively. Calibration D was made with a different tip and at 25°.

An examination of these calibration curves shows the high sensitivity of this method of analysis. Assuming that the galvanometer can be read to at least one-half of a scale division (0.5 mm.), the corresponding limit of error in the oxygen concentration is of the order of 5 ×

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[9] Vosburgh, THIS JOURNAL, **49**, 2223 (1927).

[10] Treadwell and Hall, "Analytical Chemistry," Vol. II, 7th edition, John Wiley and Sons, Inc., New York, 1928, p. 650.

10^{-7} mole per liter. The experimental points fall on the straight line within these limits. It is quite convenient to use the dropping mercury electrode with samples of about 10 cc.; and for a sample of this size the actual change which can be measured is of the order of 5×10^{-9} mole total change in oxygen concentration. At room temperatures this corresponds to 1.2×10^{-4} cc. or to 0.112 cu. mm., or 1.6×10^{-7} g. Expressed in another way the dissolved oxygen can be determined to 0.016 part per million by weight. These estimates of the sensitivity of the method are substantiated by the curves and particularly the data of Table I.

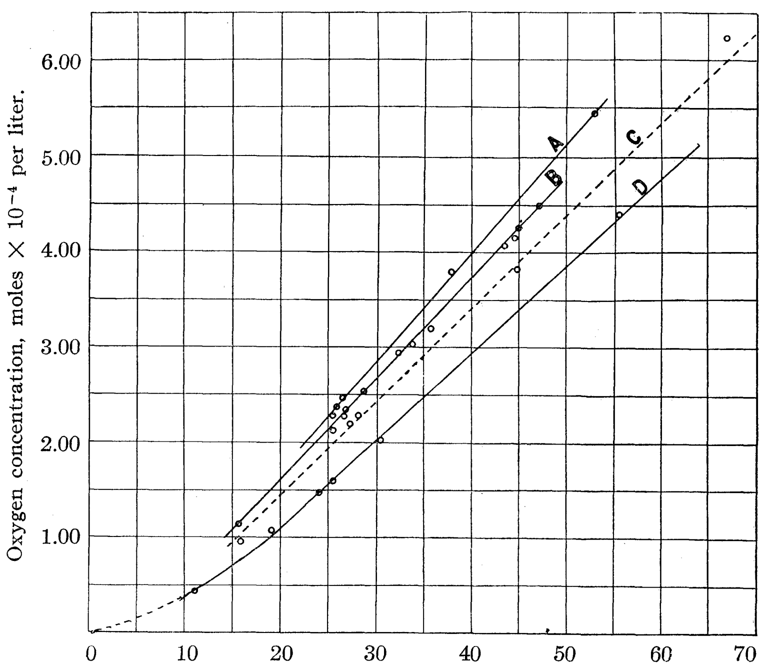

Fig. 4.

A simple calculation shows that the passage of current during the reading of the galvanometer deflections is far too small to cause detectable change in concentration by electrolysis.

The straight line relation between concentration and current apparently fails to hold below a concentration of about 5×10^{-5} mole per liter. The straight lines do not extrapolate to zero current at zero concentration, an observation which has been discussed by several investigators. In curve D of Fig. 4 special effort was made to determine the relation between concentration and current in this region. The Winkler method loses its sensitivity at these low concentrations and hence the true situation is difficult to determine. The curve bends toward the axis so that it extrapolates to zero, and this fact has been checked by other determinations. Despite this complexity, it is possible to use the method outlined here for low concentrations of oxygen by interpolating on the curve even where the straight line relationship does not hold.

The limitations of this simplified method should be summarized. The substitution of two empirically-determined voltages for the complete polarogram is possible only after a complete voltage–current curve has been plotted, and the proper voltages checked by independent chemical or physical determinations of the concentration of dissolved oxygen. However, after these voltages have been established it is no longer necessary to determine these complete curves. The preliminary curves can be prepared, manually, with simple apparatus. Calibration must be carried out for each cell and tip, and for each new type of solution unless it can be shown that no interfering substances are present. However, such calibrations are necessary, also, in the complete polarographic method. Calibration can be effected by direct chemical analysis as with the Winkler method, or by removal of oxygen by the bubbling of hydrogen and the addition of measured quantities of oxygen. It might be argued that, with this calibration method, a single voltage rather than two voltages would be sufficient, but the zero point of the galvanometer fluctuates with temperature and accidental variations in the amount of iron and other easily reducible substances give large fluctuations in the galvanometer deflections even at 0.1 volt. The fluctuations are cancelled out by taking the difference between two voltages, 1.0 and 0.1 v., for example, when analyzing for oxygen. The maximum deflections of the galvanometer are taken at a given voltage and these maxima are read easily when the mercury is dropping at the rate of one drop every second or second and a half. Although this rate may be considered somewhat rapid for producing a "theoretical" curve, it has been shown to be entirely satisfactory for the method described here.

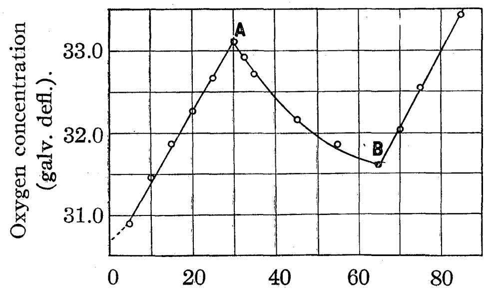

Fig. 5.

Applications

The accuracy and the quick response of this method is clearly shown in Fig. 5 where the photosynthesis of algae is protrayed. In this experiment light from a 500-watt projection lamp was filtered through 9 cm. of 0.025 *N* cupric sulfate and a Corning No. 243 filter. This red light at about 3500 ergs per second per sq. cm. was passed into a vessel containing *chlorella pyrenoidosa* suspended in Warburg nutrient solution, 16,000,000 cells per cc. The steady evolution of oxygen is indicated by the straight line with a positive slope. At point A, the light was turned off and photosynthesis stopped, but the respiration of the algae continued. The negative slope shows that oxygen is being consumed by the respiration. It is of interest to note that the rate of respiration, *i. e.*, the slope of the line, is greatest just after removal of the light. It was, in fact, to study this rate of respiration just after the exposure to light that this method was developed. Chemical analysis and differential manometric methods have failed to give information of any degree of definiteness or consistency about this rate of respiration immediately after exposure to light. When the light is turned on again at B, the photosynthesis immediately releases oxygen and the net effect of respiration and photosynthesis is a uniform increase in concentration of oxygen as before. The slopes of the oxygen concentration–time curves during exposure to light are identical within experimental error.

Before using this method it was necessary to prove that mercury is not toxic to chlorella—at least not in the concentration to which this method subjects the algae. Algae were cultured in the presence of 1 cc. of purified mercury of the grade used in the dropping mercury electrode. The algae grew normally along with many controls which were a part of the regular culture stock maintained for experimental purposes. No differences were noticed in the appearance of the algae grown in the presence of and in the absence of mercury, nor was there any noticeable difference in the total growth at the end of seventeen days. The algae which were grown in the presence of mercury respired and photosynthesized in the same way as those which were grown in the absence of mercury. Likewise, Mr. Albert E. Dimond of the Botany Department, who furnished the yeast used in some of these experiments, found that yeast is not affected by the presence of the mercury in these experiments.

Other applications of the analysis of oxygen by the dropping mercury electrode method are given in Fig. 6. Curves A, B, C, and D are for the respiration of yeast. They show how the respiration rate increases with the concentration of cells and with the addition of glucose. Curve E is for the oxygen uptake of homogenized rat liver tissue in the presence of sodium succinate four hours after the rat had been killed. The volt–current curve for this material is shown in Fig. 1, D. Curves F and G give the respiration rates of red blood cells from chickens. F and G are for the same cells, but G was obtained with a suspension in which the concentration of cells is about one-third that of F. Curve H shows the respiration of the red cells of dog's blood in vitro and it is particularly interesting because the respiration is so slight that it can be followed by other methods only with great difficulty. Accordingly, the de-

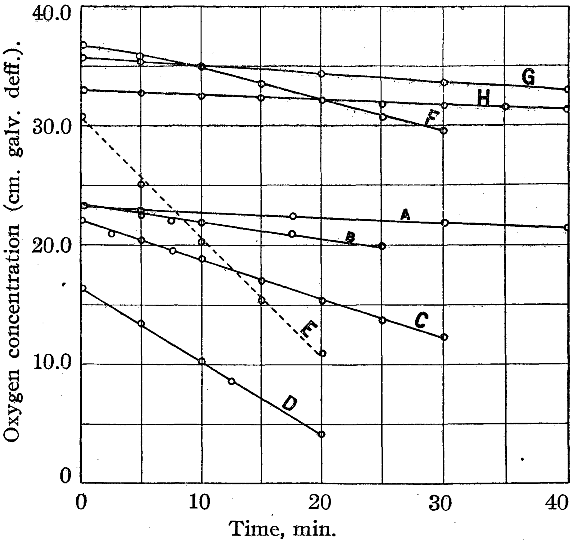

Fig. 6.—A. Yeast in physiological salt solution—3 × 10^6 cells/cc. B. Yeast in physiological salt solution + 1% glucose—3 × 10^6 cells/cc. C. Yeast in physiological salt solution + 6% glucose—3.3 × 10^6 cells/cc. D. Yeast in physiological salt solution + 6% glucose—6.6 × 10^6 cells/cc. E. Homogenized liver tissue in Krebs phosphate buffer + sodium succinate. (7.13 g. rat liver + 400 ml. buffer solution + 0.5 g. Na succinate.) F. Chicken's red blood cells—Ringers bicarbonate buffer—9 × 10^7 cells/cc. G. Chicken's red blood cells—Ringers bicarbonate buffer—3 × 10^7 cells/cc. H. Dog's red blood cells—Ringers bicarbonate buffer—60 × 10^7 cells/cc.

TABLE I

RESPIRATION OF DOG'S BLOOD

60 × 10^7 cells per cc. Temperature, 24.5°. According to the calibration of the electrode 1-cm. deflection = 3.88 cu. mm. of O_2. Over-all uptake of O_2, 7.56 cu. mm. Average uptake of O_2, 0.84 cu. mm. in five minutes.

Time, min.	Galvanometer deflection, cm.	Time, min.	Galvanometer deflection, cm.
0	33.10	25	31.95
5	32.90	30	31.75
10	32.60	35	31.70
15	32.40	40	31.45
20	32.20	45	31.15

tails of the experimental measurements are given in Table I and the volt–current curve for the dog's blood is shown in Fig. 1 at curve C.

When the chicken and dog blood are put on the same basis of concentration of cells, it is seen that chicken blood takes up in thirty minutes twenty times as much oxygen as the dog blood. The cells of the chicken bloods are nucleated while those of the dog blood are not.

Measurements were made on the dog blood cells at the same time using a Barcroft–Warburg manometer. However, the oxygen uptake was too small to be measured with any accuracy by the manometric method.

Another application of the method described here lies in the determination of the oxygen content of soils. This analysis has been beset with many difficulties and the values which have been obtained have little significance according to many workers in soil culture. The methods described here may be used, by determining first the oxygen content of a given volume of 0.1 *N* potassium chloride solution, and then determining the oxygen content after adding a sample of soil and allowing equilibrium to be established. In one sample of loam, 33 cu. mm. of oxygen was found to be associated with 1 g. of soil with a moisture content estimated as 30%.

The apparatus is portable and it can be made adaptable to field use such as determining the oxygen content of lakes at different depths.

There are other fields of study in biology which might be attacked with this precise method of oxygen analysis such for example as the study of the border line between aerobic and anaerobic bacterial action, the respiration of small amounts of tissue and nerve material, the accurate measurement of the respiration of cancer cells and the study of the influence of drugs and various diseases on the respiration of blood.

Although this investigation has been limited to the determination of dissolved oxygen, it is likely that other substances can be determined in the same simple way. Calibration curves with galvanometer deflections plotted against concentration are plotted at several different voltages and that voltage (or rather the difference in current between two voltages) is selected which gives a straight line for a calibration curve. Aside from giving the confidence which results from a straight line relationship over a wide range of concentration, this method renders unnecessary any expensive recording apparatus and enables one to make an analysis on systems undergoing rapid chemical or biological change.

The authors are glad to acknowledge the support given this investigation by the Research Committee of the Graduate School and the Wisconsin Alumni Research Foundation. They are indebted to Professor B. M. Duggar of the Botany Department in whose laboratory much of the work was done. They wish to thank Professor V. W. Meloche for his helpful interest and for the use of a polarograph in a preliminary test. They appreciate the help given by Mr. A. Axelrod in the measurements with the Barcroft manometer and by Mrs. N. Dimond in preparing the algal cultures.

Summary

1. A method using simple apparatus is described for measuring the concentration of dissolved oxygen. A dropping mercury electrode is used and galvanometer deflections are measured at two predetermined voltages. The deflections are plotted against solutions of known concentrations giving a calibration curve which is a straight line.

2. The limitations of the method are pointed out and the method is illustrated with the photosynthesis and respiration of algae and with the respiration of yeast and blood cells and with animal tissue.

MADISON, WISCONSIN

RECEIVED AUGUST 8, 1938

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF GENERAL ELECTRIC COMPANY]

Salted-Out Protein Films

BY IRVING LANGMUIR AND VINCENT J. SCHAEFER

Proteins can be adsorbed from aqueous solutions onto a plate, covered by barium stearate multilayers, which has been conditioned[1,2] by previously dipping it into a solution of thorium nitrate. When a 1% solution of insulin is applied in this way to a conditioned plate and this is then washed in distilled water, and dried, a film of a thickness of about 45 Å. is obtained. However, if the protein solution is washed off the plate with an 0.8% sodium chloride solution instead of with water and the plate is then washed with distilled water and dried, the film thickness is much greater, ranging from 70 to about 200 Å. The variations in thickness seem to depend upon the rapidity of mixing the salt solution with the underlying protein solution.

These results suggested that the increased thickness due to the application of the salt solution directly to the protein solution on the plate was caused by the concentration gradient in the solution while the salt diffused into the insulin solution. Confirmation of this hypothesis was obtained from experiments in which 0.8% sodium chloride was added to the insulin solution before applying this to the conditioned plate. After washing this off with sodium chloride solution and then with water, the normal thickness of about 45 Å. was found.

The effect seems to be analogous to the Ludwig–Soret effect in which a temperature gradient causes a migration of a solute to the cold part of a solution. The theory of this phenomenon has not been satisfactorily worked out. A simple explanation often given is that the molecules of the solute are bombarded by the solvent molecules with greater intensity on the high temperature side than on the low temperature side. Such an explanation seems particularly useful in accounting for the Soret effect in air commonly manifested by the slow accumulation of dust particles at cold spots on the ceiling of a room.

According to S. Chapman[3] particles having a large diameter compared to the free path of the molecules in a liquid should distribute themselves in such a way that cD is constant throughout the solution, c being the concentration of the particles and D the diffusion coefficient. Thus, since the diffusion coefficient increases with temperature, the concentration should be less in the hotter parts. Bruzs[4] attempts to develop a thermodynamic theory and concludes that the Soret coefficient σ depends upon the entropy and the partial molar specific heats. There are, however, practically no experimental data for checking this theory.

Hartley,[5] after discussing the preceding theories, advances reasons for believing that the relative solubilities of the solute in the solvent, at different places in the tube, are important in determining the Soret coefficient.

In a second paper,[6] Hartley considers the distribution of solute molecules in a solvent of graded composition. Apparently in all cases if there is one component A originally uniformly distributed throughout a solvent, the effect of a concentration gradient in a second component B is to drive the molecules of A toward the region where B has a low concentration. We shall designate this as the carrying effect.

Hartley believes that there are three factors that determine the magnitude of this forced migration. First there is the Chapman effect, according to which the particles should migrate toward the region where the diffusion coefficient is lowest. Thus, if the presence of a substance B increases the diffusion coefficient of substance A, A should tend to move into the region where B has a low concentration. It seems improbable, however, that the general effect of dissolved substances should be to raise the diffusion coefficient of other substances, so that Chapman's theory seems inadequate as a general explanation of the carrying effect.

As a second factor, Hartley considers the effect of the added substance B on the solubility of A.

The third factor he describes as a "push effect." The larger molecules are subjected to greater bombardment by diffusing molecules than small ones.

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(1) I. Langmuir and V. J. Schaefer, THIS JOURNAL, **59**, 1406 (1937).

(2) I. Langmuir and V. J. Schaefer, *ibid.*, **59**, 1762 (1937).

(3) S. Chapman, *Proc. Roy. Soc.* (London), **A119**, 34 (1928).

(4) B. Bruzs, *Z. physik. Chem.*, **A162**, 31 (1932).

(5) G. S. Hartley, *Trans. Faraday Soc.*, **27**, 1 (1931).

(6) G. S. Hartley, *ibid.*, **27**, 10 (1931).

Hartley assumes that the pressure exerted is approximately proportional to the mean cross-sectional area of the large molecules. Thus an enormous push effect is to be expected in the case of colloidal particles. This simple explanation of the "push effect" cannot be generally valid, for it would indicate that a sphere the size of a baseball placed at the boundary between a molar salt solution and overlying pure water should be forced upward with a force of about 1000 lb. It is obvious, however, that any pressure difference greater than that due to gravity will be equalized by a flow of liquid. It is only when the particles are of a size comparable to the free path of the molecules of the liquid that an appreciable push effect can exist.

Recently Seastone[7] found it impossible to spread monolayers of tobacco mosaic virus by Gorter's method on the surface of water adjusted to a *p*H corresponding to the isoelectric point of the protein. At *p*H 1 there was a small amount of spreading corresponding to about 0.1 sq. m. per mg. Since the protein solution when applied sank to the bottom of the tray and so could diffuse only slowly to the surface, Seastone attempted to spread the protein on a solution of higher density, using for this purpose a 25–90% saturated ammonium sulfate solution. The protein solutions, and even distilled water, spread with almost explosive rapidity on such strong salt solutions, for these have surface tensions that exceed that of pure water by several dynes per cm. With 90% saturated ammonium sulfate at *p*H 7.1, a film of virus covering an area of 0.06 sq. m. per mg. was obtained. Measurements of the virus activity proved that little or none of the tobacco virus remained in the liquid under the film. If this film has a density 1.3 and if it contains all the protein applied to the solution, its thickness should be 126 Å. In another case Seastone reports that a film of a thickness of 1000 Å. was obtained by applying tobacco mosaic virus to a 50% saturated ammonium sulfate solution. He suggests that these thick films may correspond to monolayers in which the rod-shaped molecules of diameter 150 Å. lie flat in the surface in some cases and lie with their long axes perpendicular to the surface in other cases.

The work of Gorter and Philippi shows that many proteins spread to give films of thicknesses from 7 to 20 Å. under compressions to 0 to 10 dynes per cm. Some samples of tobacco virus sent to us over a year ago by Dr. Stanley gave films of approximately this thickness. About six months ago, Dr. Stanley sent us some new samples of 1.9% tobacco virus purified by ultracentrifuge sedimentation. With a spreading technique which we had used previously, which was a modification of Gorter's, we were unable to obtain monolayers. When this solution of tobacco virus was spread upon ammonium sulfate solution we obtained very thick films, ranging from 100 to 2000 Å.

Our experiments showed clearly that the film thickness was not determined by the molecular diameter but depended on the concentration of the salt solution and on the amount of protein applied in relation to the area available for spreading.

When a drop of tobacco virus solution is placed upon a concentrated ammonium sulfate solution, the drop spreads over the surface because the surface tension of the water is less than that of the salt solution. We have observed that one drop of distilled water (0.05 ml.) spreads on a saturated ammonium sulfate solution to form a film 5×10^{-4} cm. thick and of an area of about 100 sq. cm., as shown by the pushing back of a film of indicator oil on the surface of the solution. A pressure of only one dyne per cm. causes the immediate collapse of the circular area covered by the water film.

The rate of diffusion of salt from a solution into an overlying layer of initially pure water can be calculated by methods used in problems of heat conduction.[8]

Consider a salt solution of concentration c_0 on which is placed at time $t = 0$, a layer of water of thickness b. Then, if x is the depth below the surface, the concentration c is initially 0 between $x = 0$ and $x = b$, and is c_0 for $x > b$. The concentration gradient has a maximum value at $x = b$ which is given (for not too large values of t) by

$$\mathrm{d}c/\mathrm{d}x = (c_0/2)(\pi D t)^{-1/2}$$

where D is the diffusion coefficient of the salt.

For values of x small compared to b, the concentration gradient is at first very small but rises to a maximum and then decreases toward zero. The maximum value of $\mathrm{d}c/\mathrm{d}x$ occurs when $t = b^2/6D$ and is given by

$$(\mathrm{d}c/\mathrm{d}x)_{\text{max.}} = 0.93 c_0 x/b^2$$

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[7] C. V. Seastone, *J. Gen. Physiol.*, **21**, 621 (1938).

[8] Ingersoll and Zobel, "Mathematical Theory of Heat Conduction," Ginn and Co., New York, N. Y., 1913; see especially Eq. (25) on p. 70.

At this time the concentration at the surface $x = 0$ is only $0.084c_0$; at $x = b/2$ it is $0.198c_0$ and at $x = b$ it is $0.5003c_0$. The concentration gradient at $x = b/2$ is then $0.45c_0/b$.

The diffusion coefficient D for salts in water is of the order of magnitude of 10^{-5} cm.^{2}/sec. Thus the maximum concentration gradients close to the surface will occur within less than a second, even if the water film has a thickness as great as 0.08 mm., which corresponds to 0.8 ml. per 100 sq. cm.

Although the concentration gradient reaches its maximum within such a short time, the actual concentration of salt in the surface (at $x = 0$) approaches its limiting value very slowly. Thus to reach $0.9c_0$ will require a time $32b^2/D$ and to reach $0.99c_0$ takes $t = 3200b^2/D$. With $b = 5 \times 10^{-3}$ cm., $D = 10^{-5}$ cm.^{2}/sec. One hundred and sixty seconds would be required for $c = 0.9c_0$ and four and one-half hours for $c = 0.99c_0$.

The thick films of tobacco virus observed by Seastone and confirmed by our experiments thus appear to be essentially salted-out films in which the protein is forced to the surface by the concentration gradient of the salt until the protein concentration becomes so high as to cause a crystallization of the protein into a thin sheet.

Recent work[9,10] has shown that highly purified tobacco virus solutions, if stronger than 2%, separate into two phases on standing. The lower layer, usually water clear, is liquid crystalline; the upper layer, which is slightly turbid, shows, on gentle agitation, anisotropy of flow.

X-Ray examination has shown that in the denser phase the rod-shaped molecules lie with their axes parallel, but in a plane perpendicular to this direction the molecules are arranged in a hexagonal close packed lattice with a spacing which varies continuously from 150 to 600 Å., depending upon the concentration of the solution. The lower limit of 150 Å., obtained when the water content is very low apparently corresponds to the diameter of the molecular rods.

The forces that hold the molecules apart in the hexagonal lattice are recognized as being electrostatic forces associated with the negative charges on the molecules. The intervening water must therefore carry an excess of ions of the opposite polarity. The spindle-shaped crystals of tobacco virus observed by Stanley and others have been shown to have a similar structure and are thus tactoids in which the distance between molecules depends on the water content.

We believe that in our experiments the concentration gradient of ammonium sulfate forces the tobacco virus to the surface in such concentration that this denser phase appears. Probably the molecules are arranged with their axes parallel to the surface and in transverse directions are packed in a hexagonal lattice.

Films Salted-Out onto Plates.—The salted-out films of insulin produced on a plate by applying a few drops of insulin solution and then washing this off by pouring over it a salt solution were very non-uniform in thickness. We attempted in several ways to develop a technique of producing uniform films.

Using one method, we saturated filter paper, blotting paper or silk fabrics with an insulin solution, applied this in one or more layers onto a wet, conditioned barium stearate multilayer and placed on top of this other layers of porous paper or fabric wetted with salt solution. After two minutes the layers of paper were lifted off, the film was washed with water and dried, and the thickness was determined by matching the color of the specularly reflected light with that given by a barium stearate stepped color gage.[11,12] With 0.05 ml. of 0.1% insulin on 3 sq. cm. filter paper covered with paper saturated with 90% saturated ammonium sulfate solution, a film 220 Å. thick was produced.

This represents nearly 20% of the protein applied to the paper. With more concentrated insulin solutions (up to 10%) film thicknesses, in some cases as great as 650 Å. were obtained, but the fraction recovered was much less. The films produced by this method were usually of unsatisfactory uniformity.

The best method we have found for producing salted-out films directly on a plate is as follows. A prepared plate covered with barium stearate multilayers is conditioned by thorium nitrate so as to render it hydrophilic and it is then dipped into a solution of the protein. It is important that the plate first should be rendered hydrophilic for otherwise when it is dipped into the protein solution a film is deposited on the down trip.

The plate is lifted from the protein solution at a rapid uniform rate, the adhering liquid is allowed to drain for a few seconds and the surplus removed from the lower corner of the plate by filter paper. The plate is then quickly immersed into a strong salt solution in a beaker and allowed to stand for a few minutes. It is then taken out of the salt solution and dipped successively for twenty seconds into each of several beakers containing 1% tannic acid solution. The plate is then washed thoroughly in distilled water, dried and the thickness of the protein film is measured optically.

The tannic acid renders the protein film insoluble so

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[9] F. C. Bawden, N. W. Pirie, J. D. Bernal and I. Fankuchen, *Nature*, **138**, 1051 (1936).

[10] J. D. Bernal and I. Fankuchen, *ibid.*, **139**, 923 (1937).

[11] K. B. Blodgett and I. Langmuir, *Phys. Rev.*, **51**, 964 (1937).

[12] I. Langmuir, V. J. Schaefer and H. Sobotka, THIS JOURNAL, **59**, 1751 (1937).

that it can be washed with water without loss. Salted-out films of insulin, however, suffer no loss, even without the tannic acid treatment. When tannic acid is used with insulin the film is 12 Å. thicker. We assume that with other proteins the use of tannic acid gives a similar increment of thickness.

The thicknesses of films of insulin, salted-out from a 0.5% insulin solution by applying sodium chloride solutions, increase from 90 Å. with 0.3% salt to a maximum of 340 Å. with 1% salt, decreasing to 190 Å. at 3% and to 140 Å. with salt solutions between 10 to 35%. Variation of the *p*H of the salt solution between 4 and 7 gave little or no change in thickness.

Salted-out films of pepsin (Eli Lilly's, 8000 units per gram), formed by using saturated ammonium sulfate solutions at *p*H from 2 to 5 gave 100 Å. from a 0.1% protein solution, and up to 600 Å. with a 5% protein solution. With a 0.5% pepsin solution, thicknesses of only 50 Å. were obtained with ammonium sulfate up to 25% saturated, and the thickness increased from 150 to 225 Å. as the concentration of the sulfate solution was raised from 50 to 100% saturation.

The salted-out films produced in this way were very uniform, but scattered a good deal of light (more than the films produced by the use of impregnated filter paper).

Films Salted-Out on the Surfaces of Salt Solutions.—A tray is filled with a strong solution of some salt such as ammonium sulfate, or magnesium sulfate and its surface is cleaned in the usual way. Barriers are placed across the tray to delimit a definite area.

A graduated 1-ml. hypodermic syringe is filled with the protein solution and by a micrometer screw the plunger is forced down a definite distance so as to deliver a given volume of solution. By Gorter's method the protein solution is introduced from the needle just under the surface of the salt solution. Because of the relatively high density of the salt solution, it is equally satisfactory to let drops of the protein solution fall upon the surface. Another method, which we call the "band method," consists in distributing the protein solution along a line near the edge of a thin nickel or platinum band which has a length equal to the width of the tray and has been cleaned by heating in a flame. Before the protein solution has dried, the band is lowered slowly edgewise into the tray close to one end of the delimited area.

The protein solution applied by either of these methods spreads rapidly over the salt solution, and the protein is driven to the surface by the concentration gradient. If the bottom of the tray has been made black (by black Bakelite varnish, baked on, or by a sheet of black glass) and the thickness of the protein film on the solution exceeds about 200 Å., it is visible because of the increased reflection from the surface. There is usually a part of the surface farthest from the point of application that is covered by an invisible monolayer, 10–20 Å. thick, which was formed from the first portion of the applied protein solution and which was pushed against the barriers and so retarded the further spread of the protein solution. A surface pressure of about 15 dynes per cm. can be observed against a movable barrier under these conditions.

The salted-out film on the surface should be allowed to age for two minutes so that it may reach its maximum thickness and stability.

Optical Measurement of Thickness.—Sometimes the salted-out protein films on the salt solutions are so thick, 1000–7000 Å., that interference colors are seen. There are two convenient methods of producing films of known thickness on water which serve as comparison standards. A few drops of 10% sulfuric acid applied to the edge of a barium stearate multilayer (49 to 120 layers) on glass creeps under the film and detaches it so that it may be floated off onto water in a tray. Since water has a lower refractive index (n = 1.33) than the film (n = 1.50), the interference colors are complementary to those observed when the same film is on chromium or on glass of refractive index higher than 1.55.

Table I gives the number of layers and the thickness of barium stearate multilayers on water which give various colors when examined at an angle of incidence of 45°.

The second method consists in spreading a weighed amount of indicator oil (partially oxidized lubricating oil) on water and compressing the film between barriers to confine it to known areas so that the thickness can be calculated. The relation between the thickness and the color of the oil films was approximately the same as that of the stearate films given in Table I.

TABLE I

COLORS OF THIN OIL OR STEARATE FILMS ON WATER OBSERVED WITH UNPOLARIZED LIGHT AT i = 45°

Color	No. of layers	Thickness, Å.
Gray	33	800
Faint yellow, first order	49	1200
Yellow	57	1400
Dark yellow	65	1600
Yellow-red	73	1800
Bluish-red	81	2000
Purple-blue	89	2200
Blue	97	2400
Bluish-green	105	2600
Yellow-green	115	2800
Yellow, second order	122	3000

A salted-out film produced by applying 0.3 ml. of a 1% solution of commercial egg albumin in successive drops to the central portion of a 100-cm. area of a 90% saturated ammonium sulfate solution gave at the point of application a disk of about 5-cm. diameter showing a light yellow color, while on the solution. The film around this disk showed only a gray color. Some of the film from the colored disk, transferred to a chromium plate by the "lift method" (to be described later), fixed by dipping into 1% tannic acid, then washed and dried, gave a purple-blue, about the same as that given by 45 layers of barium stearate on chromium observed at i = 50°. A portion of the same film transferred to a fused quartz plate, n = 1.46, showed a yellow color. On a microscope slide (n = 1.51), the color was light blue, while on lead glass (n = 1.6) the film gave an intense blue color. These data show that the film had a refractive index between 1.46 and 1.51, probably close to 1.48, and that the thickness was about 1100 Å. The refractive index of protein calculated from that of solutions is usually found to be approximately

1.58. It has been shown previously[13] that built-up films of egg albumin gave a refractive index for Na light of 1.50. Thus it is probable that the salted-out films and the built-up films contain water or air which lowers the refractive index. Experiments show that paper wet with a drop of octane held above a thick salted-out protein film on water or over the same film deposited on a chromium plate produces striking changes of color just like those observed by bringing these vapors in contact with skeletonized barium stearate films. These facts seem to indicate that these thick protein films are skeleton films which contain a considerable proportion of water or air.

Similar films of 1200 Å. thickness were produced by applying 0.5 ml. of a 1% solution of crystalline pepsin (Northrop) to 90% saturated ammonium sulfate.

Dr. W. M. Stanley gave us a 1% solution of some centrifuged monodispersed tobacco mosaic virus. When 0.1 ml. was applied to 100 sq. cm. of 90% saturated ammonium sulfate solution, a grayish colored film of considerable rigidity was formed covering an area of about 55 sq. cm. This was deposited upon a chromium plate and fixed in 1% tannic acid. After washing and drying, the film, when examined with the R_s ray at large angles of incidence, showed a second-order yellow corresponding to a thickness of 120 barium stearate layers or 2900 Å. At an angle of incidence $i = 45°$, this gives a purple color. Thus we should expect the film on water before deposition on the plate to have shown the complementary color, *viz.*, a second-order yellow (see also Table I). During the growth of the film, the colors should have changed from first-order yellow through purple, blue-green, to second-order yellow. Actually, however, the films on water show only a strong grayish reflection, which forms a strong contrast with a clean water surface.

The probable explanation of the absence of interference colors of the tobacco virus films on water is a graded lower boundary which does not provide the definite reflection needed for interference. When the film is deposited on a plate, fixed, washed and dried, the upper surface which was previously the lower surface now has a definite boundary and gives good interference colors.

With several proteins, egg albumin, pepsin, urease, edestin and horse globulin, we have observed that the salted-out films formed are of a composite type. Thus, if a drop of a 1% solution of one of these proteins is applied to the center of the clean surface of a 90% saturated ammonium sulfate solution about 100 sq. cm. in area, a faintly visible gray film instantly covers the surface followed within a few seconds by the formation in the central part of a circular area 2 to 5 cm. in diameter which first appears black (similar to a clean surface). This area is soon filled in with a grayish film, starting at the outer edge and gradually filling the interior with a uniform film which gradually increases in reflecting power. A second drop applied to the same place sinks into the salt solution and then rises and dissolves this film, producing a black region as previously described. This is followed by the appearance of a film similar to the previous one in formation but much thicker, often showing intense interference colors extending even into second- or third-order colors, depending largely on the purity and concentration of the protein solution used.

A large area of the film on the surface, including the colored spot, is now deposited on a chromium plate and is fixed by gently flooding over the surface a 1% tannic acid dissolved in 90% ammonium sulfate saturated solution. After washing and drying, it is usually found that interference colors are seen not only on the central disk but also far out into the surrounding area. Within the disk the thickness of the film as determined by the colors observed after deposition agrees with that determined from the color seen on the salt solution. The portions surrounding the disk, however, now give colors which correspond to very great thicknesses, often as large as 7000 Å.

These phenomena seem to show that these salted-out protein films are essentially composite and consist of two layers, a *diffuse layer* which has an indefinite lower boundary and thus produces no interference effects while on the solution, and a second or *compact layer* which overlies the diffused layer on the solution and which has a definite lower boundary giving good interference colors. The compact layer is of uniform thickness within the central disk and gradually decreases with increasing radii over the surrounding surface. The diffuse film is far thicker than the compact film and decreases steadily in thickness as the radius increases. Originally, while the film is on the solution, the diffuse film has a maximum thickness under the central disk; but while depositing this on the plate and subsequently fixing it with tannic acid, the thickest parts of this diffuse film usually break away, within a circular area, leaving within this only the compact film on the plate. By agitating the salt solution under the film or by more vigorous treatment with tannic acid fixing solution, the area from which the diffuse film is removed may be increased greatly without altering the thickness of the compact film.

The thickest compact films are obtained by using protein solutions of very high purity. For example, we find that solutions of pure crystalline egg albumin (given by Dr. P. A. Levene) give far thicker compact films and form them in far less time than when an impure egg albumin is used.

The compact film, which is usually very uniform in thickness over the central disk, acts as though it were a single crystal sheet; the diffuse film frequently may be seen upon stirring the underlying solution as a veil which scatters an appreciable amount of light and can be moved about under the compact film. It perhaps consists of a suspension of very fine crystals.

With insulin we have not been able to produce these composite films. When this protein is applied to a 90% ammonium sulfate solution, a white cloudy precipitate is formed but no coherent film. On 1% ammonium sulfate the insulin spreads to form a monolayer. When a 1% insulin solution is applied to an unlimited area of a 1% sodium chloride solution, an insulin monolayer is formed, but with a restricted area the pressure builds up to $F = 18$ dynes per cm. and a circular grayish area appears, which after deposition on a plate gives a thickness of 115 Å. It is not necessary to fix this deposited film with tannic acid, for it can be washed gently with water without loss. However, the salted-out film formed on the salt solution gradually decreases in thickness to 50 Å. if left for five minutes before deposition.

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[13] K. B. Blodgett, *J. Phys. Chem.*, **41**, 975 (1937); see p. 980.

In many experiments we have made estimates of the total amount of protein which can be recovered in the salted-out films by transferring them to metallic surfaces, or we have determined the protein content per sq. cm. by a method which we shall describe later involving the production of monolayers on another water surface. In general, with pure crystalline egg albumin, tobacco virus and pepsin, there is a very high recovery in the film.

With impure proteins such as commercial egg albumin or pepsin, the fraction of applied protein which is recovered in the salted-out film is much lower. Apparently there is a purification of the crystallizable protein involved in the formation of the salted-out film, so that the yield serves to measure the crystallizable protein content.

Properties of Salted-Out Films.—The thick salted-out films of protein, particularly the compact ones, possess considerable mechanical strength and are relatively incompressible. When subjected to moderate pressure, they can be lifted off the solution on a loop of platinum wire.

A film produced from crystalline egg albumin, on an ammonium sulfate solution, having a thickness of 1000 Å. and showing a light yellow interference color, was found to be under a pressure of $F = 23$ dynes per cm. at the time it was formed. On raising the pressure to 30 dynes per cm. the area decreased only 2%, corresponding to a compressibility of 0.0030 for each dyne per cm. On raising the compression to $F = 50$, the area decreased 17%, corresponding to a compressibility of 0.0080. At this higher pressure groups of parallel wrinkles began to appear, especially when slight shearing stresses were applied. At $F = 54$, the whole surface became wrinkled and collapse set in. For comparison we note that a monolayer of egg albumin on water decreases to half its area when F is raised from 1 to 25 and to one-quarter the original area at $F = 34$. In the F range from 23 to 30 the compressibility was 0.07 for the monolayer as compared to 0.003 for the salted-out film.

Transference of Salted-Out Films to a Water Surface.—If a piece of nickel or platinum foil cleaned and made hydrophilic by heating in a Bunsen flame, is lowered into a salt solution covered by a salted-out protein film under compression of $F = 30$ dynes per cm. produced by a drop of oleic acid, and is then raised out of the solution, the film is deposited on the foil as a hydrous B-film. If, now, before the water film under the protein film has dried, the foil is lowered into clean water in another tray, the protein film escapes onto the water surface.

Salted-out films of many proteins, such as pepsin, insulin and egg albumin, when transferred in this way to water, which preferably has its *p*H adjusted to the isoelectric point of the protein, spread out apparently without appreciable loss to form typical monolayers. By measuring A_2, the area of the monolayer at some value of F, such as 16 dynes per cm., and determining the thickness T_2 of the monolayer at the same compression, we can calculate the weight, W_2, of the protein transferred to the water by the relation

$$W_2 = 1.3 \times 10^{-5} A_2 T_2 \qquad (1)$$

where W_2 is expressed in mg. and T_2 in Å.

The thickness T_2 can be measured optically after depositing the monolayer on a barium stearate multilayer film of critical thickness (45–47–49 layers), preferably by the "lift method" in which the plate is lowered horizontally onto the monolayer (H-layer) and then after the surface has been cleaned, raised from the water. By this method a single monolayer of A_L-type is deposited.

The thickness T_1 of the original salted-out film can now be calculated from the equation

$$T_1 = A_2 T_2 / A_L \qquad (2)$$

where A_L is the area of the "lifted film" taken from the salted-out film. Our experience has been that this is usually a more accurate method of determining T_1 than a direct optical measurement of the salted-out film on the water or on a plate upon which it may be deposited. The reason for this is that the optical measurements are often difficult because of a relatively large amount of scattered light from the thick protein films. The method, however, is not applicable to tobacco virus and other proteins which do not spread to form monolayers.

Table II gives a summary of data obtained in studies of salted-out films of various proteins on 90% saturated ammonium sulfate solutions. The insulin (L) was a pure crystalline product obtained from Eli Lilly and Company, while the pepsin (L) was a commercial grade from the same source having an activity (skim milk test) of 8000 units per gram. A similar test of the activity of Northrop's crystalline pepsin (N) gave 50,000 units per gram. The egg albumin (L) was also an impure commercial product.

The third column gives the concentration of the protein solution in percentage by weight. A measured volume of this solution (for example, 0.18 ml. in Experiment 1, and 0.033 ml. in Experiment 2) which contained the weight W_1 of protein as given in mg. in Col. 4 was applied in the middle of the delimited area (Col. 5) by Gorter's technique. The sixth column gives the approximate area of the salted-out film that was produced; Col. 7 gives A_L, the area of the salted-out film that was deposited onto a plate and subsequently transferred to the surface of water (at the isoelectric point of the protein) in another tray where it gave the area A_2 (Col. 8) when subject to a

TABLE II

SALTED-OUT PROTEIN FILMS ON 90% SATURATED $(NH)_2SO_4$

$T_2 = 16$ Å. at $F = 16$ dynes/cm.

1 Expt.	2 Protein	3 % by weight	4 W_1, mg.	5 Delimited area, sq. cm.	6 A_1, sq. cm.	7 A_L, sq. cm.	8 A_2, sq. cm. $F = 16$	9 T_1, Å.	10 β
1	Insulin (L)	0.1	0.18	300	170	4	18	72	0.88
2		1.0	.33	300	95	4	63	252	.94
3		10	2.50	300	110	4	340	1340	.77
4	Pepsin (L)	0.1	0.148	300	80	4	6	24	.17
5		1.0	.96	300	100	4	15	60	.081
6		10	9.6	300	50	4	127	510	.035
7	Pepsin (L)	10	2.7	300	30	4	42	170	.025
8		10	4.8		30	4	50	200	.016
9	Insulin (L)	1	1	50	40	5	217	700	.37
10		1	1	100	90	5	185	600	.70
11		1	1	200	140	5	110	350	.64
12	Pepsin (L)	1	1	50	30	5	53	170	.066
13		1	1	100	50	5	30	96	.062
14		1	1	200	100	5	73	116	.150
15	Egg albumin (L)	1	1	100	90	12.5	180	230	.27

compression of $F = 16$ dynes per cm. The thickness T_2 was found in the various experiments to range from 15 to 18 Å., so we have taken the average value $T_2 = 16$ Å. The thickness T_1 of the salted-out film, as given in Col. 9, was calculated by Eq. (2) from A_2, T_2, and A_L.

The last column gives β, the fraction of the protein applied to the salt solution which was recovered in the salted-out film. This was calculated by the equation

$$\beta = 1.3 \times 10^{-5} A_1 T_1 / W_1 \qquad (3)$$

Examination of the data in the table shows that with a large delimited area, Experiments 1 to 3, from 77 to 94% of the insulin was found in the salted-out film, but with the L-pepsin only from 8 to 17% was recovered, the highest fraction being obtained with the most dilute protein solution. The fraction recovered was not greatly dependent on the amount of protein solution applied (Experiments 6, 7 and 8). The thickest films were obtained with the most concentrated solutions (Experiments 3 and 6) and when the largest amounts of the protein solution were applied (Experiments 6, 7 and 8). In Experiments 9 to 14 the delimited areas were purposely varied. The fraction recovered is somewhat less when the available spreading area is restricted, but the thickness T_1 is made greater in this way (Experiments 9 and 12).

The high percentage of recovery from the insulin compared with pepsin suggested that this might be due to the difference in purity of the two proteins. We therefore made some experiments with a crystallized egg albumin obtained from P. A. Levene and a crystallized pepsin from J. H. Northrop. With these very high percentages of recovery were obtained. Films of various thicknesses, ranging from 100 up to 7000 Å., could be obtained by regulating the amount of protein in the delimited area.

The Activity of Pepsin in Salted-Out Films.—Uniform salted-out films of pepsin were produced by applying pepsin solutions to 90% saturated ammonium sulfate solutions. The thickness of the film was measured optically after depositing it on a chromium plate. Another portion of the film was deposited on a plate of known area and the protein was washed off with 2 ml. of 0.1 *M* acetate buffer, *p*H 5, into a test-tube containing 1 g. of powdered skim milk in 4 ml. of the same acetate buffer, and the clotting time at 37° was noted. The weight of the protein on the plate was calculated from the area, and thickness, assuming a density 1.3. In this way the activity per gram was determined. Similar tests of activity were made by introducing known weights of protein directly into the milk solution.

The results showed that Northrop's pepsin (50,000 units per gram) gave salted-out films having at least 90% of the activity of the original protein. On the other hand, with a commercial grade of pepsin (8000 units per gram) salted-out films were obtained which gave (per gram) four times the activity of the impure pepsin applied to the salt solution, although they were still only about 60% as active as the crystalline pepsin.

The production of salted-out films may thus prove to be a rapid and convenient microtechnique for purifying small amounts of various proteins. By the choice of the proper salt and concentration it should be possible to separate proteins from one another and to measure the amounts.

Summary

When a glass or metal plate is dipped into a protein solution, then into a concentrated solution of a salt such as ammonium, sodium or magnesium sulfate, or sodium chloride, a compact film of protein often 200–1000 Å. thick is salted out onto the plate. This can be fixed by 1% tannic acid and can then be washed with water without loss. After it has dried the thickness can be determined optically by interference colors. Insulin films, formed by using 1% sodium chloride solution, need no tannic acid treatment.

Salted-out protein films, in some cases up to 7000 Å. in thickness, are formed on the surface of salt solutions by applying a few drops of the protein solution. These can be deposited as hydrous B-films or as lifted A_L films onto plates or small pieces of metal foil, and they can thus be transferred to clean water surfaces where the amount of the protein can be measured from the area of the monolayer produced, or they can be fixed by tannic acid, washed and dried and the amount of protein per sq. cm. determined optically.

The refractive index of dried salted-out films of crystalline egg albumin was found to be 1.48. This low value and the power of the film to absorb hydrocarbon vapors indicate that the dried film has a skeleton-like structure.

The formation of these films at the surface of the solution or on a plate is aided by the concentration gradient in the salt solution. This carrying effect is analogous to the Ludwig–Soret phenomenon by which a solute originally uniformly distributed through a solution tends to concentrate in a portion of the solution which is cooled.

SCHENECTADY, N. Y. RECEIVED AUGUST 12, 1938

NOTES

Esters of Chlorosulfonic Acid[1]

BY W. W. BINKLEY WITH ED. F. DEGERING

While the lower alkyl esters of chlorosulfonic acid have been prepared, they have not been purified by redistillation and there is some disagreement in the values of the physical constants which have been reported.[2] We have therefore again prepared these substances and have purified them by careful rectification using a modified Podbielniak column and have redetermined with care certain of their physical constants.

The esters were prepared by adding dropwise one-fifth mole of the absolute alcohol to one-fifth mole of sulfuryl chloride contained in a test-tube 20 cm. long immersed in an ice-bath, the sulfuryl chloride being agitated by a brisk current of dry air drawn through it. A rough separation of the alkyl chlorosulfonate from the dialkyl sulfate was first accomplished by distillation under diminished pressure at the lowest possible temperature. The distillate was then rectified under diminished pressure in a jacketed electrically heated column which has a continuous nichrome wire gage No. 18 for packing.[3] An average yield of 50% based on the alcohol was obtained. The characteristic physical constants for these esters and other analyses are collected in Table I.

The chlorine content was estimated by a modified Fajans method[4] after the ester was allowed to decompose in a pressure bottle containing calcium carbonate. Sulfur was determined by the method of Carius.

All the lower normal esters of this series are lachrymators. The tear-producing effect decreases as the length of carbon chain is increased.

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[1] Abstracted from a portion of a thesis submitted by W. W. Binkley in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry, June, 1939.

[2] Bushong, *Am. Chem. J.*, **30**, 212 (1903).

[3] Podbielniak, *Ind. Eng. Chem., Anal. Ed.*, **5**, 119 (1933).

[4] Mellon, "Methods of Quantitative Chemical Analysis," The Macmillan Co., New York, 1937, p. 297.

TABLE I

	Methyl	Ethyl	*n*-Propyl	*n*-Butyl
Sp. gr. at 25°	1.48	1.35	1.28	1.23
Ref. index 20°	1.414	1.416	1.422	1.427
B. p., °C.	48.1 at 29 mm.	42.3 at 10 mm.	53.2 at 10 mm.	69 at 10 mm.
% S, calcd.	24.53	22.18	20.18	18.65
% S, found	24.8 ± 0.2	22.0 ± 0.2	20.4 ± 0.2	18.3 ± 0.2
% Cl, calcd.	27.13	24.54	22.38	20.56
% Cl, found	27.0 ± 0.1	24.5 ± 0.1	22.2 ± 0.1	20.5 ± 0.1

They are colorless liquids, insoluble in water, but quite soluble in the common organic solvents.

DEPARTMENT OF CHEMISTRY
PURDUE UNIVERSITY
LAFAYETTE, INDIANA

RECEIVED JULY 11, 1938

Nitrogen-Terminated Conjugated Systems and Maleic Anhydride

BY FELIX BERGMANN

The ability of 9-vinylphenanthrenes to condense with maleic anhydride[1] induced us to investigate whether conjugated systems consisting of a cyclic C–N double bond and an exocyclic ethylenic linkage would add maleic anhydride. 2-Styrylquinoline gave a well-defined reaction product, which, however, besides the components, contained one molecule of water, and therefore was styrylquinolinium maleate. This became obvious in its reaction with diazomethane, yielding dimethylpyrazoline-4,5-dicarboxylate.[2] Analogous observations have been made recently by La Parola[3] in the case of antipyrine and pyramidone. For comparison purposes, we studied the interaction between maleic anhydride and cinnamylidene-aniline, which contains the nitrogen-terminated conjugated system entirely in an open chain. Here, too, the reaction involves one molecule of water (from the air), but the maleate, presumably formed as above, is unstable and decomposes spontaneously into cinnamic aldehyde and maleanilic acid, HOOCCH=CHCONNH-C_6H_5.

Experimental

2-Styrylquinoline[4] (1.2 g.) and **maleic anhydride** (0.5 g.) were heated on the water-bath or in xylene solution for some minutes. The mixture turned yellow at once and deposited on cooling yellow crystals, which were recrystallized from xylene or butyl acetate. 2-Styrylquinolinium maleate formed long, silky needles, m. p. 165–167°. *Anal.* Calcd. for $C_{21}H_{17}O_4N$: C, 72.6; H, 4.9. Found: C, 72.8; H, 5.3. The salt was kept in contact with an excess of ethereal diazomethane solution; on evaporation a crystalline mass was obtained which was triturated with light petroleum (b. p. 80–100°) and recrystallized from the same solvent. Dimethyl pyrazoline-4,5-dicarboxylate was obtained in the form of leaflets, m. p. 103–105°. *Anal.* Calcd. for $C_7H_{10}O_4N_2$: C, 45.2; H, 5.4; N, 15.1. Found: C, 44.8; H, 5.5; N, 15.6.

Cinnamylidene-aniline[5] (1 g.) and **maleic anhydride** (0.5 g.) were heated together on the water-bath; the mixture turned brown, then red and an intense odor of cinnamic aldehyde developed. After fifteen minutes, benzene was added, whereupon maleanilic acid crystallized, yield 300 mg.; from butyl acetate as rhombohedra, m. p. 210°.[6] *Anal.* Calcd. for $C_{10}H_9O_3N$: C, 62.8; H, 4.7; N, 7.3. Found: C, 62.5; H, 4.5; N, 7.7. Diazomethane gave as above the expected methyl ester-anilide of pyrazoline-4,5-dicarboxylic acid, from xylene or butyl acetate; crystals, m. p. 175° (dec.). *Anal.* Calcd. for $C_{12}H_{13}O_3N_3$: N, 17.0. Found: N, 17.4.

THE DANIEL SIEFF RESEARCH INSTITUTE
REHOVOTH, PALESTINE

RECEIVED JULY 12, 1938

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(1) E. Bergmann and F. Bergmann, THIS JOURNAL, **59**, 1443 (1937).

(2) Von Pechmann, *Ber.*, **27**, 1888 (1894); v. Pechmann and Burkard, *ibid.*, **33**, 3590 (1900).

(3) La Parola, *Gazz. chim. ital.*, **67**, 645 (1937).

(4) Skraup and Boehm, *Ber.*, **59**, 1013 (1927).

(5) Doebner and v. Miller, *ibid.*, **16**, 1665 (1883).

(6) The highest m. p. recorded before is 198° [Auwers and Schleicher, *Ann.*, **309**, 347 (1899)]. A preparation made according to Anschütz [*Ber.*, **20**, 3214 (1897)] showed m. p. 210°, after recrystallization from butyl acetate or butyl alcohol.

The Calculation of the Dissociation Constant of Weak Acids in H_2O–D_2O Mixtures

BY FRANK BRESCIA

From the exchange equilibria

$$2DCl + QH_2 = 2HCl + QD_2 \qquad K_1 = 14.64 \quad (1)$$

$$QH_2 + D_2O = QD_2 + H_2O \qquad K_2 = 0.96 \quad (2)$$

$$H_2O + D_2O = 2HDO \qquad K_3 = 3.27 \quad (3)$$

Korman and La Mer[1] have calculated the equilibrium constant for the process, $D^+ + H_2O = H^+ + HDO$, to be $K_4 = 7.1$. Their derived equation for the calculation of dissociation constants of weak acids in H_2O–D_2O mixtures

$$K_M = K_D \left[1 + 7.1 \frac{C_{H_2O}}{C_{HDO}} \Big/ 1 + 7.1 \left(\frac{K_D}{K_H}\right) \frac{C_{H_2O}}{C_{HDO}}\right] \quad (5)$$

contains, therefore, the factor 7.1. K_M is the dissociation constant of the acid in the mixtures of H_2O–D_2O, K_D is the dissociation constant of

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(1) Korman and La Mer, THIS JOURNAL, **58**, 1396 (1936).

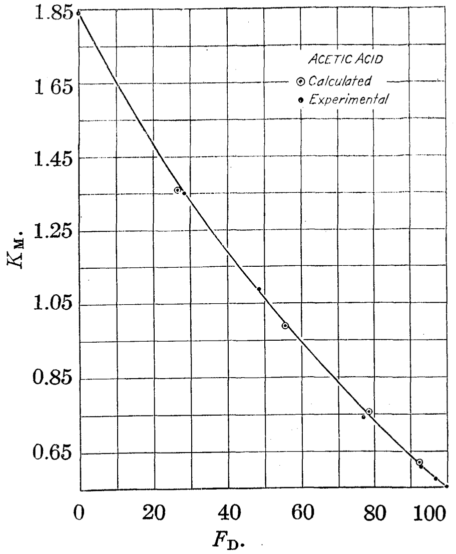

Fig. 1.—Acetic acid: ◉, calculated; ●, experimental.

the heavy acid, and K_H is the dissociation constant of the light acid. This equation, tested by Chittum and La Mer,[2] does not give the same K_M constants as those calculated from the conductance data. The sag of the experimental curve for acetic acid is opposite from that predicted by equation (5).

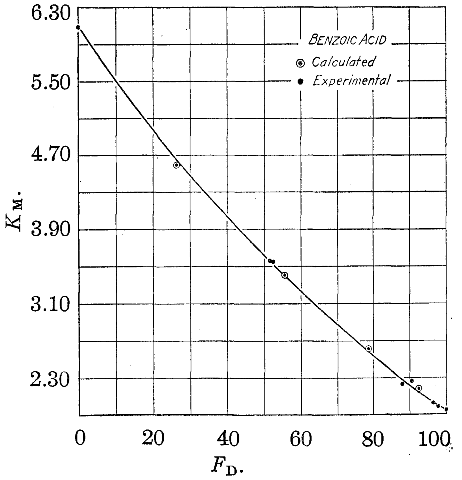

Fig. 2.—Benzoic acid: ◉, calculated; ●, experimental.

The value of K_4 can now be arrived at by an independent method. K_4 (column 4, Table I) has been calculated from the customary $K_3 = 3.27$[3] and from the values of C_{H^+} and C_{D^+} (columns 2 and 3, Table I), obtained through kinetic measurements of a specific hydrogen-ion catalyzed reaction: hydrolysis of ethyl orthoformate in mixtures of $H_2O–D_2O$.[5] The average value thus obtained, 3.76, is much smaller than the previous value, 7.1. Equation (5) is, therefore, corrected to

$$K_M = K_D \left[1 + 3.76 \frac{C_{H_2O}}{C_{HDO}} \Big/ 1 + 3.76 \left(\frac{K_D}{K_H}\right) \frac{C_{H_2O}}{C_{HDO}}\right] \tag{6}$$

TABLE I

(1) F_D	(2) $C_{H^+} \times 10^7$	(3) $C_{D^+} \times 10^7$	(4) K_4
26.40	3.68	0.624	3.99
55.60	1.93	1.16	3.72
78.49	0.827	1.49	3.46
92.51[4]	0.303	1.65	3.86

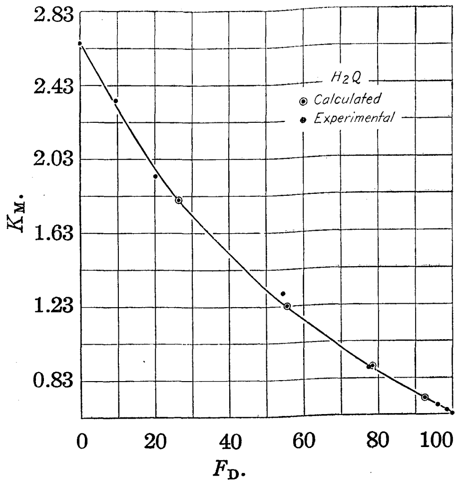

Fig. 3.—H_2O: ◉, calculated; ●, experimental.

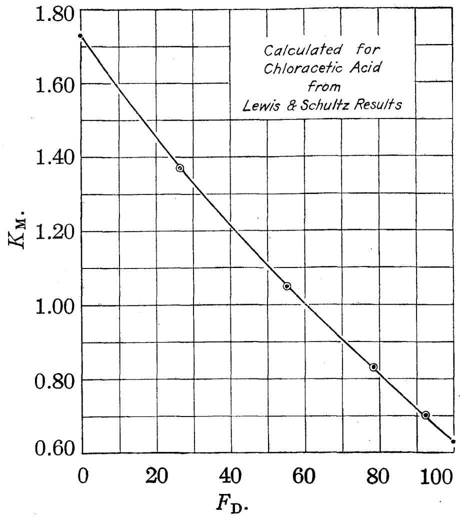

Fig. 4.—Calculated for chloroacetic acid from the results of Lewis and Schultz.

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(2) Chittum and La Mer, THIS JOURNAL, **59,** 2425 (1937).

(3) Topley and Eyring, *J. Chem. Phys.*, **2,** 217 (1934).

(4) The rate constant used to calculate this value of C_{H^+} and C_{D^+} was taken from the experimental curve in preference to the slightly lower determined value since the calculation in this region of F_D is very sensitive to small changes in the rateconstant. $F_D = \Delta S(100)/0.1079$ = fraction of deuterium in the solvent.

(5) Brescia and La Mer, THIS JOURNAL, **60,** 1962 (1938).

TABLE II

SUMMARY OF CALCULATED VALUES USING EQUATION (6) AND OF EXPERIMENTAL DATA

F_D	$K_M \times 10^5$ HAc Exptl.[6]	$K_M \times 10^5$ HAc Calcd.	$K_M \times 10^5$ HB Exptl.[7]	$K_M \times 10^5$ HB Calcd.	$K_M \times 10^{11}$ H_2Q Exptl.[7]	$K_M \times 10^{11}$ H_2Q Calcd.	$K_M \times 10^3$ ClHAc Exptl.[8]	$K_M \times 10^3$ ClHAc Calcd.
0.0	1.84	(1.84)	6.09	(6.09)	2.66	(2.66)	1.73	(1.73)
9.61					2.35			
25.18					1.94			
26.40		1.36		4.60		1.81		1.37
28.4	1.352							
48.4	1.088							
51.45			3.56					
52.42			3.55					
54.69					1.30			
55.60		0.988		3.41		1.23		1.05
77.1	0.741							
77.49					0.889			
78.49		.756		2.61		0.895		0.827
87.99			2.23					
92.51		.622		2.18		.722		.700
93.0	.608							
96.00					(.684)			
96.51			2.03					
97.0	.575							
97.87			1.99					
98.67					.657			
100	(.555)	(.555)	(1.95)	(1.95)	(.639)	(.639)	(0.631)	(.631)

The K_M values, calculated from the revised equation (6), are now in very good agreement with the experimental results. These are summarized in Table II and plotted in Figs. 1, 2, and 3. The predicted slope for chloroacetic acid is given in Fig. 4; no experimental data for comparison are available. The value of K_D for salicylic acid is extrapolated with equation (6) from the average value $K_M = 0.24 \times 10^{-3}$, a. d. 12%, at $F_D = 91.7$, and from the average $K_H = 0.98 \times 10^{-3}$, a. d. 2%, determined by Korman and La Mer.[1] The K_D thus calculated is 0.21×10^{-3} which also has not yet been determined experimentally.

It is apparent that true values of hydrogen and deuterium ion concentrations are obtainable from kinetic data when tested by means of acid dissociation constants.

(6) (Acetic acid) Chittum and La Mer, THIS JOURNAL, **59**, 2524 (1937).

(7) (Benzoic acid and hydroquinone) Rule and La Mer, *ibid.*, **60**, 1974 (1938).

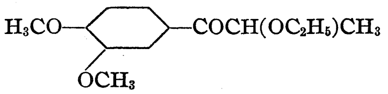
(8) (Chloroacetic acid) Lewis and Schultz, *ibid.*, **56**, 1913 (1934).

DEPARTMENT OF CHEMISTRY
THE CITY COLLEGE
THE COLLEGE OF THE CITY OF NEW YORK
NEW YORK, N. Y.
RECEIVED AUGUST 25, 1938

The Structure of Lignin

BY A. B. CRAMER, M. J. HUNTER AND HAROLD HIBBERT

In a recent note[1] the isolation of a new aromatic ketone ($C_{13}H_{18}O_4$) was described. This has now been identified (by direct synthesis and mixed melting point determination) as α-ethoxypropioveratrone



The synthesis (after numerous unsuccessful attempts, and using a variety of methods) was accomplished as follows:

Veratrole + propionyl chloride ⟶ Propioveratrone ⟶
α-Brompropioveratrone ⟶ Acetate of α-hydroxypropioveratrone
↙ ↘
α-Hydroxypropioveratrone ⟶ α-Ethoxypropioveratrone

The synthetic compound melted at 81–82°; a mixed melting point with natural compound gave no depression. The melting point of the 2,4-dinitrophenylhydrazone of the natural compound is 134–136°; synthetic compound, 134–136°; the mixed melting point also showed no depression.

DIVISION OF INDUSTRIAL
AND CELLULOSE CHEMISTRY
MCGILL UNIVERSITY
MONTREAL, CANADA
RECEIVED OCTOBER 18, 1938

(1) Cramer, Hunter and Hibbert, THIS JOURNAL, **60**, 2274 (1938).

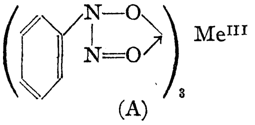
The Classification of Chelating Groups

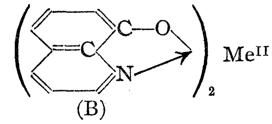
BY HELMUT M. HAENDLER AND BRADFORD P. GEYER

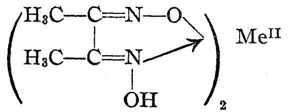
In the course of preliminary work on organic analytical reagents which form inner complex compounds with metal ions, it was found advisable to devise a system for the classification of chelating groups present in various organic compounds to serve as a basis of comparison. The available classifications, in particular that of Diehl,[1] are too unwieldy for rapid grouping and comparison. In addition to classifying the organic compounds now known, any system should also present information concerning possible reagents. The common method of indicating the number of members in the completed chelate ring is too cumbersome, in view of the recent increases in both number and variety of compounds possessing groups capable of chelation.

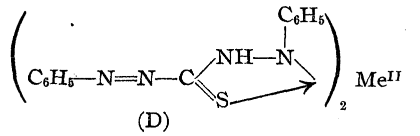
TABLE I

Group designation	Representative compound
C-N, SH	Mercaptobenzothiazole
C-NH, SH	Rubianic acid
C-NOH, OH	Benzohydroxamic acid
N-$NONH_4$, O	Cupferron (A)
C,C-N, NOH	Phenyl α-pyridyl ketoxime
C,C-N, OH	8-Quinolinol (B)
C,C-N, SH	8-Quinolinethiol
C,C-NH, SH	Thionalide
C,C-NH_2, OH	Glycocoll
C,C-NOH, NOH	Dimethylglyoxime (C)
C,C-NOH, O	α-Nitroso-β-naphthol
C,C-O, OH	Oxalic acid
C,C-O, SH	Thioglycolic acid
C,C-OH, OH	Catechol
C,C-OH, S	Thiohydantoic acid
C,N-NH, NOH	Nitrosoguanidine
C,N-NH_2, OH	Hydrazinecarboxylic acid
C,N-NH_2, SH	Dithizone (D)
C,C,C-N, NH	Chlorophyll type
C,C,C-NOH, OH	Salicylaldoxime (E)
C,C,C-O, OH	Alizarin
C,C,N-N, NH	Phthalocyanine
C,C,N-NH, NH	Biguanidine
C,C,N-NH, NH_2	Biuret
C,C,N-NH, O	Dicyandiamidine (F)


(A)


(B)


(C)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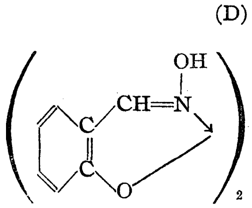
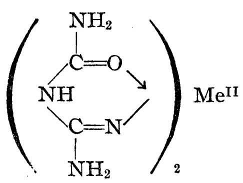

(E)


(F)

In this classification the two functioning groups, which supply the primary and secondary valences involved in the general formation of a chelate ring, and the atom or atoms linking these two groups form the basis of the system. Compounds with identical chelating groups have the same group designation, regardless of the structure of the remainder of the molecule. The group designation is derived as follows: (*a*) The atom or atoms connecting the two functional groups are expressed by their conventional symbols, arranged alphabetically. (*b*) The functioning groups are given by their symbolic representations in alphabetical order of the atoms by which they are attached to the original compound before chelation.

In salicylaldoxime, for example, the functional groups are linked by three carbon atoms, and these functional groups are the oxime and hydroxyl radicals. Consequently, the classification is C,C,C-NOH, OH.

The accompanying list gives in order of increasing complexity the designations of the more common chelating groups and the names of representative compounds containing such groupings. For the sake of clarity, structural formulas illustrating some of the inner complexes formed are also given. It is evident that exact knowledge of the structure of the chelate compound formed is not essential for this method, insofar as the primary and secondary valence connections are concerned. No attempt is made to designate these linkages as to type, and compounds are arranged solely on the basis of general structure.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF WASHINGTON
SEATTLE, WASHINGTON

RECEIVED JULY 29, 1938

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[1] H. Diehl, *Chem. Rev.*, **21**, 39–111 (1937).

Dynamic Isomerism of Acetaldehyde 2,4-Dinitrophenylhydrazone

BY W. M. D. BRYANT

In earlier papers the writer[1,2] presented conclusive evidence based on optical crystallographic measurements that there are at least two distinct crystalline modifications of acetaldehyde 2,4-

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[1] Bryant, THIS JOURNAL, **55**, 3201 (1933).

[2] *Ibid.*, **58**, 2335 (1936).

dinitrophenylhydrazone, and refuted the contention of Campbell[3] that the second modification is merely a product contaminated with the dinitrophenylhydrazone of another carbonyl compound. On the basis of the evidence then available the relationship between these two crystal modifications was assumed to be one of polymorphism. However, a new melting point study using a Kofler and Hilbck micro heating stage[4] has been completed and the results indicate dynamic isomerism rather than polymorphism as the true relationship. This explanation was proposed by Allen and Richmond[5] on the basis of some work by Bredereck[6] with substituted furfural derivatives, and is in accord with the new experimental results.

Experimental

The new melting point observations were made using a Kofler and Hilbck micro heating stage[7] mounted on the object stage of a chemical microscope equipped with a 10X Reichert heat resisting objective. By this means thermal changes in individual crystals could be followed and the temperatures read by means of a calibrated thermocouple. Melting points by this method were found accurate to ±2° and precise to ±0.5°. The samples of acetaldehyde 2,4-dinitrophenylhydrazone employed were prepared during the two earlier investigations.

Acetaldehyde 2,4-dinitrophenylhydrazone I (previously called the "stable form") recrystallized five times from 95% ethanol[1] was found to melt sharply without transition at 168–170° in agreement with 168.5° obtained previously by the more precise macro method. Above 115° in the initial heating a slight sublimate of orange lozenge-shaped crystals appeared and was recognized as the II modification (previously designated as "metastable"). These crystals melted at 156–157°. A few of these crystals in contact with modification I began melting at slightly lower temperature. The resulting liquid noticeably eroded plates of the I form below their regular melting temperature. In another experiment the sublimate was the I form (plates) and melted at the higher temperature (168–170°). On slowly cooling the liquid phase after complete fusion, the II form often reappeared first, usually at 130–140°; on reheating, this form was in equilibrium with the liquid at 148°, a slight change of temperature being sufficient to induce either growth or solution. In cases where the I form reappears first, the fusion or solution process begins at 150–155° and complete solution occurs between 155 and 160°. The above behavior is typical of a system in which the two compounds are, strictly speaking, different chemical entities but mutually convertible one into the other.

A sample of derivative recrystallized once from benzene[2] had an initial melting point of 148–151°. Crystals (mainly the II modification) reappeared at 131° and were completely fused (or dissolved) at 149.5°. After several repetitions the fusion temperature was lowered to 142°.

The above observations indicate that acetaldehyde 2,4-dinitrophenylhydrazone exists in two chemically different forms (dynamic isomers), the ordinary form (I) melting sharply near 169° and a form (II) obtained by sublimation melting at 157°. Crystallization of the melt produces a mixture (probably an equilibrium mixture) melting near 148°. The derivative recrystallized from benzene although optically identical with the I modification melts near 149° as does the "equilibrium mixture," hence must contain traces of a catalyst (possibly sulfuric acid) capable of inducing a rapid isomerization. This accounts for the low melting points sometimes observed.[2] In the writer's earlier experiments[1] slow isomerization was mistaken for a more fundamental thermal breakdown and hence not given the attention it deserved.

AMMONIA DEPARTMENT
E. I. DU PONT DE NEMOURS & CO., INC.
WILMINGTON, DELAWARE
RECEIVED OCTOBER 3, 1938

Structure of Lignin

BY M. J. HUNTER, A. B. CRAMER AND HAROLD HIBBERT

In a recent note[1] the isolation of an aromatic ketone, $C_{13}H_{18}O_4$, from spruce wood by organic solvent extraction was reported and the additional presence of derivatives containing the syringyl group from hard woods noted.

Using maple wood and similar organic solvent extraction, there is obtained a mixture of two ketones, having in the pure state the empirical formulas $C_{12}H_{16}O_4$ and $C_{13}H_{18}O_5$, respectively, which can be readily separated by conversion into their *p*-nitrobenzoates.

One of these corresponds to the ester from the ketone previously reported, while the new crystalline *p*-nitrobenzoate is derived from the second ketone, the latter being related to the former by possessing an additional methoxyl group. They are apparently present in approximately equal amounts.

The theoretical conclusion drawn previously that hard woods differ from soft in having present in the building unit not only the guaiacyl but also the syringyl radical has thus been substantiated.

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[3] Campbell, *Analyst*, **61**, 391 (1936).

[4] Kofler and Hilbck, *Mikrochemie*, **9**, 38 (1931).

[5] Allen and Richmond, *J. Org. Chem.*, **2**, 222 (1937).

[6] Bredereck, *Ber.*, **65**, 1833 (1932).

[7] This instrument manufactured by the optical firm of C. Reichert, Vienna, was obtained from Pfaltz and Bauer, Inc., Empire State Building, New York City.

[1] THIS JOURNAL, **60**, 2274 (1938).

The compound containing the syringyl radical was characterized as follows: melting point, 141–142.5°. *Analysis* of the *p*-nitrobenzoate. Calcd. for $C_{20}H_{21}NO_8$: C, 59.5; H, 5.3; N, 3.47; OCH_3, 23.1. Found: C, 59.5; H, 5.28; N, 3.5; alkoxyl as OCH_3, 23.0.

Presence of the carbonyl group was confirmed by preparing the 2,4-dinitrophenylhydrazone of the ester. Calcd. for $C_{26}H_{25}N_5O_{11}$: N, 12.0. Found: N, 11.9.

These two products undoubtedly are to be regarded as important constituents of the building unit of the lignin molecule.

DIVISION OF INDUSTRIAL AND CELLULOSE CHEMISTRY
MCGILL UNIVERSITY
MONTREAL, P. Q., CANADA
RECEIVED OCTOBER 3, 1938

The Dimerization of 3-Phenylindene

BY C. S. MARVEL AND H. A. PACEVITZ

Blum-Bergmann has reported[1,2] a dimer of 3-phenylindene (m. p. 207–209°) as a by-product in a reaction in which 3-phenylindene was treated with lithium. No exact method of producing or isolating the dimer was described. We have tried to obtain the same compound for comparison with an isomeric hydrocarbon melting at 210–211°.[3] Various combinations of conditions have been used but none yielded the dimer reported. A different dimer melting at 157° has, however, been obtained.

Dimer of 3-Phenylindene.—A mixture of 30 cc. of 47% hydrogen iodide solution and 2 g. of 3-phenylindene was shaken for sixteen hours. A dark brown solid separated out. This was separated and dissolved in about 400 cc. of low-boiling petroleum ether (b. p. 40–60°). The ether solution was concentrated to about 100 cc., at which point some crystals separated. The product was twice recrystallized from petroleum ether. The yield was 1.9 g. of a product melting at 156–157°.

Anal. Calcd. for $C_{30}H_{24}$: C, 93.6; H, 6.4; mol. wt., 384. Found: C, 93.55, 93.48; H, 6.36, 6.45; mol. wt. (Rast), 357, 359.

In a similar manner 2 g. of 3-phenylindene and 25 cc. of fuming stannic chloride gave 1.7 g. of dimer melting at 156–157°.

Heating 3-phenylindene with equal parts of sirupy phosphoric acid and water, with glacial acetic acid, with concentrated sulfuric acid or a mixture of sulfuric acid and hydrochloric acid did not cause it to dimerize.

Treating a benzene solution of 3-phenylindene with metallic lithium in an atmosphere of nitrogen for several days did not produce a dimer.

Heating the dimer to 350° caused some charring but no 3-phenylindene was found in the distillate.

CHEMICAL LABORATORY OF THE
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS
RECEIVED JULY 15, 1938

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[1] Blum-Bergmann, *Ann.*, **484**, 26 (1930).

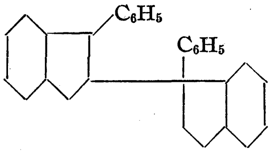
[2] Through the kindness of Dr. E. Bergmann we have obtained a sample of the dimer of 3-phenylindene melting at 210–211°. This product proved to be a different hydrocarbon from the hydrocarbon of the same composition and melting point reported by Farley and Marvel,[3] since a mixture of the two melted at 185–190°.

[3] Farley and Marvel, THIS JOURNAL, **58**, 32 (1936).

The Dimerization of 3-Phenylindene

BY E. BERGMANN

The preceding Note by Marvel and Pacevitz has been made accessible to me through the courtesy of the Editor. The dimeric 3-phenylindene had only occasionally been obtained and its structure therefore had not been elucidated. Although the mechanism by which indene is dimerized[1] would lead only to one dimer of 3-phenylindene, there may be other ways, too, of dimerization. An experiment has shown that the two substances, m. p. 210–211° and 156–157°, respectively, are not allyl isomeric forms, as they are not interconvertible by means of sodium ethylate solution.



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[1] E. Bergmann and Taubadel, *Ber.*, **65**, 463 (1932).

THE DANIEL SIEFF RESEARCH INSTITUTE
REHOVOTH, PALESTINE
RECEIVED AUGUST 30, 1938

β,β′,β″-Trichlorotriethylamine

BY J. PHILIP MASON AND DALE J. GASCH

In the course of some other work, we had occasion to make trichlorotriethylamine and its hydrochloride. By a slight modification of the procedure used by Ward,[1] we were able to increase the yield of the hydrochloride from 70 to 92%.

Two moles (238 g.) of thionyl chloride dissolved in 150 ml. of benzene was added to 0.5 mole (92.7 g.) of triethanolamine hydrochloride in a 1-liter round-bottomed flask equipped with a reflux condenser and a gas absorption trap. The mixture was heated to 55° and kept at that temperature for three hours. The benzene and excess thionyl chloride were distilled under diminished pressure at 50°. In order to decompose the last portion of thionyl chloride, about 50 ml. of ethyl alcohol was added. The mixture was warmed for

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[1] Ward, THIS JOURNAL, **57**, 914 (1935).

ten to fifteen minutes and then the alcohol was distilled. This step was found desirable because otherwise charring occurred when acetone was added to recrystallize the product. The residue was recrystallized from boiling acetone; yield, 106.3 g. (88%). By concentrating the acetone filtrate, a second crop of crystals (4.5 g.) was obtained, bringing the total yield up to 92%. McCombie and Purdie[2] made trichlorotriethylamine hydrochloride directly from triethanolamine and thionyl chloride, using chloroform as a solvent, and obtained a yield of 73.8%.

The free trichlorotriethylamine, obtained in the usual way from the hydrochloride, had a b. p. of 143–144° at 15 mm., which is 6° higher than that reported by McCombie and Purdie[2] at the same pressure.

Anal. Calcd. for $C_6H_{12}Cl_3N$: Cl, 52.1; mol. wt., 204.5. Found: Cl, 51.6, 51.8; mol. wt. (benzene), 205.9.

The amine was almost colorless when freshly distilled, but turned to a light brown color on standing for sixty hours. The color darkened on longer standing. Crystals, which were not identified, appeared in the liquid after standing for a month. Ether solutions of the amine darkened more slowly and no crystals were observed. Instead, a small amount of dark brown material was deposited from an ether solution which had been kept for two months. No attempt was made to identify this material.

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[2] McCombie and Purdie, *J. Chem. Soc.*, 1217 (1935).

CHEMISTRY LABORATORY
BOSTON UNIVERSITY
BOSTON, MASS.
RECEIVED SEPTEMBER 3, 1938

The Catalytic Reaction between Sodium Nitrite and Dichlorodiethylenediamine Cobaltic Chloride

BY J. P. MCREYNOLDS AND JOHN C. BAILAR, JR.

In the course of stereochemical studies on the complex inorganic compounds, it was observed that racemic dichlorodiethylenediamine cobaltic chloride reacts almost instantaneously with sodium nitrite according to the equation $[Coen_2Cl_2]^+ + 2NaNO_2 \longrightarrow [Coen_2(NO_2)_2]^+ + 2NaCl$[1] but that the material which has been resolved into its optical antipodes reacts very slowly. This resolution is carried out through the α-bromocamphor-π-sulfonate, which is reconverted to the chloride by means of hydrochloric acid in alcohol and ether. The active product is then washed with alcohol and ether.[2] It was found that washing the racemic material with alcohol and ether caused it to lose its reactivity toward sodium nitrite. The washings contained cobaltous ion. That cobaltous ion catalyzes the reaction in question was demonstrated easily.[3]

Werner has noted[4] briefly that traces of acids catalyze this reaction but no other example of such catalytic substitution has been reported for compounds of this type. A study was therefore made to determine the mechanism of the reaction. Two compounds which seemed possible intermediates are sodium cobaltinitrite, $Na_3Co(NO_2)_6$, and sodium cobaltonitrite, $Na_2Co(NO_2)_4$. Sodium cobaltinitrite was found to have no catalytic effect in this reaction. On the other hand, the cobaltonitrite ion could be precipitated (as the potassium salt) from mixtures which had been catalyzed artificially by addition of cobaltous ion. This seems to point to the intermediate formation of sodium cobaltonitrite.

The mechanism postulated for this catalysis must explain the very rapid replacement of chloro by nitro groups and the apparent absence of oxygen to cobalt linkages at any step in the reaction. This latter requirement is evidenced by the fact that at no time is there any indication of a red coloration such as is found in nitrito cobalt compounds. The isolated intermediate and the almost instantaneously formed product both have the yellow color characteristic of the nitrogen to cobalt bond. Further, nitrite complexes of trivalent cobalt have been prepared and characterized. They are stable in solution for a considerable period, changing to nitro complexes quite slowly.

The explanation offered here involves a shift of the electrons upon the nitrogen to allow it to form a coördinate bond to both trivalent and bivalent cobalt. This is a very unstable arrangement and is broken up immediately, leaving the nitrogen attached to the trivalent cobalt. This latter step seems quite logical since the trivalent cobalt complexes are very much more stable than those of bivalent cobalt. It must be assumed that

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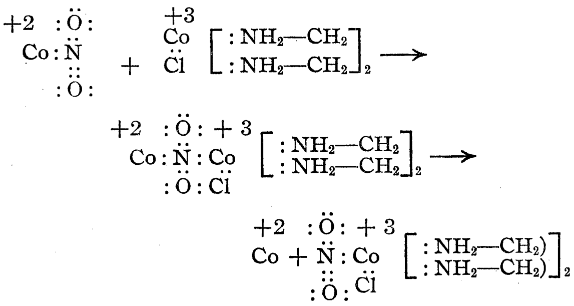
[1] The symbol "en" represents ethylenediamine.

[2] Bailar and Auten, THIS JOURNAL, **56**, 774 (1934).

[3] The traces of cobaltous ion present in the racemic material evidently are produced during the conversion of the *trans* form of the complex to the *cis* form by evaporation of the solution and subsequent heating of the residue in the oven. A dry sample of optically active material unreactive to sodium nitrite became reactive after several hours of such heating. It lost a large part of its optical activity during the heating.

[4] Werner, *Ber.*, **34**, 1734 (1901).

one chloride group ionizes from the cobaltic complex momentarily or that the coördination number of the cobaltic ion may exceed six, at least for an instant. On the first assumption, the mechanism of the catalytic reaction may be as follows



$$\overset{+2}{\mathrm{Co}}:\underset{:\ddot{O}:}{\overset{:\ddot{O}:}{\ddot{N}}} + \overset{+3}{\mathrm{Co}}\,\mathrm{Cl}\left[\begin{matrix}:NH_2-CH_2\\ :NH_2-CH_2\end{matrix}\right]_2 \longrightarrow$$

$$\overset{+2}{\mathrm{Co}}:\underset{:\ddot{O}:}{\overset{:\ddot{O}:}{\ddot{N}}}:\overset{+3}{\underset{\mathrm{Cl}}{\mathrm{Co}}}\left[\begin{matrix}:NH_2-CH_2\\ :NH_2-CH_2\end{matrix}\right]_2 \longrightarrow$$

$$\overset{+2}{\mathrm{Co}} + \underset{:\ddot{O}:}{\overset{:\ddot{O}:}{\ddot{N}}}:\overset{+3}{\underset{\mathrm{Cl}}{\mathrm{Co}}}\left[\begin{matrix}:NH_2-CH_2)\\ :NH_2-CH_2)\end{matrix}\right]_2$$

It is possible that the familiar coördination compounds of metal ions with ethylene compounds and with azo compounds are formed in the same way—by the shift of a pair of electrons from the double bond to an adjacent atom.

The catalyzed reaction, when applied to optically active starting material, lends further evidence in favor of such a mechanism since the product always has a much lower activity than that formed through the uncatalyzed reaction.

A further investigation was carried out to determine the possibilities of extending this type of catalysis to other substitutions. All attempts to catalyze the substitution of oxalate or thiocyanate groups for chloro groups by the addition of metallic ions failed to show positive results. The ions used were nickelous, ferric, aluminum, stannous and cobaltous, all of which tend to form unstable complex ions. This study showed that cobaltous ion is unique among those tried in producing the catalytic substitution of the nitro group.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS

RECEIVED JULY 25, 1938

Ammonium Chloride–Sodium Sulfide Solutions for Organic Nitro Reductions and for Inorganic Qualitative Analysis

BY M. J. MURRAY AND D. E. WATERS[1]

Two disadvantages in the use of ammonium sulfide as reducing agent for organic nitro compounds have been: (1) the length of time consumed in saturating the ammonium hydroxide with hydrogen sulfide, and (2) the indefinite amounts of materials used. Both of these disadvantages are overcome by preparing a solution containing equivalent amounts of ammonium chloride and crystalline sodium sulfide ($Na_2S\cdot 9H_2O$). This solution is added to the nitro compound dissolved in ammonium hydroxide or alcohol and ammonium hydroxide. The mixture can be heated at once until excess hydrogen sulfide has escaped, and from this point the isolation of the reduction product is the same as in standard procedures.

The reagent was tested most thoroughly on the reduction of *p*-nitrobenzoic acid. The yields were consistently higher than on parallel runs using hydrogen sulfide and ammonium hydroxide. The melting point and the neutralization equivalent showed the product to be one of high purity. Reduction by sodium polysulfide, sodium sulfide alone, and sodium hydrogen sulfide gave yields inferior as to both quality and quantity. Other compounds reduced by the sodium sulfide–ammonium chloride reagent were: *p*-nitrophenylacetic acid,[2] 3-nitrophthalhydrazide,[3] and *m*-dinitrobenzene.[4] In each case the yield equaled or exceeded that reported in the reference given.

A second use of this rapid method for the preparation of ammonium sulfide is in the making up of solutions of ammonium polysulfide for inorganic qualitative analysis. A solution of approximately known strength can be prepared in a few minutes as follows: equivalent amounts of ammonium chloride and crystalline sodium sulfide ($Na_2S\cdot 9H_2O$) are dissolved in a small volume of water, powdered sulfur is added, and the mixture warmed to promote solution. Then ammonium hydroxide is added and the solution diluted to the desired strength. Concentrations are not given here because textbooks do not agree as to the optimum strength.[5] Attention should also be directed to the fact that few laboratory assistants make up the ammonium polysulfide solutions as strong as called for because of the difficulty of completely saturating the ammonium hydroxide with hydrogen sulfide. For this reason solutions prepared by the short method just described will be, in general, considerably more concentrated than ordinarily

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(1) Present address. Transylvania College, Lexington, Ky.

(2) "Organic Syntheses," Coll. Vol. I, 1932, p. 44.

(3) Huntress, Stanley and Parker, *J. Chem. Ed.*, **11**, 143 (1934).

(4) Gattermann and Wieland, "Laboratory Methods of Organic Chemistry," 22nd edition, The Macmillan Co., New York, N. Y., 1932, p. 162.

(5) Curtman and Lehrman, *J. Chem. Ed.*, **6**, 2203 (1929), recommend a definite strength but it is doubtful whether such a high concentration is advisable in all procedures.

made up, and it may be advisable to redetermine which strength is best for the particular scheme of analysis being used.

Ammonium polysulfide prepared by the rapid method has been used successfully in this Laboratory over a period of three years for the separation of Divisions A and B in Group II.

DEPARTMENT OF CHEMISTRY
LYNCHBURG COLLEGE
LYNCHBURG, VA.

RECEIVED AUGUST 26, 1938

The Interaction between Methylene Radicals and Hydrogen

BY CHARLES ROSENBLUM

The photolysis of ketene in the presence of hydrogen points to a reaction between methylene radicals and hydrogen, in contrast with the relative stability[1] of methylene toward ketene itself and toward ether vapor. The reactants, 100 mm. of ketene and 225 mm. of hydrogen, were irradiated in a cylindrical quartz vessel (volume 130 cc.) by a "hot" mercury arc for about forty-five minutes, and the resultant gas mixture analyzed. Although a constricted arc was used throughout, a hydrogen–mercury vapor filter[2] for resonance radiation was interposed as an added precaution against the lamp as a source of hydrogen atoms. A mixture of ethylene and hydrogen did not react when exposed to the arc under these conditions.

Irradiation of ketene alone[3] results in an increase in volume due to the formation of carbon monoxide and ethylene as the sole gaseous products, this increase falling below the theoretical value after longer exposures because attendant polymerization creates a gaseous hydrocarbon deficiency. The reaction which occurs in the presence of hydrogen differs markedly from the above in that it is characterized by a volume decrease. This can be accounted for only if the gaseous hydrocarbon is saturated and some saturated liquid (or solid) hydrocarbons of low vapor pressure are formed, which implies a disappearance of hydrogen.

Analysis confirmed these expectations fully. Of the ketene decomposed in the presence of hydrogen at 35°, 1% yielded methane, 74% was recovered as a gas with an average composition[4] $C_{2.56}H_{7.12}$, and 25% yielded a residue of low volatility. At 200° the methane content corresponded to 9.6% of the decomposed ketene, the gaseous fraction with a mean composition[4] $C_{2.68}H_{7.36}$ represented 69%, and the residue accounted for 21% of the ketene present originally. In both cases, the average composition of the residual polymeric product was C_4H_{10}. The mean composition and quantity of this polymer were deduced from the carbon and hydrogen deficiencies in the balance sheet of initial and final gaseous components of the reaction system. The amounts of condensed product calculated in this manner agreed well with the observed volume decreases.

The experiments indicate that the direct association of methylene radicals and molecular hydrogen to form methane is inappreciable. The profound change in the nature of the products when hydrogen is present suggests that the interaction in question is

$$CH_2' + H_2 = CH_3 + H$$

Such a reaction yielding methyl radicals and atomic hydrogen would account for the formation of saturated and higher molecular weight hydrocarbons.[5] The methylene radical has been represented as energy rich (CH_2') since present accepted views as to bond energies would suggest that the reaction of a normal methylene radical with hydrogen would be endothermic. The energy of the radical must arise from the photoenergy absorbed during the dissociation process.

A secondary source of methyl radicals might be a reaction between methylene radicals and methane already formed

$$CH_2 + CH_4 = 2CH_3$$

This would be less endothermic than the reaction with hydrogen. The low yields of methane, increasing at higher temperatures, do not appear to support this view.

The source of methane is probably an interaction of methyl radicals with hydrogen[6] or hydrocarbons[7] which is known to take place readily at or above 150–160°. The recombination of methyl radicals to form ethane would account for the

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(1) Pearson, Purcell and Saigh, *J. Chem. Soc.*, 409 (1938).

(2) Morikawa, Benedict and Taylor, *J. Chem. Phys.*, **5**, 212 (1937).

(3) Norris, Crone and Saltmarsh, *J. Chem. Soc.*, 1533 (1933); THIS JOURNAL, **56**, 1644 (1934); Ross and Kistiakowsky, *ibid.*, **56**, 1112 (1934).

(4) Shown by cracking over a nickel catalyst in an excess of hydrogen.

(5) Summarized in Bonhoeffer and Harteck, "Grundlagen der Photochemie," Theodor Steinkopff, Dresden-Blasewitz, Germany, 1933, p. 264; also Jungers and Taylor, *J. Chem. Phys.*, **6**, 325 (1938).

(6) Cunningham and Taylor, *J. Chem. Phys.*, **6**, 359 (1938); Taylor and Rosenblum, *ibid.*, **6**, 119 (1938).

(7) Unpublished work of J. O. Smith, Princeton, 1938.

prominence of this constituent in the gaseous product.

Details of the temperature effect, which so far indicates a very small temperature coefficient for the photo-decomposition of ketene in hydrogen,[8] as well as the influence of varying concentrations of reactants and the addition of hydrocarbons, are being investigated.

[8] See also Ross and Kistiakowsky[3] in the absence of hydrogen.

FRICK CHEMICAL LABORATORY
PRINCETON UNIVERSITY
PRINCETON, NEW JERSEY
RECEIVED AUGUST 22, 1938

Potassium Acid Phthalate as a Buffer for Use with the Hydrogen Electrode

BY JOHN RUSSELL AND R. ELIOT STAUFFER

Several investigators[1] have reported in the literature that accurate measurements on 0.05 molar potassium acid phthalate cannot be made with the hydrogen electrode. On the other hand, Clark[2] states that repeated experiments have shown measurements on phthalate buffers to be reliable. Recently, MacInnes and co-workers[3] again have intimated that phthalate solution is unstable and cannot be measured satisfactorily with the hydrogen electrode, especially at 38°.

Our experience in this connection definitely supports Clark's statement, and, since the 0.05 *M* phthalate is so convenient a buffer for use in *p*H standardization, we are submitting the following data as evidence for the stability and reproducibility of hydrogen electrode potentials observed in it. We have used the following type of cell for *p*H measurements in these Laboratories (Pt) H_2; Solution X: 3.5 *N* KCl: 3.5 *N* KCl, satd. Hg_2Cl_2; Hg_2Cl_2; Hg, with 0.05 *M* phthalate as solution X in this cell both at 25 and 40°.

An essential feature in the design of the cell, which we hope to describe in detail later in connection with other studies, is the possibility of creating a very reproducible and constant junction between the potassium chloride bridge solution and solution X. Equally important in the obtaining of consistent and accurate measurements is the elimination of rubber connections in contact with the hydrogen supply or solution X, and the use of hydrogen prepared electrolytically in glass and passed over a hot platinum gauze catalyst in a fused silica tube. As a result, the cell in question has yielded highly reproducible and constant e. m. f. values with phthalate and other buffers. A few of these for phthalate at 40° are given in Table I.

TABLE I

ELECTROMOTIVE FORCE MEASUREMENTS OF POTASSIUM ACID PHTHALATE (0.05 *M*) WITH THE HYDROGEN ELECTRODE AT 40°

Reference half-cell	Phthalate soln.	E. m. f., v.	Date
A	1 X	0.49500	8-28-36
B	2 Y	.49504	9-21-36
B	2 Y	.49503	9-24-36
B	2 Y	.49496	9-28-36
B	3 X	.49503	9-25-36
B	3 X	.49501	9-28-36
C	4 Z	.49494	1-20-37
D	5 X	.49502	5- 5-37
	Average	.49500	

These measurements cover a period of about nine months during which four different calomel half-elements and bridging solutions were prepared, and five different phthalate solutions from three commercial sources of potassium acid phthalate were used. Each value in the table represents an average of values obtained by two or more platinum electrodes whose differences were rarely more than a few hundredths of a millivolt. Table II taken from a typical page of data shows that the e. m f. of the cell using phthalate as solution X remains substantially constant for periods as long as four hours after creating the liquid junction. The junction was formed as soon as the solution reached the temperature of the thermostat (*ca.* fifteen minutes).

TABLE II

CONSTANCY OF HYDROGEN ELECTRODE AND JUNCTION POTENTIALS WITH 0.05 *M* PHTHALATE BUFFER AT 40°

Hours after formation of junction	E. m. f., v.
0	0.49495
0.5	.49501
1	.49504
2	.49505
4	.49506

These data indicate that in our experience 0.05 *M* potassium acid phthalate can be used very satisfactorily as a buffer with the hydrogen elec-

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[1] I. M. Kolthoff and F. Tekelenburg, *Rec. trav. chim. Pays-Bas.*, **46**, 39 (1927); E. T. Oakes and H. M. Salisbury, THIS JOURNAL, **44**, 948 (1922); C. Z. Draves and H. V. Tartar, *ibid.*, **47**, 1226 (1925).

[2] W. Mansfield Clark, "The Determination of Hydrogen Ions," 3rd ed., The Williams and Wilkins Company, Baltimore, Md., 1928, p. 437.

[3] D. A. MacInnes, D. Belcher and T. Shedlovsky, THIS JOURNAL, **60**, 1099 (1938).

trode at temperatures as high as 40° for even the most precise work.

Eastman Kodak Company
Rochester, N. Y.
Received August 24, 1938

The Preparation of *m*-Bromobenzaldehyde

By Floyd T. Tyson

For work in progress in this Laboratory it was necessary to prepare *m*-bromobenzalaminoacetal by the interaction of *m*-bromobenzaldehyde with aminoacetal. The *m*-bromobenzaldehyde was prepared by the reduction of *m*-nitrobenzaldehyde by stannous chloride and hydrochloric acid, followed by diazotization and conversion to bromobenzaldehyde by the Sandmeyer method as originally described by Einhorn and Gernsheim[1] and modified by Buck and Ide.[2] In these procedures, no attempt is made to isolate the intermediate *m*-aminobenzaldehyde from admixture with stannic chloride and hydrochloric acid.

Analysis of the *m*-bromobenzalaminoacetal yielded uniformly low results for halogen calculated as bromine and very high results for carbon and hydrogen. These analytical values were in accord with the assumption that much of the chloro compound was present with the bromo compound.

The *m*-bromobenzaldehyde used for the preparation of the impure *m*-bromobenzalaminoacetal was analyzed for halogen and the halogen calculated as bromine. The analytical values obtained were in agreement with the theoretical values for bromobenzaldehyde. However, analyses of the *m*-bromobenzaldehyde preparations for both chlorine and bromine proved the presence of both chlorine and bromine. The amounts of chlorine indicated a percentage of chlorobenzaldehyde ranging from 20 to 72 depending upon details of procedure.

Since *m*-nitrobenzaldehyde should be a convenient source for the preparation of pure *m*-bromobenzaldehyde, a procedure has been devised which will be published elsewhere, in which the presence of chlorides in the reaction mixture was avoided.

Experimental

The following table summarizes data obtained in the analysis of products resulting from the attempted preparation of pure *m*-bromobenzaldehyde from *m*-nitrobenzaldehyde as described in the literature. The preparations analyzed were fractionated; b. p. 92–97° (6 mm.).

Table I

Prepn.	Analyses, % Cl	Analyses, % Br	Calcd. % chlorobenzaldehyde present
1	18.17	11.86[3]	72.0
	18.31	11.57[4]	
2	5.11	34.50[3]	20.3
3	6.78	31.58[3]	26.9

Preparation No. 1 was made as described by Buck and Ide.[2] Preparation No. 2 was made as No. 1 except that the hydrobromic acid was added to the cuprous bromide mixture before mixing with the diazotized solution. Preparation No. 3 was made as described by Einhorn and Gernsheim.[1]

The analytical results reported in the following table were calculated on the erroneous assumption that the mixtures of silver chloride and bromide actually obtained in the analyses of preparations No. 1, 2 and 3 (Table I) were pure silver bromide. The satisfactory agreement with the values for *m*-bromobenzaldehyde may explain the fact that the preparations as recorded in the literature[1,2] were reported as essentially pure.

Table II

Prepn.	% Br found as assumed	% Br calcd. for *m*-bromobenzaldehyde
1	43.12	43.19
2	43.18	
3	43.25	

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(1) Einhorn and Gernsheim, *Ann.*, **284**, 141 (1894).

(2) Buck and Ide, *Org. Syntheses*, **13**, 30 (1933).

(3) Analyses made by the method of displacement of bromine from weighed silver chloride and bromide by chlorine as described in "Quantitative Analysis of Inorganic Materials," by N. Hackney, J. B. Lippincott, Philadelphia.

(4) Analysis made by the method of Baubigny [*Compt. rend.*, **136**, 1197 (1903)] as described by Hackney.[4]

Department of Chemistry
Temple University
Philadelphia, Pa.
Received July 6, 1938

The Optical Rotation of a Grignard Reagent

By Frank C. Whitmore and Benjamin R. Harriman

Frequent use is made of the Grignard reaction in preparing optically active compounds from optically active halogen compounds, but not to our knowledge has the rotation of an optically active Grignard reagent been measured previously. Porter[1] observed a very small rotation in an ethereal solution of methyl-*n*-hexylmagnesium

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(1) Porter, This Journal, **57**, 1436 (1935).

bromide which he had prepared from active methyl-*n*-hexyl bromide. He ascribed this activity to unchanged bromide.

Since the position of the functional halogen atom relative to the asymmetric carbon atom determines the degree to which the product is racemic, we sought a halide in which the halogen was on the carbon atom next to the asymmetric carbon atom. Optically active 1-bromo-2-methylbutane, "active amyl bromide," was selected because it was prepared easily from the readily available optically active 2-methyl-1-butanol, which J. H. Olewine of this Laboratory has obtained by the fractionation of fusel oil through a 100-plate column.[2] Since the conversion of this bromide to another compound through the intermediate Grignard reagent gives a product which is only partly racemic, it was thought that rotation measurements on Grignard reagents made from this and similar halides might throw light on the mechanism of such racemizations and on the structure of the Grignard reagent itself. With this in mind a manipulative procedure for measuring the rotation of the Grignard reagent was evolved.

Obviously it was necessary to be assured of the absence of any excess halide. This could be done either by using an excess of magnesium or by removing the excess halide after the Grignard reagent was made. Grignard reagents were made by the first method under the most careful conditions for the exclusion of air and moisture, and a special polarimeter tube with optical Pyrex sealed-in windows was made to hold the volatile ethereal solution. However, what appeared to be finely dispersed magnesium rendered the solutions too dark for measurement.

The alternative method of using an excess of the optically active halide produced clear Grignard reagent solutions. Di-*n*-butyl ether (b. p. 141°) was used as the solvent so that the excess active amyl bromide (b. p. 120°) could be removed by distillation under reduced pressure. The Grignard reagent solution freed from excess halide was then transferred with a pipet to an ordinary polarimeter tube, in which measurement of its optical rotation readily was made. Specific rotations were calculated from data obtained by titrating the Grignard reagent with standard hydrochloric acid. Molecular rotations are given below as being non-committal as to the structure of the Grignard reagent. It is significant that the molecular rotation of the Grignard reagent was slightly greater than that of the active amyl bromide from which it was prepared.

The following is a typical run. Active 1-bromo-2-methylbutane, $[M]^{25}_D$ +5.06°, was prepared with phosphorus tribromide from active 2-methyl-1-butanol $[M]^{25}_D$ −4.35°. Using an excess of this bromide with di-*n*-butyl ether as the solvent, the corresponding Grignard reagent was then prepared in the ordinary way. After distilling off the excess bromide under reduced pressure, a clear active Grignard reagent, $[M]^{25}_D$ +5.36°, was obtained.

SCHOOL OF CHEMISTRY
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STATE COLLEGE, PENNA.

RECEIVED AUGUST 29, 1938

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[2] Olewine, THIS JOURNAL, **60**, 2569 (1938).

COMMUNICATIONS TO THE EDITOR

THE STRUCTURE OF CELLULOSE ETHERS OBTAINED BY THE METHYLATION OF CELLULOSE MATERIALS DISPERSED IN QUATERNARY AMMONIUM BASES

Sir:

The methylation of cellulosic materials dispersed in certain quaternary ammonium bases has been reported[1] to proceed as a homogeneous molecular cellulose reaction. The structure of the apparently homogeneous water-soluble methylcellulose prepared in this manner was thought to be similar to the water-soluble methylcellulose obtained by Traube, Piwonka and Funk[2] on methylating a cellulose–copper hydroxide–sodium hydroxide complex. However, since no chemical evidence was presented to substantiate this conclusion, researches on the structure of these partially methylated cellulosic materials have been undertaken in this Laboratory.

The methylation of both wood pulp and ash-free viscose rayon dispersed in 1.8 *N* dimethyldibenzylammonium hydroxide with dimethyl sulfate, according to the procedure of Bock,[1] yields methylated cellulosic materials containing 12 to 16% methoxyl, corresponding to 0.7 to 0.9 methyl group to each $C_6H_{10}O_5$ unit of cellulose. Acetylation of this material with acetic anhydride in pyridine solution, followed by methyl alcoholysis at 125° in the presence of 1% dry hydrogen chloride gave a mixture of partially methylated methylglucosides and α- and β-methylglucosides. The latter crystalline constituents were isolated from the mixture in yields of 30–35%, which after purification was found to be largely α-methylglucoside, m. p. 164–165°; sp. rot. +157.8° (H_2O). The sirupy constituents representing 65–70% of the total alcoholysis mixture, after acetylation with acetic anhydride in pyridine solution, were subjected to distillation under high vacuum. The following fractions were obtained:

Fraction	B. p., 0.1 mm.	% OCH_3	% Yield[a]
I	130–140°	29.5	25–30
II	140–150°	22.5	20–25
III	160–175°	19.5	5–10

[a] Yield based on original weight of acetylated product.

Evidence that Fraction I contained traces of trimethylmonoacetyl methylglucoside (OCH_3, 44.6%) mixed with the predominating dimethyldiacetyl methylglucoside (OCH_3, 30.4%) was shown by the fact that further fractional distillation yielded a fraction (b. p. 130–140°) with a methoxyl content of 31.7%. Fraction II yielded a small amount of crystalline 2-methyltriacetyl α-methylglucoside (OCH_3, 18.5%) with melting point 120–121°, remaining constant when mixed with an authentic specimen.[3] Fraction III yielded crystalline 2-methyltriacetyl α-methylglucoside (m. p. 120–121°), tetraacetyl β-methylglucoside (m. p. 104–105°) and a sirupy product presumably dimethyldiacetyl methylglucoside.

Acetolysis of the methylated wood pulp and viscose rayon (OCH_3, 13.5%) in a manner similar to that described by Lieser[4] gave a 5% yield of cellobiose octaacetate (m. p. 224–225°; sp. rot., +41.5° ($CHCl_3$)).

These experiments confirm the assumption of Bock[1] that the "water-soluble" methylated cellulosic materials obtained by use of the quaternary ammonium bases are very similar in structure to those obtained by Traube, Piwonka and Funk.[2] The results indicate, however, that methylation proceeds by diffusion of dimethyl sulfate into a particle structure, from which it follows that the cellulose component of these materials is not molecularly dispersed in quaternary ammonium bases but rather is dispersed as particles. Slit ultramicroscopic observations[5] of cellulosic materials dispersed in quaternary ammonium bases and of the methylated product dispersed in water verify the above conclusion by showing the presence of microscopic particles approximately 1 μ in diameter.

This work is being extended to other partially methylated cellulosic materials.

CELLULOSE DEPARTMENT
CHEMICAL FOUNDATION
BOYCE THOMPSON INSTITUTE
FOR PLANT RESEARCH
YONKERS, NEW YORK
JACK COMPTON

RECEIVED OCTOBER 19, 1938

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[1] L. H. Bock, *Ind. Eng. Chem.*, **29**, 985 (1937).

[2] W. Traube, R. Piwonka and A. Funk, *Ber.*, **69**, 1483 (1936).

[3] W. N. Haworth, E. L. Hirst and E. G. Teece, *J. Chem. Soc.*, 2858 (1931).

[4] Th. Lieser, *Ann.*, **483**, 132 (1930).

[5] *Cf.* J. Compton, THIS JOURNAL, **60**, 1807 (1938).

THE RELATIVELY INERT OXYGEN ATOM OF DIGOXIGENIN, SARMENTOGENIN AND THE STEROID COMPOUNDS OF THE ADRENAL CORTEX

Sir:

We have recently described [THIS JOURNAL, **60,** 1493, 2566 (1938)] a series of *etio*-cholanic acids and esters with oxygen atoms at C-3 and C-12. Steiger and Reichstein [*Helv. Chim. Acta*, **21,** 828 (1938)] have prepared from digoxigenin a similar series of acids which were thought to have oxygen atoms at C-3 and C-11. Since the 3,*x*-diketo-4-*etio*-cholenic acids derived from digoxigenin and from corticosterone proved to be different, they considered it doubtful that an oxygen atom occupied C-11 in the acids derived from digoxigenin. Through the courtesy of Professor Reichstein we have been able to compare directly the methyl diketo-*etio*-cholanates and the methyl diketo-4-*etio*-cholenates from the two sources. The results given in the table show that the properties of the esters from the two sources are identical. We conclude that Reichstein's acids are identical with those derived from desoxycholic acid and that the inert oxygen atom of digoxigenin, which was assigned to C-11 by Tschesche and Bohle [*Ber.* **69,** 793 (1936)], is actually at C-12.

	Acid or ester	From digoxigenin		From desoxycholic acid	
		M. p., °C.	$[\alpha]^{19}D$	M. p., °C.	$[\alpha]^{25}D$
1	Methyl diketo-*etio*-cholanate	171–172[a]	138.3 ± 2	169–170[a]	142 ± 3
2	Methyl diketo-4-*etio*-cholenate	236–238[b]	185 ± 2	236–238[b]	190 ± 6
3	Diketo-*etio*-cholanic acid	170		178	
4	Dihydroxy-*etio*-cholanic acid	280–286		283–286	
5	Methyl dihydroxy-*etio*-cholanate	180–183		145–146	

[a] Mixtures melted at 169–170°.

[b] Mixtures melted at 236–237°.

The other comparisons of the table are less satisfactory since the specific rotations of these compounds of Reichstein were not known and specimens were not available for mixed melting point determinations. The melting points of the diketo-*etio*-cholanic acids are in reasonable agreement, since we have found, as has Reichstein, that the acid is very difficult to purify. The methyl dihydroxy-*etio*-cholanates appear to be different since the melting point of our ester was sharp and could not be raised by distillation or recrystallization. Accepting this difference, epimerism at C-12 is indicated since the configuration of both esters at C-3 is α (no precipitation with digitonin). This difference is not certain, however, since the corresponding acids melt at the same point.

It has been generally accepted since the work of Tschesche and Bohle [*Ber.* **69,** 2497 (1936)] that digoxigenin and sarmentogenin differ only in the configuration at C-9. Inasmuch as some of the adrenal steroids contain an oxygen atom which corresponds in almost all respects with the inert oxygen atom of sarmentogenin, it has been assumed [Marker, THIS JOURNAL, **60,** 1725 (1938)] that they had a configuration at C-9 like that of sarmentogenin which was supposed to have a *cis* linkage of rings B and C instead of the normal or *trans* linkage. Marker [THIS JOURNAL, **60,** 1061 (1938)] has made the same assumption for his urane compounds. There is now no need to assume such a configuration at C-9 for sarmentogenin to explain its difference from digoxigenin, although such a possibility is by no means excluded. Consequently, such an assumption for the adrenal compounds has no basis. Indeed, all the evidence [Reichstein, *Helv. Chim. Acta*, **19,** 402 (1936); **20,** 978 (1937); **21,** 161 (1938)] points to a normal steroid skeleton with an oxygen atom at C-11.

DEPARTMENT OF BIOCHEMISTRY H. L. MASON
THE MAYO FOUNDATION W. M. HOEHN
ROCHESTER, MINNESOTA

RECEIVED OCTOBER 22, 1938

ABSENCE OF COMBINED FATTY ACID IN CEREAL STARCHES

Sir:

The common cereal starches contain fatty material which cannot be extracted by solvents such as petroleum ether, ethyl ether or carbon tetrachloride. From this behavior, T. C. Taylor and his co-workers assumed that the fatty acid must be present as an ester of the carbohydrate substance. His later work indicated that the α-amylose fraction of the starch was characterized by—and owed its insolubility to—this esterification with fatty acid.

Recent investigations in these Laboratories show that the fatty acids in corn, wheat and rice starches can be removed completely by Soxhlet extraction with certain water-miscible fat solvents, particularly methanol, the cellosolves, and 80% dioxane. The de-fatted starch retains its characteristic granule structure and optical birefringence, and gelatinizes in hot water to give a paste of normal high viscosity. By treatment with alcoholic oleic acid, such de-fatted starch can be reimpregnated with fatty acid, and this added fat cannot be extracted by hydrocarbon type solvents.

Hence, it appears that free fatty acid is distributed throughout the starch granule as an extraneous impurity. To explain selective extraction, it is suggested that only those fat solvents bearing hydrophilic groups can penetrate into the granule, hydrocarbon types merely washing the surface. This investigation is being continued, and final results will be reported in detail at an early date.

CORN PRODUCTS REFINING COMPANY
EDGEWATER, N. J. THOMAS JOHN SCHOCH
RECEIVED SEPTEMBER 23, 1938

PANTOTHENIC AND NICOTINIC ACIDS AS GROWTH FACTORS FOR LACTIC ACID BACTERIA

Sir:

In a previous publication the preparation of highly active concentrates (1 unit in 0.5 γ) of an essential growth factor for lactic acid bacteria has been described [Snell, Strong and Peterson, *Biochem. J.*, **31,** 1789 (1937)]. Considerable difficulty has been encountered in attempts to further purify this factor, and a long series of fractionation procedures resulted in only about a two-fold increase in activity (1 unit in 0.20 γ).

Recently, information became available [R. J. Williams, papers presented before the American Chemical Society at Milwaukee, Wisconsin, Sept. 5–9, 1938, and private communications] which revealed a striking similarity between the properties of the above growth factor and pantothenic acid [Williams, *et al.*, THIS JOURNAL, **55,** 2912 (1933)]. Both are water-soluble, nitrogenous, organic, hydroxy acids, easily destroyed by aqueous acids or alkalies, but relatively resistant to the action of light, nitrous acid, bromine, and mild oxidizing agents. Through the kindness of Dr. R. J. Williams it has now been possible to subject two samples of pantothenic acid to our bacterial test. One preparation, A, contained approximately 40%, and the other, B, 83% calcium pantothenate. The following results were obtained on *Lactobacillus casei* as the test organism:

	γ Added per 10 cc. medium				Cc. 0.1 *N* acid produced per 10 cc. medium			
Supplement	a	b	c	d	a	b	c	d
Sample A	0.0	0.05	0.1	0.5	0.5	1.4	3.5	7.0
Sample B	.0	.02	.05	.3	.5	1.3	3.3	7.8

These and other tests indicated that sample A contained one unit in approximately 0.13 γ, and that B possessed about twice this activity.

Sample B was further tested on *Bacillus lactis acidi*, *Lactobacillus arabinosus*, *Lactobacillus pentosus*, *Lactobacillus delbrückii*, *Bacillus brassicae*, *Streptococcus lactis*, *Leuconostoc mesenteroides*, and *Propionibacterium pentosaceum*, and proved to be highly active for each organism. All of these organisms had previously been shown to require the growth factor. It appears certain that the active substance in our concentrates is identical with pantothenic acid, and that our best preparation contained approximately 26% pantothenic acid.

In addition to pantothenic acid some lactic acid bacteria seem to require nicotinic acid as well. Six species tested were found to grow very poorly or not at all in an acid-hydrolyzed casein medium containing both riboflavin and pantothenic acid. When small amounts of nicotinic acid were added to this medium, a marked improvement in growth and acid production occurred in some cases.

	γ Nicotinic acid added per 10 cc. medium				Cc. 0.1 *N* acid produced per 10 cc. medium			
Organism	a	b	c	d	a	b	c	d
L. casei	0.0	0.1	0.3	0.5	2.2	4.1	5.4	6.6
L. arabinosus	.0	.1	.3	.5	1.7	4.7	...	5.2

From the above data it appears that nicotinic acid is also an essential growth factor for at least two species of lactic acid bacteria.

DEPARTMENT OF BIOCHEMISTRY ESMOND E. SNELL
COLLEGE OF AGRICULTURE FRANK M. STRONG
UNIVERSITY OF WISCONSIN WILLIAM H. PETERSON
MADISON, WISCONSIN
RECEIVED SEPTEMBER 24, 1938

ORIENTATION OF HIGH MOLECULAR WEIGHT LINEAR POLYMERS IN UNSTRETCHED FILMS

Sir:

Recent electron diffraction studies by Storks[1] furnish definite evidence that unstretched films of polyethylene sebacate consist of relatively small crystallites which are oriented with their long axes approximately in the plane of the film, and with limited rotation around this axis, "probably due in part to the presence of carbonyl groups along the chain." Further, Storks points out that such films will probably show a preferred orientation until the film thickness exceeds the average chain length; only beyond this point do high molecular weight linear polymers exhibit truly amorphous Debye–Scherrer ring patterns,

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(1) Storks, THIS JOURNAL, **60,** 1753 (1938).

This work is in complete accord with a theory of partially oriented film structure proposed by us, which was advanced to explain qualitatively the results of film continuity studies.[2]

We have shown previously that the minimum coating weight of certain linear polymers on several metals varies essentially inversely as the average chain length.[2] If the chains made a 90° angle with the surface, a direct ratio of minimum coating weight to chain length would obviously be approximated. A system of oriented chains *parallel* to the surface would give a minimum coating weight independent of chain length. At any angle between zero and 90° which the chains make with the surface, a fixed chain length would give a coating weight directly related to the sine of the angle with the surface. Now, it is obvious from the work of Langmuir and others that a chain having only a single terminal polar anchoring group would tend to stand on end; with additional polar groups along the chain, the effective polarity gradient along the polymer would vary with the type and distribution of such groups. Assuming a relatively uniform distribution along the chain,[3,4] then the chain would incline at an angle with the surface which was directly related to the polarity gradient. Finally, with uniform distribution of polar groups along the chain, the longer the chain the smaller would be this polarity gradient. Accordingly, the longer the chain the smaller would be the angle it makes with the surface and as a result, an increase in chain length would reduce the minimum coating weight. This was actually found by experiment.[2]

This line of reasoning had already led us to make electron diffraction studies, with inconclusive results. Storks' results obviously reopen this method of attack. They furnish independent confirmation of our theory of partial orientation in what are usually considered to be wholly amorphous films.

Unfortunately, our film continuity studies depend upon a specific method, namely, that of conductivity through discontinuous films. In the near future attempts will be made to get an independent check of this work by studying the diffusion of hydrogen through thin films on palladium and of helium through thin films on glass.

CONTRIBUTION FROM THE STONER-MUDGE, INC., INDUSTRIAL FELLOWSHIP
MELLON INSTITUTE OF INDUSTRIAL RESEARCH
PITTSBURGH, PA., AND G. H. YOUNG
THE PENNSYLVANIA STATE COLLEGE W. K. SCHNEIDER
STATE COLLEGE, PA. J. G. ASTON

RECEIVED AUGUST 13, 1938

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[2] Young, *et al.*, *Ind. Eng. Chem.*, **29**, 1277, 1280 (1937); **30**, 685 (1938). See also paper to appear shortly.

[3] Flory, THIS JOURNAL, **59**, 466 (1937).

[4] Marvel, *et al.*, *ibid.*, **60**, 280, 1045 (1938).

NEW BOOKS

Catalysis from the Standpoint of Chemical Kinetics. By GEORG-MARIA SCHWAB, University of Munich. Translated from the First German Edition, with additions from the recent literature by the author, by HUGH S. TAYLOR, Princeton University, and R. SPENCE, Leeds University. D. Van Nostrand Company, Inc., 250 Fourth Ave., New York, N. Y., 1937. xi + 357 pp. 39 figs. 16 × 23.5 cm. Price, $4.25.

The German edition [reviewed in THIS JOURNAL, **54**, 3017 (1932)] of Dr. Schwab's "Katalyse," which appeared in 1931, ably filled the need for an ordered and condensed theoretical treatment of the whole field of catalysis, both homogeneous and heterogeneous. The present translation, delayed by "the difficult economic conditions in the world," closely adheres to the original arrangement and purpose, but has been brought up to date by the addition of new material to the extent of some 15%. The result is a book admirably suited to graduate courses in catalytic theory, and useful to the prospective investigator as an orientation into the many unsolved problems in this field.

The reader is assumed to be familiar with the principles of theoretical chemistry, including the kinetics of uncatalyzed reactions, and with elementary mathematics. The emphasis is on the significance of theories as applied to selected examples rather than on formal mathematical statements. The treatment of the various types of catalysis is organized on a systematic rather than historical basis. Experimental examples are frankly chosen for their value in illuminating general principles, and details are naturally minimized. The book is about equally divided between homogeneous catalysis (in gases and solutions) and heterogeneous catalysis (of gas reactions). Bio-catalysis is treated briefly; technical aspects of catalysis are excluded, as is also experimental technique.

Some idea of the current activity in catalytic investigation may be obtained from the fact that the 457 citations to the literature in the original text have grown in six years to 735. The increase is especially marked in heterogeneous catalysis, where new sections on "activated adsorption," "quantum mechanics of activated adsorption," etc., appear. All the original citations are retained but in the main the effort to incorporate the newer material into the old has been reasonably successful. The translation is mostly clear in spite of the fact that few liberties have been taken with the original text.

A few points are discussed in a way which may seem inadequate to the specialist, for example: entropy of activation, *absolute* rates of adsorption and of catalysis, determination of surface areas, adsorption by poisoned catalysts, catalysis of gas–solid reactions by solids. But on the whole the book should be as stimulating to the specialist as it will be indispensable to others interested in an authoritative survey of this vigorous branch of theoretical chemistry.

Arthur F. Benton

Lehrbuch der Chemie. Teil II. Organische Chemie. (Textbook of Chemistry. Part II. Organic Chemistry.) By Walter Hückel, Professor at the University and Institute of Technology, Breslau. Akademische Verlagsgesellschaft m. b. H., Markgrafenstrasse 6, Leipzig C 1, Germany, 1937. xvi + 602 pp. 38 figs. 16.5 × 24 cm. Price, RM. 16; bound, RM. 18.

This text is an introduction to organic chemistry for the general student, with special attention given to the needs of the pre-medical group. Sections of importance for these students are marked.

The special quality of this book lies in its spirit and choice of material, rather than in any novel order of presentation. The material is chosen with unusual discrimination. The classification by homologous series is well explained, and thereafter only examples of live current interest are used to illustrate types of compounds. The work is distinguished by the logical presentation which would be expected by all who know Professor Hückel's writings. There is frequent reference to the experimental methods behind the structures and interpretations presented.

While it may not be practicable to use a German text in the instruction of first-year American students, this book will be welcome for the way in which it combines an interesting story with the teaching of a logical science.

P. D. Bartlett

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(1) **Collateral Readings in Inorganic Chemistry.** (2) **Readings in Elementary Organic Chemistry.** Edited by L. A. Goldblatt, University of Pittsburgh. D. Appleton-Century Co., 35 West 32d St., New York, N. Y., 1937 and 1938. 21.5 × 27.5 cm. (1) viii + 225 pp. Price, $1.35. (2) viii + 150 pp. Price, $1.25.

A chemistry major student on departing from a small college or large university should carry with him a thorough grounding in the fundamentals of chemistry and a humble realization that there is much more to his chosen science than has been given in his lectures and textbooks. The one is a function of faculty and curriculum; the other requires in addition a judicious consultation of the original literature, and its acquisition frequently is rendered difficult by linguistic and library limitations as well as the problem of intelligent selection. In these photo-reproductions of the original articles (with notes and translations where needed), Professor Goldblatt has gone far toward solving the problem, presenting a comprehensive selection of recent inorganic and organic papers ranging from the "Fathers of the Chemical Revolution" to the Dow Process for Bromine from Sea Water, and from Wöhler's "Artificial Preparation of Urea" to the Use of Isotopes in the Study of Intermediary Metabolism, with plentiful dashes of general seasoning in the form of Nobel Laureates, Eminent Chemists, Summary Articles and Market Reports. The experiment seems worth while and its continuance, by revised selection editions, will depend upon the academic acceptance accorded these two inexpensive paper-bound volumes.

Allen D. Bliss

Traité de Pharmacie Chimique. (Treatise on Pharmacological Chemistry.) By P. Lebeau, Professor in the Faculty of Pharmacy of Paris, and G. Courtois, Assistant in the Faculty of Pharmacy of Paris. Vol. I. Chimie Minérale et Chimie Organique. Vol. II, Parts 1 and 2. Chimie Organique. Second edition. Masson et Cie., Éditeurs, 120 Boulevard Saint-Germain, Paris VI^e, France, 1938. 17.5 × 25 cm. Vol. I: xxviii + 1206 pp. Price, fr. 280. Vol. II: xxviii + 2128 pp. Price, fr. 460.

The rapid development during the last few years of the study of chemical medication compelled the authors considerably to increase the bulk of the second edition of their textbook on pharmacological chemistry. It is presented now in three volumes, a total of 3334 pages.

The first volume is still, as in the previous edition, devoted to the study of therapeutical material classified under inorganic chemistry and the acyclic part of organic chemistry, excluding the nitrogen derivatives.

The second volume consists of two parts. The first one deals with pharmaceutical substances of the cyclic group, both cyclic and acyclic nitrogen compounds, terpenic derivatives, and finally with the chemically well-defined substances of the hormone, vitamin and organo-mineral group. The second volume describes the therapeutically valuable substances of the heterocyclic, the alkaloid, the glucoside and the proteic groups.

The authors give special consideration in their work to phytopharmacy, to which they lend a very particular importance. The profession of pharmacist, in France, is quite distinct from what it is in this country so that it is evident that the requirements of a textbook on pharmaceutical chemistry will be different also.

The present work is primarily intended as a textbook and corresponds to a regular course in pharmaceutical chemistry as given at the Faculty of Pharmacy of the University of Paris.

Rather complete references to the literature are given so as to allow for more thorough study of the properties of the different pharmaceutical compounds. This makes the Treatise of equal value to both the student and the pharmaceutical practitioner.

The first part of the work, dealing with mineral chemistry, is different from the usual textbook on general chemistry only in that more emphasis is given to the pharmaceutical aspect of the different substances described. It seems as if it would have been wise to pay even more attention to the pharmacological side and to reduce considerably the description of chemical properties and modes of preparations. The sequence of descriptions follows closely the trend in books of general chemistry. The relation between chemical structure and physiological activity has, however, been stressed by the authors as often as possible.

The recent advances in the field of vitamin and hormone investigation are only briefly described and the achievements of the last two years are practically entirely omitted. It might be stated once more, in this respect, that the aim of the authors was not to publish a monograph, but to provide the student with a textbook as a help to his course on the subject. Sufficient bibliography, including reference to more specialized textbooks, is given, however, so as to provide the student with all facilities for further study on a given subject.

The presentation of the subject matter of this book is very good indeed.

V. DESREUX

A Textbook of Biochemistry. By ROGER J. WILLIAMS, Ph.D., D.Sc., Professor of Chemistry, Oregon State College. D. Van Nostrand Company, Inc., 250 Fourth Avenue, New York, N. Y., 1938. x + 525 pp. 17 figs. 14.5 × 22 cm. Price, $6.00.

The book includes five sections: biochemical materials, Chapters 2–5; tissue composition, Chapter 7; food composition, Chapter 8; bodily mechanisms for promoting and regulating chemical change, Chapters 9–14; metabolism, Chapters 15–23. There is a glossary and an index.

The conventional description of fats, proteins, and carbohydrates is well balanced with proper attention to chemical properties on the one hand and biochemical significance on the other. Other materials of biochemistry usually are considered in relation to function rather than structure to the bewilderment of the student accustomed to the orderly system of organic chemistry. The author has wisely arranged these diverse substances in Chapter 5 according to chemical constitution, postponing until later questions of function.

Tables showing the chemical make-up of tissues are assembled in Chapter 6 from 166 sources. There are a few errors, some data of doubtful validity and no analyses are reported of extra- and intracellular phases of muscle, but it is a unique and valuable compilation.

Excellent chapters in the later sections cover the subjects of permeability, chemical mediation of nerve impulses and chemotherapy. It is the opinion of the reviewer that the first of these could be improved by including, with some elaboration, the discussion of colloid osmotic pressure given in Chapter 6—Colloidal Properties. Concealed in the latter chapter is an incomplete account of the physicochemical properties of proteins. Neither here nor elsewhere is the role of proteins as buffers explained except for the special case of hemoglobin.

There are remarkably few errors. On p. 179, Steffanson's experiences are said to indicate that very high protein diets may be quite satisfactory. Actually, Steffanson became sick on a lean meat diet but thrived on a fat meat diet despite a moderate ketosis. His protein intake did not exceed that of the American soldier in active service. On p. 346, the small intestine is said to be 30 feet long. This is the length after death; a sound passed naturally through the gastro-intestinal tract of a healthy man shows a length of 7 or 8 feet from mouth to rectum. On p. 487 it is said that Cinchona bark has been used to treat malaria for two centuries. Presumably it had been used for centuries by the Indians before the first authenticated use in treating the wife of the governor of Peru about 1630.

The author is tolerant in his discussion of new theories and shows good judgment in evaluating current trends in biochemistry. He questions, for example, the validity of the assumption that the faster the rate of growth and the greater the body size, the better for the race, whether of rats or men.

D. B. DILL

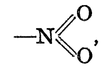
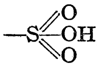
Textbook of Organic Chemistry. By GEORGE HOLMES RICHTER, Assistant Professor of Organic Chemistry, the Rice Institute. John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y., 1938. viii + 711 pp. 83 tables. 15.4 × 23.5 cm. Price, $4.00.

Professor Richter set himself the task of writing a book "directed specifically to that large body of ambitious students who wish to study beginning organic chemistry and gain more than a superficial knowledge of the subject." He has accomplished his purpose admirably; his book should prove most useful in a full year's elementary course; indeed, it contains far more material than one could hope to cover in the usual first course.

The order of the subject matter is the conventional one: after a very brief introduction in which types of valence and structural formulas are discussed, follow aliphatic hydrocarbons, saturated and unsaturated, alcohols, ethers, aldehydes and ketones, etc. The various homologous series are well illustrated by excellent tables giving pertinent physical properties of the more important members, with the result that such data are kept at an absolute minimum in the text with a consequent increase in readability.

Adequate consideration is given to compounds of industrial significance and to naturally occurring substances; these are to be found as illustrations of the particular classes to which they belong. Granting that this method of treatment is desirable up to a certain point, we are not entirely sure that the very early introduction of formulas as complex as those of the carotenes and the sex hormones is not objectionable from the pedagogic standpoint.

An unusually large number of substances find mention, and the choice of material is, on the whole, good. If Professor Richter has erred at all, he has attempted to give too complete a picture of organic chemistry in a book written specifically for ambitious beginners. Each chapter closes with a list of review questions which cover the subject matter very fully.

In one minor respect the author is not consistent: he points out carefully the objections to the formulation of the nitro group as  $-\mathrm{N}{\genfrac{}{}{0pt}{}{\nearrow \mathrm{O}}{\searrow \mathrm{O}}}$, and of sulfonic acids, etc., as  $-\mathrm{S}{\genfrac{}{}{0pt}{}{\nearrow \mathrm{O}}{\searrow \mathrm{O}}}\!-\mathrm{OH}$, and then proceeds to use the rejected formulas freely.

The book is clearly and interestingly written, it contains very few typographical errors, and is a very complete and accurate survey of the chemistry of organic compounds with emphasis on their nomenclature, structure synthesis, reactions and properties.

NATHAN L. DRAKE

Introduction to Physiological Chemistry. By MEYER BODANSKY, Ph.D., M.D. Fourth Edition. John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y., 1938. ix + 686 pp. 15.5 × 24 cm. Price, $4.00.

The Fourth Edition brings this very satisfactory "Introduction to Physiological Chemistry" largely up to date. In each chapter some of the material has been rewritten, and several chapters have been entirely rewritten. As a whole, it takes into account work published in 1937, both in the text and in the many references. All this has been done with the addition of only twenty-five pages, but, as the type is smaller, the actual addition is substantially greater than appears at first sight. There are very few typographical errors or errors of commission, and, although any reader having intimate knowledge of the subjects included would probably write the subject coming within his special competence differently, it is none the less a thoroughly sound and satisfactory introduction to the wide variety of subjects covered under the general title bio-chemistry.

RONALD M. FERRY

Organic Syntheses. An Annual Publication of Satisfactory Methods for the Preparation of Organic Chemicals. Vol. XVIII. By R. C. FUSON, C. F. H. ALLEN, W. H. CAROTHERS, L. F. FIESER, W. W. HARTMAN, J. R. JOHNSON, C. R. NOLLER and A. H. BLATT. John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y., 1938. v + 103 pp. 15.5 × 24 cm. Price, $1.75.

Like the preceding members of this series, the present volume contains carefully tested methods for the preparation of a selected group of organic compounds. As will be noticed from the table of contents, the continued increase in biochemical interest is represented by several classical examples. Here, under "Barbituric Acid" might have been mentioned Hakon Lund's recently (1935) described method of condensation by means of magnesium methylate. As further indication of modern trends, the introduction of fluorine, and of selenium, into organic compounds is exemplified each by one substance.

The list of new preparations is as follows: 2-acetothienone, acetylenedicarboxylic acid, allylamine, barbituric acid, betaine hydrazide hydrochloride, β-bromoethylamine hydrobromide, α-chloroanthraquinone, α,β-dibromosuccinic acid, 4,4′-difluorobiphenyl, 3,4-dihydro-1,2-naphthalic anhydride, diphenyl selenide, diphenylselenium dichloride and triphenylselenonium chloride, ethyl benzoylacetate, ethyl α-phenylacetoacetate, *n*-ethyl-*m*-toluidine, *l*-histidine monohydrochloride, α-hydrindone, malonic acid, methyl benzyl ketone, methyliminodiacetic acid, 1,2-naphthalic anhydride, *p*-nitrobenzaldehyde, phenoxthin, α-phenylacetoacetonitrile, 2-phenylpyridine, potassium anthraquinone-α-sulfonate, protocatechualdehyde, taurine *p*-tolylcarbinol.

A recent number of "Nature" contains a review of this volume, and it is a pleasure to endorse the statement, "In all respects this latest member of the series maintains the high standard of its predecessors."

M. GOMBERG

The Origin of Life. By A. I. OPARIN. Translated with Annotations by SERGIUS MORGULIS. The Macmillan Company, New York, 1938. 270 pp. $2.75.

Probably there is no biologist or philosopher who has not at some time considered the basic question of biology, "How did life come to be?" In general they must be satisfied with the statement that somehow, somewhere on the surface of the earth special conditions, and perhaps an "accident," started the stream of life in motion. Few have attempted to expand the discussion past the limits of a few paragraphs. Oparin, however, has evolved a fascinating hypothesis and has expanded it into an exceedingly readable volume, one which challenges and provokes the thought of the scientist and which unquestionably will stimulate a certain amount of experimental investigation, although Oparin does not hold out much hope that experimental investigations based on the hypothesis will lead to its confirmation or rather will lead to the creation of life.

Oparin's viewpoint is radically different from most discussions of the subject of which the reviewer is aware. Most discussions presuppose an atmosphere in which carbon dioxide is highly concentrated and from which enormous quantities of carbon dioxide could be drawn by plants with the corresponding liberation of oxygen by the photosynthetic process. The great rise of the plant kingdom, culminating in the carboniferous era, is thus explained, and most hypotheses account for the tropical temperatures at that time by assuming a blanketing effect of the higher carbon dioxide content of the atmosphere.

Oparin begins his discussion of the origin of life by discussing the origin of the planetary systems. He points out that if the planets arose from the sun because of tides raised on the sun by the passage of another star, the gaseous masses which eventually became the planets would have had to pass through a progressive evolution as the masses cooled. He points out that the primary atmosphere of the earth must have been devoid of oxygen because the earth's crust is still far from being saturated with oxygen, and at the higher temperatures this lack of oxygen saturation by the lithosphere must have been still more pronounced. He, therefore, regards the free oxygen in the atmosphere as having arisen in a much later epoch and to have been formed secondarily as the result of the activity of living organisms. Furthermore, he regards the nitrogen of the atmosphere as being principally of secondary origin and concludes that the nitrogen must originally have been present in the form of nitrides and of ammonia. He points out that at high temperatures carbon and hydrogen would preferentially unite to form hydrocarbons and that carbon would react with mineral elements to form carbides. As the temperatures became lower, water vapor and superheated water would react with the carbides to form hydrocarbons and with the nitrides to form ammonia. His primary atmosphere would then consist of a great variety of hydrocarbons, of ammonia, and of water vapor. As the cooling proceeded, the water would condense into the oceanic pools, the ammonia would largely dissolve in the water, and this mixture would be saturated with a variety of hydrocarbons.

As supporting evidence of this portion of his thesis, he cites Russell to the effect that the original oceans on Jupiter probably consisted of aqua ammonia, and as the temperature fell still lower, the water froze out, so that today at a temperature of −100°, ice exists at the bottom of Jupiter's oceans and that this ice is covered with liquid ammonia, that the clouds on Jupiter are apparently clouds of ammonia snow, and that when we pass to Neptune at −200° the ammonia is solidified and the clouds now are clouds of methane snow.

Up to this point Oparin has introduced no radically new hypothesis. He now points out, however, that the biocatalysts or the enzymes characteristic of living organisms in general only speed up reactions which take place very slowly in the absence of the catalyst. In the evolution of the planets there would be the opportunity for hydrocarbons and their oxidation products, aldehydes, alcohols, ketones, and organic acids, to interact with each other in an aqueous ammoniacal medium over long eons of time. He therefore believes that under the conditions which then prevailed most of the types of organic compounds, and which we now know to be characteristic of plants and animals, originated by the processes of this chemical interaction. This evolutionary process lasted for an incalculably long period of time. Condensations and polymerizations built up complex organic molecules. These probably reached colloidal size long before that phenomenon which we know as life came into being. Oparin suggests that relatively complex proteins may have originated *de novo* in this manner. He even accounts for the origin of optically active organic compounds and the specialized groupings around an asymmetric carbon atom by calling attention to the fact that sky light is plane polarized and that when this passes into an aqueous medium it is transformed into circularly polarized light, and then he cites experimental evidence that circularly polarized light preferentially decomposes either the *d*- or the *l*-form of a racemic mixture of organic compounds having appropriate absorption bands.

He continues with his thesis, assuming that certain of these organic colloids are positively charged and that others are negatively charged, and argues from the observation of Bungenberg de Jong that coacervate droplets would separate as a distinct phase. Here then we have what are essentially single cells but as yet incapable of self-propagation. He concludes, however, that since enzymes are in all probability chemical compounds with particular space configurations, there should be no essential reason why enzymes should not arise in the same way that the primary organic compounds arose and that a coacervate system containing enzymes possibly represents the primary living cell.

From this point on the argument is somewhat more hypothetical and is based on the assumption that those coacervate systems more nearly adapted to the environment tended to persist and become stabilized, whereas those coacervate systems less adapted to the environment were eliminated and disappeared by a process of "natural selection." Those systems which persisted probably grew at the expense of the nutrilites in the aqueous environment, and those which possessed enzymes characteristic of anaerobic respiration found a source of energy in the interaction of organic substances with water molecules. In this way carbon dioxide and other products of fermentation were liberated into the atmosphere. This started a new cycle of reactions, since new building stones were available, and from these new series of reactions Oparin postulates the synthesis of certain special pigments which, when possessed by the coacervate system, rendered that particular system capable of utilizing the energy of sunlight for initiating and controlling chemical reactions. Such systems became the primitive life forms.

The above is only a very brief and cursory review of a very fascinating hypothesis. Many chemists will want to read this volume over and over again. Every physiologist and biochemist should call it to the attention of his students, for while it is purely a hypothesis, there are many proven facts interwoven into the network, and in some places where the gaps in knowledge are great, it may be possible to supply at least a part of the missing links by further investigations.

ROSS AIKEN GORTNER

Colorimetric Methods of Analysis Including Some Turbidimetric and Nephelometric Methods. Vol. II. Organic and Biological. By FOSTER DEE SNELL and CORNELIA T. SNELL. D. Van Nostrand Company, Inc., 250 Fourth Avenue, New York, N. Y., 1937. xxiv + 815 pp. 49 figs. 16.5 × 23.5 cm.

In this second volume the authors have collected methods of colorimetric and nephelometric analysis applicable to organic and biological substances. They have also collected methods for the comparison and evaluation of the colors of various products such as oils and sugar solutions. The book is complete up to 1936.

As in the first volume, a number of methods are given for each substance, five, for example, being given for benzene. The general plan of Volume I is also continued. After a brief general description of each method, detailed directions for the preparation of samples are given. Then the procedure is described carefully and finally there are directions for preparing standards.

Although complete critical treatment of all of the methods described is impossible in a volume of this scope, a great deal of very valuable criticism and discussion of interferences has been collected from the literature and included in the book. Thus thirteen references are quoted on the determination of methanol and methoxy groups as formaldehyde by Schiff's reagent, and no less than sixty-four on the determination of cholesterol by acetic anhydride. Incidentally, this bibliography in the form of footnotes is most convenient and accessible. Would that all compilers of chemical information would thus make short the path from datum to reference! The index is also complete and accurate.

The first chapter on hydrocarbons is followed by one on alcohols and then by a chapter on sterols. Next there are three chapters on aldehydes and ketones and then thirteen chapters on acids and related compounds, ranging from formic to abietic acid. Then follow chapters on hemoglobin, proteins, nitrogen in various forms, phenols, urea and related compounds, miscellaneous amines, imines, and nitro compounds. Five chapters on carbohydrates, four on alkaloids and one each on glucosides, halogen derivatives, and compounds with inorganic radicals, are included. Then there are two chapters on enzymes, one on hormones and one on vitamins. Finally a chapter on the measurement of bleaching power introduces a section of nine chapters on the measurement of color and turbidity itself in oils, sirups, extracts, pigments, etc. In this section various special instruments adapted to particular types of color measurement are described.

The authors may feel sure that a wide circle of chemists will be grateful to them for the labor of preparing this very useful and comprehensive survey of colorimetric and nephelometric methods.

C. H. Greene

An Outline of Organic Chemistry. By Ed. F Degering, Purdue University, R. E. Nelson, Purdue University, and J. R. Harrod, Ohio Northern University, and seventy-seven Assistant Editors. Revised edition. Barnes and Noble, Inc., 105 Fifth Avenue, New York, N. Y., 1937. 317 pp. 14 × 21.5 cm. Price, $2.25.

If at first one is inclined to regard this volume as just a soft short-cut for the student to a pass mark in a course in organic chemistry, a careful perusal of the book promptly corrects such a view. It represents a sincere effort on the part of a group of teachers to aid students in understanding what is to many a difficult subject, but it is no sugar-coated pill. Sixteen standard texts have been drawn upon in preparing the outline, and a pagination chart enables one to use it with any one of these texts in lieu of note taking in class. Throughout an effort has been made to indicate conditions and reagents requisite for the performance of each reaction. In addition to the usual material referred to in a one-year course, the book contains excellent special chapters contributed by authorities. The chapter on nomenclature, edited by Patterson, should aid in the gradual, and welcome, unification and simplification of naming schemes employed by American chemists. *Chemical Abstracts* usage is recommended. Lucas' excellent chapter on electronics makes evident to the beginning student in organic chemistry the fact that a knowledge of electrons and protons should not be relegated to limbo after a good course in Freshman chemistry. Careful attention to the brief, but good, section on pronunciation will spare users from censure (readily recalled by the reviewer from his student days) for the use of "damned Teutonisms." An excellent, *informative*, 17-page index is included. The publishers present with the book an "omission list," the use of which, without change, would in the reviewer's opinion lead to a pretty thin broth kind of elementary organic chemistry course. The outline, with no omissions, presents somewhat too much "red meat" for most students to digest in one year. The material given is very well organized, misprints and other errors are remarkably few, and the book work is very well done.

This little volume is interesting, stimulating, and should prove helpful to students and instructors alike.

G. Albert Hill

Qualitative Analyse mit Hilfe von Tüpfelreaktionen. Theoretische Grundlagen, praktische Ausführung und Anwendung. (Qualitative Analysis with the Aid of Spot Tests. Theory, Development and Application.) Third, revised edition. By Dr.-Ing. Fritz Feigl, Professor in the University of Vienna. Akademische Verlagsgesellschaft m. b. H., Sternwartenstrasse 8, Leipzig C 1, Germany, 1938. xii + 554 pp. 27 figs. 16 × 24 cm. Price, RM. 28; bound, RM. 30.

All chemists who are familiar with the first (1930) [This Journal, **53**, 1621 (1931)] and second (1935) [*ibid.*, **58**, 863 (1936)] editions of this valuable work will be gratified to note the publication of this third edition. Although the total number of pages has increased from 513 (2nd edition) to 554 (3rd edition), yet substantial improvements in the typographical arrangements of the numerous tables have permitted the inclusion of much more material than would correspond to the page increase alone.

As in the previous editions the book is divided into two major divisions designated as theoretical (140 pp.) and special (373 pp.). Both are generously documented with references to the original literature. The first will be particularly welcomed since it was omitted completely from the recent English translation of the second edition [*ibid.*, **60**, 734 (1938)]. Following a brief but adequate description of the general technique of "spot testing," the special part devotes itself to the particular methods for the detection of metals (127 pp.), the detection of acids (66 pp.), systematic investigation of inorganic mixtures (21 pp.), application of spot tests to qualitative organic analysis (104 pp.), tests for purity, technical testing and mineral examination (50 pp.) and finally to an extensive tabular review of the content of the special part.

As a work to which continual reference will gladly be made by workers in organic as well as inorganic chemistry, the present edition well deserves the attention of all chemists who may hitherto have overlooked this valuable assistant.

E. H. Huntress

Second Report on Viscosity and Plasticity. Prepared by the Committee for the Study of Viscosity of the Academy of Sciences at Amsterdam. Nordemann Publishing Company, Inc., 215 Fourth Avenue, New York, N. Y., 1938. viii + 287 pp. 80 figs. 19 × 27 cm. Price, $7.50.

The book consists of a series of six articles surveying various topics relating to the viscous and plastic deformation of liquids and solids. The contributors are J. M. Burgers, F. M. Jaeger, R. Houwink, C. J. van Niewenburg, and R. N. J. Saal.

In the first article, Chapter I, recent investigations on the structure of liquids are reviewed by Burgers. The results of X-ray scattering studies and the calculation of radial distribution functions receive particular attention. In the article by Jaeger, viscosity data on pure liquids and liquid mixtures are discussed in connection with a number of theoretical and semi-empirical formulas. Certain problems relating to the theory of lubrication are touched upon.

The article by Burgers, Chapter III, on the motion of small particles suspended in a viscous liquid is of particular interest to chemists because of its bearing on the molecular shape of proteins and of polymers of high molecular weight. The author develops in a rather simple manner an approximate theory of the influence of elongated particles on the viscosity of a liquid in which they are suspended. By employing a method due to Oseen for the calculation of the velocity field in a viscous liquid in laminar flow, under the influence of external forces, he is able to avoid much of the intricacy of the exact hydrodynamical treatment of Jeffery and others.

In Chapter IV, by Houwink, the various factors influencing the yield value of crystalline solids, amorphous solids, and suspensions are investigated. The last two chapters are concerned with the techniques of plasticity and viscosity measurements. In the article on plastometers by van Niewenburg a survey of the types of instruments in use is undertaken, and the significance of plasticity measurements is discussed. The author concludes that no plastometers of present design allow an unambiguous determination of the fundamental relation between the rate of shear in an element of the sample and a simple shearing stress acting through it. In the final chapter by Saal, types of technical capillary viscosimeters in current use are described.

The report provides a unified and critical survey of a large amount of material on viscous and plastic phenomena. It will certainly prove to be a source of useful information on the subject. It is perhaps to be regretted that certain of the latest theoretical developments in the theory of viscosity have not been included.

JOHN G. KIRKWOOD

Tables of Reagents for Inorganic Analysis. In English, German and French. First Report of the "International Committee on New Analytical Reactions and Reagents" of the "Union Internationale de Chimie": C. J. van NIEUWENBURG (Delft) President, W. BÖTTGER (Leipzig), F. FEIGL (Vienna), A. S. KOMAROVSKY (Odessa), N. STRAFFORD (Manchester). Akademische Verlagsgesellschaft m. b. H., Sternwartenstrasse 8, Leipzig C 1, Germany, 1938. xxiv + 409 pp. 18 × 25 cm. Price, RM. 34; bound, RM. 36.

It should be clearly understood that this report deals only with reagents for use in *qualitative* inorganic analysis, and that the reagents that are covered are those that have been introduced in the period 1911–1936, inclusive. Spectroscopic methods, flame color reactions and methods of separation or concentration are not mentioned. Neither are the older standard reagents, unless they have been reinvestigated during this period.

The types of reactions described are those involving precipitation, color, catalysis, and certain miscellaneous operations. The procedures cover spot tests on drop plates or paper, micro tests under the microscope or in the micro test tube, and macro tests in the ordinary test tube.

Data are presented by an extensive use of symbols and abbreviations under the six general columns (1) cation or anion, (2) name and formula of the reagent, (3) type of reaction, (4) procedure, (5) sensitivity, and (6) remarks on compounds that are known to yield similar reactions or to interfere in the test. Extensive references to the literature are given under each test.

The section on cations deals with tests for some 57 elements plus the ammonium ion, while that on the anions covers some 38 anions. Finally, there is a very complete subject index listing the reagents and the tests in which they are used.

The book is a very worth while addition to texts on inorganic analysis, and is a mine of information for those who are prospecting or working in the field of qualitative analysis.

G. E. F. LUNDELL

The Elements of Physical Chemistry. By F. W. GODDARD, M.A., F.C.S. and E. J. F. JAMES, M.A., D.Phil. Longmans, Green and Co., 114 Fifth Avenue, New York, N. Y., 1938. viii + 251 pp. 66 figs. 13.5 × 20 cm. Price $1.80.

The two British authors state in their preface: "This introduction to the study of Physical Chemistry is intended for the use of students preparing for Higher Certificate, First Medical, and University Entrance Scholarship Examinations. It is assumed that such students will have acquired a knowledge of elementary physics and chemistry up to the standard of School Certificate on Matriculation." In American colleges and in teacher training schools it could well find a place in a course following general chemistry, or as an introduction to the regular course in physical chemistry. The book is distinctly an elementary treatment of the subject. Little, if any, calculus is involved. The pitch is about right for our American type of pre-medical courses in physical chemistry, but the dearth of illustrative material drawn from the biological field probably renders this text unsuited for such a purpose It is a bare skeleton outline cut almost to the bone.

The scope of the book is indicated by the chapter headings: I, The Atomic and Molecular Theory; II, Valency and the Structure of Atoms; III, The Gaseous and Liquid State; IV, Solution; V, Osmotic Pressure and Allied Phenomena; VI, Law of Mass Action; VII, Thermochemistry; VIII, Electrolysis and Electrolytic Dissociation; IX, Catalysis; X, Colloids.

The exposition is extremely clear, and the whole book is well organized. Every chapter is followed by a well-chosen list of good questions and problems (two hundred and fifty altogether). The answers are supplied at the end of the book. There is also a supplementary list of miscellaneous questions. An author index, subject index, and atomic weight, four-place log and anti-log tables, are also given.

EDWARD MACK, JR.

Laboratory Methods of Physical Chemistry. By JOSEPH J. JASPER, Assistant Professor of Chemistry, Wayne University. Houghton, Mifflin Company, 2 Park Street, Boston, Massachusetts, 1938. xix + 312 pp. 34 figs. 15 × 22.5 cm. Price $2.50.

This textbook is one of the series edited by Professor H. T. Briscoe. Following the Editor's Introduction, a Preface, Table of Contents and List of Figures, there are Preliminary Remarks to the Student, and the Chapters: I, Errors of Measurement and Corrections; II, Gases; III, Liquids; IV, Optico-Chemical Methods; V, Solutions; VI, Colloidal Systems; VII, Thermochemistry; VIII, Homogeneous Equilibrium; IX, Chemical Kinetics; X, Phase Equilibrium in Chemical Systems; XI, Electrical Conductance; XII, Transference Numbers; XIII, Electromotive Force; XIV, Photochemistry; Bibliography and Index. Altogether, Professor Jasper gives directions for about sixty experiments. The directions are clear and adequate and are featured by (1) the excellent figures, (2) helpful discussion of the pertinent theory at the beginning of every experiment, and (3) by specific instructions for treatment of results at the end.

It is perhaps somewhat surprising, or perhaps not surprising, to teachers of physical chemistry to find that several of the available laboratory manuals are constructed so nearly on the same pattern. Resemblances in the skeleton outline of book structure may be inevitable because of the necessity of acquainting the student with a representative set of the highly standardized laboratory techniques of the physical chemist. The author of such a textbook no doubt feels almost compelled to present the usual type of directions for making the classical measurements of molecular weight, surface tension, viscosity, electrical conductivity, hydrogen ion concentration, etc., etc., through the whole list.

If a dozen, or several dozen, authors and their publishers are to give birth to laboratory manuals of physical chemistry, it is to be hoped that some distinctive flavor of originality may be found in a few of the new-born. Surely the vast literature of experimental physical chemistry, with its enormous wealth of illustrative material suitable for textbook use, has scarcely been sucked quite dry. Nor have the resources upon which the alert pedagogue may draw for setting forth the meaning and limitations and possibilities of the experimental method, and for arousing and sustaining the interest of the student, necessarily been exhausted.

The present book is a good one. It should find a wide adoption and usefulness, as have some of the other books which it resembles.

The author, the editor and the publishers are to be congratulated on its very fine appearance, and on the excellent job of book-making that they have done.

EDWARD MACK, JR.

The Fine Structure of Matter. Part II. Molecular Polarization. Part III. The Quantum Theory and Line Spectra. By C. H. DOUGLAS CLARK, D.Sc., A.R.C.S., A.I.C., D.I.C., Assistant Lecturer in Inorganic Chemistry in the University of Leeds. John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y., 1938. 14.5 × 22.5 cm. Part II: lxxii + 241 pp. 35 figs. Part III: lxxii + 185 pp. 29 figs. Price, $4.50 each.

The chapter headings in the two volumes under review are the following: Part II, Molecular Polarization: Dielectric Constants, The Debye Theory of Polarization, Molecular Refraction, Polar Molecules, Molecular Fields; Part III, The Quantum Theory and Line Spectra: The Quantum Theory, The General Principles of Line Spectra, The Multiple Structure of Lines, Line Spectra and the Periodic Classification.

In the opinion of the reviewer, a reader unfamiliar with the subjects could not gain an understanding of molecular polarization and line spectra by the study of these books, although the author in his preface suggests that Part III might serve as an introduction to the study of spectra. The style in which the books are written is incoherent and confusing, and the author has not given a consecutive account of the topics treated. Unrelated subjects are grouped together as, for example, on page 285, where reference is inserted in a section on the additivity of molecular refraction values to a method of calculating the refractive index of nickel arsenide from its reflective power in air and in cedarwood oil. The lack of clarity in the discussions is due in part to the inclusion of references to outmoded suggestions as well as to the more satisfactory recent theories and to unreliable as well as reliable values of experimental quantities.

The theoretical parts of the books are poor; although a detailed mathematical discussion (pages 452–455) is given of Debye's old calculation, now unimportant, of the value 64° for the H–O–H angle in the water molecule (the actual value being 105°), no derivation of the Debye fundamental equation relating molecular polarization and dipole moment is given in the chapter headed "The Debye Theory of Polarization" or elsewhere in the book. In several pages of discussion of the Clausius–Mossotti equation mention is made of the electric displacement in cylindrical cavities, but the significant step of evaluating the factor $^1/_3$ in the equation with use of a spherical cavity is omitted, the reader being left unenlightened as to the nature of the "certain assumptions, in accordance with the classical theory," which are involved.

The volumes are made somewhat unsatisfactory for reference purposes by the Author's selection of 1934 as the closing date for literature references, and by the existence of many errors. Fluorescent scattering and Raman scattering are said to require a decrease in frequency of the light. A figure showing experimental values of the molecular refraction of alkali halide crystals is confusingly described as based on estimates of $R_{\text{crystal}} - R_{\text{free gas ion}}$. Typographical errors such as CH_2OH for CH_3OH, SiF_6 for SeF_6, $Te(NO_3)_2$ for $Te(NO_3)_4$, and HeII for HeII occur rather frequently.

The books are not recommended either to readers interested in learning about the subjects treated or to those seeking a convenient guide to the literature.

LINUS PAULING

BOOKS RECEIVED

September 15, 1938–October 15, 1938

SAUL B. ARENSON. "The Solution of Problems in Quantitative Analysis." Lithoprinted by Edwards Brothers, Inc., Ann Arbor, Mich. 41 pp. $0.35.

JAMES E. BELCHER and GUY Y. WILLIAMS. "A Course in Qualitative Analysis Based on Macro and Semi-Micro Methods." Houghton Mifflin Co., 2 Park St., Boston, Mass. 265 pp. $2.40.

WILLIAM H. CHAPIN and LUKE E. STEINER. "Second Year College Chemistry." Fourth edition. John Wiley and Sons, Inc., 440 Fourth Ave., New York, N. Y. 407 pp. $3.00.

REGINALD ALDWORTH DALY. "Architecture of the Earth." D. Appleton-Century Co., 35 West 32d St., New York, N. Y. 211 pp. $3.00.

EDWARD F. DEGERING and ASSOCIATE EDITORS. "The Quadri-Service Manual of Organic Chemistry." Houghton Mifflin Co., 2 Park St., Boston, Mass. 221 pp. $2.25.

HAROLD G. DIETRICH and ERWIN B. KELSEY. "Laboratory Manual to Accompany 'Introductory General Chemistry' (Brinkley)." Revised edition. The Macmillan Company, 60 Fifth Ave., New York, N. Y. 118 pp. $1.90.

L. ERHARD, Editor. "Blätter für Geschichte der Technik." Verlag von Julius Springer, Linkstrasse 22–24, Berlin W 9, Germany. 80 pp. RM. 4.

O. GATTY and E. C. R. SPOONER. "The Electrode Potential Behavior of Corroding Metals in Aqueous Solutions." Oxford University Press, 114 Fifth Ave., New York, N. Y. 504 pp. $8.00.

L. A. GOLDBLATT, Editor. "Readings in Elementary Organic Chemistry." D. Appleton-Century Co., Inc., 35 West 32d St., New York, N. Y. 150 pp. $1.25.

P. H. GROGGINS, Editor-in-Chief. "Unit Processes in Organic Synthesis." Second edition. McGraw-Hill Book Co., Inc., 330 West 42d St., New York, N. Y. 769 pp. $6.00.

GEORGE HEVESY AND F. A. PANETH. "A Manual of Radioactivity." Second edition. Translated by Robert W. Lawson. Oxford University Press, 114 Fifth Ave., New York, N. Y. 306 pp. $5.50.

HANS HOHN. "Chemische Analysen mit dem Polarographen." Verlag von Julius Springer, Linkstrasse 22–24, Berlin W 9, Germany. 102 pp. RM. 7.50.

A. JENNY. "Die elektrolytische Oxydation des Aluminiums und seiner Legierungen." Verlag von Theodor Steinkopff, Residenzstrasse 32, Dresden-Blasewitz, Germany. 224 pp. RM. 14; bound, RM. 15.

WALTER L. KUBIĚNA. "Micropedology." Collegiate Press, Inc., Iowa State College, Ames, Iowa. 243 pp. $3.00.

EUGENE W. NELSON. "The Magic Wand of Science." E. P. Dutton and Co., Inc., 300 Fourth Ave., New York, N. Y. 213 pp. $2.00.

ARTHUR A. NOYES and MILES S. SHERRILL. "A Course of Study in Chemical Principles." Second edition, rewritten. The Macmillan Company, 60 Fifth Ave., New York, N. Y. 554 pp. $5.00.

CARL OPPENHEIMER. "Die Fermente und ihre Wirkungen. Supplement, Band II, Specieller Teil—Hauptteil XVIII–XX, Lieferung 10." W. Junk Verlag, Den Haag, Nederland. 160 pp. 10 Dutch florins.

ERICH PIETSCH. "Sinn und Aufgaben der Geschichte der Chemie." Verlag Chemie, G. m. b. H., Corneliusstrasse 3, Berlin W 35, Germany. 33 pp. RM. 0.90.

CARL L. A. SCHMIDT, Editor. "The Chemistry of the Amino Acids and Proteins." Charles C. Thomas, 220 East Monroe St., Springfield, Ill. 1031 pp. $7.50.

W. SEITH and K. RUTHARDT. "Chemische Spectralanalyse." Verlag von Julius Springer, Linkstrasse 22–24, Berlin W 9, Germany. 103 pp. RM. 7.50.

CHAPLIN TYLER. "Chemical Engineering Economics." Second edition. McGraw-Hill Book Company, Inc. 330 West 42d St., New York, N. Y. 241 pp. $3.00.

L. ZECHMEISTER and L. v. CHOLNOKY. "Die chromatographische Adsorptionsmethode." Second edition. Verlag von Julius Springer, Linkstrasse 22–24, Berlin W 9, Germany. 354 pp. RM. 19.80.

"Outfits for Absorption Spectrophotometry. Photographic, Visual, Photoelectric." Sixth edition. Adam Hilger, Ltd., 98 St. Pancras Way, Camden Road, London N. W. 1, England. 63 pp.

"Spectrographic Outfits for Metallurgical and General Chemical Analyses." Ninth edition. Adam Hilger, Ltd., 98 St. Pancras Way, Camden Road, London N. W. 1, England. 63 pp.

JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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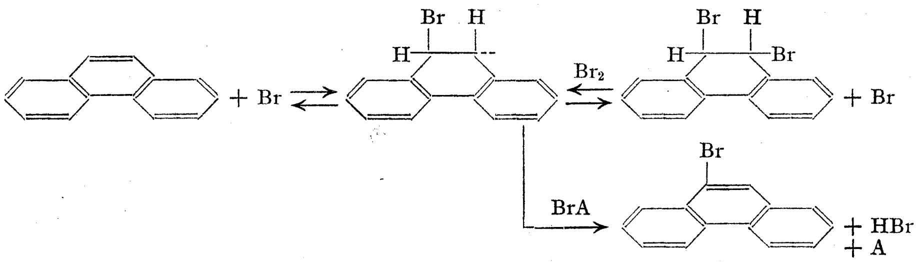
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

The Mechanism of Aromatic Bromination[1]

BY CHARLES C. PRICE AND CLYDE E. ARNTZEN

From previous investigations of the effect of iodine on the reaction between bromine and phenanthrene[2] it was concluded that the bromine substitution reaction proceeded in the following manner, A representing the necessary bromination catalyst.



Since the central ring of phenanthrene obviously differs from the usual aromatic type in that it forms a stable addition product, it remained to prove that this mechanism could be applied to aromatic compounds in general.

It was pointed out in a previous paper[2] that Bruner's[3] extensive measurements of the iodine-catalyzed bromination of benzene with this reactant as solvent could be reinterpreted very accurately according to the rate expression

$$d[C_6H_5Br]/dt = k[Br_2]^{3/2}[I_2]^{5/2}$$

Any dependence of the rate on the benzene concentration could not be detected in his experiments since the benzene was in such excess as to remain essentially unchanged during the course of the reaction.

A study of the iodine-catalyzed bromination of phenanthrene has shown it to obey the same kinetics as the similar reaction of benzene investigated by Bruner. The only difference is that it was not feasible to work with a large enough excess of phenanthrene for its concentration to remain unchanged during the course of the reaction. The rate expression therefore includes dependence on the hydrocarbon concentration as well as bromine and iodine.

$$d[C_{14}H_9Br]/dt = k[C_{14}H_{10}][Br_2]^{3/2}[I_2]^{5/2}$$

The values for the constant, *k*, calculated with the concentrations expressed in moles per liter, are summarized in Table I for various bromine, iodine and phenanthrene concentrations. The fact that for both benzene and phenanthrene the rate of bromination is dependent on the bromine concentration to the three-halves power and the iodine concentration to the five-halves power proves beyond reasonable doubt that the mechanisms for the two reactions are identical. We may therefore write the bromination of benzene according to the following scheme, omitting, of course, a dibromide such as is formed in the case of phenanthrene.

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[1] Presented before the Division of Organic Chemistry at the Dallas meeting of the American Chemical Society, April 19, 1938.

[2] Price, THIS JOURNAL, **58**, 2101 (1936).

[3] Bruner, *Z. physik. Chem.*, **41**, 514 (1902).

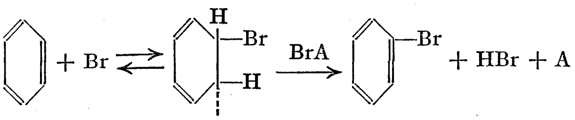


TABLE I

THE REACTION OF PHENANTHRENE AND BROMINE IN THE PRESENCE OF IODINE

$[I_2]^a$	$[Br_2]^a = [C_{14}H_{10}]$	$k^b \times 10^{-5}$	K_{25}^c	K_{IBr}^d
0.00204	0.0322	0.67		
.00204	.0644	.66	192	..
.00408	.0322	.64	133	..
.00408	.0644	.68		
.00613	.0322	.60	103	15
.00715	.0322	.60		
.00817	.0161	.59	94	16.5
.00817	.0322	.59	92	20
.00817	.0644	.65	96	19.5
.01022	.0322	.57	50	30
.01226	.0644	.54	37	24

[a] Total concentration expressed in moles per liter. [b] $d[C_{14}H_9Br]/dt = k[C_{14}H_{10}][Br_2]^{3/2}[I_2]^{5/2}$. [c] $K_{25} = [C_{14}H_{10}Br_2]/[C_{14}H_{10}][Br_2]$ (= 230 in absence of iodine). [d] $K_{IBr} = [IBr]/[Br_2]^{1/2}[I_2]^{1/2}$. K_{25}(Calcd.) = 19.9.

The catalyst may function in the reaction not only, as has been indicated, by the removal of hydrogen from the active intermediate, but also in the production of the active bromine which acts as the initiator of the reaction by producing this active intermediate. Thus the total effect of iodine on the rate of reaction may be divided into an effect on the equilibrium of the first step, the formation of the intermediate, in addition to catalysis of the second step, the removal of the hydrogen.

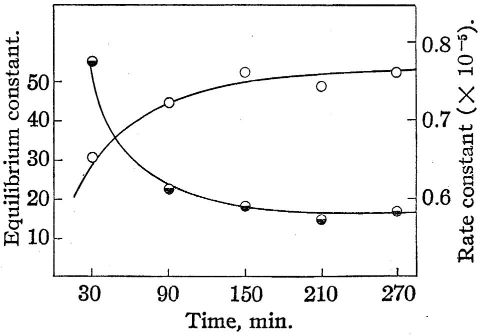
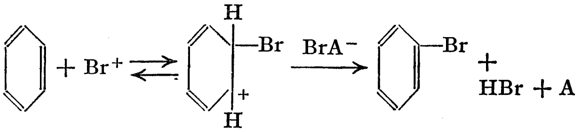


Fig. 1.—Phenanthrene and bromine concentration 0.0322 *M*; iodine 0.0102 *M*; equilibrium constant for addition ○; rate constant for substitution ◒.

Since iodine has a decidedly inhibitory effect on the addition of bromine to phenanthrene,[2] which is a photochemical[4] chain reaction propagated by bromine atoms, it may well be that the iodine-catalysis of the first step in the bromination is the production of positive bromine *ions* rather than bromine atoms. The intermediate in this case would have a positive charge and would be that proposed by Pfeiffer and Wizinger.[5]



The fact that benzene reacts with bromine photochemically to form an addition product while the catalytic reaction leads to substitution is in agreement with this proposal. The photochemical addition most certainly proceeds by an atomic mechanism, leaving an ionic intermediate as the most probable for catalytic substitution in the absence of light.

The kinetics of the reaction are incapable of distinguishing between the atomic and the ionic mechanisms, proving only that the same mechanism holds for both benzene and phenanthrene.

The experiments were all performed in the dark using painted flasks to exclude light. Bromine was purified as in previous experiments;[6] the iodine was resublimed and the phenanthrene prepared from its recrystallized dibromide by treatment with zinc dust in alcohol,[4b] m. p. 99–99.5°.

Standard solutions of the three reagents were mixed and the samples for individual titrations immediately placed in small (5-cc.) glass-stoppered flasks and sealed with paraffin to prevent loss of hydrogen bromide. After a specified interval the flasks were opened under distilled water containing potassium iodide. The liberated iodine was titrated with sodium thiosulfate to the disappearance of its color, then the acid with carbonate-free sodium hydroxide using phenolphthalein as indicator. From these data the course of both addition and substitution can be determined since the decrease in bromine concentration is a measure of both reactions while the acid is produced by substitution alone.

It was found in every case that the rate constant for the substitution reaction did not become truly constant until the equilibrium of the addition reaction had been established. In Fig. 1 are plotted the rate and equilibrium constants at various times for a typical experiment to illustrate this point. The rate constants of Table I are, therefore, the average of the individual con-

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[4] (a) Kharasch, White and Mayo, *J. Org. Chem.*, **2**, 574 (1038); (b) Price, Arntzen and Weaver, THIS JOURNAL, **60**, 2837 (1938).

[5] Pfeiffer and Wizinger, *Ann.*, **461**, 132 (1928).

[6] Price, THIS JOURNAL, **58**, 1834 (1936).

stants for each experiment after the attainment of the equilibrium of the addition reaction.

In Table I the penultimate column lists the values for the equilibrium constants for the addition of bromine to phenanthrene at the various iodine concentrations. They show a steady decrease with increasing iodine concentration which may be accounted for by the reaction of bromine and iodine to form a bromoiodide

$$Br_2 + I_2 \rightleftharpoons BrI$$

which would reduce the actual concentration of bromine molecules but not the bromine titer. Insertion of the titer value for bromine, a larger value than is actually effective, would cause a variation in the manner noted for the equilibrium constant.

In fact, since the true value for the equilibrium constant, $K_{25} = [C_{14}H_{10}Br]/[C_{14}H_{10}][Br_2] = 230$, is known, and since the concentrations of both the phenanthrene and its dibromide may be calculated from the experimental data, it is possible to calculate from this the value for the free molecular bromine concentration. With this value known, as well as the total iodine and total bromine concentrations (Br_2 + BrI) it is possible to calculate the equilibrium constant, $K_{IBr} = [BrI]/[Br_2]^{1/2}[I_2]^{1/2}$, for the bromine–iodide reaction in carbon tetrachloride solution, the values for which are given in the final column of Table I. The calculation is for the last determination in each experiment, which should be at equilibrium. No calculation could be made for the experiments at lower iodine concentration since the equilibrium of the addition reaction had not been established at the last measurement.

Bodenstein and Schmidt[7] have determined the value for this equilibrium constant at elevated temperatures in the gas phase and derived the following expression for its dependence on the temperature

$$\log \frac{1}{4K^2} = \frac{3.676}{4.57 \times T} - 0.50$$

Calculation of the equilibrium constant at 25° from this expression gives a value of 19.9, agreeing well with the experimentally determined values, especially since a fairly large experimental error (10–15%) could easily be involved.

Summary

The kinetics of the iodine-catalyzed bromination of phenanthrene have been determined as identical with those of benzene. This is offered as proof of the identity of mechanism for the bromination of aromatic compounds in general with that previously proposed for phenanthrene.

This mechanism involves addition of a positive bromine ion to the unsaturation of the aromatic nucleus followed by catalytic elimination of a hydrogen ion to yield the substitution product.

It has been found that the equilibrium for the bromine-iodine reaction in carbon tetrachloride solution agrees with the determinations of Bodenstein and Schmidt for the gas phase reaction at considerably higher temperatures.

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[7] Bodenstein and Schmidt, *Z. physik. Chem.*, **123**, 30 (1926).

URBANA, ILLINOIS RECEIVED JULY 1, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

The Reaction of Bromine with Various Samples of Phenanthrene

BY CHARLES C. PRICE, CLYDE E. ARNTZEN AND CLAY WEAVER

No entirely satisfactory method for the purification of phenanthrene has as yet been developed. Selective oxidation with nitric acid[1] and with chromic acid,[2] as well as treatment with maleic anhydride,[3] have been recommended for the removal of anthracene. Treatment with sodium has been found effective for the removal of fluorene[4] or sulfur-containing compounds.[5]

We have found the following series of reactions convenient for preparing samples of phenanthrene of a high degree of purity from relatively impure starting material.

$$C_{14}H_{10} + Br_2 \longrightarrow C_{14}H_{10}Br_2 \xrightarrow[\text{alcohol}\ (60°)]{\text{Zn dust in}} C_{14}H_{10} + ZnBr_2$$

The chief advantage offered is that the phenanthrene dibromide may be recrystallized to remove impurities which could not be separated from phenanthrene itself by crystallization. The prod-

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[1] Cohen and Cormier, THIS JOURNAL, **52**, 4363 (1930).

[2] W. E. Bachmann, *ibid.*, **57**, 557 (1935).

[3] Clar, *Ber.*, **65**, 852 (1932).

[4] Jeanes and Adams, THIS JOURNAL, **59**, 2615 (1937).

[5] Schroeter, *Ber.*, **57**, 2025 (1924).

uct so obtained (A) melted at 99–99.5°, three degrees higher than the starting material, which had been purified by oxidation[2] but not by treatment with sodium.

Dihydrophenanthrene was a possible impurity in this product since some of the dibromide might decompose with evolution of hydrogen bromide even though the temperature was kept well below its usual thermal decomposition point (90–100°). Consequently some of the material (A) was treated with selenium for eight hours at 300–320°, distilled and twice recrystallized. This treatment raised the melting point only half a degree but completely altered the behavior of the material toward bromine.

Phenanthrene purified from coal tar as described previously[6] and the sample (A) prepared by the present method react with bromine photochemically[7] at nearly the same rapid rate. The sample from selenium treatment, however, in spite of the higher melting point, was found to react only very slowly, although it finally attained the same equilibrium for the addition reaction as the other samples. This is in agreement with experiments using synthetic phenanthrene,[8] which also had been treated with selenium. This material was found to melt high (m. p. 100.7–101°), and to react with bromine only very slowly.

That the difference in the behavior of these various samples of phenanthrene was not due to the absence of fluorene or anthracene in the selenium-treated samples (which may have been present as an impurity in the material reacting with bromine), was demonstrated by addition of these hydrocarbons to such samples, the mixtures showing the same characteristics as the original material.

It was of interest to note that anthracene, which catalyzes several reactions of bromine in the dark,[9] did not cause the chain addition of bromine to phenanthrene. The course of the reaction of bromine with a mixture of phenanthrene and anthracene appeared, in this case, to be the addition of one molecule of bromine to phenanthrene for each molecule reacting with anthracene. The results of these experiments are summarized in Table I. The fact that all the phenanthrene samples behave similarly in this instance indicates that the material which inhibits the photochemical addition (bromine atom mechanism) has no effect on the dark, anthracene-catalyzed reaction (bromine cation mechanism).

TABLE I

THE DARK REACTION OF PHENANTHRENE AND ITS DIBROMIDE WITH BROMINE IN THE PRESENCE OF ANTHRACENE

[Phenanthrene] = [Br_2] = 0.03 *M*; time, 60 minutes.

[Anthracene]	Δ[Br_2]	Δ[Br_2] for anthracene	Δ[Br_2] for phenanthrene
....	0.0005	....	0.0005
0.0005[a]	.0025	0.0010	.0015
.00065[b]	.0030	.0013	.0017
.00075[c]	.0033	.0015	.0018
[Phenanthrene Dibromide] = 0.03 *M*; [Br_2] = 0.003 *M*; time, 30 minutes			
....	−0.0003	....	−0.0003
0.00065	− .0001	0.0013	− .0014

[a] Phenanthrene sample (A). [b] Phenanthrene sample (A) treated with selenium. [c] Gesellschaft für Teerverwertung phenanthrene.

Furthermore, it was found that addition of selenium-treated phenanthrene to that reacting with bromine gave a mixture which would not react. These various facts are interpreted as indicative of the presence of an inhibitor in the phenanthrene treated with selenium, in spite of its higher melting point. However, since the photobromination of this hydrocarbon is a chain reaction of considerable length,[6] it would require but small amounts of a chain-breaking impurity to account for the results.

Several qualitative tests have been made for the purity of the various samples of phenanthrene. These are summarized in Table II.

These color tests indicate that the samples prepared by the present method are much purer than the starting material and seem quite similar to a sample of the highly purified hydrocarbon from the Gesellschaft für Teerverwertung.

Experimental

Crude phenanthrene (10 g.) with a melting point of 94–96° was dissolved by warming in 50 cc. of purified[6] carbon tetrachloride[10] and, after cooling in ice, treated with 4 cc. of bromine in portions. The reaction mixture was allowed to stand in sunlight at 0° for an hour. The dibromide, 13 g. (65%), was recrystallized by dissolving in the minimum amount of benzene (150 cc.) at 40–45°,[11] adding an equal amount of petroleum ether (60–90°), and cooling in an ice-salt bath to −15°. The pure dibromide, crystallizing as colorless plates with a greenish tinge, was collected by filtration, yield 10 g., m. p. 98–99°, with decomposition. Its

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[6] Price, THIS JOURNAL, **58**, 1834 (1936).

[7] All rates mentioned are for the photochemical reaction unless specified otherwise.

[8] Fieser and Hershberg, THIS JOURNAL, **57**, 2192 (1935).

[9] (a) Price and Thorpe, *ibid.*, **60**, 2839 (1938); (b) Price and Weaver, unpublished work.

[10] The reaction of bromine with phenanthrene in commercial carbon tetrachloride was found to proceed much more slowly and a much poorer yield of the dibromide was obtained.

[11] Since anthracene dibromide is very unstable even at room temperature, it should be decomposed completely by this treatment.

TABLE II

COLOR TESTS ON VARIOUS HYDROCARBON SAMPLES

Compound	H_2SO_4 Cold	H_2SO_4 Warm	H_2SO_4–HNO_3[a]	H_2SO_4–40% Formalin[a]
Phenanthrene				
(1) Crude	Yellow	Dark yellow	Red-black	Blue crystals (tan soln.)
(2) Sample (A)	None	Very pale blue	Clear red	Blue crystals (colorless soln.)
(3) (A) treated with Se				
(4) Commercial[b]				
Anthracene[c]	Yellow	Black		Dark brown-black soln.
Fluorene[b]	None	None	Pale yellow	Deep purple soln. (5 min.)

[a] The hydrocarbon was suspended in sulfuric acid and one drop of the second reagent was added.

[b] Gesellschaft für Teerverwertung.

[c] Martin, THIS JOURNAL, **58,** 1438 (1936).

solution in 200 cc. of alcohol was treated with 7.5 g. of zinc dust at 50–60° for twelve hours, the reaction mixture filtered while hot, evaporated to 50–60 cc. and set aside to crystallize. The yield was 4.6 g. (90%) of colorless plates melting at 99–99.5° after one recrystallization.

A portion of this material was heated with selenium to 300–320° for eight hours, distilled under diminished pressure and twice recrystallized from alcohol to give a sample melting at 99.5–100°.

Summary

Phenanthrene of a high degree of purity may be obtained by conversion to the dibromide followed by regeneration of the hydrocarbon on treatment with zinc dust.

Phenanthrene which has been treated with selenium apparently contains an impurity inhibiting the photochemical addition of bromine.

Anthracene has been found to catalyze an equimolecular but not a chain addition of bromine to phenanthrene in the dark.

URBANA, ILLINOIS RECEIVED JULY 1, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

A Chemically-Catalyzed cis-trans Isomerization

BY CHARLES C. PRICE AND RALPH S. THORPE

The anthracene-catalyzed bromination of dioxane[1] can be accounted for only by assuming that the reaction between bromine and anthracene produces active bromine. Since many photochemical reactions of bromine presumably proceed through active bromine atoms produced by the dissociation of a bromine molecule on absorption of light, and since the same intermediate has been proposed for several reactions of hydrogen bromide in the presence of peroxides,[2] it was proposed to use one of these reactions to test the possibility that the active bromine produced by the anthracene–bromine reaction in the dark might behave in a similar manner.

The particular reaction studied was the conversion of a maleic ester to the corresponding fumaric ester. Wachholtz and Schmidt[3] have reported previously the photochemical isomerization of the ethyl and methyl esters, respectively, in the presence of bromine. Both investigators agree that the mechanism must be a chain reaction with a length of several hundred, initiated by the photochemical dissociation of bromine molecules to atoms. They represent the course of the reaction as

$$Br_2 + h\nu \longrightarrow 2Br$$
$$M + Br \longrightarrow (MBr) \longrightarrow F + Br$$

More recently Kharasch[2] has proposed a bromine atom intermediate for the peroxide-catalyzed rearrangement of isostilbene to stilbene in the presence of hydrogen bromide, and, on this basis, has extended this proposal of a bromine atom mechanism to the well-known effect of peroxides in reversing the usual mode of addition of hydrogen bromide to many olefinic double bonds.

The investigation reported herein is on the conversion of ethyl maleate to ethyl fumarate by bromine and anthracene in carbon tetrachloride solution.

Experimental.—The reactions were all carried out in purified carbon tetrachloride solution.

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(1) Price and Weaver, unpublished work.

(2) Kharasch, Mansfield and Mayo, THIS JOURNAL, **59,** 1155 (1937).

(3) (a) Wachholtz, *Z. physik. Chem.*, **125,** 1 (1929); (b) Schmidt, *bid.*, **B1,** 205 (1930).

Ethyl maleate was prepared from the anhydride according to the directions of Wachholtz.[3a] Bromine and anthracene were added to a solution of 1 cc. of the ester in 2.5 cc. of carbon tetrachloride in a painted flask. The bromine color had always faded completely at the end of the reaction so the mixture of the two isomeric esters was obtained by fractional distillation under diminished pressure. The effective removal of carbon tetrachloride was demonstrated by the index of refraction of the ester mixture. Analysis for the percentage conversion was most convenient according to the method developed by Kistiakowsky and Smith[4] with the modification that no special apparatus was necessary for the determination. The production of cloudiness in the clear solution of 0.4 cc. of ester mixture in 0.6 cc. of liquid petroleum could be reproduced readily to within 0.5° using only the naked eye in ordinary daylight. Analysis by this method was accurate to within 1% and scarcely more difficult than an ordinary melting point determination. The results of these various determinations are summarized in Table I.

TABLE I

CONVERSION OF ETHYL MALEATE TO ETHYL FUMARATE BY BROMINE AND ANTHRACENE IN CARBON TETRACHLORIDE

Expt.	Mole % $C_{14}H_{10}$	Mole % Br_2	Time, hours	% ethyl fumarate
9	...	...	48	1
6	...	2.6	312	2
18	...	1.3	27	1
5[a]	...	2.6	288	100
19[a]	...	1.3	26	100
2	5.2	2.6	91	97.5
7	5.2	2.6	24	100
8	2.6	1.3	27	91
10	2.6	1.3	16	81
12	2.6	1.3	5	93
13	2.6	1.3	1	75
14	2.6	1.3	0.5	68
15	2.6	1.3	.25	77
20	2.6	1.3	.08	70
16, 17[b]	2.6	1.3	.5	18, 22

[a] These experiments were exposed to light. [b] In these experiments the bromine-anthracene reaction was completed *before* the ester was added.

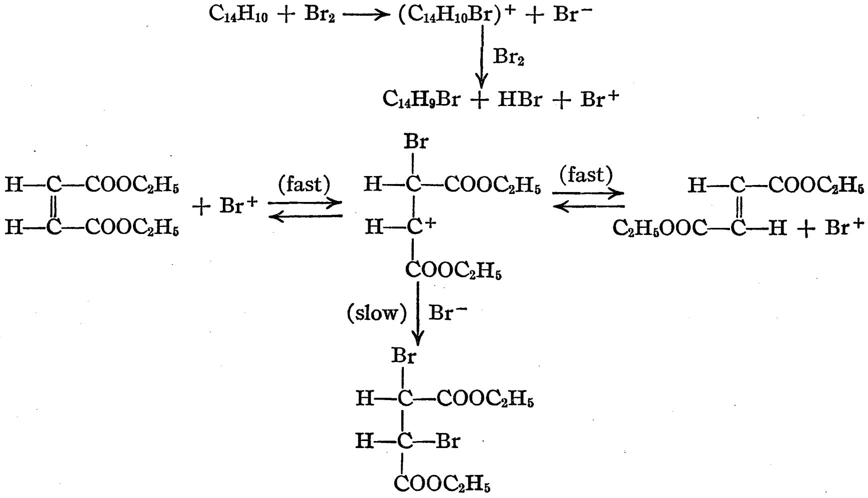
Discussion of Results.—Inspection of this table shows that ethyl maleate was converted rapidly in good yield to ethyl fumarate by the combined action of bromine and anthracene in carbon tetrachloride solution with light rigorously excluded. That the isomerization was indeed due to the combined effect of bromine and anthracene is demonstrated by Experiments 6 and 18 in which bromine alone caused no isomerization in the dark, even after a week, while the reaction in the presence of anthracene requires at most but a few minutes. The photochemical reaction reported by Wachholtz and Schmidt was observed in Experiments 5 and 19 in which bromine alone, exposed to sunlight, caused complete isomerization.

The small proportion of anthracene (1.3%) which was capable of isomerizing a large portion of the maleate is indicative of a fairly long chain mechanism for the conversion in agreement with the previous reports for the photochemical reaction.[3]

Two mechanisms appear plausible for this *cis-trans* isomerization. A bromine atom, as in the photochemical reaction, may be the active intermediate. If such were the only alternative, anthracene must react with bromine in the dark to produce bromine atoms.

$$C_{14}H_{10} + Br_2 \longrightarrow C_{14}H_{10}Br + Br$$

An alternative mechanism, however, involves a bromine cation as active intermediate. In this regard, it may be mentioned that the bromination of dioxane in the presence of anthracene may be best accounted for on the basis of the production



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(4) Kistiakowsky and Smith, THIS JOURNAL, **56**, 638 (1934).

of an active bromine cation by the reactions between anthracene and bromine in the dark. On this basis, the conversion of *cis* to *trans* isomers in the dark might then be represented by the series of reactions shown.

The isomerization would thus be a true chain reaction since the bromine cation is constantly regenerated after each conversion.

These results indicate that bromine cations, as well as bromine atoms, may cause rapid isomerization about an olefinic bond. This latter reaction, therefore, must be applied with reservation as a criterion for the presence of bromine atoms.

Summary

The reaction of bromine with anthracene in the dark has been found to catalyze the isomerization of ethyl maleate to ethyl fumarate.

The mechanism of this conversion has been formulated with a positively charged bromine ion as an intermediate.

The subsequent limitation of *cis–trans* isomerization as a criterion for the presence of bromine atoms is pointed out.

URBANA, ILLINOIS RECEIVED JULY 1, 1938

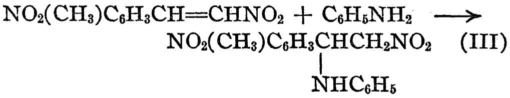
[A CONTRIBUTION FROM THE PEARSON MEMORIAL LABORATORY OF TUFTS COLLEGE]

The Action of Ammonia and Aromatic Amines on 4-Methylnitrostyrene and Related Compounds

BY DAVID E. WORRALL

Nitrostyrene has been shown[1] to react with aniline in a manner characteristic of α,β-unsaturated compounds, forming ultimately a saturated β-anilino derivative. That the additive capacity of the unsaturated system toward such substances is slight became apparent when it was discovered that comparatively few reacted in this way, if at all. An attempt[2] to facilitate the reaction by working with a substance incapable of polymerization, namely, bromonitrostyrene, was fruitless as the presence of halogen promoted the formation of Schiff bases. Similar results were obtained by Musante[3] working with nitrostyrenes containing methoxy or oxymethylene groups. A study has now been made of the effect of substituents on the alkylated nitrostyrene, $CH_3C_6H_4CH{=}CHNO_2$ (I).

The ability to add organic bases is entirely lost on the introduction of a methyl group into the ring of nitrostyrene, although the tendency for polymerization or hydrolysis is not greatly changed. It is true that a condensation product of the amine and aldehyde is formed when I reacts with an alcoholic solution of phenylenediamine or benzidine, a reaction that may be interpreted as resulting from the decomposition of an intermediate addition product. Since no reaction takes place with anhydrous benzene as a solvent, it seems apparent that the product is rather the result of hydrolysis and condensation. The additive power of I is not increased by the introduction of bromine in the side chain, but the presence of a nitro group in the ring partially restores the lost reactivity. Addition compounds are formed with aniline and *p*-toluidine, but not with phenylhydrazine.

(II)  (III)

$$NO_2(CH_3)C_6H_3CH{=}CHNO_2 + C_6H_5NH_2 \longrightarrow NO_2(CH_3)C_6H_3\underset{NHC_6H_5}{\underset{|}{CH}}CH_2NO_2$$

p-Phenylenediamine reacts in a similar manner, both functional groups being involved. With ammonia the reaction is somewhat different inasmuch as the primary addition product reacts further with a second molecule of II.

$$2NO_2(CH_3)C_6H_3CH{=}CHNO_2 + NH_3 \longrightarrow IV$$
$$(NO_2(CH_3)C_6H_3CH[CH_2NO_2])_2NH$$

The introduction of bromine into the side chain of II again cuts down the ability to form addition compounds. No reaction takes place in the absence of water and with wet reagents only unchanged components or products resulting from hydrolysis or destructive decomposition are present.

The nitrostyrene (V) obtained from nitroethane and toluic aldehyde contains an alkyl group in the side chain next to the nitro group as well as in the ring. It shows no tendency to

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[1] Worrall, THIS JOURNAL, **49**, 1598 (1927). This particular substance was first prepared, in another manner, by Tönnies, *Ber.*, **20**, 2986 (1887), although the true structure was pointed out later by Wieland, *ibid.*, **36**, 2564 (1903).

[2] Worrall, THIS JOURNAL, **43**, 919 (1921).

[3] Musante, *Gazz. chim. ital.*, **67**, 579 (1937).

polymerize or form addition compounds. The introduction of bromine into the side chain on carbon next to the ring has no effect but nitration produces a substance again capable of reacting, by addition, with *p*-toluidine. The presence of the methyl group in the side chain, however, has a hindering effect as the nitro derivative does not form an addition compound with *p*-phenylenediamine.

The introduction of a phenyl group into the side chain produces a nitrostilbene, a substance showing no tendency to react by addition or polymerization. It is converted by alcoholic ammonia into an isoxazolone oxide.[4]

Experimental

α-Nitro-β-[4-methylphenyl]-ethylene I.—While toluic aldehyde may be condensed with nitromethane through the action of alkali,[5] it was found more convenient in working with smaller quantities (0.25 to 0.5 g. mole) to use a modification of the method of Knoevenagel.[6] The two components were heated under a reflux condenser by steam in the presence of 5% of the equivalent amount of amylamine for forty minutes. The yield by either method after crystallization from two volumes of alcohol was slightly better than 60%. A much better yield was obtained on heating with alcoholic amylamine but the product was contaminated with a small amount of polymer difficult to remove. I separated from alcohol in long light yellow needles, m. p. 102°.

Anal. Calcd. for $C_9H_9NO_2$: C, 66.3; H, 5.5. Found: C, 66.0; H, 5.5.

A gelatinous precipitate difficult to filter separated from a warm alcohol solution of I in the presence of ammonia or an aliphatic amine. Considerable discoloration may take place especially with ammonia. No good solvent was found for the polymer which dried out after thorough washing with hot alcohol to a white powder. It gradually decomposed above 230°.

Anal. Calcd. for $(C_9H_9NO_2)x$: C, 66.3; H, 5.5. Found: C, 66.5; H, 5.6.

Ammonia did not react with a dry benzene solution of I. Amylamine in the absence of solvents reacted vigorously, producing a tar from which 4-methylbenzalamylamine and nitromethane were isolated and identified.

I gave no evidence of reacting with aniline. On long standing the oily residue was found to consist of a mixture of unchanged components. Similar results were obtained with phenylhydrazine and *p*-toluidine. No reaction took place between I and *p*-phenylenediamine dissolved in dry benzene even after the mixture had been heated to boiling and then kept at room temperature for a day. Unchanged amine separated out. These same substances did react in warm alcohol, but as the product was insoluble in alcoholic potash and was unchanged on heating with this same reagent, it was not an addition product but a Schiff base. Recrystallized from glacial acetic acid, it appeared as tiny brownish-yellow needles, m. p. 188–189°.

Anal. Calcd. for $C_{22}H_{20}N_2$: C, 84.6; H, 6.4. Found: C, 84.3; H, 6.5.

Similar results were obtained with benzidine.

α-Nitro-β-(4-methylphenyl)-ethylene Dibromide.—Ten grams of I was brominated in chloroform by heating for an hour under a reflux condenser. The oily residue after removal of solvent hardened on cooling. A small portion was crystallized from ligroin, separating in colorless tablets, m. p. 79–80°.

Anal. Calcd. for $C_9H_9O_2NBr_2$: Br, 49.5; Found: Br, 49.3.

α-Nitro-α-bromo-β-[4-methylphenyl]-ethylene.—The crude dibromide reacted spontaneously and smoothly with a warm alcohol solution of potassium acetate. After standing for a short time the new substance was isolated, separating from alcohol as lustrous yellow plates, m. p. 67–67.5°.

Anal. Calcd. for $C_9H_8BrNO_2$: Br, 33.1. Found: Br, 32.8.

It did not polymerize in the presence of alcoholic ammonia, neither was it observed to react with *p*-toluidine or *p*-phenylenediamine. The corresponding chlorine derivative obtained in a similar manner as narrow yellow plates melting at 78–78.5° was also non-reactive.

Anal. Calcd. for $C_9H_8ClNO_2$: C, 54.7; H, 4.1. Found: C, 54.3; H, 4.2.

α-Nitro-β-[2-nitro-4-methylphenyl]-ethylene.—The product obtained by nitrating 25 g. of I using fuming acid and maintaining the temperature slightly below 20° was recrystallized from alcohol: yield 23 g.; m. p. 121–122°, after several crystallizations. It was identified as the 3-nitro derivative of I by an analysis and an examination of the oxidation product, obtained by the action of potassium permanganate, which did not depress an authentic sample of 3-nitro-*p*-toluic acid. The substance previously prepared by Hanzlik and Bianchi[7] by the nitration of *p*-methylcinnamic acid and recorded as melting at 117–118° probably contained some of the 2-nitro isomer. The original filtrate yielded 8.5 g. of material melting at 70–75°. By repeated crystallizations a small quantity of tiny pale yellow needles was obtained that had a constant melting point, 96–97°.

Anal. Calcd. for $C_9H_8N_6O_4$: C, 51.9; H, 3.8. Found: C, 51.5; H, 3.9.

It was unchanged by nitric acid while the melting point was depressed by the 3-nitro isomer. It seems safe to conclude that the substance was the 2-nitro derivative of I, although it still may have contained some of the isomer.

α-Nitro-β-anilino-β-[3-nitro-4-methylphenyl]-ethane III was obtained by heating, until solution was complete, the two components in the presence of alcohol. Crystals gradually formed on standing. III separated from alcohol as small yellow prisms, m. p. 98–99°. As with all of these addition compounds, some decomposition took place at the melting point which accordingly varies depending upon the rate of heating. III was soluble in alcoholic potash.

Anal. Calcd. for $C_{15}H_{15}N_3O_4$: C, 59.8; H, 5.0. Found: C, 59.5; H, 5.0.

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[4] Worrall, This Journal, **57**, 2299 (1935).

[5] *Org. Syntheses*, **9**, 66 (1929).

[6] Worrall, This Journal, **56**, 1556 (1934).

[7] Hanzlik and Bianchi, *Ber.*, **32**, 2287 (1899).

α-Nitro-β-toluidino-β-[3-nitro-4-methylphenyl]-ethane.—Prepared in a similar manner it separated from alcohol as bright yellow sparkling plates, m. p. 135–136°, dec.

Anal. Calcd. for $C_{16}H_{17}O_4N_3$: C, 61.0; H, 5.4. Found: C, 60.7; H, 5.4.

N,N′-(α,α′-[3-Nitro-4-methylphenyl]-β,β′-dinitro-diethyl)-*p*-phenylenediamine.—Yellow crystals quickly formed on heating II and *p*-phenylenediamine in alcohol until dissolved. No good solvent was found although the substance crystallized from acetone as tiny pale yellow plates, melting with decomposition at 152–153°. It was dissolved readily by alcoholic potash.

Anal. Calcd. for $C_{24}H_{24}N_6O_8$: C, 55.0; H, 4.6. Found: C, 55.4; H, 4.8.

II readily formed a polymer with alcoholic ammonia, an amorphous powder melting with decomposition at 198–200°. It was not examined further.

α,α′-([3-Nitro-4-methylphenyl]-β,β′-dinitrodiethyl)-amine, IV.—It was obtained by dissolving 2 g. of II in 100 cc. of dry benzene which was then saturated with dry ammonia. The mixture after standing for several hours in a closed container was allowed to evaporate spontaneously to a small bulk. The nodular crystalline aggregates that appeared were crystallized from alcohol. This must be done cautiously and in small lots as the substance is destroyed easily by hot alcohol solutions. Small colorless flat needles melting at 147° with decomposition were obtained. IV was insoluble in alcoholic potash and was not observed to form a salt with acids, although it was soluble in concd. hydrochloric acid.

Anal. Calcd. for $C_{18}H_{19}N_5O_8$: C, 49.9; H, 4.4. Found: C, 50.1; H, 4.5.

α-Nitro-β-bromo-β-[3-nitro-4-methylphenyl]-ethylene.—Ten grams of the bromine derivative of I was nitrated, the product crystallizing from a moderately large volume of alcohol in clumps of small pale yellow needles, m. p. 105°.

Anal. Calcd. for $C_9H_7BrN_2O_4$: C, 37.6; H, 2.4. Found: C, 38.1; H, 2.7.

Repeated crystallization from alcohol of the residue left in the original mother liquor produced eventually a substance that separated from ligroin as tiny yellow needles, m. p. 82–83°. This isomer, the 2-nitro derivative, on analysis gave data identical with those reported for the 3-nitro compound and in the one experiment tried did not form an addition compound. Only negative results were obtained in attempts to form addition compounds of the new 3-nitro derivative with aromatic amines, or to obtain a polymer. The odor of bromonitromethane was evidence that some hydrolysis occurred, but even with phenylenediamine no Schiff base was isolated from the black tar that formed.

α-Nitro-β-chloro-β-[3-nitro-4-methylphenyl]-ethylene.—Nitration of the chlorine derivative of I resulted in small pale yellow needles (from alcohol), m. p. 107–108°.

Anal. Calcd. for $C_9H_7ClN_2O_4$: C, 44.5; H, 3.3. Found: C, 44.9; H, 3.1.

No search was made for the isomer probably present. All attempts to form addition compounds with the chloro derivative were fruitless.

α-Nitro-α-methyl-β-[4-methylphenyl]-ethylene, V.—This substance obtained from nitroethane and toluic aldehyde using amylamine separated from petroleum ether as yellow prismatic needles, m. p. 55°; yield approximately 50%.

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.8; H, 6.2. Found: C, 67.4; H, 6.1.

All attempts to form addition compounds using ammonia, *p*-toluidine and *p*-phenylenediamine failed, also attempts to prepare a polymer. A small amount of V was brominated in the customary manner and the oil-like product heated under a reflux condenser with potassium acetate for four to five hours. The mixture was worked up yielding a pale yellow oil. With this impure sample only negative results followed attempts to form an addition compound with toluidine.

α-Nitro-α-methyl-β-(3-nitro-4-methylphenyl)-ethylene, VI.—Nitration of V gave a substance separating from ligroin as narrow yellow plates, m. p. 72–73°.

Anal. Calcd. for $C_{10}H_{10}N_2O_4$: C, 54.1; H, 4.5. Found: C, 54.0; H, 4.7.

α-Nitro-α-methyl-β-(*p*-toluidino)-β-[3-nitro-4-methylphenyl]-ethane.—*p*-Toluidine formed an addition compound with VI after several hours. It separated from alcohol in clusters of bright golden platelets, m. p. 109–110°, dec.

Anal. Calcd. for $C_{17}H_{19}N_3O_4$: C, 62.0; H, 5.8. Found: C, 62.1; H, 5.8.

On mixing VI with a warm alcohol solution of *p*-phenylenediamine a black tar quickly formed from which, by digestion with warm alcohol, a crystalline product was obtained. It crystallized from acetone in tiny hair-like pale yellow crystals, m. p. 254–255°. As it was stable toward alkali and therefore not an addition compound, the substance was not examined further.

3,5-Diphenyl-4-(4-methylphenyl) Isoxazolone Oxide.—A suspension of 10 g. of 4-methylnitrostilbene in 50 cc. of alcohol was saturated with ammonia. The melting point of the product, removed at the end of an hour, indicated a mixture. It was heated with hydrochloric acid to destroy the condensation product of aldehyde, phenylnitromethane and ammonia otherwise difficult to remove.[6] The residue separated from a large volume of alcohol in long slender needles, m. p. 171–172°.[8]

Anal. Calcd. for $C_{22}H_{19}O_2N$: C, 80.2; H, 5.8. Found: C, 80.2; H, 5.9.

Dibenzoyl-4-methylphenylmethane Monoxime.—The filtrate from VII after steam distillation and crystallization from ligroin yielded a small amount of needle-like crystals, easily soluble in alcohol, m. p. 160–161°.

Anal. Calcd. for $C_{22}H_{19}NO_2$: C, 80.2; H, 5.8. Found: C, 79.8; H, 5.9.

It is quickly changed by hot hydrochloric acid into the corresponding isoxazole.

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[8] Meisenheimer and Matarbeiter, *Ann.*, **468**, 254 (1929), obtained, as a by-product in the preparation of 4-methylnitrostilbene, a small amount of white needle-like crystals melting at 168° and sparingly soluble in methyl alcohol. Based on an analysis the formula $C_{21}H_{19}NO_2$ was deduced for the unknown substance, which was probably VII.

3,5-Diphenyl-4-(4-methylphenyl)-isoxazole was obtained from VII by the action of hot alcoholic potash as needles, m. p. 198°.

Anal. Calcd. for $C_{22}H_{17}NO$: C, 84.9; H, 5.5. Found: C, 84.7; H, 5.5.

5-(4-Bromophenyl)-4-(4-methylphenyl)-3-phenylisoxazolone Oxide.[9]—A suspension of 3 g. of *p*-bromophenylnitromethane and VII in 50 cc. of alcohol was saturated with ammonia. The product after an hour was dissolved in alcohol separating as feathery needles, m. p. 182–183°; yield 2.5 g.

Anal. Calcd. for $C_{22}H_{18}NO_2Br$: C, 64.7; H, 4.4. Found: C, 65.1; H, 4.6.

5-(4-Bromophenyl)-4-(4-methylphenyl)-3-phenylisoxazole.—Obtained from the isoxazolone oxide it separated from alcohol in hair-like needles, m. p. 175°.

Anal. Calcd. for $C_{22}H_{16}BrNO$: C, 67.7; H, 4.1. Found: C, 67.6; H, 4.3.

Summary

It has been shown that the presence of an alkyl group in the aromatic ring of nitrostyrene prevents addition reactions with ammonia and aromatic amines, but does not stop polymerization. An alkyl group in the side chain partially blocks the addition reaction and completely stops the tendency to polymerize. Halogen has a similar effect. Both reactions are suppressed by a phenyl group in this position. The presence of a nitro group in the ring partially restores the addition tendency, but has no noticeable influence on polymerization.

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[9] It has been assumed that this substance resulted rather than the isomeric 3-(4-bromophenyl)-5-phenyl derivative; see Kohler and Richtmyer, THIS JOURNAL, **50**, 3092 (1928).

[A CONTRIBUTION FROM THE PEARSON MEMORIAL LABORATORY OF TUFTS COLLEGE]

The Action of *p*-Toluidine and *p*-Phenylenediamine on Substituted Nitrostyrenes

BY DAVID E. WORRALL AND FREDERIC BENINGTON

It was shown in a previous communication[1] that the tendency of a nitrostyrene to form an addition compound with an aromatic amine, which is rather limited in the mother substance, may be modified by the introduction of certain groups into the molecule. In the hope of finding a more active combination, a number of unsaturated nitro compounds have been prepared and a study made of their additive power. *p*-Toluidine and *p*-phenylenediamine, most powerful of the primary aromatic amines for reactions of this type, were selected to test the reactivity.

The results clearly indicate that an addition reaction between an aromatic amine and a substituted nitrostyrene is relatively uncommon and even more circumscribed than with the parent substance. No reaction takes place with the unsaturated nitro compounds prepared from aldehydes containing hydroxy, methoxy or methylene oxy groups. The presence of a nitro group in the ring on the contrary enhances the additive capacity and even may restore the lost activity of a substituted nitrostyrene. Halogen also has a favorable influence as the most active substance in the list contains a chlorine as well as a nitro substituent. *p*-Phenylenediamine is more reactive than *p*-toluidine with these particular substances.

α-Nitro-β-(2-methoxyphenyl)-ethylene.—This substance, prepared by condensing *o*-methoxybenzaldehyde with nitromethane in the presence of triethylamine,[2] separated from alcohol in the form of yellow prismatic crystals, m. p. 50°.

Anal. Calcd. for $C_9H_9NO_3$: C, 60.3; H, 5.0. Found: C, 60.1; H, 5.1.

α-Nitro-β-(2-methoxy-4-nitrophenyl)-ethylene.—The product obtained by the action of fuming nitric acid crystallized from alcohol as yellow plates, m. p. 175–176°.

Anal. Calcd. for $C_9H_8N_2O_5$: C, 48.2; H, 3.6. Found: C, 48.7; H, 3.9.

The isomeric 2-nitro-4-methoxy compound obtained in a similar manner formed microscopic canary yellow crystals from alcohol, m. p. 145–146°.

Anal. Calcd. for $C_9H_8N_2O_5$: C, 48.2; H, 3.6. Found: C, 47.9; H, 3.8.

The following procedure was used in testing the addition ability of the nitrostyrenes with *p*-phenylenediamine and *p*-toluidine. To a filtered solution containing the correct amount of the base in alcohol was added 1 g. of the unsaturated compound. The mixture was heated until all of the solid phase had disappeared, adding more solvent if necessary. The addition product usually appeared within a few minutes. No good solvent was found for the phenylenediamine derivatives although they are somewhat soluble in acetone. The crude products were purified by thorough extraction with hot alcohol. The 2-nitro and 3-nitro derivatives may have contained traces of colored impurities. All melted with decomposition and were dissolved readily by alcoholic potash. Shaking

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[1] THIS JOURNAL, **60**, 2841 (1938).

[2] Worrall, *ibid.*, **56**, 1556 (1934).

TABLE I

p-PHENYLENEDIAMINE ADDITION COMPOUNDS[3]

-Nitrostyrene	Appearance	M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
2-Nitro	Brownish-red plates	147	$C_{22}H_{20}N_6O_8$	53.2	4.0	53.5	4.4
3-Nitro	Red microscopic cryst.	168	$C_{22}H_{20}N_6O_8$	53.2	4.0	52.9	4.3
4-Nitro	Yellow microsc. cryst.	172	$C_{22}H_{20}N_6O_8$	53.2	4.0	53.1	4.2
2-Methoxy-4-nitro	Orange plates	157–158	$C_{24}H_{24}N_6O_{10}$	51.8	4.3	52.1	4.2
2-Nitro-4-chloro	Golden plates	156–157	$C_{22}H_{18}Cl_2N_6O_8$	46.7	3.2	46.4	3.5

with concd. hydrochloric acid caused disappearance of color. The white microscopic crystals of the salt that promptly appeared were analyzed in one instance (3-nitro derivative) and found to agree with the calculated value.

α-Nitro-β-(*p*-toluidino)-β-(2-nitro-4-chlorophenyl)-ethane.—Obtained in the customary manner it crystallized from alcohol in the form of brownish-yellow plates, m. p. 136–137°, dec. It was observed to form a hydrochloric acid salt.

Anal. Calcd. for $C_{15}H_{14}ClN_3O_4$: C, 53.4; H, 4.2. Found: C, 53.1; H, 4.1.

No reaction was observed between toluidine and the other nitrostyrenes reacting with *p*-phenylenediamine. Negative results with both *p*-toluidine and *p*-phenylenediamine followed attempts at addition with the following: 2-methoxy, 4-methoxy, 2-nitro-4-methoxy, 2,4-dimethoxy, 2,4-dimethoxy-6-nitro, 3-methoxy-4-hydroxy, 3,4-oxymethylene and 4-chloronitrostyrenes. Furfurylidene also was without action.

Summary

p-Phenylenediamine forms addition compounds with the three mononitro, 2-methoxy-4-nitro and 2-nitro-4-chloronitrostyrenes. *p*-Toluidine acts similarly with 2-nitro-4-chloronitrostyrene. Neither substance reacts with other nitrostyrenes prepared from the common aldehydes.

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[3] In naming these substances they may be regarded as substituted phenyl derivatives of N,N′-[(α,α-diphenyl)-β,β′-dinitrodiethyl]-*p*-phenylenediamine.

[CONTRIBUTION FROM THE PEARSON MEMORIAL LABORATORY OF TUFTS COLLEGE]

The Action of Aromatic Amines on 4-Nitro-2-chloronitrostyrene

BY DAVID E. WORRALL

In a recent investigation relating to the additive capacity of substituted nitrostyrenes,[1] it was disclosed that the 2-nitro-4-chloro derivative represented an unusually active combination as measured by *p*-toluidine and *p*-phenylenediamine. The isomeric 2-chloro-4-nitro compound (II) has been found to be much more reactive, so the present communication is concerned with a study of this capacity toward a variety of organic bases containing mobile hydrogen.

II is decidedly more reactive in some respects than nitrostyrene itself. It forms, for example, addition compounds with *o*- and *m*-toluidines as well as *p*-anisidine. On the other hand, it does not react, at least under similar experimental conditions, with aniline or β-naphthylhydrazine, both of which add to nitrostyrene. It is believed that the failure to obtain similar compounds with II is the consequence of an increased tendency for destructive oxidation–reduction reactions originating in the nitro groups. This also explains the formation of black tars when II is heated with hydrazine or hydroxylamine and the rapid destruction of the ammonia addition product by alcohol.

Experimental

α-Nitro-β-(2-chlorophenyl)-ethylene (I).—Obtained by the action of triethylamine[2] it crystallized from alcohol as long yellow needles, m. p. 48°.

Anal. Calcd. for $C_8H_6ClNO_2$: C, 52.3; H, 3.3. Found: C, 52.1; H, 3.5.

α-Nitro-β-(2-chloro-4-nitrophenyl)-ethylene (II).—The product from the nitration of 10 g. of I separated from alcohol in the form of slender pale yellow needles, m. p. 149–150°, yield 7.5 g.

Anal. Calcd. for $C_8H_5ClN_2O_4$: C, 42.0; H, 2.2. Found: C, 41.9; H, 2.5.

α-Bromo-α-nitro-β-(2-chloro-4-nitrophenyl)-ethylene (III).—Five grams of II after bromination was treated with alcoholic potassium acetate producing after crystallization from alcohol 3.5 g. of yellow prismatic needles, m. p. 132–133°.

Anal. Calcd. for $C_8H_4BrClN_2O_4$: C, 31.2; H, 1.3. Found: C, 31.1; H, 1.6.

In a similar manner I was changed into the monobromo derivative, yellow needles melting at 60–61°.

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[1] Worrall and Benington, THIS JOURNAL, **60**, 2844 (1938).

[2] Worrall, THIS JOURNAL, **56**, 1556 (1934). No polymer formation observed.

TABLE I

β-DERIVATIVES OF α-NITRO-β-(2-CHLORO-4-NITROPHENYL)-ETHANE

Substance	Formula	Cryst. form	M. p., °C.	Analyses, % Calcd. C	H	Found C	H
o-Toluidino	$C_{15}H_{14}ClN_3O_4$	Golden narrow plates	117–118	53.6	4.2	53.7	4.3
m-Toluidino	$C_{15}H_{14}ClN_3O_4$	Golden narrow plates	127–128	53.6	4.2	54.1	4.4
p-Toluidino	$C_{15}H_{14}ClN_3O_4$	Golden narrow plates	130–131	53.6	4.2	54.0	4.5
p-Anisidino	$C_{15}H_{14}ClN_3O_5$	Yellow plates	88–89	51.2	4.0	50.8	4.1
Phenylhydrazino	$C_{14}H_{13}ClN_4O_4$	Orange prisms	133–134	49.9	3.9	49.6	4.0
p-Tolylhydrazino	$C_{15}H_{15}ClN_4O_4$	Golden plates	127–128	51.3	4.3	51.3	4.5
DERIVATIVES OF (α,α'-DI-(2-CHLORO-4-NITROPHENYL)-β,β'-DINITRODIETHYL)							
Ammonia	$C_{16}H_{13}Cl_2N_5O_8$	Pale yellow narrow plates	118–119	40.5	2.8	40.4	3.1
p-Phenylenediamine	$C_{22}H_{18}Cl_2N_6O_8$	Brownish-yellow platelets	201–202	46.7	3.2	46.9	3.5
Benzidine	$C_{28}H_{22}Cl_2N_6O_8$	Yellow microscopic	137–138	52.4	3.4	52.7	3.6

Anal. Calcd. for $C_8H_5BrClNO_2$: C, 36.6; H, 1.9. Found: C, 37.0; H, 2.2.

N,N'-(α,α'-Di-(2-chlorophenyl)-β,β'-dinitrodiethyl)-*p*-phenylenediamine.—*p*-Phenylenediamine, but not *p*-toluidine, formed an addition compound with I, separating from an alcohol solution of the components as irregular yellow plates melting with decomposition at 147–148°.

Anal. Calcd. for $C_{22}H_{20}Cl_2N_4O_4$: C, 55.6; H, 4.2. Found: C, 56.1; H, 4.5.

α-Bromo-α-nitro-β-(2-chloro-4-nitrophenyl)-β-*p*-toluidino-ethane.—III reacted in alcohol with *p*-toluidine producing gold yellow platelets, m. p. 138°, dec. A slight odor of monobromonitromethane was noticed.

Anal. Calcd. for $C_{15}H_{13}BrClN_3O_4$: C, 44.3; H, 3.1. Found: C, 43.5; H, 3.3.

No addition reactions were observed with aniline or *m*-toluidine, but *p*-phenylenediamine produced tiny brownish needles. This material which melted indefinitely with marked decomposition gave a poor analysis and was not examined further.

A uniform procedure was used with II. Five-tenths gram of the nitro compound was weighed out carefully, together with the equivalent amount of the base and a few cc. of alcohol. The mixture was heated until solution was completed. The reaction, if it went at all, usually started in a few minutes. The phenylenediamine reaction started in less than one minute, while the *o*-toluido compound did not form for an hour. The products were recrystallized from alcohol, except those obtained with the diamines which were thoroughly washed with hot alcohol. The substance obtained from ammonia, using dry benzene as a solvent,[3] was decomposed rapidly by alcohol; therefore it was crystallized from a benzene-ligroin mixture. All of the above-mentioned addition products melted with decomposition.

Negative results ensued with aniline, *m*-anisidine, β-naphthylamine, β-naphthyl- and *m*-tolylhydrazines, and *m*-phenylenediamine. Destructive decomposition occurred with hydroxylamine, hydrazine, and piperidine.

Summary

4-Nitro-2-chloronitrostyrene is unusually reactive with aromatic amines and for the first time (with a nitrostyrene) addition compounds have been obtained with *o*- and *m*-toluidines as well as *p*-anisidine.

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[3] THIS JOURNAL, **60**, 2843 (1938).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

The Mechanism of Carbohydrate Oxidation. XXIV.[1] The Action of *aldehydo-d*-Glucose and of *aldehydo-d*-Galactose in Alkaline Solutions[2]

BY ROY JOSEPH PLUNKETT AND WILLIAM LLOYD EVANS

When *d*-glucopyranose and *d*-galactopyranose are treated with aqueous solutions of potassium hydroxide, lactic acid is formed in amounts which are dependent upon the concentration of the alkali used and the temperature employed. Shaffer and Friedemann[3] have found that the yields of lactic acid obtained from alkaline solutions of dihydroxyacetone are also a function of the concentration of the triose.

The reaction mechanism, which has been used to account for lactic acid formation in alkaline solutions of certain hexoses and other carbohydrates, involved a rupture of the oxidic structure with the resulting intermediate formation of the corresponding aldehydo structure. The next stage of the reaction assumed the fragmentation of the hypothetical hexose enediols[4] derived from the *aldehydo* sugar thus formed, an action which has been postulated as the third one in the series of changes resulting in lactic acid formation. This latter step should yield pyruvic aldehyde, the precursor of lactic acid, and, in addition, other products of fewer carbon atoms than the original carbohydrate. This has been found to be true. Nef[4] and Schmidt[5] have postulated mechanisms for the rupture of the hypothetical enediols formed by alkaline solutions of reducing sugars.

The discovery of *aldehydo-d*-glucose and *aldehydo-d*-galactose pentaacetates by Wolfrom[6] has made it possible to test the validity of the postulate that the *aldehydo* sugars, if formed as intermediates in the alkaline fragmentation of reducing carbohydrates, should yield lactic acid as one of the reaction products. To establish the validity of this assumption experimentally was the principal objective of this study.

Experimental Part

1. ***aldehydo-d*-Glucose Pentaacetate and *aldehydo-d*-Galactose Pentaacetate.**—These compounds were prepared according to the methods of Wolfrom.[6]

2. **Reagents.**—All reagents used throughout these experiments were examined for their purity by appropriate physical and chemical methods.

3. **Apparatus.** (a) **Volatile Acid Distillation.**—A 500-ml. round-bottomed flask, bearing a small separatory funnel and an aspirator, was connected through a Kjeldahl bulb and an adapter to the top of an upright coil condenser. The delivery end of the condenser dipped into a layer of water about 1 cm. in thickness contained in a 750-ml. suction flask. Heat was supplied through a water-bath and the whole system was evacuated by means of a water pump.

(b) **Extraction Apparatus.**—Modified Soxhlet[7] apparatus was used to extract the lactic acid.

(c) **Volumetric Apparatus.**—All volumetric apparatus was carefully calibrated by the usual well-known methods.

4. **Analytical Procedures.** (a) **Determination of Lactic Acid.**—The procedure for lactic acid was essentially the same as that reported by Nadeau, Newlin and Evans.[8] Only the procedure used for *β-d*-glucopyranose pentaacetate will be described since the same procedure with slight modifications was used throughout this work.

A small glass vial (18 × 50 mm.) was charged with *β-d*-glucopyranose pentaacetate (2.4385 g. = $^1/_{160}$ mole) and placed upright in a 150-ml. carbon dioxide flask containing 12.5 ml. of potassium hydroxide solution of the desired concentration. The flask was closed with a rubber stopper bearing two outlet tubes and a copper wire. The wire was used to hold the vial and its contents in an upright position until the time of mixing. The flask was then evacuated and filled with nitrogen gas, which had been scrubbed with ferrous sulfate and alkaline pyrogallol to remove any oxygen. The evacuation and introduction of nitrogen was repeated twice. The flask and its contents were then placed in the thermostatically controlled water-bath and then allowed to come to the temperature equilibrium. After ten minutes the copper wire was pulled out and the contents of the vial spilled into the potassium hydroxide solution. The flask and contents were agitated in the thermostat for a period of forty-eight hours (except in the case of the time runs) after which the flask was removed, a 5-ml. sample of the contents pipetted into a tared weighing bottle and the density determined. After the density determination the sample was returned to the flask, the stopper, pipet and bottle washed with distilled water, and the potassium hydroxide neutralized with 12.5 ml. of phosphoric acid of the appropriate molarity.

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[1] Number XXIII of this Series, Harry Gehman, Leonard C. Kreider and Wm. Lloyd Evans, THIS JOURNAL, **58**, 2388 (1936).

[2] Abstracted from a thesis presented by Roy Joseph Plunkett to the Graduate School of The Ohio State University in partial fulfilment of the requirements for the degree, Doctor of Philosophy.

[3] P. A. Shaffer and T. E. Friedemann, *J. Biol. Chem.*, **86**, 345 (1930).

[4] J. U. Nef, *Ann.*, **335**, 191 (1904); **357**, 214 (1907); **376**, 1 (1910); **403**, 204 (1913).

[5] Otto Schmidt, *Chem. Rev.*, **17**, 137 (1935); *Ber.*, **68**, 60, 795 (1935); *cf.* C. Neuberg, *ibid.*, 505.

[6] M. L. Wolfrom, THIS JOURNAL, **51**, 2188 (1929); **52**, 2464 (1930).

[7] W. L. Evans, R. H. Edgar and G. P. Hoff, *ibid.*, **48**, 2665 (1926).

[8] G. F. Nadeau, M. R. Newlin and W. L. Evans, *ibid.*, **55**, 4957 (1933).

The vial was then removed and the neutral solution treated with carboraffin, filtered, transferred to a 500-ml. round-bottomed flask and evaporated to dryness under a water pump vacuum at 50°. Forty ml. of water (in 10-ml. portions) were added to the residue and evaporated off to effect the completeness of the removal of acetic and formic acids. The residue was dissolved in a small amount of water (50–100 ml.) and transferred to the Soxhlet extractor, after which the aqueous solution was extracted for forty-eight hours with ether. The Sy flask contained a few grams of zinc carbonate and 50 ml. of water in addition to the ether. At the end of the forty-eight hour period the ether was evaporated off and the aqueous solution treated with carboraffin and boiled for a few minutes to complete the reaction between the zinc carbonate and lactic acid. The carboraffin and excess zinc carbonate were filtered off and the filtrate transferred to a 4-inch (10-cm.) evaporating dish and evaporated to dryness on a water-bath maintained at a temperature of about 50°. The crystallized zinc lactate trihydrate was treated with a minute amount of cold water and about 2 ml. of cold 95% ethanol and cooled to 0°. The crystalline salt was transferred to a tared Gooch crucible and washed with a few ml. of anhydrous ether. The salt was dried at 40–45° in a vacuum oven and examined quantitatively for its water of hydration and zinc oxide content. The filtrate and washings were evaporated for a second crop of zinc lactate trihydrate.

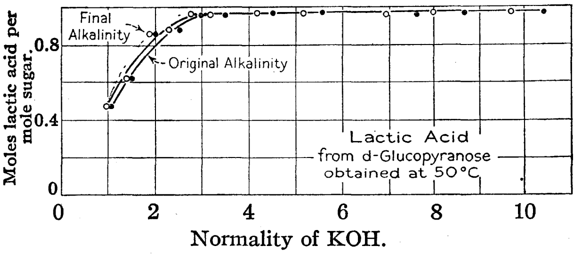

Fig. 1.—Lactic acid yields from *d*-glucopyranose expressed as a function of the original alkali normality and the final normality obtained after applying the necessary correction due to the expansion of the reaction mixture.

(b) **Saccharinic Acids.**—The aqueous solutions remaining after the extraction of lactic acid were evaporated to dryness and the residue freed from moisture by drying in a vacuum oven at 65°. The dried residue was placed in a bottle, covered with about 50 ml. of absolute ethanol, the bottle stoppered, and then allowed to stand for several days at room temperature. The mixture was next digested on the hot-plate for two to three hours and filtered through a Büchner funnel, the phosphate residue being washed with absolute ethanol. The filtrate and washings were transferred to a 250-ml. beaker, water added, and the alcohol evaporated off. An excess of zinc carbonate was added and the mixture digested on the hot-plate for several hours. This was necessary because it was found by titration that the saccharinic acids were present in the form of their lactones, which hydrolyzed slowly. After the completion of the reaction between the saccharinic acid and zinc carbonate the excess zinc carbonate was filtered off, the filtrate concentrated to low volume and transferred to a tared crucible. The liquid in the crucible was evaporated to dryness, the crucible weighed and the zinc saccharinate roasted to zinc oxide and the crucible reweighed. The ratio of zinc oxide/zinc saccharinate indicated that the saccharinic acids were largely $C_6H_{12}O_6$, *i. e.*, rearranged hexoses.

5. **Effect of Expansion on Alkali Normality.**—In comparing the lactic acid yields obtained from the pentaacetates of *d*-glucopyranose and *d*-galactopyranose with those of *d*-glucopyranose and *d*-galactopyranose themselves, it was desired to plot the amount of lactic acid produced as a function of the normality of the alkali. To make the data comparable it was necessary to apply a correction factor to the alkali concentration used with the pentaacetates to account for the potassium hydroxide used up in neutralizing the acetic acid formed by the hydrolysis of the acetates.

In this manner, using equivalent quantities of the various sugars, it was thought that the amount of sugar and the alkali concentration in the solutions were comparable. However, in some preliminary experiments by Mr. L. C. Kreider,[9] of this Laboratory, and ourselves, it was noted that when β-glucopyranose pentaacetate was dissolved in potassium hydroxide there was an appreciable expansion in volume. Thus it became necessary to determine experimentally the magnitude of this expansion for the acetylated sugars and for the sugars themselves and to make suitable corrections for the change in alkali normality before strict comparisons could be made.

From the density of the solutions and the weight of materials originally used, the volume and the potassium hydroxide concentration of the reacting solution were calculated easily. This value is only as accurate as our method used in determining the density. The density measurements could be reproduced within 1%, which is sufficiently accurate for this work. The expansion in all cases for the pentaacetyl derivatives was found to be approximately 18%, while that of *d*-glucopyranose was approximately 8%. Our experience shows that the volume change was inappreciable during the time of the experiment.

In Fig. 1 are shown the effects of the correction for such expansion on the character of the lactic acid curve obtained from *d*-glucopyranose at 50°, while in Fig. 2 similar data are plotted for β-*d*-glucopyranose pentaacetate. The curves for *d*-glucopyranose and β-*d*-glucopyranose pentaacetates are not greatly changed, except in the points being shifted in a direction parallel to the potassium hydroxide axis. However, the curve for *aldehydo*-*d*-glucose pentaacetate is altered quite appreciably (Fig. 3). The same relationships are true at least qualitatively for all of the experimental data herein reported.

In connection with the density determinations it should be pointed out that Powell[10] in studying the velocity of decomposition of dextrose and fructose by alkalies, measured the change in volume during the reaction by means of a very delicate dilatometer. He noted that for a reaction volume of about 15 ml. (sugar concn. = 0.4 *M*) the expansion was of the order of magnitude 0.15 ml. This expansion would lie within our experimental error.

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[9] Harry Gehman, L. C. Kreider and W. L. Evans, THIS JOURNAL, **58**, 2388 (1936).

[10] C. W. R. Powell, *J. Chem. Soc.*, **107**, 1335 (1915).

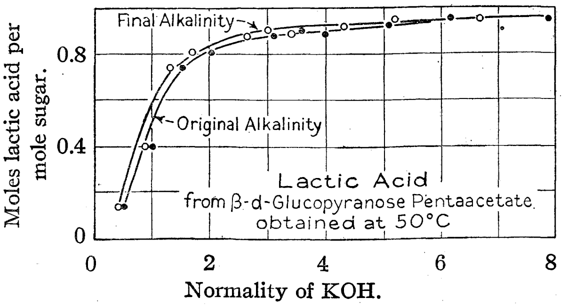

Fig. 2.—Lactic acid yields from *β-d*-glucopyranose pentaacetate expressed as a function of the original alkali normality and the final normality obtained after applying the necessary correction due to the expansion of the reaction mixture.

The increase in volume of our solutions caused a decrease in the sugar concentration. We were interested to learn if this decrease would have any effect on the lactic acid production. To check this point, varying amounts of *d*-glucopyranose (2.0000–2.5000 g.) were treated with 25 ml. of 3.221 N potassium hydroxide. The amount of lactic acid produced is 0.95 mole per mole of *d*-glucopyranose over this range of concentration. Thus the lowering of the sugar concentration by the increase in volume had no effect on lactic acid production, under our experimental conditions. These results are in quantitative agreement with those of Shaffer and Friedemann,[3] who found that the yield of lactic acid from 5 N sodium hydroxide solutions containing 100–500 mM. equivalents of glucopyranose is 1.05–1.01 moles. The concentration of sugar in our experiments was in no case far removed from 500 mM. equivalents.

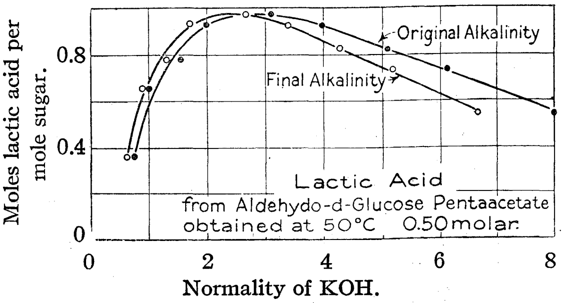

Fig. 3.—Lactic acid yields from *aldehydo-d*-glucose pentaacetate expressed as a function of the original alkali normality and the final normality obtained after applying the necessary correction due to the expansion of the reaction mixture.

The Effect of Time on the Lactic Acid Production.—In a comparative study of this type it is necessary that the reactions proceed to completion. At first it was thought that the differences in lactic acid production might be due to different reaction rates. This point was cleared up by running *d*-glucopyranose, *β-d*-glucopyranose pentaacetate and *aldehydo-d*-glucose pentaacetate in approximately 3 N potassium hydroxide for various periods of time from five minutes to forty-eight hours. Reference to Fig. 4 shows that the yield of lactic acid increases rapidly with time, reaching a constant value in about four hours. The quantitative differences between the three curves are obvious in Fig. 4. The data show definitely that the reaction was completed in the forty-eight-hour period.

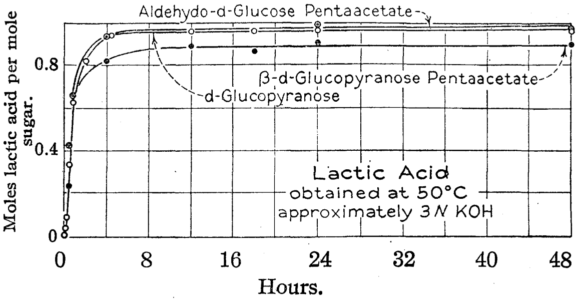

Fig. 4.—Lactic acid yields obtained from alkaline solutions of *d*-glucopyranose, *β-d*-glucopyranose pentaacetate and *aldehydo-d*-glucose pentaacetate expressed as a function of time.

Discussion

Lactic Acid Formation from *aldehydo*-Hexoses.—The data obtained in this experimental study concerning the behavior of *aldehydo-d*-glucose pentaacetate and *aldehydo-d*-galactose pentaacetate in alkaline solutions show conclusively that lactic acid is formed in these reactions under the same conditions as were used in obtaining this acid from *d*-glucopyranose and *d*-galactopyranose, respectively. *Therefore, it is clear that the mechanism which postulates the intermediate formation of aldehydo structures from the respective pyranoid structures in the production of lactic acid from the sugars seems to be well founded.*

Marchlewski[11] and collaborators found that alkaline solutions of glucose, galactose, maltose and arabinose give strong absorption bands in the ultraviolet, but after neutralization the original continuous spectrum is restored. The band in the region of about 2700 Å. is characteristic for alkaline solutions of the above carbohydrates and is attributed to the formation of an aldehyde group.

Effect of Temperature and Alkali Normality on Lactic Acid Formation.—Since it was necessary to use *aldehydo-d*-glucose pentaacetate and *aldehydo-d*-galactose pentaacetate in these experiments, it followed that one each of the *d*-glucopyranose pentaacetates and *d*-galactopyranose pentaacetates should be employed throughout for comparative purposes. We chose *β-d*-glucopyranose pentaacetate and the *β-d*-galactopyranose

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[11] (a) Gabryleski and Marchlewski, *Biochem. Z.*, **261**, 393 (1933); *C. A.*, **27**, 4218 (1933); (b) Marchlewski and Urbanczyk, *Biochem. Z.*, **262**, 248 (1933); *C. A.*, **27**, 5004 (1933).

pentaacetate in each case by reason of their more favorable solubilities.

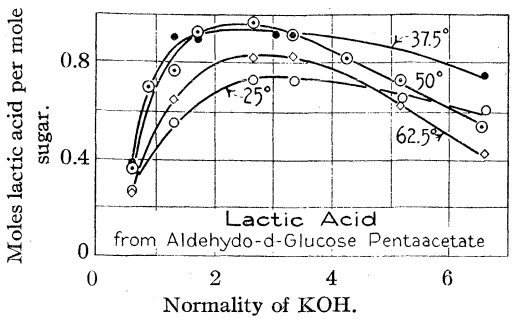

Fig. 5.—Lactic acid yields obtained from alkaline solutions of *aldehydo-d*-glucose pentaacetate at 25, 37.5, 50 and 62.5°.

(a) The yields of lactic acid obtained from the *aldehydo-d*-glucose pentaacetate under varying alkali normalities at 25, 37.5, 50 and 62.5° are shown in Fig. 5, while the comparative data obtained from *β-d*-glucopyranose pentaacetate under the same experimental conditions are shown in Fig. 6.

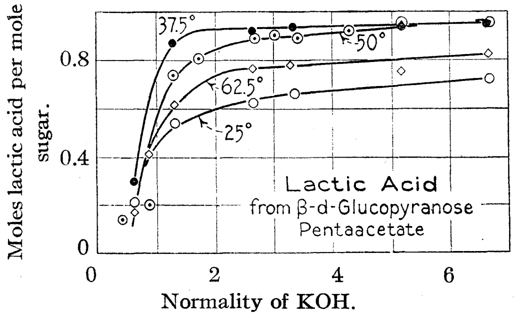

Fig. 6.—Lactic acid yields obtained from alkaline solutions of *β-d*-glucopyranose pentaacetate at 25, 37.5, 50 and 62.5°.

From these two figures it is seen that in some respects *d*-glucopyranose pentaacetate and *aldehydo-d*-glucose pentaacetate differ quite markedly in their behavior in alkaline solutions of the same alkali normality and the same temperature. The diminishing yields of lactic acid from the aldehydo form of the sugar after the range 2–3.5 N has been passed are in marked contrast to those obtained from the pyranoid form. From limited experimental data available in this Laboratory it has become increasingly evident that these diminishing yields of lactic acid from *aldehydo-d*-glucose pentaacetate are compensated for by the increasing yields of saccharinic acids, while the increasing yields of lactic acid obtained from *d*-glucopyranose pentaacetate are on the contrary accompanied by diminishing yields of the saccharinic acids.[3] This relationship is shown in Fig. 7 for which the data have been gathered by a method which leaves much to be desired. This same general relationship was observed by Gehman, Kreider and Evans[9] in a study of the products obtained by the action of mixtures of cellobiose octaacetate and dihydroxyacetone monoacetate in alkaline solutions. In this connection it also should be noted that Hoff[7] obtained crystalline *d*-galacto-α-saccharinic acid lactone from alkaline solutions of *d*-galactopyranose in yields which increased with the temperature and the alkali normality.

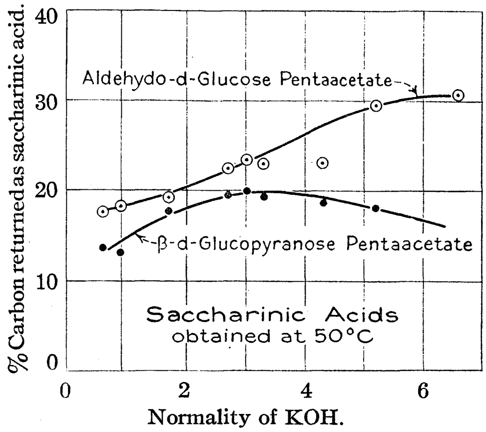

Fig. 7.—Saccharinic acids obtained from alkaline solutions of *aldehydo-d*-glucose pentaacetate and *β-d*-glucopyranose pentaacetate.

We may classify the reactions of reducing sugars in alkaline solutions into the following general groups: (1) they may undergo rearrangement to form saccharinic acids; (2) they may undergo the Lobry du Bruyn and Alberda van Ekenstein rearrangement to form other reducing sugars; (3) they may rearrange to form hypothetical enediols; (4) they may mutarotate; (5) they may form polymers; (6) they may fragment. The general relationship existing between the yields of lactic and saccharinic acids may be regarded as due to differences or equalities in the rates of the two reactions here shown

Fragmentation $\longleftarrow$ Reducing sugar $\longrightarrow$ Rearrangement

The fragments may undergo rearrangement to give acetic, lactic, C_4 and C_5 saccharinic acids, while the sugar itself may at the same time rearrange to the C_6 saccharinic acids. It has been pointed out by Hockett[12] that glycol aldehyde, a

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(12) W. L. Evans and R. C. Hockett. THIS JOURNAL, **52**, 4065, ref. 14 (1930).

theoretically possible fragmentation product of the saccharides, must be regarded as one of the possible sources of acetic acid when this simplest of all carbohydrates is reacted upon by alkalies, *i. e.*, acetic acid must be considered the saccharinic acid of glycol aldehyde in quite the same way as lactic acid may be regarded as the saccharinic acid of glyceric aldehyde and dihydroxyacetone.

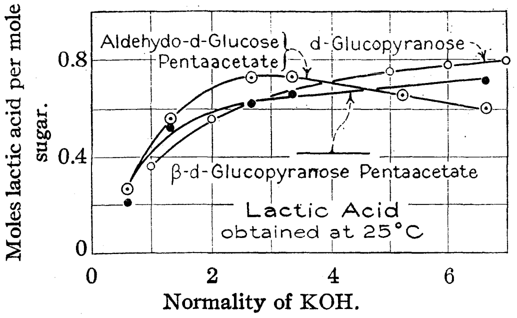

Fig. 8.—Comparison of lactic acid yields obtained from alkaline solutions of *d*-glucopyranose, *β*-*d*-glucopyranose pentaacetate and *aldehydo-d*-glucose pentaacetate at 25°.

From the above discussion it is evident that the relationship between the yields of C_6 saccharinic acids and those containing less carbon atoms must depend on many experimental factors among which are temperature, alkali normality and concentration of sugar studied. From Figs. 5 and 7 it is clear that approximately 73% of the *aldehydo-d*-glucose pentaacetate carbon has been recovered at 50° between 2–3 *N* potassium hydroxide as lactic and saccharinic acids. This is our maximum value in this series of studies. These reactions are accompanied by tar formation. Work is now in progress in this Laboratory to extend our knowledge of these complicated systems. (b) From the data in Figs. 5 and 6 it is seen that the lactic acid yields from *aldehydo-d*-glucose pentaacetate and *d*-glucopyranose pentaacetate are not necessarily at a maximum at the highest temperatures. At 37.5° and in the region of lower alkali normalities, the two compounds seem to be more sensitive than at the other temperatures studied and tend to give as high yields of lactic acid as under more drastic conditions of alkalinity.[3] This is more especially true with the pyranoid structure, while with the aldehydo form the yields at 37.5 and 50° from 0.6 *N* to approximately 4 *N* are almost the same. It is to be noted that the yields of lactic acid are lower from both compounds at 62.5°, a fact in harmony with previous studies[13] on *d*-glucopyranose, *d*-mannopyranose and *d*-fructopyranose at 75°. The lactic acid data obtained by a comparative study of *aldehydo-d*-glucose pentaacetate, *d*-glucopyranose, and *β*-*d*-glucopyranose pentaacetate at 25° are shown in Fig. 8.

Although no extensive experimental studies have been made of the effect of temperature and different alkali normalities on the formation of saccharinic acids containing six carbon atoms from the hexoses except that of Hoff,[7] it may be concluded safely that the data obtained by such an inquiry will be found in general to be in accord with the views expressed above with reference to lactic and saccharinic acid formation at 50° with various alkali normalities. (c) The yields of lactic acid obtained from *aldehydo-d*-galactose pentaacetate, *d*-galactopyranose pentaacetate and *d*-galactopyranose at 25 and 50° are shown in Figs. 9 and 10, respectively. It is seen that the *aldehydo* structure seems to be more reactive than either of the two pyranoid structures which were used for comparative purposes. The *aldehydo* structure reaches a maximum production of lactic acid at a lower alkalinity at 50° than it does at 25°.

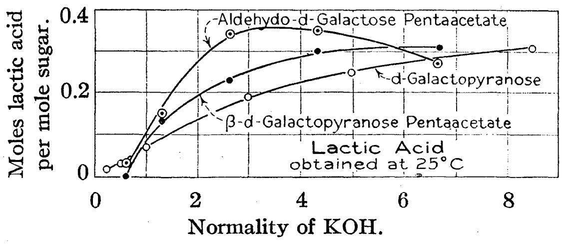

Fig. 9.—Comparison of lactic acid yields from alkaline solutions of *d*-galactopyranose, *d*-galactopyranose pentaacetate and *aldehydo-d*-galactose pentaacetate at 25°.

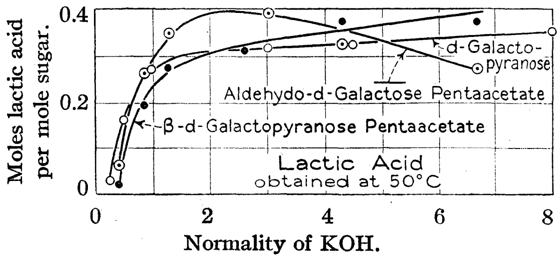

Fig. 10.—Comparison of lactic acid yields from alkaline solutions of *d*-galactopyranose, *d*-galactopyranose pentaacetate and *aldehydo-d*-galactose pentaacetate at 50°.

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[13] (a) W. L. Evans and J. E. Hutchman, THIS JOURNAL, **50**, 1496 (1928); (b) W. L. Evans and D. C. O'Donnell, *ibid.*, **50**, 2543 (1928).

(d) Although the galactose series does not yield as much lactic acid as the glucose series under our experimental conditions the data obtained by Hoff[7] show that the formation of *d*-galacto-α-metasaccharinic acid at 50° increases rapidly with increasing alkali normalities, a fact in harmony with the views expressed above. Whether there is a higher concentration of the *aldehydo* form of galactose under these conditions has not been established.

Effect of Potassium Acetate on Lactic Acid Formation.—Since potassium acetate is formed in all of these reaction mixtures, it became necessary to determine the extent of its influence on the formation of lactic acid. This was done by studying the yields of this acid obtained from *d*-glucopyranose, *aldehydo*-*d*-glucose pentaacetate, β-*d*-glucopyranose pentaacetate, and a mixture of *d*-glucopyranose and potassium acetate equal to that produced by the hydrolysis of the pentaacetates, at 50° and at various alkali normalities. The data obtained in these experiments are shown in Fig. 11. An examination will show that in general there is a close correspondence in the results obtained in the pyranoid structures, especially in the case of the two pentaacetates. At the higher alkalinities the yields of lactic acid from the pyranoid structures tend to become more nearly identical, *i. e.*, the data are within the limits of the experimental error.

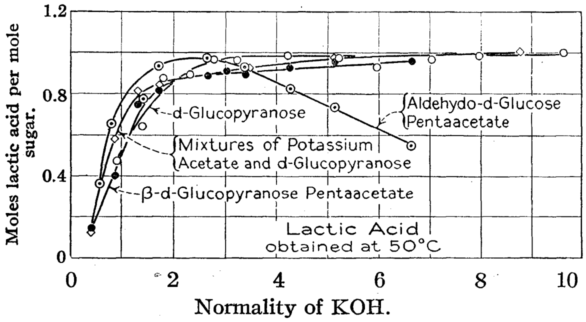

Fig. 11.—Comparison of the yields of lactic acid obtained from alkaline solutions of *d*-glucopyranose, β-*d*-glucopyranose pentaacetate, *aldehydo*-*d*-glucose pentaacetate, and mixtures of potassium acetate and *d*-glucopyranose.

Acknowledgment.—The authors wish to express their indebtedness to Drs. Leonard C. Kreider and Harry Gehman for valuable assistance rendered during the progress of this work.

Conclusions

1. (a) A comparative study has been made of the yields of lactic acid obtained from *d*-glucopyranose pentaacetate and *aldehydo*-*d*-glucose pentaacetate at 25, 37.5, 50 and 62.5° in potassium hydroxide solutions ranging from 0.5–6 *N*. (b) A similar study was made with *d*-galactopyranose pentaacetate and *aldehydo*-*d*-galactose pentaacetate at 25 and 50°.

2. Lactic acid was obtained as a reaction product from the *aldehydo* structures as well as from the pyranoid structures, a fact which supports the postulate that pyranose sugars are converted into *aldehydo* ones as intermediate compounds in the mechanism involved in the formation of lactic acid in alkaline solutions.

3. The most striking difference in the yields of lactic acid obtained from the pyranoid and *aldehydo* structures of both glucose and galactose lies in the maximum point reached by the *aldehydo* structures after which there is a marked decrease in the yield of this acid.

4. (a) In the glucose series the difference in lactic acid yields between the *aldehydo* and pyranoid structures has been attributed to a concurrent production of the isomeric saccharinic acids at such rates as to produce this effect. (b) At 50°, it was found that the yields of lactic acid obtained from *d*-glucopyranose pentaacetate and *aldehydo*-*d*-glucose pentaacetate bear an inverse relation to their respective yields of the saccharinic acids.

5. At 50°, the *aldehydo*-*d*-glucose pentaacetate yielded the maximum amount of its carbon as lactic and saccharinic acids, namely, approximately 73% between 2–3 *N* potassium hydroxide.

6. At 37.5° and the lower alkali normalities, *d*-glucopyranose pentaacetate seems to be more sensitive toward alkalies than at either 25, 50 or 62.5°.

COLUMBUS, OHIO RECEIVED AUGUST 29, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DEPAUW UNIVERSITY]

The Composition of the Seeds of *Asimina triloba*

BY J. L. RIEBSOMER, JOHN BISHOP AND CHARLES RECTOR

The mature fruit of *Asimina triloba* (common name papaw) required for this investigation was collected from woodlands in Putnam County, Indiana, about October 1, 1937, and the seeds were extricated from the pulp almost at once and allowed to air dry at room temperature. Each fruit contains from two to twelve flat, oblong, dark brown seeds, the average weight of which is 0.7 g. The air-dried seeds were ground carefully and dried at 100–110° for an hour in a carbon dioxide atmosphere. The loss in weight indicated a moisture content of 5.1%. The dried material was then extracted quantitatively with petroleum ether (b. p. 30–60°) and found to contain about 38% of a reddish-brown fatty oil. The unextracted residue was a slightly gray powder.

Experimental

Analysis of the Fatty Oil of Papaw Seed.—The usual physical and chemical characteristics of this oil were determined by standard methods[1] and are as follows: sp. gr. (25°/25°), 0.9296; ref. ind. (Abbe 25°), 1.4728; iodine no. (Hanus), 113.5; sap. value, 194.0; mean mol. wt. satd. acids, 307.9; mean mol. wt. unsatd. acids, 308.2; iodine no. unsatd. acids, 117.8; iodine no. satd. acids, 14.0; unsatd. acids (basis of oil) (by the lead-salt method) (corrected %), 85.5; satd. acids (basis of oil) (corrected %), 5.6; unsap. matter, %, 0.80; Reichert–Meissl no., 1.05; acid value, 6.4; acetyl value, 18.11.

Composition of the Unsaturated Acids.—The unsaturated acids (270 g.) were converted into the methyl esters and distilled at 4 mm.: yield 228 g.; b. p. 175–182°. The narrow boiling point range indicated that the mixture contained acids with the same number of carbon atoms.

Two and one-half grams of the unsaturated methyl esters was reduced catalytically with hydrogen. The product was saponified and the acid thus produced, recrystallized once from 95% alcohol, melted at 68–70°. The unsaturated acids were thus shown to consist of only eighteen-carbon-atom acids.

Linolenic and more highly unsaturated acids were found to be absent by adding bromine to a cold ether solution of the unsaturated acids. Another sample was dissolved in petroleum ether, cooled to −5° and bromine added slowly with stirring. A precipitate formed, was filtered off and recrystallized once from glacial acetic acid. The melting point of the product was 112.5–113.5°. This indicated qualitatively the presence of linoleic acid.

The ozonolysis method of Riebsomer and Johnson[2] was applied to 175 g. of the unsaturated methyl esters, and the methyl esters from this process fractionally distilled from a modified Claisen flask with the following results: at a pressure of 14 mm., the fractions had boiling points and weights of (1) 53–57°, 7.4 g.; (2) 57–88°, 4.7 g.; (3) 88–99°, 15.8 g. At a pressure of 4–5 mm., the fractions had boiling points and weights of (4) 60–121.5°, 21.8 g.; (5) 121.5–127.5°, 54.8 g.; (6) 127.5–155°, 30.0 g.; (7) 155–167°, 11.9 g.; (8) 167–177°, 9.4 g.; undistillable, 15.4 g.

Fractions 3 and 4 were put together and redistilled into three fractions which are designated as fractions 3a, 3b, and 3c. At a pressure of 14.5 mm., these fractions had boiling points and weights of (3a) 85–91°, 5.4 g.; (3b) 91.5°, 21.1 g.; (3c) residue, 11 g.

For the examination of the various fractions densities were determined at 20°, converted to densities at 4°; refractive indices were determined at 20° using the Abbe refractometer. The refractive index and density of fraction 1 were 1.407, 0.8858. The ester was saponified and the acid distilled, b. p. 106–107° at 18 mm.; found for the refractive index and density of the acid, 1.4150, 0.9211; reported for caproic acid, 1.4138, 0.927. The anilide prepared from this acid melted at 94.5–95°. Mixed m. p. of known caproic anilide (m. p. 96°) was 94.5–95.5°. These data established the identity of fraction 1 as methyl caproate.

Fractions 2 and 3a were small and each boiled over a wide range. Their refractive index, density and saponification equivalents all indicated them to be a mixture of methyl caproate and methyl pelargonate found in fraction 3b.

For fraction 3b the refractive index and density were 1.4210 and 0.8792. The ester was saponified and the acid distilled, b. p. 142–144° at 18 mm.; neut. equiv. acid, found 157.0; calculated for pelargonic acid, 158.1; refractive index and density: 1.4309, 0.905; reported for pelargonic acid; 1.433, 0.907. The anilide prepared from this acid melted at 55–55.5°. Reported for the anilide of pelargonic acid 56°. These data indicated this fraction to be methyl pelargonate.

Fraction 3c.—The b. p. of fraction 3c and its saponification equivalent (137.6) indicated it to be a mixture of the methyl esters of pelargonic and azelaic acids.

The refractive index and density for fraction 5 were 1.4361, 0.9974; reported for dimethyl azelate, 1.436, 1.005. The ester was saponified and the acid recrystallized from water. It melted at 106.5°; mixed m. p. with known azelaic acid (m. p. 106.5°) showed no depression; neut. equiv. of the acid 95.1; calculated for azelaic acid 94.1. Fraction 5 was thus shown to be dimethyl azelate.

In a similar manner, fraction 6 was demonstrated to be essentially dimethyl azelate.

Fractions 7 and 8 were relatively small and boiled over large ranges. Saponification equivalents, refractive indices, and density determinations indicated them to con-

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[1] Jamieson, "Vegetable Fats and Oils," Monograph Series No. 58, The Chemical Catalog Co., Inc., New York, 1932.

[2] Riebsomer and Johnson, THIS JOURNAL, **55**, 3352 (1933).

sist largely of dimethyl azelate admixed with the methyl esters of some 18 carbon monobasic acids which had not been cleaved by ozonolysis.

The three significant fractions for establishing the composition of the original unsaturated acids are 1, 3c, and 5, which were shown to contain, respectively, caproic, pelargonic, and azelaic acids.

Using the same reasoning as employed by Riebsomer and Nesty[3] these products were taken to mean that the only acids present in the unsaturated acids were oleic and linoleic. This is another case in which the double bonds in the natural occurring linoleic acid are found in the 9, 10, and 12, 13, positions, which is in accord with previous findings.[3]

The iodine number of the unsaturated acids was 117.8, which makes it possible to calculate the percentage of oleic and linoleic acids.

	In unsatd. fraction	In oil % acid	In oil % glyceride
Oleic acid	69.5	59.4	62.1
Linoleic acid	30.5	26.1	27.1

The Saturated Acids

The neutral equivalent of the saturated acids (307.9) indicated that the mixture contained some acids with more than 18 carbon atoms. Twenty grams of the saturated acids was converted into the methyl esters and were fractionally distilled at 4 mm. using a modified Claisen flask. The fractions had boiling points, weights, and saponification equivalents of (1) 160–175°, 12.5 g., 208.0; (2) 175–190°, 5.5 g., 317.7; residue 1.5 g.

The saponification equivalent of fraction 1 suggested a mixture of methyl palmitate and methyl stearate. This material was redistilled into three fractions. The first 1.2 g. of distillate (fraction 1a) was collected, the next 6.5 g. (fraction 1b) was collected, and the last 2.0 g. to distil was collected separately (fraction 1c). Fraction 1a was saponified and the acid recrystallized three times from ethyl alcohol. The m. p. of the acid was 60–61°. Mixed m. p. with palmitic acid was 61–62°; the m. p. of the anilide 88–88.5°. Mixed m. p. with known anilide of palmitic acid showed no depression. Fraction 1c was saponified and recrystallized from alcohol. The m. p. of the acid was 67–69°. Mixed m. p. with stearic acid 68–70°. These data were interpreted to mean that fraction 1 consisted of palmitic and stearic acids.

Fraction 2 (b. p. 175–190°) was saponified and, after three crystallizations of the acid from ethyl alcohol, a small amount of acid was left with a m. p. of 68–70°. A mixed m. p. with stearic acid showed no depression. The saponification equivalent (317.7) of this fraction indicated that another acid with a molecular weight greater than that of stearic acid was present, but it was not isolated from this fraction.

The residue (1.5 g.) was saponified, the acid dissolved in ethyl alcohol, decolorized with charcoal, and allowed to crystallize. On the second crystallization 0.3 g. of an acid was isolated; m. p. 76–77°. A mixed m. p. with an authentic specimen of arachidic acid (m. p. 76–77°) showed no depression, from which it was concluded that arachidic acid was present.

These data do not permit a very accurate calculation of the percentages of the saturated acids, but if we assume fraction 1 to be a mixture of palmitic and stearic acids, fraction 2 to be a mixture of stearic and arachidic acids, and the residue to be largely arachidic acid it is then possible to obtain the percentages shown in the accompanying table. These assumptions are admittedly not entirely valid, especially since no account has been taken of the small amount of unsaturated acids present.

	In satd. fraction	% acid	% glyceride
Palmitic acid	41.5	2.3	2.4
Stearic acid	31.8	1.8	1.9
Arachidic acid	26.6	1.5	1.54

Glycerol was shown to be present by conversion into the tribenzoate.

Estimation of Nitrogen, Crude Fiber, and Ash Content of the Seeds.—A Kjeldahl nitrogen determination on the ground dried seeds showed 0.1805% of nitrogen present. This would correspond to 1.128% of protein.

Crude fiber was determined on the dried meal after extraction of the oil. The percentage of crude fiber calculated on the basis of the dried seeds was 20.0%.

The ash content calculated on the basis of the dried seeds was 1.3%.

The authors wish to express their appreciation to Dean William M. Blanchard of this department who was instrumental in securing funds for this work from the National Research Council and from Mr. J. K. Lilly of Indianapolis, Indiana.

Summary

1. The seeds from *Asimina triloba* have been analyzed.

2. These seeds contain about 38% of a fatty oil which consists of the glycerides of oleic, linoleic, palmitic, stearic, and arachidic acids.

3. The protein, crude fiber, and ash content of the seeds have been determined.

GREENCASTLE, INDIANA RECEIVED MARCH 31, 1938

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[3] Riebsomer and Nesty, THIS JOURNAL, **56**, 1784 (1934).

[CONTRIBUTION FROM THE BIOLOGICAL LABORATORIES, HARVARD UNIVERSITY]

Further Studies on the Electrical Properties of Stearate Films Deposited on Metal

BY ELIOT F. PORTER AND JEFFRIES WYMAN, JR.

I. Introduction

In two previous communications[1,2] we have discussed a variety of phenomena associated with the contact potentials of multilayer stearate films built on metal slides by dipping the slides through stearate monolayers spread on liquid surfaces. Langmuir[3] recently has pointed out the advantages of interpreting these phenomena on the hypothesis that the potentials are due to the production of surface charges. He also has outlined a mathematical analysis of the electrostatic forces brought into play in consequence of the potentials while the films are being dipped. This analysis suggests that by introducing an arbitrary voltage between the submerged metal slides and the liquid it should be possible to modify the behavior of the films and to control the potentials which they develop, and Langmuir refers to observations pointing to this. Thus, speaking in terms of the surface charge hypothesis, he states that "By applying potentials of a few volts between the plate and the metallic tray during the deposition of stearate monolayers it has been found possible to alter the surface charge σ on X or Y films and to obtain either positive or negative values of σ over wide ranges of *p*H."

In the present paper we describe a variety of experiments which reveal new phenomena associated with the films, and which have a bearing on the problem of the source and nature of the potentials, particularly in relation to the surface charge hypothesis.

II. Effects of Liquids on Potentials Associated with the Films

In this section we discuss studies on the effect of dipping films into various liquids, as well as electromotive force measurements involving films covered with liquids. In these electromotive force measurements, owing to the very high resistance of the circuits due to the films themselves and in some cases to the liquids as well, it was impossible to make direct measurements with a potentiometer. For this reason we employed a bridge circuit of the type described by Du Bridge,[4] involving an F. P. 54 Pliotron.

We already have pointed out[2] that dipping an X film of high contact potential into water or the aqueous substrates from which films are obtained does not greatly alter its subsequent contact potential in air. Nevertheless while the film is under the liquid its electrical behavior is like that of a film of zero potential. The same is true of Y films and X films of lower potential. Thus the e. m. f. of the arrangement

X or Y film/liquid/X or Y film

is always very close to zero, irrespective of the contact potentials of the films. This is illustrated by the case of two X films of potentials 1.79 and 0.175 v. separated by a few drops of a solution used for forming X films. The voltage of the combination was close to zero, *i. e.*, 0.055–0.075. If we think of the potential as due to internal charges, or to the orientation of dipoles within the film, the effect may be interpreted as due to the accumulation of a layer of compensating free charge, or of oriented dipoles, at the outer face of the film while it is in contact with the liquid. On the other hand, if we regard the potential as due to the presence of a layer of free charge on the surface, we may think of this effect as due to the surface being discharged by contact with the liquid. It is then, of course, necessary to assume that the surface of the film is recharged by the act of separating it from the liquid, since contact potentials persist after the slides are dipped into aqueous solutions. This result at once raises the question whether a similar neutralization takes place when other liquids are substituted for water or aqueous solutions. We have made a number of observations to answer this question.

When films are immersed in benzene there is no evidence of neutralization of the potentials. This is illustrated by the case of an X film originally of potential 5.6 v. separated from a Y film of potential 0.19 v. by a layer of benzene. The voltage from left to right[5] of the combination

X film (5.6 v.)/C_6H_6/Y film (0.19 v.)

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[1] Porter and Wyman, THIS JOURNAL, **59**, 2746 (1937).

[2] Porter and Wyman, *ibid.*, **60**, 1083 (1938).

[3] Langmuir, *ibid.*, **60**, 1190 (1938)

[4] Du Bridge, *Rev. Sci. Instruments*, **4**, 532 (1933).

[5] *I. e.*, the voltage of the metal plate coated with film on the right minus that of the plate on the left. This convention is used throughout in expressing the voltage of such combinations

varied from +5.4 to +4.0 over a period of three hours, showing some tendency to fall, but rising each time the benzene was renewed close to the initial value. The sign of the voltage agrees with the orientation of the films. After the observation was over the potentials of the two films were measured in air and found to be 4.9 and 0.29. In this and all following cases we adopt the convention that the number in brackets following the word "film" refers to the original contact potentials of the film in air. Measurements of other pairs of films all gave the same results, *e. g.*

X film (3.10 v.)/C_6H_6/X film (0.18 v.)

Voltage varied between +2.7 and +1.3 over a period of about fifty-two minutes, showing some tendency to drop but returning close to the original value when the benzene was renewed. After the measurements the potential of the left-hand X film in air was about 2.70.

When chloroform is substituted for benzene, neutralization is complete as in the case of water and aqueous solutions. For example the voltage from left to right of the combination

X film (4.9 v.)/$CHCl_3$/Y film (0.29 v.)

was −0.14. The potentials of the films in air after the measurements were 1.8 and 0.29. The same type of neutralization is produced by mixtures of chloroform and benzene containing about 60% or more by weight of chloroform but not by those containing less, as may be seen by the following three examples:

(1) X film (2.8)/C_6H_6 + $CHCl_3$ (25%)/X film (0.34)
Voltage +2.3 − +2.2 over a period of twenty-five minutes
Potentials of films after measurements 2.5 and 0.35

(2) X film (2.6)/C_6H_6 + $CHCl_3$ (50%)/X film (0.35)
Voltage +2.1 − +1.0 over a period of forty-five minutes
Potentials of films after measurements 1.7 and 0.16

(3) X film (1.9)/C_6H_6 + $CHCl_3$ (59%)/Y film (0.22)
Voltage fell quickly from 0.73 and reached a value of 0.01 in twenty-five minutes
Potentials of films after measurements 1.0 and 0.20

Other observations were made by placing small drops of mercury on films and making contact with them by means of a fine platinum wire. The voltages of the combination

Film/Hg/Pt

are always small and independent of the potentials of the films, as may be seen by the following examples, in which the different values of the voltage belong to different parts of the film

X film (2.6)/Hg/Pt, voltage +0.25, +0.15, +0.13, +0.19
Y film (−0.20)/Hg/Pt voltage 0, +0.20, 0

Contact with mercury has little or no effect on the subsequent potential of the films. This point was tested by dipping films into a beaker of mercury the surface of which had been scraped clean. After an X film having an initial potential of 3.0–3.2 v. was dipped repeatedly its potential was found to be 3.4–3.7 v. A color comparison showed that none of the film had been removed. In another case several layers were found to have been removed by continued dipping but there was no significant change in the potential. The same result is obtained when Y films are dipped in mercury. On the other hand, it may be seen from the data given above that prolonged contact with chloroform reduced the potentials of X films considerably. Contact with benzene, however, reduces the potentials only slightly.

If warm moist air is blown over the films so as to produce water condensation on the surface while the contact potentials are being measured there is no appreciable change, although, as we have pointed out, immersion in water leads to neutralization of the potential.

We have referred to the fact that when X and Y films are made electrodes in a glow discharge, they develop very large contact potentials. These are positive or negative according to the direction of the discharge. In the case of Y films these "discharge potentials" are abolished by dipping the films into water and aqueous substrates; in the case of X films a residual potential, amounting to several volts or more, always remains after dipping and seems to have the same degree of permanence as the native potentials of X films. Like the spontaneous potentials, these potentials are neutralized while the films are under water. Dipping into benzene wholly fails to reduce such "discharge potentials" in the case of both X and Y films. The same is true of dipping into mercury, although when several of the outermost layers are removed there is some reduction in the "discharge potentials," *e. g.*, in one case when 4 layers were removed from an X film a reduction from +13 to +7.4 v.; in another when several layers were removed from a Y film a reduction from about +15 to +4 or 5 v. The same results are obtained when the potentials are negative. Such removal of layers generally occurs the first time a slide is dipped; if subsequently a new "discharge potential" is impressed on the film and it is dipped in mercury no film is removed and there is no reduction of potential. When Y films are dipped in chloroform the "discharge potentials" are at once reduced to zero, although no film is removed. On the other hand "discharge potentials" of X films are completely unaffected by dipping in chloroform. Nevertheless, measurements of the voltages of combinations like those discussed above show that while X and Y films are in contact with mercury and chloroform the "discharge potentials" are always neutralized.

III. Effect of Applied Voltages

In this section we shall present a detailed investigation of the effects of applying a voltage between the plate and the liquid subphase while films are being built. Under the conditions of our experiments such voltages give rise to currents of the order of several milliamperes which may be read easily by placing a milliameter in series with the voltage source. In accordance with Langmuir's hypothesis such currents might be expected to have a marked effect on potentials by modifying the density of the surface charge. Langmuir has referred to observations suggesting this.[6] In any case, quite apart from the concept of surface charge and its relation to the current flowing, simply on the basis of Langmuir's general analysis of the electrostatic forces acting during the formation of films, it would be expected that applied voltages would alter the contact angles and the upper limiting potentials of the films, and perhaps also the slope of the potential–thickness curves throughout the whole process.

Since it is well known that metallic ions even at very low concentrations have marked effects on the properties of built-up stearate films,[7] an attempt was made to eliminate as far as was conveniently possible all sources of contamination of the solutions by traces of metallic ions. For this reason glass trays and glass barriers were substituted for the usual metal trays and barriers. Water for making up solutions was redistilled through a Pyrex glass still. In the earlier experiments the films were built on stainless steel slides, but in the greater part of the work a platinum slide was substituted to avoid complications due to possible electrolytic effects under the influence of applied voltages. Contact with the solution was made with a platinum wire. The source of voltage applied between the slide and solution was either a storage battery or dry cells.

To prevent large changes in *p*H, especially when working in the alkaline range, the solutions were buffered with borates.[8] The following solutions were used:

(1) 1.33×10^{-3} *M* H_3BO_3; 1.33×10^{-3} *M* NaOH; 0.12×10^{-3} *M* Ca $(Ac)_2{\cdot}2H_2O$; *p*H = 10.9; for X layers

(2) 1.87×10^{-3} *M* H_3BO_3; 0.93×10^{-3} *M* NaOH; 0.4×10^{-3} HCl; 0.12×10^{-3} *M* $Ca(Ac)_2{\cdot}2H_2O$; *p*H = 8.6; for X layers

(3) Same as (2) but with the addition of 2.0×10^{-6} *M* $CuCl_2{\cdot}2H_2O$, for Y layers

(4) 1.33×10^{-3} *M* H_3BO_3; 0.67×10^{-3} *M* NaOH; 0.67×10^{-3} *M* HCl; 0.12×10^{-3} *M* $Ca(Ac){\cdot}2H_2O$; and with or without 2.0×10^{-6} *M* $CuCl_2{\cdot}2H_2O$; *p*H = 7.4–7.7; for Y layers

(5) 1.33×10^{-3} *M* H_3BO_3; 0.67×10^{-4} *M* NaOH; 0.67×10^{-3} *M* HCl; 0.36×10^{-4} *M* $BaCl_2{\cdot}2H_2O$; 2.0×10^{-6} $CuCl_2{\cdot}2H_2O$; *p*H = 7.4; for Y layers

During the deposition of X layers, unless otherwise indicated, the slides were kept submerged in the solution for ten seconds on each dip. This procedure usually favors the deposition of more uniform X layers than can be obtained by more rapid dipping. Castor oil was used to keep the monolayer under constant compression. The experiments were conducted at room temperature, which varied between 19–24°.

A. Effects on X and Y Films Deposited on Stainless Steel.—If stainless steel slides are used for deposition of the film with an applied voltage, reproducible results can be obtained only for a certain length of time which seems to depend to some extent on the magnitude as well as on the polarity of the voltage. Invariably, however, in time the slide begins to show signs of electrolytic action such as small pits and there may even be an evolution of gas while the slide is submerged with an applied voltage in the course of depositing films. This occurs most rapidly when the voltage is high—22 v. was the highest voltage used in the work—and when the slide is attached to the positive pole of the battery. A slide affected in this manner is useless for further work without repolishing. The potentials of X films deposited on such slides fail to rise in the usual way with increase in number of layers, perhaps due to metallic ions escaping from the steel and becoming incorporated in the stearate films. It was pos-

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[6] See quotation, p. 2855.

[7] Langmuir and Schaefer, THIS JOURNAL, **59**, 2400 (1937).

[8] Sørensen's borate buffers given by W. Mansfield Clark in "The Determination of Hydrogen Ions," Williams and Wilkins Co., Baltimore, Md., 3d edition, 1928.

sible, however, by using new steel slides for only one or two films and working at relatively low voltages to obtain very consistent results.

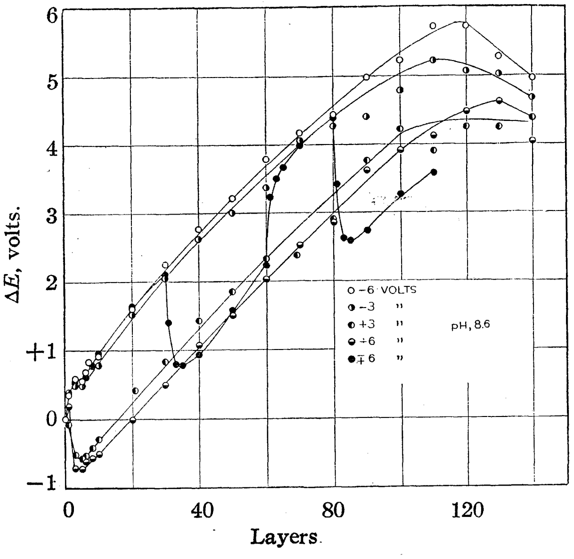

Fig. 1.

Figure 1 shows the change of contact potential with increase in number of layers for X films formed from solution (2), *p*H 8.6, on stainless steel at four different applied voltages, +3, +6, −3, −6 v. It should be noted that in all cases discussed in this paper we call the applied voltage positive when the positive pole of the battery is attached to the slide. The most striking characteristic of these curves is that from layer 5 to layer 90 they are parallel, *i. e.*, have equal slopes. Between 0 and 5 layers, however, the curves obtained with positive and negative applied voltages behave quite differently. The potentials of films made with positive voltages drop sharply, *e. g.*, to −0.6 v. for a voltage of +3, and to −0.7 v. for a voltage of +6. On the other hand, the potentials of films made with negative voltages rise, *e. g.*, to +0.5 for a voltage of +3 v. and to +0.5 for a voltage of +6. This initial behavior gives rise to the separation of the two parallel sets of curves.

The potential curve for a film formed without an applied voltage is not shown in this figure, but a typical curve lies between the positive and negative curves, although not necessarily parallel to them, usually more nearly coinciding at the start with the negative voltage curves and as the number of layers increases crossing over to the positive voltage curves. The curve for ∓6 v. in the figure was obtained by changing the direction of the applied voltage at 30, 60 and 80 layers. From 0–30 layers, with −6 v. applied, the curve is coincident with the −6 v. curve. On reversing the polarity the potential drops rapidly to the +6 v. level and becomes approximately coincident with the +6 v. curve. On changing back to −6 v. the potential rises steeply and this time coincides with the −3 v. curve. On reversing the polarity once more at 80 layers the curve drops below the +6 v. curve but becomes parallel with it at a lower potential level. Similar results have been obtained on substrates containing carbonates instead of borates.

In Fig. 2 are plotted the potential changes due to the X layers alone of the first four curves of Fig. 1, the contribution to the potential of the first five Y layers being in each case eliminated by subtracting from the actual potential the potential observed after the deposition of the last Y layer. The resulting curves are all the same within the experimental variation.

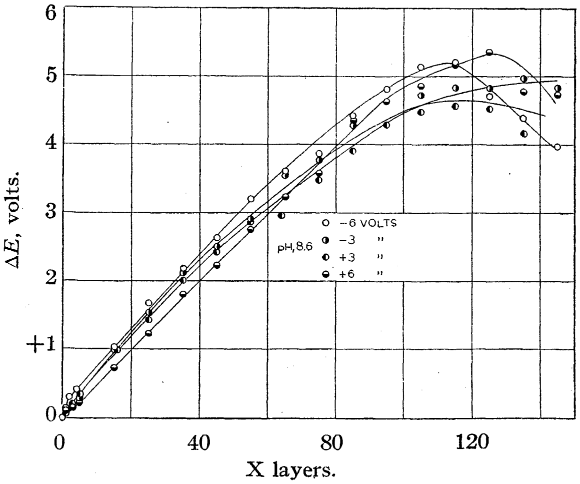

Fig. 2.

The effect of an applied voltage on Y films formed from solution (5), *p*H 7.4, is shown in Fig. 3.

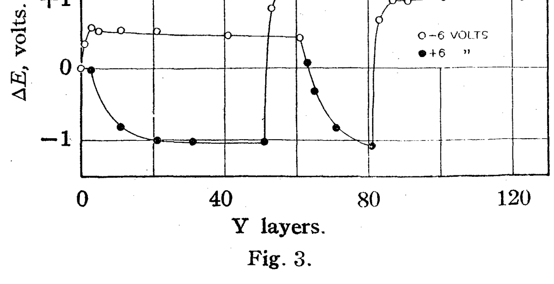

Fig. 3.

With −6 v. the potential rises to a maximum of +0.6 v. at three layers and declines from then on slightly as the thickness of the film increases to 61 layers. At this point the voltage is reversed and the potential drops rapidly to −1.1 v. at 81 layers. Return to the original voltage causes a sudden rise in potential to an approximately constant value of +1.0 v. from 87–123 layers. If we start with +6 v. the sequence is reversed as may be seen from the figure.

The separation of the two curves in Fig. 3 before reversing the polarity of the applied voltage amounts to 1.5 v., which is approximately the magnitude of the separation of the +6 and −6 v. curves for X films in Fig. 1. In both the curves of Fig. 3 there is an over-compensation when the polarity of the applied voltage is changed from +6 to −6 v. This may be a phenomenon similar to the over-compensation observed in Fig. 1 after the last change in polarity from −6 to +6 v. in the ∓6 volt curve.

B. X and Y Films Deposited on Platinum.—Essentially the same results are obtained with a platinum slide. However, in this case it is possible to work with higher applied voltages. In Fig. 4 potential curves are given for two X films deposited on platinum from solution (2), *p*H 8.6.

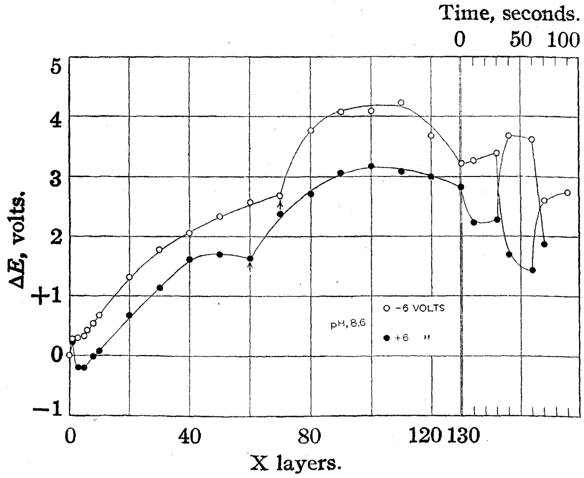

Fig. 4.

The first four layers after the initial layer are Y layers. The curves for +6 and −6 v. are very nearly linear and parallel between 5 and 40 layers. At thicknesses greater than 40 layers the curves cease to be linear but have the same general configuration. The two arrows in the figure indicate points after which a fresh monomolecular layer was spread on the substrate in the tray used for building the films. The increase of slope following renewal of the monomolecular layer in the tray is like what is always observed when there are traces of contaminating ions in the subphase. Apparently such ions slowly diffuse into the surface layer and impair its ability to form X films of high potential.

Figure 5 shows potential–layer curves for four films deposited on platinum from solution (1) at *p*H 10.9 with applied voltages of +6, −6, +22 and −22 v. The curves are in every way very similar to those in Fig. 4 at *p*H 8.6.

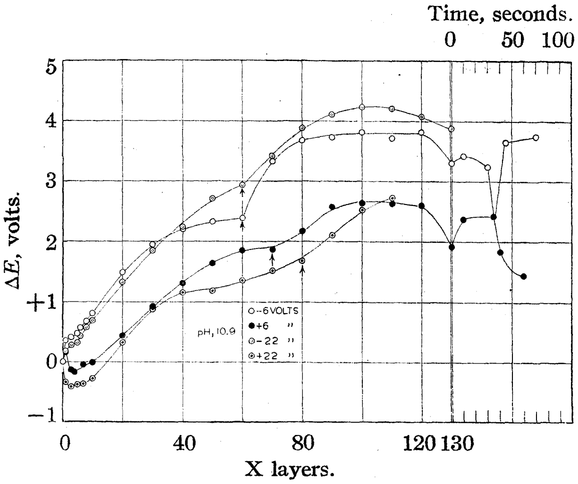

Fig. 5.

In Fig. 6 the six lower curves show the potential change due to the first 55 X layers of the films represented in Figs. 4 and 5. The point for the last Y layer in each case is taken as the origin. The six curves all fall together and the slopes are all the same, within the random variation among the films. This is like the situation shown in Fig. 2 for films on steel slides. In both cases the average slope is 58 mv. per X layer. Thus the increase of potential due to the addition of each successive X layer, at least up to a total of 55 layers, is independent of the metal on which the films are deposited, the *p*H of the substrate, and the sign and magnitude of the applied voltage.

As we have already pointed out, reversal of the applied voltage during the deposition of X or Y layers causes a sudden shift of contact potential from a value on the characteristic potential layer curve for the original voltage to a value on the curve for the reversed voltage. This shift, however, does not depend on the deposition of layers, but can be brought about equally well by reversing the applied voltage and dipping the slide into the substrate through a clean surface free of the monolayer. A few seconds in the liquid with reversed voltage is sufficient to establish the new value. The potential can be changed back and forth from one curve to the other many times in this manner, just as when layers are being deposited. If the applied voltage is not reversed there is practically no change in contact potential when the slide is submerged in the substrate, as the first two points indicate. At the right-hand sides of Figs. 4 and 5 are given what we will call potential–time curves illustrating this phenomenon. In these curves "time" refers to the total length of time that the slides were submerged with the applied voltage.

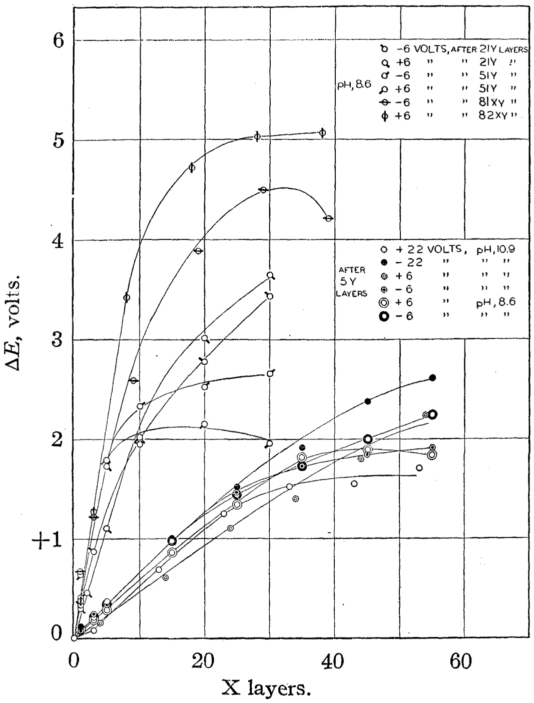

Fig. 6.

Potential–layer curves for Y films on platinum with applied voltages of +6 and −6 v. are shown in Fig. 7. Two different solutions were used: solution (3), *p*H 8.6, with copper; solution (4), *p*H 7.7, without copper. The small initial differences between the two pairs of curves from solutions (3) and (4) are due probably to the difference in *p*H rather than the copper content of the solution, for curves similar to the pair without copper at *p*H 7.7 are obtained at the same *p*H with copper. Comparison of these results with those for steel slides given in Fig. 3 shows that the nature of the underlying metal has only a slight effect on the shapes of potential curves of Y films, the curves for steel becoming horizontal, those for platinum continuing to rise or fall slightly. It is significant that the separation of the two Y film curves at 5 layers for applied voltages of +6 and −6 is about 0.6–0.7 v., which is also the separation of the parallel portions of the curves for X films on platinum obtained with the same applied voltages, shown in Figs. 4 and 5.

Potential–time curves for Y films submerged with an applied voltage are given at the right-hand side of Fig. 7. These are in general similar to those in Figs. 4 and 5 for X layers, which we have already described. The bracketed points are identical, the origin of the time curve having been displaced to the right merely for convenience in plotting.

It may be recalled that during the first dip of a chemically clean slide into a substrate covered with a monolayer, only a single layer is deposited on the slide under all conditions. This layer is formed when the slide is withdrawn from the liquid and seems to be different from either an X or a Y layer. Germer and Storks[9] have shown that the polar groups of this layer are attached to the metal surface of the slide. The effect of an applied voltage on the potential associated with such layers is somewhat different from that observed in the case of X and Y films. If the applied voltage is between +6 and −6 v., the initial layer always causes an increase in the contact potential but by a somewhat smaller amount for positive than for negative voltages. We have

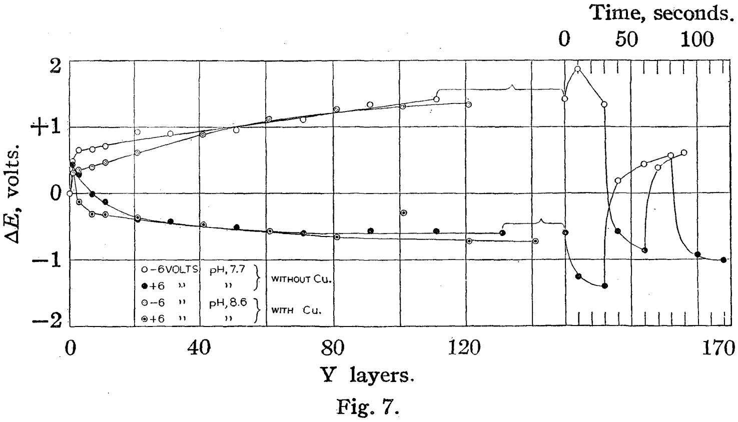

Fig. 7.

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(9) Germer and Storks, *Proc. Natl. Acad. Sci.*, **23**, 390 (1937).

not investigated applied voltages between +6 and +22 v. but at +22 v. the initial layer produced a decrease in contact potential. These effects are apparent in certain of the figures already presented. Presumably there is some critical positive voltage, for any given set of conditions of substrate and temperature, at which the initial layer produces no change in contact potential.

C. Composite Films Deposited on Platinum.—It will be recalled that the addition of X layers to a Y film causes a steep rise of potential to values characteristic of a pure X film of the same total thickness, that the addition of Y layers to an X film causes a sudden drop of potential to the Y film level and that by alternating blocks of X and Y layers it is possible to shift the potential back and forth between the curves for pure X and Y films. The question arises as to the effect of an applied voltage on these phenomena.

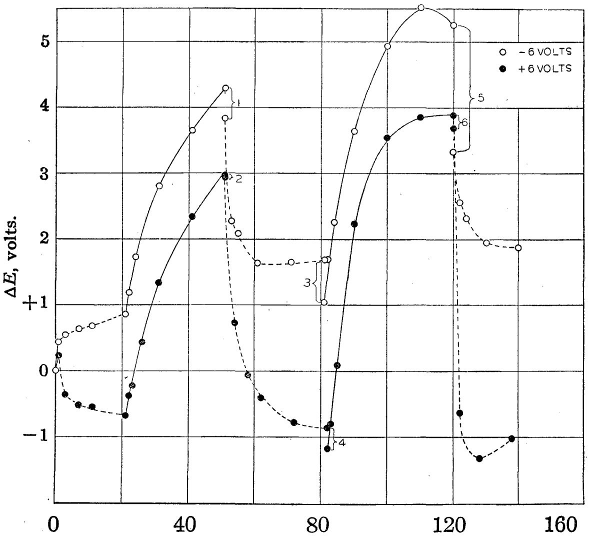

Fig. 8.—- - - - Y layers; ——— X layers.

Two sets of results bearing on this question are given in Figs. 8 and 9. The X layers were obtained from solution (2); the Y layers from solution (4), with copper. Two curves are shown in each figure, one for +6 v. and one for −6 v. In each case Y layers were deposited first and the potential curves obtained were in every way similar to those already described. In the experiment shown in Fig. 8 after 21 Y layers had been laid down X layers were deposited. During this process the potentials rose steeply, the curves for +6 and −6 v. being very nearly parallel. After a total of 51 layers, Y layers were again deposited and the potentials dropped sharply to approximately the values for pure Y films of the same total thickness formed with the corresponding applied voltages. At a total of 81 to 82 layers X layers were added once more. This time the potential rose considerably more steeply and to a higher value than before, after 21 Y layers. Finally, after a total of 120 layers, one more block of Y layers was deposited with much the same results as before. In the experiment shown in Fig. 9, 51 Y layers were deposited before the addition of X layers. The X layers then produced a steeper rise of potential than the first block of X layers at +6 or −6 v. in Fig. 8.

From these results it appears that with an applied voltage the alternation of blocks of X and Y layers is accompanied by a shift of potential back and forth between the curves for pure X and Y films obtained with that voltage. The situation is like that observed in the absence of such a voltage. The rate of increase of potential when X layers are deposited on underlying Y layers is greater the greater the total thickness of the film but it does not depend on the applied voltage. This point is shown by the upper group of curves in Fig. 6. These curves are obtained by plotting the potential against the number of layers for each block of X layers in the experiments shown in Figs. 8 and 9. In each case the origin is the point corresponding to the last preceding Y layer. The curves for a block of X layers added to a Y film of 21 layers are the same for applied voltages of +6 and −6 v., and have an initial slope of 240 mv. per layer. Those for a block of X layers

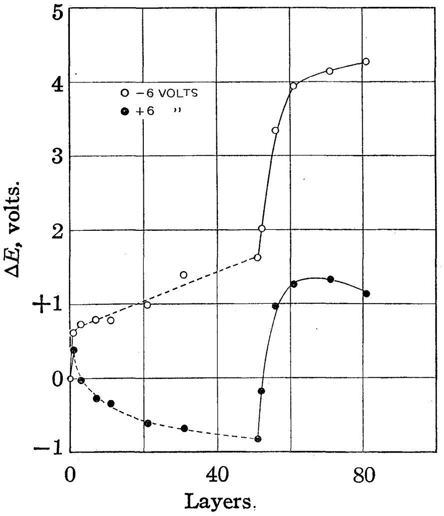

Fig. 9.—- - - - Y layers; ——— X layers.

added to a Y film of 51 layers at +6 and −6 v. have a slope of 360 mv. per layer; those for a block of X layers added to a film of 81 or 82 total layers at +6 and −6 v., a slope of about 430 mv. per layer or greater.

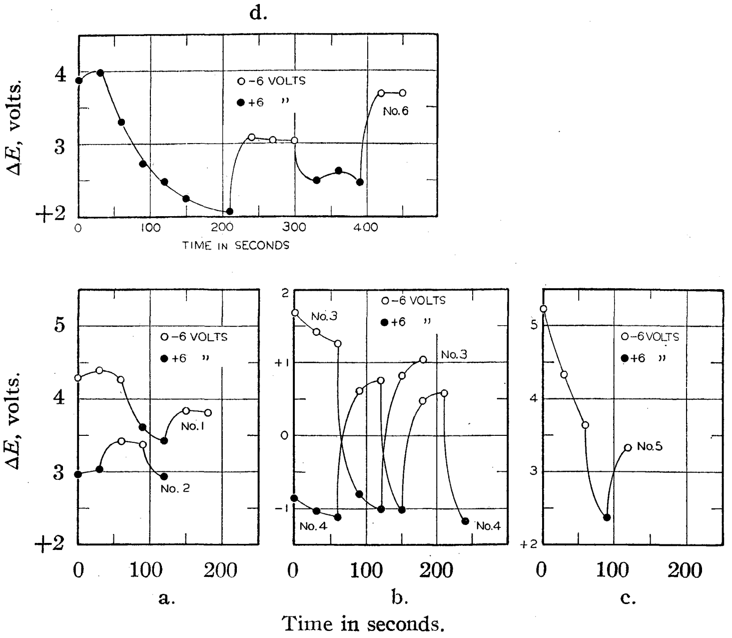

Fig. 10.

The treatment of the films represented in Fig. 8 between the numbered, bracketed points involved submerging them in the substrates with an applied voltage without the deposition of layers. During this treatment the behavior of these composite films is much like pure X or Y films. A complex film always resembles a film made up entirely of the kind of layer last deposited, as shown by Fig. 10.

The composition of the substrates used had no detectable influence in these phenomena.

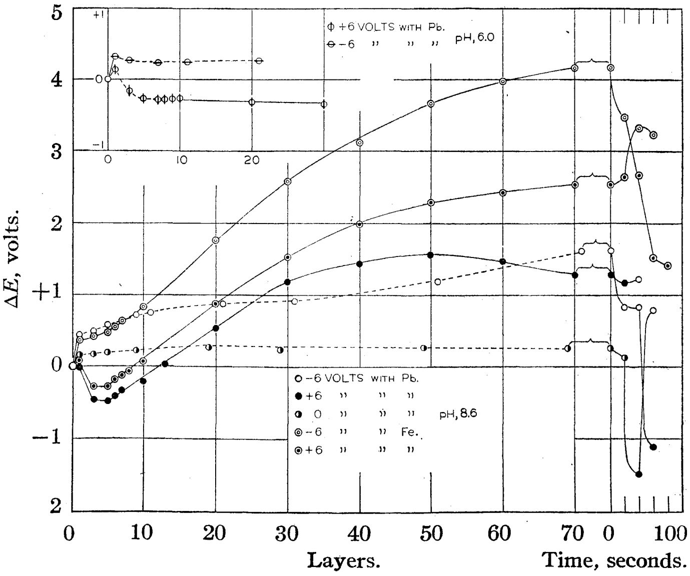

Fig. 11.—- - - - Y layers; ——— X layers.

IV. X and Y Films Deposited from Substrates Containing Iron and Lead

In the last section we described phenomena observed with films deposited on stainless steel and on platinum. Although the major effects were the same for both kinds of film, nevertheless there were certain minor differences: the potentials of simple X films on steel rose more nearly linearly and attained higher values than the potentials of X films on platinum (*cf.* Figs. 2 and 6); the potentials of Y films on steel quickly attained a constant value under the influence of an applied voltage, whereas the potentials of Y films on platinum continued to rise or fall, depending on the direction of the voltage, as the films increased in thickness. Since it is known that the properties of films are greatly affected by certain ions, even at very small concentrations, it seemed possible that these differences were due to the influence of ferric ions arising from the steel slides. In order to test this possibility, X films were deposited on platinum from solution (2) which had been made 1.4 × 10^{-5} molar in ferric chloride. The potential–layer curves of these films, which are given in Fig. 11, are quite similar to those of X films deposited on platinum from solution (2) without iron, except for a somewhat greater slope, the initial slope of these calcium–ferric stearate films being about 80 mv. per layer. Also the potential–time curves when these films are submerged in the subphase with an applied voltage are like those of films without iron. It appears then that no considerable effects are produced by the presence of ferric ions in the concentration we have used, and there must therefore be some other basis for the differences in behavior between films deposited on steel and on platinum.

On the other hand, the properties of films are greatly altered by small concentrations of lead. Langmuir[3] has reported that in the presence of lead acetate X films may be formed at *p*H 6, and that the potentials of such films are like those of Y films. On this basis he has suggested that the *p*H of the subphase is the primary factor which determines film potentials. Other observations of our own show certain curious effects of lead at other values of *p*H and with an applied voltage.

It will be recalled that films deposited from solution (2), *p*H 8.6, are always X films regardless of the applied voltage. However, when this solution was made 2×10^{-6} molar in lead acetate the films deposited on platinum were Y films with applied voltages of 0 and -6 v. and X films with a voltage of $+6$ v. The potential–layer curves of these films are given in Fig. 11. The initial slope of the X film curve (after the deposition of the last underlying Y layer) is about 80 mv. per layer, but the curve flattens out before reaching the higher values characteristic of X films without lead. The two Y film curves are much like those of other Y films formed with the same applied voltages without lead. The potential–time curves of these films, giving the effect of an applied voltage on films submerged without deposition of layers, are those characteristic of the respective types of film, X or Y.

In the insert in Fig. 11 are given the potential–layer curves for two films formed on platinum from a pure sodium acetate buffer of *p*H 6.0 containing lead acetate, 2×10^{-5} molar, with applied voltages of $+6$ and -6 v. Just as at *p*H 8.6, the film obtained with the positive voltage was an X film, the other a Y film. As in the case of the X film reported for *p*H 6 by Langmuir, the potential of this X film failed to rise above the characteristic Y level. It was noted while this film was being deposited that the contact angle as the slide was withdrawn from the liquid was considerably less than 90°, somewhat approaching the angle for a Y film. This accords with the observation based on many cases that large contact angles are associated with high contact potentials; for example, if under conditions otherwise favorable for the production of high potentials in X films, the slide is dipped too rapidly, the contact angle is small and the film fails to develop a high potential.

Curiously enough, when films are formed on stainless steel under these same conditions, *i. e.*, with a sodium acetate buffer of *p*H 5.9–6.0 and a concentration of lead acetate 2×10^{-5} molar, X layers are deposited at both $+6$ and -6 v. The potential of the film formed with the positive voltage becomes constant, after a few layers, at -0.5 v.; that of the film formed with the negative voltage, constant at $+0.4$ v. These potentials are the same as those of Y films obtained with the same applied voltages in the absence of lead.

The question arises whether these X films of low potential are in other respects like X or Y films. In one respect they show a striking difference from any other films, X or Y which we have studied. All other films when made electrodes in a glow discharge or subjected to X-ray treatment develop very large contact potentials, generally exceeding any values developed spontaneously by X films in the course of their formation. These low potential X films containing lead entirely fail to develop high potentials under such treatment. Two such X films of 35 layers, one formed with a positive voltage and having an initial potential of about -0.5 v., the other formed with a negative voltage and having an initial potential of about $+0.4$ v., gave, respectively, potentials of only -0.35 and -0.04 v. after the usual treatment with X-rays. When similar films were subjected to a rectified glow discharge the potentials failed to change by more than a small fraction of a volt, regardless of the direction of the discharge. There appears to be some curious feature in the structure of these lead containing X films which prevents the development of high potentials. Whether or not this may be related to the resistance of the films we will consider later.

V. Potentials Observed during the Early Stages of the Formation of X Films

It already has been observed,[2] when measurements are made after each dip during the early stages of building an X film without an applied voltage, that the potential increases in a stepwise manner, and that the contact angle alternates between 90° and values less than 90°. This effect we have attributed to the condition at the outer surface of the films where at the end of every other dip there must be an unpaired layer, presumably with its polar surface inward. As a result of the succeeding dip each such unpaired layer receives a partner, and we have suggested that during this dip it turns over so that its polar surface comes to face that of the partner, which is inward, an interpretation which accords with the X-ray spacing of the metallic ions, and the hydrophobic character of X films.

This stepwise increase of potential, which appears so significant in relation to events at the surface of the film, becomes blurred and lost as the thickness of the films increases beyond about 15 layers in the case of films formed without an applied voltage, perhaps in consequence of different areas of the same film falling out of step. When, however, the phenomenon is investigated in the case of X films formed with applied voltages, it shows up much more clearly and persists much longer. Certainly it remains undiminished up to thicknesses of 26 layers, which is as far as we have carried the measurements. The applied voltages seem to have a steadying effect on the films.

Two films were studied in this connection, both deposited on platinum from solution (2), *p*H 8.6, one with an applied voltage of +6, the other with −6 v. The results are shown in Fig. 12. X layers were formed after the fifth layer. As a result of the behavior at the addition of the seventh layer the two curves fall out of step. Corresponding to the stepwise increase of potential there was observed initially an alternation of contact angle. The rise of potential occurred with an angle of 90°. During the addition of alternate layers, when the potential failed to rise, or dropped, the angle was always less than 90°. After about 20 layers, this alternation of contact angle disappeared and the angle was always close to 90°, although the stepwise increase of potential continued undiminished.

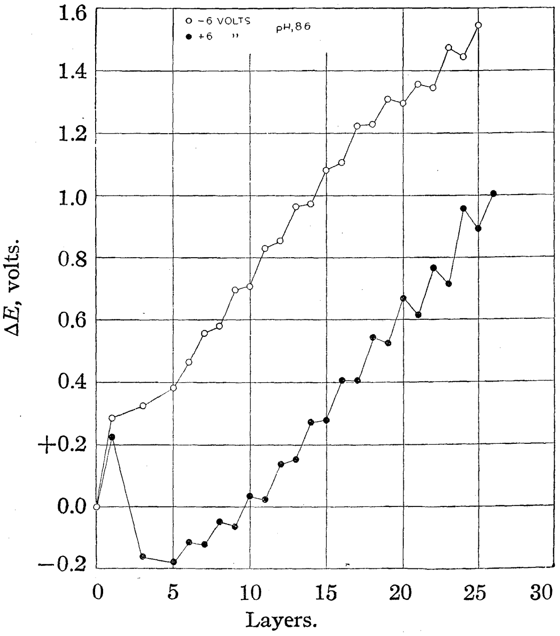

Fig. 12.

The parallel course of the two curves, after X layers begin to be formed, is very striking. It is also striking that the applied voltage has very little effect on the potential of the initial layer, and the separation of the curves for +6 and −6 v. is realized during the deposition of the two pairs of succeeding Y layers.

VI. Impedance of Films and Related Phenomena

We have referred in passing to the possibility of the resistance being different for different types of films. For example, this would be a possible reason for the fact that the large potentials produced by the X-ray treatment or a glow discharge, provided they are due to internal charges in the film, are abolished by dipping the films into aqueous solutions in the case of Y films but not in the case of X films. Again the fact that the lead films deposited at *p*H 6 never develop high potentials might be laid to a relatively low resistance. On the other hand, from attempts to measure voltages of circuits involving films in contact with conducting liquids (section II) it is evident that the d. c. resistance of all types of films must be very high. These considerations point to the importance of direct evidence on the resistance of the films, and in this section we discuss measurements bearing on this question.

An initial attempt was made to measure the impedance of the films by placing a small drop of mercury on the film, with which contact was made with a platinum wire. The binding post of the slide and the platinum wire were connected to the terminals for the unknown on an a. c. bridge and measurements attempted at 800 cycles. The results were not very satisfactory, but it was at once apparent that with high signal voltages the resistance of the films was very low, less than 1 ohm, whereas with signals of 1 or 2 v. the resistance was of the order of megohms. Evidently, the higher signals exceeded the breakdown voltages of the films.

Much more satisfactory measurements were obtained at radio frequencies with a General Radio Co. radio frequency bridge, by using as before the device of placing a small drop of mercury on the surface of the film. Two sets of measurements were made, one at a frequency of 1 megacycle (λ = 300 m.), the other at a frequency of 0.244 megacycle (λ = 1230 m.). The strength of the signal did not exceed a fraction of a volt. At the higher frequency the bridge was balanced by a condenser and power factor dial; at the lower frequency by a condenser and a series resistance. The capacity settings were very sharp; the power factor or resistance settings less so, particularly with the thicker films. A number of different mercury drops were used, but all the results given below were obtained with 3 different drops, all of very nearly the same size, 1.5–1.8 mm. in diameter. The same drop could be rolled from one place to another on a given film or from one film to another. There was considerable variation in the results obtained on the same film with different drops, or with the same drop in different places, due apparently to differences in the size of the drops and in the exact area of contact of a given drop with a film in different places. This variability was much greater for the power factor and resistance settings than for the condenser settings. Results on X and Y films deposited on stainless steel slides are given in Tables I and II. These are expressed in terms of parallel capacity, C_p, and resistance, r_p. Bracketed results were obtained with the same drop. The Y films were copper–barium stearate films formed at *p*H 7.4; the X films, of which the first four layers after the initial layer were Y layers, were calcium stearate films formed at *p*H 9.

TABLE I

Frequency 0.244 × 10^6 (λ = 1320 m.)

	n = No. of layers	C_p, μμ*F*	$r_p \times 10^{-3}$	nC_p	r_p/n
	Y Films (Cu–Ba Stearate, *p*H 7.4)				
No. 1	7	1,680	47	11,800	6,700
	17	775	200	13,200	11,900
	31	515	400	16,000	13,000
No. 3	35	468	470	16,400	13,300
	71	220	1,360	15,600	19,100
No. 2	141	97	22,200	13,700	158,000(?)
			Av.	14,500	
	X Films (Ca Stearate, *p*H 9)				
No. 2	9	1,530	83	13,800	9,200
	13	1,000	213	13,000	16,000
	21	650	504	13,700	24,000
	37	362	1,300	13,400	35,000
	37	423	951	15,700	26,000
	69	218	2,240	15,000	32,000
	133	112	4,550	14,900	34,000
			Av.	14,200	

TABLE II

Frequency 10^6 (λ = 300 m.)

	n = No. of layers	C_p, μμ*F*	$r_p \times 10^{-3}$	nC_p	r_p/n
	Y Films (Cu–Ba Stearate *p*H 7.4)				
No. 2	35	323	117	11,200	3,300
	71	167	415	12,100	5,800
	141	96	2760	13,500	19,000
No. 3	35	570	39	20,000	1,100
	71	260	153	18,500	2,160
	141	133	660	18,800	4,700
			Av.	15,800	
	X Films (Ca Stearate, *p*H 9)				
No. 2	37	395	101	14,600	2,700
	69	224	338	15,500	4,900
	133	114	2080	15,200	11,400
			Av.	15,100	

It is evident from the data in these two tables that there is no significant difference between X and Y films in respect to either capacity or resistance. Other measurements on X films of low potential deposited from a sodium acetate buffer of *p*H 6, 2 × 10^{-5} molar in lead, gave substantially the same results. In both types of film the capacity decreases with thickness, as would be expected, but the capacity multiplied by the number of layers is the same, within the experimental variation, for all the films and at both frequencies, as shown by the fourth column. Since

$$C_p = A\epsilon/4\pi nt \qquad (1)$$

in which ϵ denotes dielectric constant, n number of layers, t the thickness of a layer and A the area of the drop in contact with the film, and since t is the same for X and Y films, this result implies that the dielectric constant is also approximately the same and approximately independent of frequency. The known size of the drops agrees with a value of the dielectric constant of approximately 2.5, or a value close to that obtained for stearate in the bulk phase. Thus on the basis of t = 24 Å. and ϵ = 2.5 the average value of n C_p = 14,500 gives for the radius of the area of contact of the drop with the film a value of 0.72 mm. The over-all diameter of the drops, which should be somewhat more than twice this value, was 1.5–1.8 mm., as well as could be estimated. This estimate of the dielectric constant is of some interest in relation to the question of possible water of hydration in the films.

The fifth columns of both tables give average values of the resistance per layer. Although these values probably do not differ significantly between X and Y films, they show a definite increase with the thickness of the films. Moreover, the values obtained at 1 megacycle are definitely less than those at the lower frequency. It may be noted that a value of 20,000 ohms per layer corresponds to a specific resistance of about 2 × 10^9 ohms, having regard to the size of the drops and the thickness of the layers. The resistance of the films measured at both frequencies is far less than would be judged from the experience of measuring the electromotive force of circuits involving films covered with mercury (section II). Evidently there is a phenomenon of power absorption in the films, increasing with frequency over the range studied.

In view of this, and also to explore the question of the breakdown of the films under high voltages, various d. c. measurements were undertaken. X and Y films of different numbers of layers were covered with a drop of mercury and subjected to a variable measured voltage in series with a galvanometer, which, with the shunt turned on full, gave a deflection of 1 mm. for a current of 4.37 × 10^{-9} ampere. The readings of the galvanometer were followed as the voltage was increased. With films of about 30 layers and thicker there was no observable deflection of the galvanometer until a certain critical breakdown voltage was reached. To determine values of this voltage it was unnecessary to make use of the galvanometer. As soon as it was reached the relatively low resistance voltmeter placed in parallel with the film was automatically shorted and the needle immediately fell to zero. With thinner films there were appreciable currents almost from the start. Values of the breakdown voltage for various X and Y films are given in Table III.

TABLE III

X Films[a] (Ca Stearate, *p*H 9)

Layers	11	15	23	39	71	135
Voltage	0.5	0.5	2.0	9, 10	27, 34	60, 90
Voltage per layer	0.05	0.03	0.09	0.2	0.4	~0.5

Y Films (Cu–Ba Stearate, *p*H 7.4)

Layers	7	17	35	71
Voltage	0.1	0.6	11	29
Voltage per layer	0.01	0.03	0.3	0.4

[a] The first six layers after the initial layer were Y layers.

Apparently the breakdown voltage per layer rises sharply at a thickness of about 20 layers. It may be pointed out that a value of 1 v. per layer corresponds to a field of about five million volts per centimeter. Below the breakdown voltage the resistance of the films is very high. In the thicker films where there is no observable galvanometer deflection up to the breakdown voltage (0.4 v. per layer) the resistance between the drop and the plate must be at least 10^8 ohms per layer, corresponding to a specific resistance of the order of 10^{13} ohms. In thinner films, where there is a deflection of a fraction of a mm. with fields as low as 10^{-2} v. per layer, the resistance cannot be more than about 10^7 ohms per layer. This is suggestive of the bridge measurements, in which the resistances per layer, though all of a different order of magnitude, are found to be less for the thinner films.

In view of these values of the breakdown voltage and the very high d. c. resistances observed below these voltages, it would appear hard to explain the magnitude of the current (of the order of a milliampere or two) observed when films are submerged in aqueous liquids with an applied voltage. The answer to this paradox is found in observations like those we have just described but with a drop of tap water substituted for the mercury drop. In this case, much as in the case of the mercury drop, there is no deflection of the galvanometer until a certain "breakdown" voltage is reached; at this point a current begins to flow which soon shoots up and rises almost vertically as the voltage is further increased. There is, however, the striking difference between these and the results obtained with mercury, that the critical voltage at which the current suddenly rises is very nearly independent of the thickness of the films: for the thin films it is higher, for thick films lower, than with mercury. The behavior of X and Y films[10] is shown in Fig. 13; they are not very different. For both, however, there is a difference in the voltage–current curves depending on the direction of the voltage. When the positive pole of the battery is connected with the slide the curve shoots up more steeply than in the opposite case, in which, though the curve begins to rise at about the same voltage, it does so more slowly until it passes over a kind of shoulder. It seems likely that this difference is due to an electrical asymmetry in the film, probably asso-

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(10) Y films containing lead were not significantly different from Cu–Ba stearate Y films.

ciated with the initial layer (see for example Fig. 9). Below these breakdown voltages, the d. c. resistance of the films covered with water is, so far as we can say, as great as that of films covered with mercury. There is another contrast between the results obtained with water and mercury. With mercury drops the film seems to be ruptured permanently when the breakdown voltage is exceeded, and the resistance remains low. With water drops this is not the case, and subsequent curves obtained with the same drop in the same place on the film are about the same as the initial curve.

This very striking difference between the results obtained with films covered with water and with mercury may be due to a difference in the affinities of the two liquids for the surface, although neither water nor mercury wets the surface. It is suggestive to recall in this connection that Y films which have acquired large contact potentials as a result of a glow discharge completely lose these potentials as a result of being dipped in water, whereas the potentials remain unaffected or are only partially abolished when the films are dipped in mercury, even though several layers may be removed by the process. It is as if the water were able to penetrate the films.

VII. Discussion

In view of the spacing of the metallic ions revealed by the X-ray studies of Holley and Bernstein,[11] it is clear that the basic structure of X and Y films is the same: the layers, apart from the first layer, occur in pairs, with the polar surfaces together. On the other hand, there must be some structural differences to account for the very different properties and behavior of the two kinds of film. As a result of the great effects often produced by very small changes in the character of the substrate it seems likely that these differences are closely connected with the ionic composition of the films. If we accept the surface electrification hypothesis it would be such differences which determine whether or not the films acquire a charge when withdrawn from the substrate rather than the fact that the layers are deposited singly or in pairs. This accords with the fact that lead X films formed at *p*H 6 do not develop high potentials although the layers are deposited only one at each dip. Evidently, however, it is not the character of the whole film, but only that of the outermost layer or two which is the determining factor, since when one or two X layers are deposited on a Y film it develops the potential characteristic of an X film of the same total thickness and conversely when one or two Y layers are deposited on an X film. Moreover, when layers are successively removed from composite films the films appear to retrace their past history in respect to potential. We have seen that the characteristic potentials of all films disappear while the films are in contact with various polar liquids, but redevelop when the films are withdrawn from the liquids. Evidently the original surface charge is restored by the work of separation from the liquid, and the sign and magnitude of the charge depend on the character of the surface of the film rather than on the nature of the liquid, *e. g.*, whether chloroform, water or mercury.

On the other hand, certain other phenomena clearly depend not on the nature of the surface layer but upon that of the whole film, for example, the optical thickness of the films, the temperatures at which they soften and the change of optical thickness which accompanies softening. In all these respects X and Y films differ, and the experiments show that X augmented Y films and Y depressed X films behave like simple Y and X films, respectively.

It seems probable that, unlike the "natural" potentials of the films, potentials produced by the X-ray treatment or a glow discharge are due to the development of an internal charge in the body of the films as a result of the penetration of ions into the films. Otherwise it is hard to understand how these potentials, whether positive or negative, can persist as they do after X or Y films are dipped into mercury and several layers are removed. Even on the basis of this view, however, certain points remain obscure. Why are these potentials, whether positive or negative, abolished in the case of Y, but not of X, films as a result of dipping the films into water and chloroform? By what mechanism are they neutralized while the films are in contact with polar liquids, supposing that the internal charge is not removed? These phenomena, together with the curious behavior of the lead films, which fail to develop large potentials under any conditions, remain a difficult problem.

Consider now the experiments on the effect of a voltage applied between the slide and the liquid subphase while films are being deposited. The

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(11) Holley and Bernstein, *Phys. Rev.*, **52**, 525 (1937).

data show clearly that for all types of film an applied voltage does not affect the shape of the potential–layer curves (except for the first three layers of simple X and Y films, as in Fig. 12), but simply serves to displace the curves by a constant amount up or down depending on its direction. The absolute magnitude of the shift is nearly if not quite independent of the magnitude of the applied voltage, as well as of the type of film. From this it appears, in terms of the surface charge hypothesis, that when the films, of whatever type, are withdrawn from the liquid they acquire the same charge as in the absence of the applied voltage, but that in addition to this there is superposed an effect due to the voltage. This effect might be interpreted as due either to a polarization, possibly involving a reorientation of an underlying layer, or to the accumulation of a subsidiary charge on the surface of the film. In accordance with the latter interpretation we may think of the film as a condenser of capacity given by equation (1). Then, under the influence of the applied voltage V_f effective across the film, the film will accumulate a charge per unit area given by

$$\sigma' = \epsilon\, V/4\pi nt$$

This charge, over and above the charge σ acquired by the film independently of the applied voltage at the time it is withdrawn from the liquid, would account for the displacement of the potential–layer curve by an amount V, without its being otherwise altered. But on either interpretation it is the charge σ which determines the character of the potential–layer curves, and it follows, somewhat unexpectedly, that σ is wholly unaffected by the applied voltage.

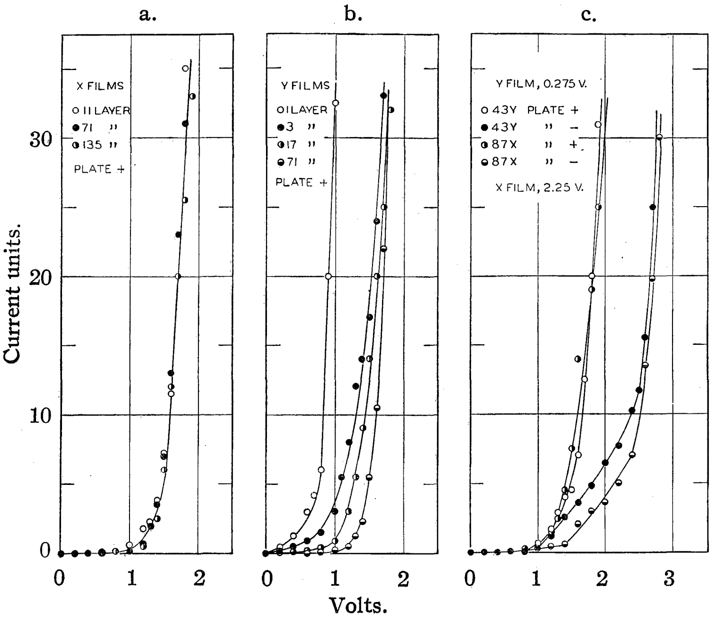

Fig. 13.—Voltage–current curves of X and Y films in contact with water.

It now remains to consider why the up or down displacement of the curves is independent of the magnitude of the applied voltage. An explanation of this is to be found in the results represented in Fig. 13. Evidently when a voltage V is applied between a point in the liquid and the submerged metal slide a voltage V_f at once begins to build up across the film. However, it may be seen from Fig. 13 that before V_f attains the value V (if V be sufficiently high) the critical point will be reached when the resistance of the film suddenly drops, and a current begins to flow. Equilibrium is then established when the current reaches such a value that the resulting voltage drop in the liquid is equal to $V - V_f$. Since after the attainment of the critical voltage, the current through the film rises sharply (see Fig. 13) it is evident that V_f should be very nearly independent of V, as it is found to be. This explanation has nothing to do with the nature of the reversible "breakdown" associated with the sudden rise of current in the film in contact with the liquid when the applied voltage reaches a certain value, but depends simply on the fact that such a process occurs.

Summary

Voltage measurements of circuits involving X and Y films in contact with polar liquids indicate that the potentials of the films are neutralized by contact with the liquids, although they reappear after the films are separated from the liquids. Similar measurements of films in contact with benzene show that in this case the potentials are not neutralized.

Contact potentials induced in X and Y films by exposure to a glow discharge are not abolished as a result of dipping the films in mercury even when several layers of the film are removed, but are abolished in the case of Y films by contact with water and chloroform.

The effect of applying an arbitrary voltage between the slide and the liquid while films are being

built is to displace the potential–layer curves up or down without altering their shape subsequent to the first three layers. The absolute magnitude of the displacement is independent of the type of film and of the magnitude of the applied voltage but the direction of displacement, up or down, depends upon the direction of the voltage. Similar shifts of potential are produced when films are immersed in the liquids under the influence of an applied voltage without the deposition of layers.

X or Y films containing lead fail to develop large contact potentials under all conditions and show certain unusual properties.

Impedance measurements at frequencies of 1 and 0.244 megacycles show no significant difference between X and Y films. They indicate a dielectric constant of about 2.5 and give evidence of power absorption. Breakdown voltages of X and Y films are the same. Breakdown voltages of films in contact with mercury increase with the thickness of the films, and correspond to fields of the order of 10^6 v./cm. Apparent breakdown voltages of films in contact with water are nearly independent of thickness and depend on the direction in which the voltage is applied. The specific d. c. resistance of both X and Y films is of the order of 10^{13} ohms.

CAMBRIDGE, MASS. RECEIVED JUNE 4, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF MICHIGAN]

The Volumetric Oxidation of Iodide and Bromide by Periodic Acid[1]

BY HOBART H. WILLARD AND LUCIEN H. GREATHOUSE

Periodic acid and periodates of the alkalies are powerful oxidizing agents in dilute aqueous solution and usually stable enough for use in volumetric analysis.

Reactions of periodates as oxidizing agents have been investigated from an early date.[2] The reaction between periodate and iodide with excess of the former

$$KI + 3KIO_4 = 4KIO_3$$

is of particular interest.[3]

The excess of periodate may be determined accurately in the presence of iodate by titrating with standard arsenite the iodine liberated from iodide in neutral solution, thus

$$KIO_4 + 2KI + 4H_3BO_3 = KIO_3 + I_2 + K_2B_4O_7 + 6H_2O$$

This principle was first stated by Péchard[4a] but the method was developed by Müller and his associates.[4b] For this purpose the solution is buffered preferably with boric acid–borax mixture.

Titrations based on these reactions have been used recently to identify polyhydric alcohols.[5]

Periodates Suitable as Reagents

Potassium Periodates.—The metaperiodate, KIO_4, commercially available, contained 79.51% of I_2O_7 compared with the theoretical value of 79.52% and was free from iodate by test with silver nitrate.[2c,6] It may be used as a primary standard for iodimetry.

The solubility of potassium metaperiodate in water was found to be as follows, in grams per 100 ml. of the saturated solutions

0°	25°	35°	45°	55°	65°
0.1546	0.5112	0.785	1.190	1.75	2.51

The specific gravity at 25° of the solution saturated at 25° was 1.00125. If the solubility at 25° as determined by Hill[7] is recalculated to grams per 100 ml. a value of 0.5106 is obtained.

The metaperiodate decomposes in solution with a strong odor of ozone. Dipotassium paraperiodate, $K_2H_3IO_6$, is much more soluble than the meta salt and more stable in solution and hence better suited for standard solutions.

Sodium Periodates.—The paraperiodates precipitated by the reaction of chlorine on iodate in alkaline solution vary in composition between $Na_3H_2IO_6$ and $Na_2H_3IO_6$.[7]

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[1] From a dissertation presented in partial fulfilment of the requirements for the degree of doctor of philosophy at the University of Michigan by Lucien H. Greathouse in 1917.

[2] (a) Ammermüller and Magnus, *Ann.*, **11**, 18–24 (1834); (b) Bengieser, *ibid.*, **17**, 254–260 (1836); (c) Langlois, *ibid.*, **83**, 153–175 (1852); (d) Selmons, *Chem. Centr.*, [3] **18**, 502–504 (1887); (e) Grützner, *Arch. Pharm.*, **234**, 634–640 (1896); (f) Péchard, *Compt. rend.*, **128**, 1101 (1899); (g) Brunner and Mellet, *J. prakt. Chem.*, [2] **77**, 33–42 (1908); (h) Willard and Greathouse, THIS JOURNAL, **39**, 2366 (1917).

[3] (a) Phillip, *Bull. soc. chim.*, [2] **12**, 350 (1869); (b) Péchard, *Compt. rend.*, **130**, 1705 (1900); (c) Garzarolli-Thurnlackh, *Monatsh.*, **22**, 955–975 (1901); (d) Müller, *Z. Elektrochem.*, **9**, 584–594, 707–716 (1903); (e) Bray, *Z. physik. Chem.*, **54**, 463–497 (1906); (f) Auger, *Bull. soc. chim.*, [4] **11**, 731 (1912).

[4] (a) Péchard, *Compt. rend.*, **128**, 1453 (1899); (b) Müller and Friedberger, *Ber.*, **35**, 2652 (1902); and Jacob, *Z. anorg. Chem.*, **82**, 308–314 (1913); and Weglin, *Z. anal. Chem.*, **52**, 755 (1913).

[5] (a) Malaprade, *Compt. rend.*, **186**, 382 (1938); *Bull. soc. chim.*, [4] **43**, 683–696 (1928); *ibid.*, [5] **1**, 833–852 (1934); (b) Fleury and Lange, *J. pharm. chim.*, [8] **17**, 107–113, 196–208, 313–326, 409–427 (1933); (c) Fleury, *ibid.*, [8] **18**, 476–481 (1933); (d) Rappaport, Reifer and Weinmann, *Mikrochim. Acta*, **1**, 290–299 (1937); Rappaport and Reifer, *ibid.*, **2**, 273 (1937).

[6] Willard and Thompson, THIS JOURNAL, **56**, 1827 (1934).

[7] Hill, *ibid.*, **50**, 2678 (1928).

The precipitate is very insoluble in excess of sodium hydroxide. The metaperiodate, $NaIO_4$, is readily soluble in water and is therefore more useful as a reagent. Analysis of a sample prepared in this work gave 85.61% of I_2O_7 as compared with the theoretical value of 85.59%. It is prepared by dissolving the paraperiodate in dilute nitric acid and recrystallizing.

Standard Solutions.—Standard arsenite was prepared in the usual way from very pure arsenious oxide and brought to a *p*H of approximately 7 by buffering with sodium bicarbonate saturated with carbon dioxide.

Standard tenth normal potassium paraperiodate was prepared by dissolving the meta salt in hot water and adding a 10% excess of potassium hydroxide.

The rates of decomposition of metaperiodate and paraperiodate in 0.05 *M* solution at about 30° are shown in Fig. 1. The sodium salt was used to obtain a metaperiodate solution of this strength. Although the paraperiodate solution gave a faint odor of ozone its loss in strength shown in Fig. 1 was probably due also to a slow precipitation by impurities extracted from the glass container by the alkaline solution.

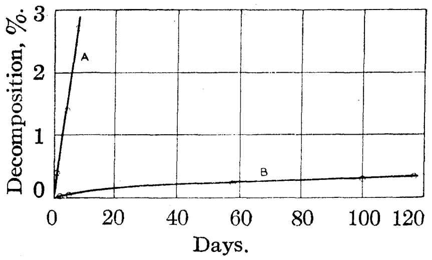

Fig. 1.—Decomposition of 0.05 *M* periodate solutions at 30°: A, sodium metaperiodate; B, dipotassium paraperiodate.

Standard solutions of periodic acid or of sodium metaperiodate acidified with one equivalent of sulfuric acid were found exceptionally stable. One such solution changed less than 0.1% after standing four months in the light and then two years in the dark. These acid solutions were not used because the reagents required were not commercially available at the time.

Determination of Iodide

If a neutral solution of iodide is oxidized to iodate by the addition of an excess of periodate, the latter can then be determined by titration with arsenite as already described. Since iodine is first liberated and subsequently oxidized the reaction must be carried out in a closed vessel.

Standard potassium iodide solution was prepared from a pure salt which had been recrystallized until free from chloride, bromide, and iodate. It was kept in an atmosphere of hydrogen and was standardized gravimetrically by precipitation with silver nitrate, with the following results:

Grams of iodine *in vacuo*, per gram of solution in air, 0.0125961 0.0125965 0.0125966 Av. 0.0125964

Influence of Temperature on the Reaction.—Experiments were made at 25, 35, 45 and 55°, following the reaction of 0.0025 mole of potassium iodide with 0.0075 mole of potassium paraperiodate in a volume of 250 ml. The standard periodate and iodide solutions were brought separately to the selected temperature, then mixed and diluted to volume quickly in a volumetric flask immersed in a thermostat at the same temperature. At suitable intervals 25-ml. samples were withdrawn, treated with borax and boric acid, then with an excess of potassium iodide solution, and titrated with 0.1 *N* arsenious acid. This titration gave residual periodate plus the oxidizing equivalent of such iodine as had been liberated but not yet oxidized to iodate. A second experiment was made at 25° but diluted to 500 ml. and 50-ml. samples withdrawn.

The results plotted in Fig. 2 indicated that at higher temperatures and with an excess of periodate the reaction would be rapid.

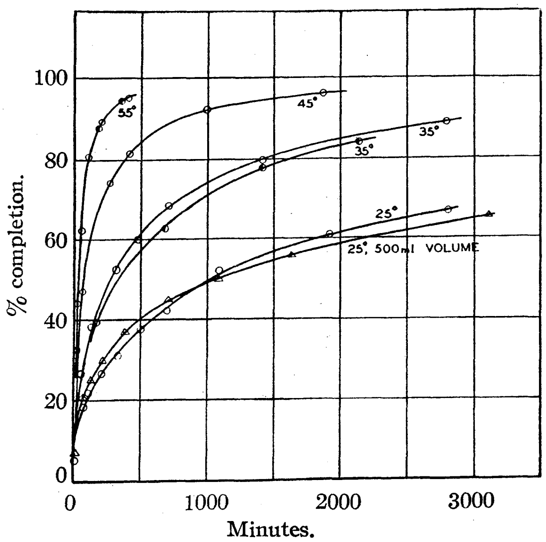

Fig. 2.—Effect of temperature on the reaction $3K_2H_3IO_6 + KI = 4KIO_3 + 3KOH + 3H_2O$: ◐, duplicate experiment; △, dilution experiment at 25°.

Determination of Iodide Alone.—One general procedure was used. Fifty milliliters of 0.1 *N* paraperiodate was introduced into a glass-stoppered 250-ml. Erlenmeyer flask. A flat-ended glass vial, containing 3 to 8 ml. of iodide solution, was lowered into the flask and placed upright on the bottom. Thus the two solutions were kept separate until the whole system was heated to the selected temperature. No other water was added except where noted. The flask was then stoppered and tilted to upset the vial and mix the solutions. After periods as noted in the tables, the reaction mixtures were cooled and excess periodate titrated.

In determinations 1 to 7 of Table I the oxidation was conducted at 70 to 80° and was complete in thirty-five to forty minutes when a small excess of periodate was used. In determinations 8 to 22 the reaction was conducted at 96 to 98° which reduced this period to about twenty minutes. After the iodine liberated at first had disappeared, the solution was neutralized with an excess of boric acid, the flask being opened and closed quickly.

In the determinations shown in Table I the factors of time, temperature and excess of periodate were varied to determine the limits within which the reaction would be

TABLE I

DETERMINATION OF IODIDE

No.	Iodine as KI taken, g.	Excess 0.1 N $K_2H_3IO_6$, ml.	Volume during oxidation, ml.	Time heated, min.	Error, mg. of iodine
1	0.0727	14.30	60	10	−0.2
2	.0767	12.41	60	7	.0
3	.0789	11.33	60	5	+ .2
4	.1004	1.16	60	30	− .1
5	.1007	1.06	60	40	− .2
6	.0964	3.12	60	35	− .2
7	.0977	2.48	60	30	.0
8	.1009	0.95	60	40	− .1
9	.1008	.96	60	40	+ .1
10	.1002	.31	60	70	.0
11	.0998	1.51	60	22	.0
12	.0996	1.64	60	21	.0
13	.0988	3.22	100	15	+ .2
14	.0985	3.38	150	15	+ .2
15	.0985	3.38	200	15	.0
16	.0987	3.28	250	15	.0
17	.0785	12.78	250	8	− .1
18	.0850	9.71	250	8	.0
19	.0923	6.33	250	8	−1.1
20	.0704	16.65	250	5	0.0
21	.0760	14.00	250	5	− .6
22	.0831	10.63	250	5	−1.7

complete. In determinations 13 to 22 the volume was increased and the time allowed for reaction progressively decreased as the excess periodate varied, until in determinations 19, 21 and 22 the reaction was incomplete.

Determination of Iodide in Presence of Bromide.—When bromide was also present, slight liberation of bromine occurred which did not affect the accuracy of the iodine determination if no bromine was lost.

The presence of bromide accelerated the reaction so that the addition of boric acid could be omitted. This avoided the procedure of opening the flask during the reaction, which would have permitted loss of bromine. In Table II, in determinations 1 and 2, 50 ml. of 0.1 N $K_2H_3IO_6$ was used but in the others, 25 ml. of 0.1 N $K_2H_3IO_6$ and 75 ml. of water were added.

TABLE II

DETERMINATION OF IODIDE IN PRESENCE OF BROMIDE

No.	Iodine taken, g.	KBr, g.	Excess $K_2H_3IO_6$, ml.	Time heated, minutes	Error, mg.
1	0.0982	0.6	1.88	15	0.0
2	.0965	.6	3.13	10	− .1
3	.0380	5.0	6.25	3	.0
4	.0382	5.0	6.15	3	+ .1
5	.0386	5.0	5.95	3	.0
6	.0415	5.0	4.69	3	− .1

The determination of small percentages of iodide in mixtures with bromides is rapid and accurate.

Recommended procedure: Measure into an Erlenmeyer flask with a ground-glass stopper standard 0.1 N paraperiodate in 10 to 25% excess over that required to oxidize the iodide in the sample to iodate. Dissolve the sample in 5–10 ml. of water in a small vial with a flat end, and set this upright within the flask. Place the flask in a steam-bath, heat to 97–98°, stopper it and upset the vial to mix the solutions.

After the disappearance of iodine, which should occur in less than five minutes, continue heating for ten minutes, then loosen the stopper, cool, and add an excess of powdered boric acid. If the iodine color reappears, replace the stopper, and return to the steam-bath for ten minutes. Any iodine color persisting either before or after the boric acid addition indicates insufficient periodate, in which case the determination will not be accurate.

When bromide is present, the reaction is faster. The addition of boric acid during the reaction is not required, and should be delayed until the solution, after reacting for fifteen minutes, has been cooled. With higher bromide concentrations, a faint bromine color may appear slowly, differing, however, from the iodine color which appears at once when oxidation is incomplete. After completion of oxidation, cool, add an excess of boric acid, then an excess of 5% potassium iodide solution, about 1 ml. for each milliliter of unreacted 0.1 N periodate being sufficient to prevent volatilization of iodine. Titrate the iodine liberated with standard arsenite. Each milliliter of 0.1 N periodate is equivalent to 0.0021153 g. of iodine.

Determination of Bromide

Periodic acid oxidizes bromide in acid solution to bromine. The reaction is complete if the bromine is removed by bubbling air through the solution. The excess periodate may then be titrated to determine bromide.

A standard solution by weight was prepared from potassium bromide purified for atomic weight work. It was standardized by precipitation as silver bromide with the following results:

Grams of bromine *in vacuo*, per gram of solution in air
0.0157740 0.0157731 0.0157770 0.0157730 Av. 0.0157743

Either the standard paraperiodate solution, as in the iodine determination, or the acidified sodium periodate solution described earlier, may be used. There are also required a 5 N sulfuric acid solution, which must be free of reducing reagents, a starch iodide indicator, and Schiff fuchsine indicator for bromine as described by Guareschi.[8]

The reaction was conducted in an Erlenmeyer flask with a ground-glass stopper, through which passed one tube connected to an aspirator and another down into the flask so that air could be drawn through the reaction mixture from several fine openings. A U-tube containing the indicator solution was connected in the suction line. The fuchsine indicator must be used instead of starch iodide if chlorine is present.

Recommended Procedure.—If iodide or other constituents oxidizable by periodate in neutral solution are present, first determine the amount of the standard reagent required for this on a separate aliquot of the solution to be analyzed. To another aliquot, placed in the reaction flask, add this amount of standard periodate, plus a volume of 10 to 35% in excess of that required for oxidation of the bromide. If much iodide is present, keep the two solutions separate until

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(8) Guareschi, *Z. anal. Chem.*, **52**, 451 (1913).

heated, then mix and oxidize as described before, which usually requires ten to fifteen minutes. Dilute to 100 ml. and acidify with 20 ml. of 5 *N* sulfuric acid in excess of that equivalent to the combined base in the bromide plus that in the standard periodate used. Heat and draw air through the solution until the bromine color disappears, then place the indicator solution in the U tube and repeat until no test for bromine is obtained. Cool, neutralize with 20 ml. of 5 *N* sodium carbonate, buffer the solution and titrate the excess of periodate.

TABLE III

DETERMINATION OF BROMIDE

No.	Bromine taken, g.	0.2 *M* KCl, ml.	Excess 0.1 *N* $K_2H_3IO_6$, ml.	5 *N* H_2SO_4, ml.	Time of heating, min.	Error bromine, mg.
1	0.3599		4.56	25	45	−0.1
2	.3600		4.54	20	55	.0
3	.3607		4.45	20	65	+ .1
4	.3401		7.48	10	90	− .6
5	.3038		11.86	10	95	+ .2
6	.2560		17.84	10	80	+ .3
7	.2001		24.84	10	55	+ .3
8[a]	.2211		22.25	18.5	150	.0
9	.3633	5	4.42	10	100	− .5
10	.3632	5	4.35	10	105	− .1
11	.3638	5	4.30	10	120	.0
12	.3621	10	4.33	10	120	+1.2
13	.3617	25	4.15	10	120	+3.1

[a] Reaction volume was 100 ml. except 300 ml. in No. 8.

Each milliliter of 0.1 *N* periodate is equivalent to 0.00792 g. of bromine.

Any considerable amount of chloride interferes but, as shown in the results of Table III, by using low acidity and a prolonged bubbling, separation from a millimole or less of chloride may be effected.

Summary

1. Potassium metaperiodate, KIO_4, can be purified readily so as to have the theoretical composition and may be used as a primary standard in iodimetry.

2. Dipotassium paraperiodate in a slightly alkaline solution, and sodium metaperiodate acidified with sulfuric acid are both stable volumetric solutions, the latter showing remarkable permanency. Metaperiodates in neutral solution decompose with noticeable rapidity.

3. Iodide may be determined in the presence of bromide, chloride, and other substances not oxidized by neutral periodate solution by oxidation to iodate with standard periodate, and titration of the excess of the latter with arsenious acid. Conditions required for a rapid reaction are shown.

4. Bromide may be determined in presence of small amounts of chloride by oxidation to bromine with standard periodate in slightly acid solution, expulsion of the bromine, and titration of the excess periodate.

ANN ARBOR, MICHIGAN RECEIVED SEPTEMBER 6, 1938

[CONTRIBUTION FROM FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

The Electron Diffraction Investigation of the Molecular Structures of Hydrogen Disulfide, Dimethyl Disulfide and Sulfur Dichloride

BY D. P. STEVENSON AND J. Y. BEACH[1]

We have investigated the structure of the gas molecules of hydrogen disulfide, dimethyl disulfide and sulfur dichloride by the electron diffraction method. The apparatus has been described elsewhere.[2] The electron wave length was 0.0590 Å., determined from transmission pictures of gold foil (*a* = 4.070 Å.). The distance from the gas nozzle to the photographic plate was 12.19 cm. The photographs were interpreted by the visual method.[3] The radial distribution method[4] and a modification[5] of the radial distribution method also were used.

Hydrogen Disulfide.—The hydrogen disulfide was prepared according to Vanino.[6] The compound was clear and colorless. The photographs were taken within an hour after the compound was made. After standing for several days at room temperature the hydrogen disulfide turned yellow. A few semiquantitative measurements of the vapor

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(1) National Research Council Fellow in Chemistry.

(2) Beach and Stevenson, *J. Chem. Phys.*, **6**, 75 (1938).

(3) Pauling and Brockway, *ibid.*, **2**, 867 (1934).

(4) Pauling and Brockway, THIS JOURNAL, **57**, 2684 (1935).

(5) Schomaker, to be published.

(6) Vanino, "Handbuch der präparative Chemie," Vol. I, 1925, p. 80.

pressure agreed with the values reported by Butler and Maass.[7] This eliminated H_2S as a possible impurity. The only other possible impurity, hydrogen trisulfide, melts at −52°. As the melting point of our preparations was less than −80° (the melting point of hydrogen disulfide is −89°),[6] not much hydrogen trisulfide could have been present. The photographs were taken with the sample at about 33°. Even if some hydrogen trisulfide had been present in our sample, because of its low vapor pressure the amount of it in the vapor phase would have been small as compared with the amount of hydrogen disulfide.

The photographs of hydrogen disulfide show six evenly spaced maxima and minima. The intensities of the maxima drop off uniformly from the first to the sixth. The observed values of s [$s_{\text{obsd.}} = (4\pi \sin \Theta/2)/\lambda$] for the maxima and minima and the visually estimated intensities of the maxima are tabulated in Table I.

TABLE I

HYDROGEN DISULFIDE

Max.	Min.	I	$s_{\text{obsd.}}$	$s_{\text{calcd.}}$	$s_{\text{calcd.}}/s_{\text{obsd.}}$
1		10	3.963	3.68	0.929
	2		5.730	5.17	.902
2		9	6.869	6.72	.978
	3		8.807	8.31	.944
3		8	9.932	9.81	.988
	4		11.822	11.39	.963
4		6	12.922	12.80	.991
	5		14.742	14.28	.969
5		4	15.898	15.76	.991
	6		17.631	17.37	.985
6		2	18.927	18.90	.999
Average (1st max., 2nd min. omitted)					0.979

Results: S–S = 2.04 Å.
H–S = 1.33 Å. (assumed)
H–S–S = 95° (assumed)

The radial distribution function obtained by treating these data by the ordinary distribution method[4] is shown in Fig. 1, curve A. The modified radial distribution function[5] is shown in Fig. 1, curve B. The ordinary radial distribution function shows a peak at 2.04 Å. representing the sulfur–sulfur distance. The modified radial distribution function shows a sulfur–sulfur peak at 2.06 Å. and a small peak at 1.36 Å., at about the expected hydrogen–sulfur distance. Knowing the sulfur–sulfur distance to be about 2.05 Å., we assume 1.33/2.08 for the ratio of the hydrogen–sulfur distance to the sulfur–sulfur distance in calculating the theoretical curve. 2.08 Å. is the radius table[8] value for the sulfur–sulfur single bond distance. The H–S–S angle was assumed to be 95°. The theoretical curve is shown in Fig. 2, curve A. The effect of the hydrogen–sulfur terms on the theoretical intensity curve is negligible. Accordingly no attempt was made to locate the hydrogen atoms. Quantitative comparison of the photographs with the theoretical intensity curve is made in Table I. The sulfur–sulfur distance is 2.04 Å. Averaging the three sulfur distances, 2.04, 2.06 and 2.04 Å., obtained from the radial distribution functions and the visual method gives a final value of 2.05 ± 0.02 Å. for the sulfur–sulfur distance in hydrogen disulfide.

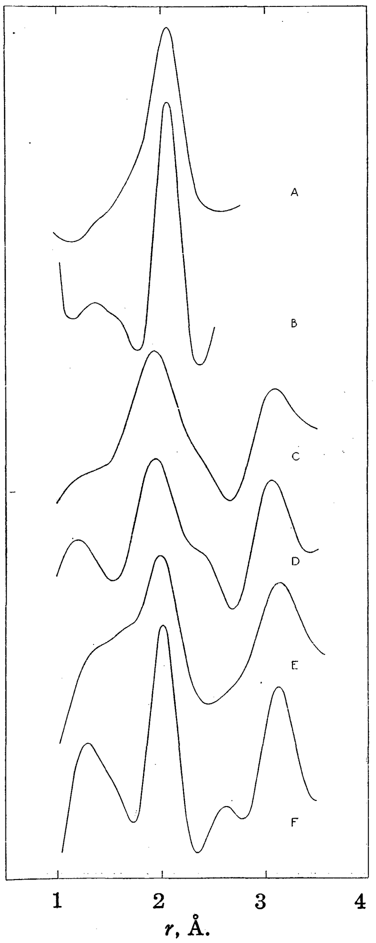

Fig. 1.—Radial distribution functions: Curve A, ordinary for H_2S_2; Curve B, modified for H_2S_2; Curve C, ordinary for $(CH_3)_2S_2$; Curve D, modified for $(CH_3)_2S_2$; Curve E, ordinary for SCl_2; Curve F, modified for SCl_2.

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(7) Butler and Maass, THIS JOURNAL, **52**, 2184 (1930).

(8) Pauling and Brockway, *ibid.*, **59**, 1223 (1937).

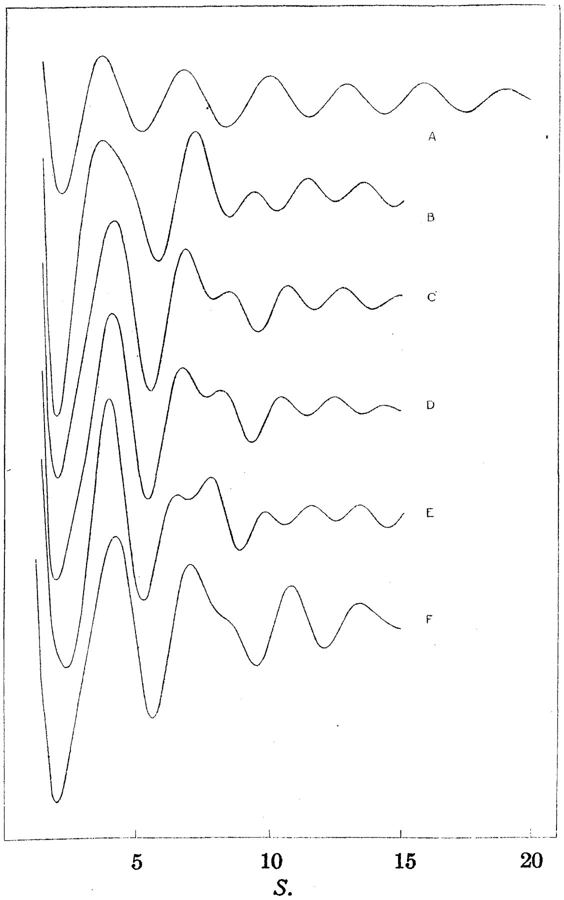

Fig. 2.—Theoretical intensity curves for H_2S_2 and $(CH_3)_2S_2$: Curve A, H_2S_2; Curve B, $[(CH_3)_2S_2]$, $\rho = 2.08/1.81$, $\alpha = 95°$; Curve C, $\rho = 2.08/1.81$, $\alpha = 105°$; Curve D, $\rho = 2.08/1.81$, $\alpha = 110°$; Curve E, $\rho = 2.08/1.81$, $\alpha = 120°$; Curve F, $\rho = 2.00/1.81$, $\alpha = 105°$.

Dimethyl Disulfide.—The method of Price and Twiss[9] for preparing disulfides was modified slightly according to the suggestions of Westlake.[10] In order to obtain the dimethyl disulfide one mole of methyl iodide and one mole of sodium thiosulfate were refluxed for an hour in an equal volume mixture of methyl alcohol and water. After cooling, potassium triiodide solution was added slowly with shaking until a faint iodine color remained for three minutes after addition. (Heat was applied near the end of the reaction in order to increase the rate.) Sodium sulfite was added to remove the excess iodine and the dimethyl disulfide was distilled out of the mixture along with water, methyl alcohol and some methyl sulfide. The dimethyl disulfide was salted out of the distillate, and distilled twice at atmospheric pressure. The boiling point (uncorr.) was 109°. Although the freshly distilled product was colorless, it developed a yellow color upon standing for a few hours, apparently losing dimethyl sulfide. The photographs were taken with the sample at 70° immediately after pumping off at room temperature any dimethyl sulfide which had formed after the distillation.

The photographs show five measurable maxima. The first two maxima are of roughly equal intensity. The third appears as a shelf on the second maximum. The fourth and fifth maxima are well defined but less intense than the first two maxima. The fourth is stronger than the fifth. The observed values of s are given in Table II, along with the intensities. The ordinary and modified radial distribution functions are shown in Fig. 1, curves C and D, respectively. Both radial distribution curves have maxima at 1.94 ± 0.01 Å. This is intermediate between a carbon–sulfur distance of 1.81 Å. and a sulfur–sulfur distance of about 2.06 Å. The two distances are not resolved. The peak at 3.08 Å. is due to the long carbon–sulfur distance. The sulfur–sulfur distance is more important in the scattering formula than the two equal carbon–sulfur distances so the peak at 1.94 Å. should be somewhat nearer the sulfur–sulfur distance than the carbon–sulfur distance. The carbon–sulfur single bond distance from the radius table[8] is 1.81 Å. The sulfur–sulfur distance then is about 2.05 Å. Later in the paper, in discussing hydrogen disulfide, we show that a sulfur–sulfur distance of about 2.05 Å. in a disulfide precludes the possibility that the molecule is pyramidal. We shall now proceed to determine more accurately the bond distances and angles of the chain molecule. The theo-

Table II

Dimethyl Disulfide

Max.	Min.	I	$s_{\text{obsd.}}$	$s_{\text{calcd.}}$	$s_{\text{calcd.}}/s_{\text{obsd.}}$
1		18	4.185	4.14	0.989
	2		5.926	5.46	.921
2		16	6.795	6.75	.993
3 (shelf)		6	8.532	8.45	.990
	4		9.797	9.49	.969
4		10	10.770	10.65	.989
	5		12.197	11.62	.953
5		5	13.240	12.71	.960
Average (1st max. and 2nd min. omitted)					0.976

Results: S–S = 2.03 Å.
C–S = 1.77 Å.
H–C = 1.09 Å. (assumed)

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(9) Price and Twiss, *J. Chem. Soc.*, **95**, 1489 (1909).

(10) Westlake, private communication.

retical intensity curve for the *trans* configuration of the molecule is indistinguishable from the theoretical intensity curve for the same molecule with free internal rotation. No attempt was made, therefore, to determine the freedom of rotation by electron diffraction, and all theoretical intensity curves were calculated for *trans* molecules. Assuming a ratio $\rho = 2.08/1.81$ for the ratio of the sulfur–sulfur to the carbon–sulfur distance we have calculated intensity curves for values of the C–S–S angle, α, equal to 95, 100, 105, 110 and 120°. These curves are shown in Fig. 2. When α is less than 105° the calculated curves are unsatisfactory in that the third maximum is not high enough on the second maximum. When ρ is greater than 105° the third maximum is too high. When ρ is decreased to 2.00/1.81 the third maximum drops in intensity. The curve for $\rho = 2.00/1.81$, $\alpha = 105$ is shown in Fig. 2. Quantitative comparison of photographs with the curve calculated for $\rho = 2.08/1.81$, $\alpha = 105°$ is given in Table II. Because there are two parameters ρ and α as well as the internal rotation and absolute size of the molecule a slightly greater probable error than usual is placed on the results. The final results obtained from the visual method and the radial distribution method are: S–S = 2.04 ± 0.03 Å., C–S = 1.78 ± 0.03 Å., C–S–S = 107 ± 3°.

Sulfur Dichloride.—The sulfur dichloride was prepared by passing excess chlorine into sulfur monochloride in the presence of a small quantity of iodine. The resulting mixture was fractionally distilled through a 30-inch (76-cm.) column. The fraction boiling between 59 and 60° was collected and again distilled immediately before the pictures were taken. Pictures were taken of a sample which boiled between 59 and 59.5° (uncorr.). The pictures were taken with the sample at about 15° within half an hour after the final distillation. Any chlorine which might have been formed after distillation by the slow reaction

$$2SCl = Cl_2 + S_2Cl_2$$

was pumped off a few seconds before the exposures were made.

The photographs show six fairly evenly spaced maxima, the intensities of which decrease uniformly from the first to the sixth. The fourth maximum is rather broad. The s values of the maxima and minima and the visually estimated intensities of the maxima are tabulated in Table III. The ordinary radial distribution function has maxima at 1.98 and 3.13 Å. The modified radial distribution function has maxima at 2.01 and 3.12 Å. The first peak at 2.00 Å. represents the sulfur–chlorine distance. The second peak is the chlorine–chlorine distance. These distances lead to a Cl–S–Cl angle of 103°. The theoretical intensity curves are shown in Fig. 3. There is only one shape parameter, the Cl–S–Cl angle. When the angle is equal to 100° or less the fourth maximum is too sharp on the theoretically calculated curves. When the angle is 110° the third maximum on the calculated curve is too high. The 120° curve is unsatisfactory because the fourth maximum is too sharp. Quantitative comparison of the photographs with the 102° 30′ and the 105° calculated curves is made in Table III. The final results are: S–Cl = 2.00 ± 0.02 Å. and Cl–S–Cl = 103 ± 2°.

TABLE III

SULFUR DICHLORIDE

Max.	Min.	I	$s_{obsd.}$	$s_{calcd.}$	$s_{calcd.}/s_{obsd.}$	$s_{calcd.}$	s_c/s_o
1		10	4.368	4.06	0.929	4.04	0.925
	2		5.704	5.42	.950	5.36	.940
2		8	6.725	6.73	1.001	6.67	.992
	3		9.099	8.71	0.957	8.73	.959
3		6	10.295	10.18	.989	10.14	.985
	4		11.774	11.50	.977	11.48	.975
4		4	12.917	12.83	.993	13.05	1.010
	5		15.243	14.98	.983	14.86	0.975
5		2	16.382	16.29	.994	16.14	.985
	6		18.202	17.59	.966	17.57	.965
6		1	19.533	19.38	.992	19.54	1.000
Average (1st max. and 2nd min. omitted)					0.984		0.983

Results: S–Cl = 2.00 Å. Cl–S–Cl = 102° 30′. Cl–S–Cl = 105°.

Discussion.—The electron diffraction data on hydrogen disulfide do not show directly whether the two hydrogen atoms are on the same or different sulfur atoms. However, from the sulfur–sulfur distance it is possible to give the answer to this question. If the hydrogen atoms are on adjacent sulfur atoms the sulfur–sulfur bond is a single bond and would be expected to have the single-bond interatomic distance. The sulfur–sulfur single-bond distance has been observed in rhombic sulfur[11] to be 2.12 Å. Pauling and Huggins[12] from a study of interatomic distances decide that the most probable sulfur–sulfur single bond distance is 2.08 Å. If the two hydrogen atoms are on the same sulfur atom the sulfur–

[11] Warren and Burwell, *J. Chem. Phys.*, **3**, 6 (1935).

[12] Pauling and Huggins, *Z. Krist.*, **87A**, 205 (1934).

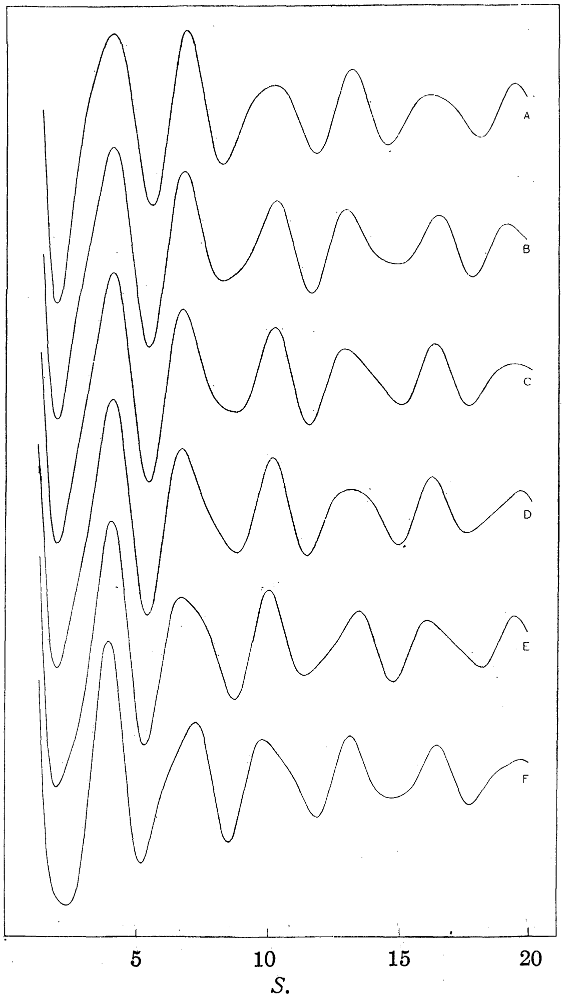

Fig. 3.—Theoretical intensity curves for SCl_2: Curve A, $\alpha = 95°$; Curve B, $\alpha = 100°$; Curve C, $\alpha = 102° 30'$; Curve D, $\alpha = 105°$; Curve E, $\alpha = 110°$; Curve F, $\alpha = 120°$.

sulfur bond will be a semipolar or dative bond. The interatomic distance for this type of bond has been observed in the case of several phosphates[13] and sulfates[14] to be about the double bond value. Electron diffraction work on $PSCl_3$,[2] $POCl_3$,[15] etc., has shown the interatomic distance for semipolar double bonds to be about the double bond value. The cause for this has been discussed.[2] The double bond sulfur–sulfur distance is 1.90 Å.[8]

The observed distance in hydrogen disulfide is 2.05 ± 0.02 Å. This is practically identical with the single bond distance, 2.08 Å. We conclude, therefore, that the hydrogen disulfide molecule is a chain molecule, the two hydrogens being on adjacent sulfur atoms. Butler and Maass[7] from a study of the refractivity and parachor of hydrogen sulfide and hydrogen disulfide have reached the same conclusion.

In treating the electron diffraction data for dimethyl disulfide we did not calculate theoretical intensity curves for pyramidal models (both methyl groups on the same sulfur atom) because of the radial distribution function. If the molecule were pyramidal the first peak on the radial distribution function would have been at about 1.86 Å. instead of at 1.94 Å., because of the shorter sulfur–sulfur distance for the pyramidal model. Accordingly theoretical intensity curves were only calculated for chain models. The sulfur bond angle of 107° in dimethyl disulfide is about the same as the angle observed for sulfur[11] (105°). The carbon–sulfur distance (1.78 ± 0.03 Å.) is equal to the radius table value (1.81) for the carbon–sulfur single bond within the experimental error. Brockway and Jenkins[16] have found 1.82 ± 0.03 Å. for the carbon–sulfur distance in dimethyl sulfide. The sulfur–chlorine distance in sulfur dichloride (2.00 + 0.02 Å.) seems slightly less than the radius table value (2.03 Å.). This effect for similar compounds has been discussed.[16]

Summary

The molecular structures of hydrogen disulfide, dimethyl disulfide and sulfur dichloride have been investigated by the method of electron diffraction. Hydrogen disulfide and dimethyl disulfide are chain molecules. In hydrogen disulfide the S–S distance is 2.05 ± 0.02 Å. In dimethyl disulfide the S–S distance is 2.04 ± 0.03 Å., the C–S distance is 1.78 ± 0.03 Å. and the C–S–S angle is 107 ± 3°. Sulfur dichloride is a bent molecule. The S–Cl distance is 2.00 ± 0.02 Å., the Cl–S–Cl angle is 103 ± 3°.

PRINCETON, N. J. RECEIVED SEPTEMBER 13, 1938

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[13] West, *Z. Krist.*, **74**, 306 (1930).

[14] Zachariasen and Ziegler, *ibid.*, **81**, 92 (1932).

[15] Brockway and Beach, THIS JOURNAL, **60**, 1836 (1938).

[16] Brockway and Jenkins, *ibid.*, **58**, 2036 (1936).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

The Conductivities of Electrolytes in Anhydrous Acetic Acid*

BY BRUCE V. WEIDNER,[1] A. WITT HUTCHISON AND G. C. CHANDLEE

The recent contributions of Kraus, Fuoss and co-workers[2] on "The Properties of Electrolytic Solutions" have furnished the first satisfactory explanation of the unusual conductance phenomena exhibited by solutions of electrolytes in solvents with low dielectric constants. Since considerable interest has been shown in recent years in the properties of solutions in anhydrous acetic acid, which has a low dielectric constant,[3] $\epsilon = 6.25$, it was thought that additional studies[4] of conductivities in this solvent might prove of value especially in view of the above contributions.

In the present investigation conductance data have been obtained for solutions of certain quaternary ammonium salts, the chlorides and nitrates of the alkali metals and sodium acetate.

Experimental

The bridge assembly, thermostat and cells, as well as the method of purification of the solvent, were described previously.[4b] The specific conductivity of the acid used in the preparation of the solutions varied from 0.37 to 0.70 × 10^{-8} mho at 25°. Recently acid with a specific conductivity as low as 0.18 × 10^{-8} mho was obtained in quantity in this way.

Lithium chloride was prepared by the method of Richards and Willard.[5]

The chlorides of sodium, potassium and ammonium and the nitrates of lithium, sodium, potassium and cesium were purified by three recrystallizations of C. P. reagents from conductivity water and dried in an oven at 120° for three days.

Sodium acetate was prepared by the method of Davidson and McAllister.[6]

The quaternary ammonium compounds[7] were prepared by passing the corresponding halide into an alcoholic solution of trimethylamine. The second crop of crystals obtained from these solutions was then twice recrystallized from pure methyl alcohol and heated to constant weight at 120°.

The stronger solutions were made by adding weighed amounts of the dry salt to a known weight of pure acetic acid. The solutions of low concentration were obtained by dilution.

Discussion of Results

The experimental results are given in Tables I to XII. The concentrations are expressed in moles per liter. In calculating the equivalent conductances no solvent correction was applied.[8] The specific conductivity of the solvent is that measured at the completion of each dilution run. The starred values are for *k*-solvent varying between 0.40 and 0.70 × 10^{-8} mho. In each case at least two different samples of the solution were measured. In addition, duplicate dilution runs were made for several of the electrolytes. These results were in very good agreement with the data listed here but were omitted in order to conserve space.

A comparison with the results of Kolthoff and Willman[4a] is possible in the case of the sodium acetate and lithium chloride solutions. The data for sodium acetate are in satisfactory agreement but those obtained for lithium chloride in the present work are definitely higher. These differences might be due to a difference in the method of the preparation of the salt. Two separate preparations of lithium chloride were studied in the present work and the data obtained were in excellent agreement.

An examination of curves in which values of Λ were plotted against $\sqrt{c}$ indicated them to be of the type previously described[8] for solutions in solvents of low dielectric constants. In the dilute range the slope of such curves is chiefly determined by the ion pair equilibrium.[9] In the more concentrated solutions the effect of triple ion formation[10] is evident. The data for tetramethyl-

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(*) Original manuscript received July 24, 1936.

[1] Present address: University of Alaska, College, Alaska.

[2] Series of publications in THIS JOURNAL and in *Trans. Faraday Soc.* Number XIX of this series, the latest to date, may be found in *Trans. Faraday Soc.*, **32**, 594 (1936). A review of the major portion of this work appears in *Chem. Rev.*, **17**, 29 (1935).

[3] Seward and Hamblet, THIS JOURNAL, **54**, 554 (1932).

[4] (a) Kolthoff and Willman, *ibid.*, **56**, 1007 (1934); (b) Weidner, Hutchison and Chandlee, *ibid.*, **56**, 1285 (1934).

[5] Richards and Willard, *ibid.*, **32**, 4 (1910).

[6] Davidson and McAllister, *ibid.*, **52**, 519 (1930).

[7] All the quaternary ammonium compounds were very kindly prepared by Mr. J. H. Jones of this Laboratory.

[8] Application of a solvent conductance correction showed a curvature in the log Λ *vs.* log *c* plots which seemed anomalous and also gave somewhat less satisfactory agreement with what might be expected from Walden's rule. Furthermore, some uncertainty exists regarding the nature of the solvent conductance. In view of these considerations it seemed best not to make a correction.

[9] Fuoss and Kraus, THIS JOURNAL, **55**, 476 (1933).

[10] Fuoss and Kraus, *ibid.*, **55**, 2387 (1933).

Table I

Lithium Chloride

k-solvent = 0.41 × 10^{-8}

C	Λ
0.02434	0.1852*
.01539	.1951*
.01084	.2243
.007224	.2512
.004100	.3089
$.0_33703$	.8449
$.0_32853$	.9470
$.0_49322$	1.538
$.0_45439$	1.928
$.0_43136$	2.436
$.0_42044$	2.916
$.0_41206$	3.627
$.0_5801$	4.30
$.0_5497$	5.29
$.0_5354$	6.11
$.0_5252$	7.16

Table II

Sodium Chloride

k-solvent = 0.45 × 10^{-8}

C	Λ
0.003764	0.1651*
.002550	.1910
.001711	.2279
$.0_35547$	.3822
$.0_33383$	.4805
$.0_32045$	.6092
$.0_31251$	.7706
$.0_47686$	.9787
$.0_44769$	1.231
$.0_42836$	1.592
$.0_41666$	2.071
$.0_41001$	2.66
$.0_5716$	3.14
$.0_5584$	3.46

Table III

Potassium Chloride

k-solvent = 0.47 × 10^{-8}

C	Λ
0.01060	0.1364*
.006675	.1620*
.004407	.1888*
.002507	.2574*
.001915	.2630*
$.0_39772$	.3602
$.0_35901$	.4543
$.0_33434$	.5853
$.0_31512$	.8636
$.0_48452$	1.159
$.0_44876$	1.533
$.0_43040$	1.907
$.0_41833$	2.442
$.0_41188$	3.01
$.0_5688$	3.95
$.0_5448$	4.95
$.0_5300$	6.12

Table IV

Ammonium Chloride

k-solvent = 0.50 × 10^{-8}

C	Λ
0.002575	0.2241
.001704	.2680
$.0_39797$	.3401
$.0_35815$	.4357
$.0_32907$	.5993
$.0_31642$	.7751
$.0_49789$	.9841
$.0_45552$	1.287
$.0_43171$	1.646
$.0_41879$	2.100

Table V

Lithium Nitrate

k-solvent = 0.39 × 10^{-8}

C	Λ
0.02736	0.2355
.009935	.2389
.002933	.3129
$.0_35423$	.4837
$.0_33279$	.5510
$.0_31501$	.687
$.0_49154$	.829
$.0_45568$	.102
$.0_43653$	1.24
$.0_42619$	1.49

Table VI

Sodium Nitrate

k-solvent = 0.43 × 10^{-8}

C	Λ
0.007934	0.2060*
.004541	.2423*
.003266	.2573
.001689	.3190
$.0_39262$	.3906
$.0_35066$	.4767
$.0_32279$	.6231
$.0_31426$	.739
$.0_48747$	.882
$.0_45053$	1.112
$.0_43165$	1.365
$.0_41875$	1.772
$.0_41120$	2.270
$.0_5819$	2.69
$.0_5522$	3.34

TABLE VII

POTASSIUM NITRATE

k-solvent = 0.47×10^{-8}

C	Λ
0.01246	0.2407*
.009466	.2435*
.006219	.2675*
.004190	.3047*
.001824	.4087
.001219	.4736
$.0_{3}5783$	.6278
$.0_{3}2121$	.929
$.0_{3}1134$	1.199
$.0_{4}6720$	1.477
$.0_{4}3910$	1.860
$.0_{4}2362$	2.32
$.0_{4}1452$	2.88
$.0_{5}906$	3.53
$.0_{5}635$	4.13
$.0_{5}433$	4.91
$.0_{5}315$	5.82

TABLE VIII

CESIUM NITRATE

k-solvent = 0.50×10^{-8}

C	Λ
0.002329	0.3938*
.001310	.5033*
$.0_{3}7033$	.6514*
$.0_{3}5932$	.7003
$.0_{3}2913$	.9454
$.0_{3}1572$	1.228
$.0_{4}9061$	1.549
$.0_{4}4917$	2.010
$.0_{4}2789$	2.59
$.0_{4}1630$	3.22
$.0_{5}957$	3.97
$.0_{5}567$	4.90
$.0_{5}432$	5.59

TABLE IX

TETRAMETHYLAMMONIUM CHLORIDE

k-solvent = 0.56×10^{-8}

C	Λ
0.1153	1.551*
.05136	0.8053*
.01970	.5264*
.01227	.5064*
.008150	.5242*
.005610	.5630*
.002749	.6995
.001771	.820
$.0_{3}5373$	1.365
$.0_{3}1062$	2.806
$.0_{4}1974$	6.12
$.0_{4}1151$	7.36
$.0_{5}647$	9.23
$.0_{5}372$	10.97
$.0_{5}250$	12.29

TABLE X

TETRAMETHYLAMMONIUM BROMIDE

k-solvent = 0.45×10^{-8}

C	Λ
0.002287	0.6813
.001247	.8505
$.0_{3}9725$	.9477
$.0_{3}6095$	1.155
$.0_{3}3223$	1.528
$.0_{3}1822$	1.976
$.0_{3}1044$	2.549
$.0_{4}679$	3.106
$.0_{4}474$	3.64

TABLE XI

TRIMETHYL-n-BUTYLAMMONIUM BROMIDE

k-solvent = 0.57×10^{-8}

C	Λ
0.008222	0.5121
.004988	.5601
.003063	.6401
.001990	.7327
.001169	.9107
$.0_{3}4954$	1.303
$.0_{3}2710$	1.692
$.0_{3}1635$	2.12
$.0_{4}9668$	2.68
$.0_{4}5736$	3.42

TABLE XII

SODIUM ACETATE

k-solvent = 0.48×10^{-8}

C	Λ
0.02966	0.05347*
.02000	.07820*
.01676	.07901*
.009629	.09637
.005797	.1195
.001482	.2167
$.0_{3}8832$	.2773
$.0_{3}4635$	.3798
$.0_{3}2498$	.5149
$.0_{3}1296$	.7160
$.0_{4}6980$	.9748
$.0_{4}3920$	1.312
$.0_{4}2465$	1.664
$.0_{4}2149$	1.973
$.0_{4}1140$	2.682
$.0_{5}549$	3.96

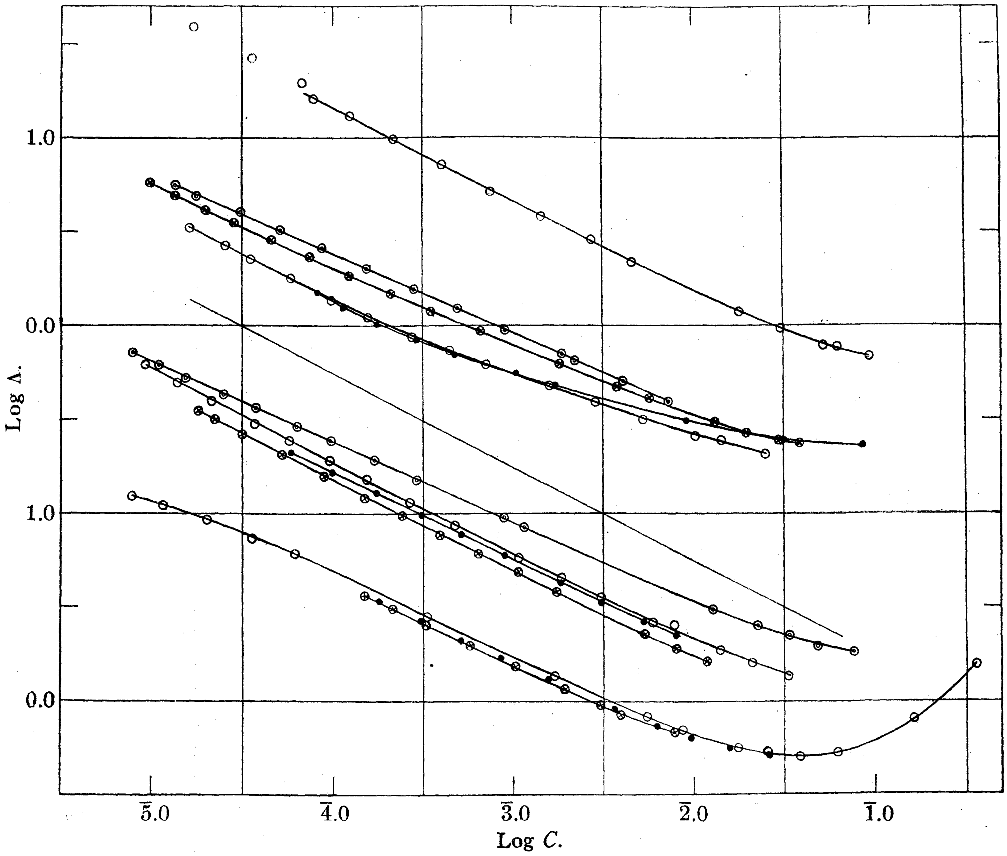

Fig. 1.—The ordinates have unit value. In plotting, the second and third groups of curves and the upper simple curve have been displaced by 1, 2 and 3 units, respectively. The straight line has a slope of $-1/2$. In the first group: ○, tetramethylammonium chloride; ⊗, tetramethylammonium bromide; and ●, trimethyl-*n*-butylammonium bromide. The second group are for the chlorides: ⊙, lithium; ○, potassium; ⊗, sodium; and ●, ammonium. The third group are nitrates: ⊙, cesium; ⊗, potassium; ●, lithium; and ○, sodium. The top curve is for sodium acetate.

ammonium chloride solutions show a distinct minimum due to this effect while in the case of the other substances investigated it is apparent that, though not reached, a minimum is being approached. More concentrated solutions were not investigated because of solubility limitations in the case of several of the materials used. Plots of log Λ against log *C*, Fig. 1, gave nearly straight lines indicative of small values for the ion pair dissociation constant.[9,11]

The limiting equivalent conductances and the ion pair dissociation constants for several of the salts were evaluated by the methods of Kraus and Fuoss.[2] Unfortunately these calculations must be based on the data obtained in the more dilute solutions where considerable uncertainty exists regarding the influence of the solvent conductances in the case of acetic acid. Because of this difficulty the numerical values obtained are of doubtful significance. The results, however, were in reasonable accord with the general predictions of the theory.

We wish to acknowledge the kindness of Professor C. A. Kraus in discussing with us certain points in regard to the interpretation of these data.

Summary

The specific conductances of a number of uni-univalent electrolytes have been determined in dilute solutions in acetic acid with a specific conductivity varying from 0.37 to 0.70 × 10^{-8} mho at 25°.

STATE COLLEGE, PENNA. RECEIVED AUGUST 23, 1938

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[11] Kraus and Fuoss, THIS JOURNAL, **55**, 21 (1933).

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

5,5-Crotyl Alkyl Barbituric Acids[1]

BY WILBUR J. DORAN AND H. A. SHONLE

A recent report from this Laboratory described a series of barbituric acids containing the unsaturated 2-methylallyl.[2] Since some of these derivatives produced an anesthesia of brief duration, we believed that the isomeric 5,5-crotyl alkyl and 5,5-(1-methylallyl) alkyl barbituric acids might also be of short duration.

Crotyl substituted barbituric acids described in the literature are 5,5-dicrotyl,[3] 5,5-crotyl allyl[4] and, since the preparation of the barbituric acids herein described was completed, 5,5-crotyl isopropyl[5] and 5,5-crotyl isobutyl barbituric acids.[5]

A representative group of 5,5-crotyl alkyl barbituric acids, prepared by treating the sodium salts of 5-monoalkyl barbituric acids with crotyl bromide, is described in this paper. The treatment of 5-monoethyl barbituric acid with crotyl bromide gave two 5,5-crotyl ethyl barbituric acids, which we believe to be the *cis* and *trans* isomers. Our crotyl isopropyl and crotyl isobutyl barbituric acids differ in melting points from those described in the I. G. Farbenindustrie patent.[5] These may also be cases of *cis* and *trans* isomers.

A barbituric acid containing the isomeric 1-methylallyl group in the 5-position, and a 2-crotyl thiobarbituric acid were included in this study.

Pharmacological results, in Table I, give the minimum anesthetic dose (M. A. D.), the minimum lethal dose (M. L. D.) and the average duration of anesthesia determined by the intraperitoneal administration of dilute solutions of the sodium salts of the barbituric acids in white rats. With few exceptions the 5,5-crotyl alkyl barbituric acids produce an anesthesia of shorter duration than the isomeric 2-methylallyl barbituric acids. 5,5-(1-Methylallyl) ethyl barbituric acid has a duration of anesthesia twice as long as that of the isomeric *cis*- and *trans*-crotyl ethyl barbituric acids, while 5-*n*-butyl 2-crotyl thiobarbituric acid produced only convulsant effect.

Experimental

The crotyl alkyl barbituric acids were prepared either by condensing the crotyl alkyl ethyl malonate with urea, or by condensing crotyl bromide with the alkyl barbituric acid, using the usual procedure for the introduction of the allyl group.

Since the action of phosphorus tribromide on crotyl alcohol produces an equilibrium mixture of crotyl and 1-methylallyl bromide (consisting of 87% of the primary isomer), it is necessary to separate these isomers by distillation procedures just prior to use.[6] Instead of using vacuum, we used atmospheric pressure for the fractionation of the crotyl bromide from this isomeric mixture. Fractionating 222 g. through a 30-cm. Widmer column during a period of two hours, we obtained as a final fraction 31.5 g. boiling at 106–108° (uncorr.) and possessing $n^{25}\text{D}$ 1.47936. It was therefore almost pure crotyl bromide.

FRACTIONATION OF 222 G. OF AN ISOMERIC MIXTURE OF CROTYL BROMIDE

Fraction	B. p., °C. (uncorr.)	Wt., g.	$n^{25}\text{D}$	% crotyl bromide
1	98–100	8.8	1.46228	11.0
2	100–101	25.3	1.47003	51.0
3	101–103	30.0	1.47218	61.5
4	103–105	33.8	1.47479	75.0
5	105–103	41.6	1.47677	86.5
6	105–106	36.3	1.47872	96.0
7	106–108	31.5	1.47936	99.5
8 Residue		10.0		
		217.3		

1-Methylallyl bromide was obtained from the equilibrium mixture of crotyl and 1-methylallyl bromides by slow fractionation through a long column at atmospheric pressure.[6] The fraction boiling at 88–90° which was used contained less than 10% of the primary bromide.

To dilute alcoholic solutions of the sodium salts of the various pure monosubstituted barbituric acids, were added molecular proportions of the freshly distilled crotyl bromide. In some instances a small amount of a copper salt was added. The reaction was completed usually after several hours of warming. The crude 5,5-crotyl alkyl barbituric acids which separated at the end of the reaction, after the alcohol solvent was removed under vacuum, were dissolved in chloroform and were freed from unreacted 5-mono alkyl barbituric acids by extracting with dilute sodium bicarbonate solution. The disubstituted barbituric acids were freed from chloroform and then recrystallized from dilute alcohol until a constant melting point was obtained.

In the case of 5,5-crotyl ethyl barbituric acid two fractions were obtained on recrystallizing from dilute alcohol, each of which had a constant melting point. The final purification of the lower melting isomer was effected by

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[1] Presented before the Division of Medicinal Chemistry at the 96th meeting of the American Chemical Society, Milwaukee, Wisconsin, September 5 to 9, 1938.

[2] Doran and Shonle, THIS JOURNAL, **59**, 1625 (1937).

[3] Braun and Schirmacher, *Ber.*, **56**, 538 (1923).

[4] Taub, Schutz and Meisenberg, U. S. Patent 1,511,919, Oct. 14, 1924.

[5] I. G. Farbenindustrie A.-G., British Patent 475,948, Nov. 29, 1937.

[6] Winstein and Young, THIS JOURNAL, **58**, 104 (1936).

TABLE I

5,5-Crotyl alkyl barbituric acid	M. p., °C.[a]	% Nitrogen Calcd.	Found		M. A. D. mg./kg.	M. L. D., mg./kg.	Average duration of M. A. D., min.
Ethyl	108–110	13.34	13.43	13.34	100	280	372
Ethyl	120–121	13.34	13.36	13.38	100	240	300
n-Propyl	160–161	12.50	12.58	12.60	130	340	120
1-Methylethyl	144–145[b]	12.50	12.46	12.76	70	180	200
n-Butyl	142–143	11.76	11.79	11.82	110	320	40
1-Methylpropyl	130–131	11.76	11.93	11.94	80	220	120
2-Methylpropyl	126–127[b]	11.76	11.92	11.77	100	300	45
1-Methylbutyl	110–113[c]	11.11	11.15	11.19	90	200	66
3-Methylbutyl	147–148	11.11	11.22	11.29	120	180	40

Ethyl 1-methylallyl barbituric acid had a M. A. D. of 125 mg./kg. and a M. L. D. of 175 mg./kg. The average duration of M. A. D. was seven hundred and twenty minutes.

[a] Anschütz thermometer used. [b] British Patent 475,948 gives a melting point of 137–138° for 1-methylethyl crotyl barbituric acid and 115° for 2-methylpropyl crotyl barbituric acid. [c] Also obtained in a hydrated form melting at 88–90°, calcd. for $C_{13}H_{20}N_2O_3 \cdot H_2O$: N, 10.37%; found: N, 10.58 and 10.65%.

recrystallization from hot water. That these are isomeric crotyl ethyl barbituric acids and not a mixture of crotyl ethyl and 1-methylallyl ethyl barbituric acids was proved by the catalytic hydrogenation of each isomer. Using Adams platinum catalyst, each isomer, after reduction, gave butyl ethyl barbituric acids which had identical melting points, and which showed no depression in melting point when mixed with each other or when mixed with a known sample of *n*-butyl ethyl barbituric acid. From this it is evident that they were isomeric crotyl ethyl barbituric acids, presumably of the *cis–trans* type. Some evidences of similar isomers were obtained with some of the other barbituric acids, but the amounts were so small that products of constant melting point were not obtained.

1-Methylallyl bromide, obtained as described above, was added immediately to a solution of a molecular amount of sodium ethylate and ethyl ethylmalonate in absolute alcohol. The solution was kept cold during the addition. It was then stoppered and allowed to come to room temperature and to stand at room temperature for two days. It was desired to avoid the use of heat during this reaction, because of the rapid isomerization rate of 1-methylallyl bromide. The crude 1-methylallyl ethyl ethyl malonate was freed from alcohol and sodium bromide, dried, and fractionated under vacuum. Two fractions were obtained, the first being 1-methylallyl ethyl ethyl malonate, boiling at about 104–108° (uncorr.) at 6 mm. and possessing $n^{25}\mathrm{D}$ 1.4333, and the second, crotyl ethyl ethyl malonate, boiling at 114–118° (uncorr.) at 6 mm. and possessing $n^{25}\mathrm{D}$ 1.4390. The identification of these malonic esters was established from the structures of the barbituric acids obtained by condensing the esters in the usual manner with urea in the presence of sodium ethylate.

The lower boiling ester gave a barbituric acid which melted at 146.5–148.0°. The anal. calcd. for $C_{10}H_{14}O_3N_2$: N, 13.34; found: N, 13.36 and 13.16. When it was reduced catalytically using Adams catalyst, a reduced barbituric acid was obtained which after crystallization melted at 165.5–166.0°. Since there was no depression of the melting point when mixed with a known sample of 5,5-secondary butyl ethyl barbituric acid, it was evident that we originally had 5,5-(1-methylallyl) ethyl barbituric acid. Crystals of the two forms of crotyl ethyl barbituric acid melting at 107° and 118–119° were obtained when the higher boiling ester fraction was condensed with urea.

5,5-Crotyl *n*-propyl, 5,5-crotyl 1-methylethyl, 5,5-crotyl *n*-butyl, 5,5-crotyl 1-methylpropyl, 5,5-crotyl 2-methylpropyl, 5,5-crotyl 1-methylbutyl, and 5,5-crotyl 3-methylbutyl barbituric acids were prepared by treating freshly fractionated crotyl bromide with the sodium salt of the appropriate monosubstituted barbituric acid.

5,5-Crotyl 1-methylbutyl barbituric acid was also prepared from urea and crotyl 1-methylbutyl ethyl malonate, which was prepared by condensing crotyl bromide with 1-methylbutyl ethylmalonate in the presence of sodium ethylate. Crotyl 1-methylbutyl ethyl malonate boiled at 140–145° (uncorr.) at 10 mm. and possessed $n^{25}\mathrm{D}$ 1.4450.

A solution of the sodium salt of 5-*n*-butyl thiobarbituric acid was treated with crotyl bromide with the expectation of obtaining 5,5-*n*-butyl crotyl thiobarbituric acid. After several hours of refluxing, part of the alcohol was taken off under vacuum and the reaction product filtered off and washed with sodium bicarbonate solution. The resulting disubstituted thiobarbituric acid was purified by several recrystallizations from dilute alcohol and had a melting point of 238–239°. The anal. calcd. for $C_{12}H_{18}N_2O_2S$: N, 11.02; found: N, 11.09 and 11.14.

Since the injection of a sodium salt of this thiobarbituric acid produced only convulsions, the possibility of substitution on an atom other than the methylene carbon had to be considered.

A portion of the *n*-butyl crotyl thiobarbituric acid was refluxed for about twenty hours in dilute alcoholic hydrochloric acid solution. The alcohol was evaporated off and the residue filtered off and recrystallized from dilute alcohol. A product melting at 203–205° (uncorr.) was obtained. When it was mixed with 5-*n*-butyl barbituric acid (m. p. 204–207°, uncorr.) there was no depression of the melting point. From these facts, it was evident that the crotyl group was attached to the sulfur and that the disubstituted thiobarbituric acid melting at 238–239° was 5-*n*-butyl 2-crotyl thiobarbituric acid.

The reaction of crotyl bromide with 5-*n*-butyl thiobarbituric acid is therefore different from its reaction with 5-*n*-butyl barbituric acid.

A similar reaction had been reported previously for alkyl, allyl and benzyl halides and 5-methyl thiobarbituric acid.[7]

Table I covers some of the physical properties of the

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(7) Nishikawa, *J. Chem. Soc. Jap.*, **56**, 1487 (1935); *ibid.*, **58**, 97 (1937).

crotyl alkyl barbituric acids described and includes a brief summary of their pharmacological response.

Summary

Crotyl ethyl, crotyl 1-methylbutyl and 1-methylallyl ethyl ethyl malonates have been prepared and characterized. A series of eight crotyl alkyl barbituric acids has been prepared, and some of their physical and pharmacological properties are described. Also 5,5-(1-methylallyl) ethyl barbituric acid and 5-*n*-butyl-2-crotyl thiobarbituric acids have been prepared and pharmacologically studied.

The presence of *cis–trans* isomers has been observed in 5,5-crotyl alkyl barbituric acids.

INDIANAPOLIS, INDIANA RECEIVED OCTOBER 5, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

The Preparation of Acetylenic Carbinols[1]

BY KENNETH N. CAMPBELL, BARBARA K. CAMPBELL AND LAWRENCE T. EBY

Acetylenic alcohols have been prepared, in general, through the Grignard reaction[2] or by condensing an acetylene with an aldehyde or ketone in an anhydrous solvent such as ether. In some cases the latter reaction has been carried out using the sodium derivative of the acetylene,[3] in others the sodium enolate of the carbonyl compounds has been used,[4] while in still other cases use has been made of condensing agents such as sodamide,[5a] potassium *t*-butylate[5b] and potassium hydroxide.[5c] None of these methods is entirely satisfactory.

Since large amounts of acetylenic alcohols were needed for other work, we investigated the preparation of these alcohols from sodium acetylide and a carbonyl compound, using liquid ammonia as a solvent. Such a method would have considerable advantages over the older methods in simplicity and ease of manipulation. At the time this work was started, there was but one reference in the literature to the use of liquid ammonia as a solvent for the reaction.[6] Later, McGrew and Adams[7] reported the preparation of ethynylethylcarbinol by a method similar to ours, and a recent series of patents[8] describes the preparation of some acetylenic carbinols in liquid ammonia solution.

We have shown that sodium acetylide in liquid ammonia will condense with many aldehydes and ketones to give the corresponding carbinols in good yields (see Table I) and the method is a general one. Comparatively small amounts of the glycols, formed by the condensation of two molecules of the carbonyl compound with one of acetylene, were obtained. The yield of the acetylenic carbinols can be increased, and that of the glycol decreased, by passing acetylene gas into the mixture during the entire course of the reaction. The reaction has been extended successfully to include the sodium derivatives of monoalkyl acetylenes. Several of the carbinols prepared in this work have not been described before. These include: 1-phenyl-3-propyn-1-ol, 3-methyl-4-nonyn-3-ol, 4-methyl-5-decyn-4-ol, 4-nonyn-3-ol and 4-methyl-5-undecyn-4-ol.

In the case of methylethylethynylcarbinol, this method of preparation was compared with others. The liquid ammonia method was found to be the most satisfactory, as it gave better yields and was carried out more easily. Although a direct comparison of methods was not carried out in other cases, the short time required, and the ease of manipulation, in the liquid ammonia method would seem to make it preferable even if, in certain cases, other methods gave better yields.

The condensation of sodium acetylide with a carbonyl compound does not seem to involve an enol form of the latter, since benzophenone and benzaldehyde will undergo the reaction. The following mechanism is suggested to explain the glycol formation, and the effect of excess acetylene gas.

$$HC\equiv CNa + R\text{—}\underset{\underset{O}{\|}}{C}\text{—}R' \longrightarrow$$

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[1] Paper XXIX on the chemistry of substituted acetylenes; previous paper, THIS JOURNAL, **60**, 1717 (1938).

[2] Iotisch, *Bull. soc. chim.*, [3] **34**, 181 (1905).

[3] Nef, *Ann.*, **308**, 264 (1899); Moureu and Desmots, *Bull. soc. chim.*, **27**, 360 (1902).

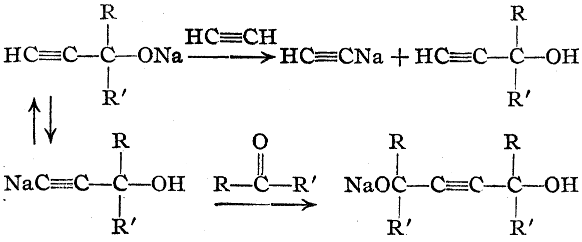
[4] Locquin and Sung, *ibid.*, [4] **35**, 597 (1924).

[5] (a) Ruzicka, *Helv. Chim. Acta*, **2**, 182 (1919); (b) Gould and Thompson, THIS JOURNAL, **57**, 340 (1935); (c) Favorsky, *Bull. soc. chim.*, **26**, 284 (1901).

[6] Bayer and Co., German Patent, 285,770; *Friedländer*, **12**, 57–58 (1914–16).

[7] McGrew and Adams, THIS JOURNAL, **59**, 1499 (1937).

[8] Kreimeier, U. S. Patents 2,106,180–2,106,182 (1936); *C. A.*, **32**, 2547 (1938).



$$\mathrm{HC{\equiv}C{-}\overset{R}{\underset{R'}{C}}{-}ONa} \xrightarrow{\mathrm{HC{\equiv}CH}} \mathrm{HC{\equiv}CNa} + \mathrm{HC{\equiv}C{-}\overset{R}{\underset{R'}{C}}{-}OH}$$

$$\uparrow\downarrow$$

$$\mathrm{NaC{\equiv}C{-}\overset{R}{\underset{R'}{C}}{-}OH} \xrightarrow{\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}R'}} \mathrm{NaO\overset{R}{\underset{R'}{C}}{-}C{\equiv}C{-}\overset{R}{\underset{R'}{C}}{-}OH}$$

The preparation of the chloride from methylethylethynylcarbinol was investigated in some detail. Gaseous hydrogen chloride at 0° reacted only slightly with the alcohol, and little or no chloride was formed. Phosphorus trichloride in pyridine gave the chloride in fair yields, but the purification was difficult. Concentrated aqueous hydrochloric acid reacted with the carbinol at room temperature to give the chloride in about 40% yields, and purification was fairly simple. A more detailed study of the preparation and reactions of such acetylenic halides is in progress.

Experimental

Preparation of Alkylethynylcarbinols.—One mole of sodium acetylide was prepared[9] by adding 23 g. of sodium to about 1 liter of liquid ammonia, contained in a 2-liter, 3-necked round-bottomed flask fitted with a mechanical stirrer, while a rapid stream of dry acetylene was passing through the solvent. The acetylene was then shut off, and one mole of the aldehyde or ketone was added dropwise, with stirring, over a period of one hour. Stirring was continued for about three hours longer, with addition of liquid ammonia from time to time to keep the liquid level at about 1 liter. If acetylene gas is passed through the reaction mixture for the entire time, the yield of carbinol is in some cases, at least, higher and less glycol is formed. The reaction mixture may be hydrolyzed immediately, but generally the liquid ammonia was allowed to evaporate (overnight) and the resulting solid was hydrolyzed with ice and water. The hydrolysis mixture was made slightly acid, with cooling, with 50% sulfuric acid, the organic layer dissolved in ether, if viscous, washed with brine and dried over magnesium sulfate. The original aqueous layer and the wash water were extracted with ether in the case of the lower, water-soluble carbinols, and the extract added to the main product. The residue remaining after evaporation of the ether was distilled under reduced pressure through a small Vigreux column. In nearly all cases some high-boiling glycol was obtained after the carbinol had distilled over.

Preparation of Alkylalkynylcarbinols.—A liquid ammonia solution of sodamide was prepared[10] from 23 g. of sodium, 0.5 g. of ferric nitrate and 1.5 liters of liquid ammonia. To this was added 1.1 moles of alkylacetylene, dropwise, with stirring, in the course of fifteen minutes, and the mixture was stirred for an additional thirty minutes. Then 1 mole of aldehyde or ketone was added dropwise over a period of one hour. Stirring was continued for three hours and the mixture was allowed to stand overnight to evaporate the ammonia. The residue was hydrolyzed with ice and water and made slightly acid with 50% sulfuric acid. The organic layer was washed with water, dried over magnesium sulfate and distilled under reduced pressure through a small Vigreux column.

Preparation of Methylethylethynylcarbinol by Other Methods. Grignard Method.—An acetylenic Grignard reagent was prepared by treating ethylmagnesium bromide (made from 34 g. of magnesium and 166 g. of ethyl bromide) with a current of dry acetylene gas for several hours. The Grignard reagent was then cooled in an ice-bath, and a solution of 72 g. of methyl ethyl ketone in an equal volume of dry ether added over a period of three hours. The mixture was hydrolyzed and worked up in the usual way. There was obtained a 6% yield of carbinol, and a 65% yield of glycol.

Potassium *t*-Butylate Method.—The procedure of Gould and Thompson[5b] was followed. Considerable difficulty was found in purifying the product, as the *t*-butyl alcohol and the carbinol tended to distill together. A 40% yield of pure carbinol was obtained.

Sodium *t*-Butylate as Condensing Agent.—Sodium *t*-butylate was prepared by adding 23 g. of sodium to a liquid ammonia solution of 150 g. of *t*-butyl alcohol. The liquid ammonia was removed by allowing the mixture to stand overnight, and then heating it for two to three hours on a water-bath to drive off excess *t*-butyl alcohol and residual ammonia. The rest of the procedure was similar to that used with potassium *t*-butylate. A 53% yield of carbinol was obtained.

Conversion of Methylethylethynylcarbinol to the Chloride.—When 50 g. of the carbinol (b. p. 78° under 150 mm., $n^{20}\mathrm{D}$ 1.4310) was saturated at 0° with dry hydrogen chloride, the product shaken with anhydrous potassium carbonate and distilled from fresh carbonate, no halogen-containing compound was obtained, and 26 g. of the carbinol, b. p. 74–78° under 150 mm., $n^{20}\mathrm{D}$ 1.4330, was recovered.

The general procedure of Juvala[11] was tried. A mixture of 60 g. of carbinol and 11 g. of pyridine was added dropwise, with stirring, at 0°, to 33 g. of phosphorus trichloride. The liquid layer was decanted, the solid residue washed with a little dry ether and the liquid and ether combined and stored over anhydrous potassium carbonate. The material was distilled under reduced pressure through a small helix-packed column from fresh carbonate to give 20 g. of an impure chloride, b. p. 50–57° (135 mm.), $n^{20}\mathrm{D}$ 1.4330–1.4386, $d^{20}{}_4$ 0.9175.

Forty grams of the carbinol was shaken for a few minutes with 200 cc. of concentrated hydrochloric acid. The layers were separated, and the organic layer was stored in a refrigerator over anhydrous potassium carbonate. The light yellow liquid was distilled through a small helix-packed column from fresh carbonate to give 30 g. of material of b. p. 51–60° (137 mm.), $n^{20}\mathrm{D}$ 1.4328–1.4390. Refractionation of this material yielded 20 g. of chloride of b. p. 51–52° (135 mm.), $n^{20}\mathrm{D}$ 1.4328–1.4331, $d^{20}{}_4$ 0.9140, *MR*D obsd. 33.13, *MR*D calcd. 32.71.

Anal. Calcd. for C_6H_9Cl: Cl, 30.41. Found: Cl, 30.36.

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[9] Vaughn, Hennion, Vogt and Nieuwland, *J. Org. Chem.*, **2**, 1 (1937).

[10] Vaughn, Vogt and Nieuwland, THIS JOURNAL, **56**, 2120 (1934).

[11] Juvala, *Ber.*, **63**, 1989 (1930).

TABLE I

YIELDS AND PHYSICAL CONSTANTS OF CARBINOLS

Acetylene	Carbonyl cpd.	Yield, %	B. p., °C.	Press., mm.	n^{20}_D	d^{20}_4	*MR* obsd.	*MR* calcd.
Acetylene	Acetone	23	60	120	1.4207	0.8618	24.74	24.81
Acetylene	Acetone	55[a]						
Acetylene	Me Et ketone	60	78	150	1.4310	.8688	29.24	29.43
Acetylene	Me Et ketone	72[a]						
Acetylene	Me *n*-Pr ketone	50	58	26	1.4338	.8620	33.88	34.05
Acetylene	Me *n*-Am ketone	40	88	26	1.4396	.8547	43.20	43.28
Acetylene	Cyclohexanone	55	74	14	1.4820	.9873	36.35	36.47
Acetylene	Acetophenone	7[b]	101	14	1.5370	1.0314	44.26	44.30
Acetylene	Benzophenone	50	M. p. 49°					
Acetylene	Benzaldehyde	45	114	12	1.5508	1.0655	39.56	39.68
1-Hexyne	Me Et ketone	55	96	18	1.4487	0.8555	48.33	47.90
1-Hexyne	Acetaldehyde	21	88	40	1.4347	.8577	38.37	38.66
1-Hexyne	Me *n*-Pr ketone	65	106	20	1.4490	.8539	52.92	52.52
1-Heptyne	Me *n*-Pr ketone	65	120	19	1.4508	.8561	57.32	57.14

[a] Acetylene gas was passed through the mixture during the entire reaction. Mr. Froning has obtained 60% yields of dimethylethynylcarbinol and 15% yields of the glycol by this method, on 5-mole runs. See J. F. Froning, Master's Dissertation, University of Notre Dame, 1938. [b] Other workers have obtained poor yields from acetophenone. See Carothers and Coffman, THIS JOURNAL, **54**, 4071 (1932).

Summary

1. A general method has been described for the preparation of acetylenic carbinols from the sodium salt of acetylene or a monoalkylacetylene, and an aldehyde or ketone, in liquid ammonia solution.
2. Several new acetylenic carbinols have been prepared and characterized.
3. The preparation of the chloride from methylethylethynylcarbinol has been described.

NOTRE DAME, INDIANA RECEIVED AUGUST 3, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY AND PHARMACOLOGY, SCHOOL OF MEDICINE AND DENTISTRY, THE UNIVERSITY OF ROCHESTER]

Relation of Refractive Index to Density in Dental Hard Tissues[1]

BY RICHARD S. MANLY[2]

In certain biological mixtures and in many mineral series, the refractive index has become valuable because it is linearly related to the density. Since in previous work[3] a number of density fractions of pure enamel and dentine had been prepared, the mean refractive indices were determined to discover any similar relations in these tissues.

The reported values for the refractive indices of enamel are in good agreement. Von Ebner[4] and Hoppe[5] report a figure of 1.627 for the ordinary ray and the former, 1.6234 for the extraordinary ray. Taylor and Sheard[6] and Eisenberg[7] noted that the refractive index of enamel prisms ranges between 1.612 and 1.625. Wishart in 1933 (personal communication) examined a few specimens of enamel and found the refractive index to be less than 1.625, usually near 1.618, but appearing to vary somewhat from that number. For two samples of normal dentine Taylor and Sheard[6] found a refractive index of 1.577 ± 0.003. No values for the refractive index of cementum have been reported.

Experimental

A "mean refractive index" was estimated by the following interpolation procedure. A few milligrams of the 60-mesh enamel or dentine powder was stirred into a drop of liquid of known refractive index and placed on a constant temperature stage under a microscope. A "sodium" filter (Eastman Kodak Co. filters nos. 64 and 73) was used over the light source. Determination of the mean refractive index, *i. e.*, the refractive index at which half the particles were higher and half lower than the liquid, was made by interpolation from the counts obtained with 3 or 4 different liquids.

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[1] This work was supported in part by the Rockefeller Foundation and in part by the Carnegie Corporation of New York.

[2] From a thesis submitted to the Division of Graduates Studies of the University of Rochester in partial fulfilment of the degree of Doctor of Philosophy, June, 1938.

[3] Manly, Hodge and Ange, *J. Dent. Research*, in press.

[4] Von Ebner, *Deut. Monatsh. Zahnhlk.*, **41**, 65 (1903).

[5] Hoppe, *Virchow's Arch. path. Anat.*, **24**, 13 (1892).

[6] Taylor and Sheard, *Proc. Soc. Exptl. Biol. Med.*, **26**, 257 (1928); *J. Biol. Chem.*, **81**, 479 (1929).

[7] Eisenberg, *Am. Dental Surg.*, **50**, 225 (1930).

The counting method employed was the Becke line test.[8,9] One hundred particles were counted for each sample in various liquids. For refractive index standards, mixtures of α-chloronaphthalene ($n^{25}\text{D}$ 1.63) and liquid petrolatum ($n^{25}\text{D}$ 1.475) were prepared whose indices ranged from 1.530 to 1.630 in steps of 0.005. Calibration was made at 25 ± 0.1° with an Abbe refractometer.

Discussion

In enamel a proportionality exists between the mean density and refractive index as shown in Fig. 1. The equation is $d = 7.69\ n - 9.494 \pm 0.001$. The probable error of n is ± 0.001, which is within the variations due to birefringence.[10] Inasmuch as mineral apatites usually have refractive indices of about 1.634, the upper limit of enamel is of interest: only 0.09% of the original enamel exhibited a refractive index greater than 1.6293.

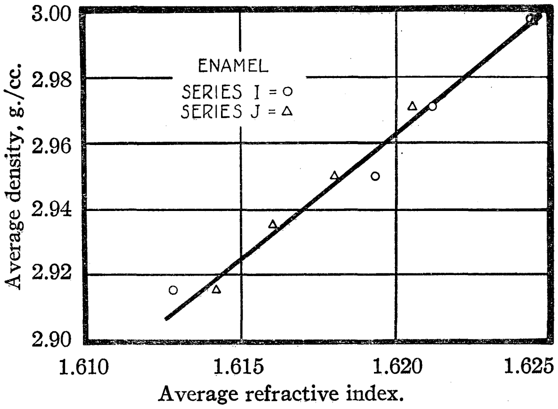

Fig. 1.—Enamel refractive index is proportional to the density.

In dentine the relation between refractive index and density is shown by the straight line in Fig. 2. The slope, 8.6, is somewhat steeper than that of enamel and the line lies 0.45 g. per cc. below the enamel curve when the latter is extrapolated to a density of 2.7. This fact suggested that the dentinal tubules were filled with air during the density and refractive index determinations. From the usual equation relating refractive index and density of a mixture[11] the volume per cent. of air, apatite, and protein in one dentine fraction (n, 1.5495; d, 2.135) was calculated. Values for density and refractive index of air, apatite and protein were taken from the literature. The calculated air space of 9 volume per cent. compares favorably with Feiler's estimation[12] of 12 to 24% tubule space. The calculated inorganic percentage was 75.0, in fair agreement with the value 78.4%, found by analysis.

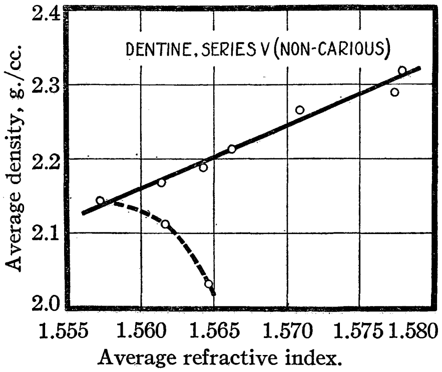

Fig. 2.—Refractive index–density relations for dentine. The two points on the dotted line are cementum.

Pulverized secondary cementum was found to have a refractive index range of 1.560 to 1.570. The two points on the dotted line of Fig. 2 are cementum, since they fall within this range and have the correct density[3] for cementum.

On vacuum drying for seven hours at 110°, an average decrease of 0.0018 was found in refractive index on six fractions of enamel. With dentine the decrease was much greater, 0.02–0.03, and the linear relationship with the original, oven-dry density was abolished. Cementum, on the other hand, behaved like enamel since the refractive index of the *oven-dry* material was decreased by only 0.001 on vacuum drying while the refractive index of *air-dry* cementum actually increased with the same treatment. As a tentative explanation for these differences in behavior, it may be assumed that neither capillary formation nor shrinkage is possible in the highly consolidated enamel, the former occurs chiefly in dentine and the latter in cementum.

A difference has been observed in the refractive index behavior of the inorganic salts of enamel and dentine. When ashed by glycol procedure[13] the refractive index of the inorganic material of dentine was 1.591–1.605, of enamel, 1.614. Heating the dentine ash or the unashed dentine for five hours at 900° raised the refractive index to 1.641–1.644, showing an essential change in structure. Enamel became opaque after five hours at

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(8) Becke, *Tschermak's mineralog. petrog. Mitt.*, **13**, 385 (1892).

(9) Larsen, U. S. Geol. Survey, Bull., Cir., Professional Papers, Water Supply Papers, No. 679, 1921.

(10) Keil, *Z. Zellforsch.*, **25**, 204 (1936).

(11) F. H. Getman, "Outlines of Theoretical Chemistry," 4th ed., John Wiley and Sons, Inc., New York, N. Y., 1928, p. 131.

(12) Feiler, *Deut. Monatsh. Zahnhlk.*, **41**, 65 (1923).

(13) LeFevre and Manly, *J. Am. Dental Assoc.*, **25**, 233 (1938).

900°, making refractive index determinations impossible.

Acknowledgment.—The author is glad to acknowledge the enthusiastic counsel of Dr. Harold C. Hodge throughout the course of the work.

Summary

1. The mean refractive indices of powdered enamel and dentine samples, with differing and known density limits, were determined by the Becke line procedure.

2. The refractive indices of dried enamel lie between 1.612 and 1.630 and are proportional to the density.

3. The refractive indices of dried dentine lie between 1.555 and 1.580 and are roughly proportional to the density when the fractions are dried under the same conditions for both determinations. Vacuum drying brought about a marked lowering of refractive index.

4. Secondary cementum exhibited a refractive index of 1.560–1.570 which was little affected by vacuum drying.

RECEIVED SEPTEMBER 9, 1938

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 668]

The Crystal Structure of Ammonium Cadmium Chloride, NH_4CdCl_3

BY HENRI BRASSEUR[1] AND LINUS PAULING

In crystalline cadmium chloride, $CdCl_2$, there are octahedral groups $CdCl_6$ condensed into layers, each chlorine atom being adjacent to three cadmium atoms.[2] Tetrahedral coördination is shown by cadmium[3] with cyanide groups in $K_2Cd(CN)_4$, and with sulfur, selenium and tellurium atoms in the sphalerite and wurtzite type crystals CdS, CdSe and CdTe, and might well occur with chlorine also. There are accordingly two types of reasonable structures for complexes with the composition $(CdCl_3)_x$, the first involving octahedra with shared corners, as for example in the cubic crystal $KMgF_3$, and the second involving rings or chains of tetrahedra, as in the metasilicates. We have determined completely the structure of the orthorhombic crystal NH_4CdCl_3, and have found it to be based on octahedral coördination about the cadmium atoms, the $CdCl_6$ octahedra being polymerized into infinite double rutile strings which extend parallel to the *c*-axis of the crystal.

Experimental Methods and Results

The crystals of NH_4CdCl_3 used in this investigation were obtained by evaporation of an aqueous solution containing equimolar amounts of NH_4Cl and $CdCl_2$. The transparent white needles used for the x-ray photographs were about 0.1 sq. mm. in cross section and 3 to 10 mm. in length. In addition to single crystals many twins were obtained; the nature of the twinning was not studied.

Crystallographic study[4] has shown the crystals to be orthorhombic, with axial ratios 0.6059:1:0.7992 and density 2.93. X-ray photographs prepared with 15° oscillation about the directions [100], [010], and [001], with use of CuKα radiation filtered through nickel, gave the following dimensions for the unit cell

$$a_0 = 8.96 \pm 0.02 \text{ Å.}$$
$$b_0 = 14.87 \pm 0.03 \text{ Å.}$$
$$c_0 = 3.97 \pm 0.01 \text{ Å.}$$

These lead to the axial ratios 0.603:1:0.267, in good agreement with the crystallographic values, after dividing the crystallographic *c*-axis by three. All indices used in this paper refer to the X-ray axes a_0, b_0, c_0 given above.

The observed reflections show the lattice to be simple. The absence of prism reflections $\{h0l\}$ with h odd and $\{0kl\}$ with $k + l$ odd provides strong evidence that the space group is $D_{2h}^{16}-Pnam$ or its subgroup $C_{2v}^{9}-Pna$. In the absence of any observed deviation from holohedral habit of the crystals, we have assumed the space group to be D_{2h}^{16}; this assumption is given later justification by the derivation of a satisfactory atomic arrangement based on the holohedral space group.

The Atomic Arrangement

The sets of equivalent positions provided by $D_{2h}^{16}-Pnam$ are

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(1) Fellow of the Belgian-American Educational Foundation.

(2) L. Pauling, *Proc. Natl. Acad. Sci.*, **15**, 709 (1929); L. Pauling and J. L. Hoard, *Z. Krist.*, **74**, 546 (1930).

(3) R. G. Dickinson, THIS JOURNAL, **44**, 774 (1922).

(4) H. Traube, *Z. Krist.*, **29**, 602 (1898); A. Johnsen, *N. Jahrb. Mineral.*, **2**, 115 (1903).

4a: $000,\ 0\tfrac{1}{2}0,\ \tfrac{1}{2}0\tfrac{1}{2},\ \tfrac{1}{2}\tfrac{1}{2}\tfrac{1}{2}$
4b: $00\tfrac{1}{2},\ 0\tfrac{1}{2}\tfrac{1}{2},\ \tfrac{1}{2}00,\ \tfrac{1}{2}\tfrac{1}{2}0$
4c: $xy\,1/4,\ \tfrac{1}{2}+x\ \tfrac{1}{2}-y\,1/4,\ \tfrac{1}{2}-x\ \tfrac{1}{2}+y\,3/4,\ \overline{xy}\,3/4$
8d: $xyz,\ \tfrac{1}{2}+x\ \tfrac{1}{2}-y\ z,\ \tfrac{1}{2}-x\ \tfrac{1}{2}+y\ \tfrac{1}{2}+z,\ \overline{xy}\ \tfrac{1}{2}+z,\ \overline{xyz},\ \tfrac{1}{2}-x\ \tfrac{1}{2}+y\ \bar{z},\ \tfrac{1}{2}+x,\ \tfrac{1}{2}-y\ \tfrac{1}{2}-z,\ xy\ \tfrac{1}{2}-z$

The unit cell contains 4 NH_4CdCl_3, the number of molecules calculated from the cell dimensions and density being 3.99. The possibility that 8 Cl occupy the positions 8d is ruled out by the small value 3.97 Å. of c_0, since the distance $c_0/2 = 1.99$ Å. between non-bonded chlorine atoms is very much less than that found in any crystal. It was noted, moreover, that the intensities of the X-ray reflections indicate strongly that all of the atoms are in planes $c_0/2$ apart. An arrangement of this type leads to the same structure factor for all the reflections ($hk0$), ($hk2$), ($hk4$), etc., and also for all the reflections ($hk1$), ($hk3$), etc.; and it was observed that on oscillation photographs the intensities of the reflections with $l = 2$ and $l = 4$ reproduce those with $l = 0$, but somewhat diminished because of the larger scattering angles, and that similarly the intensities of the reflections with $l = 3$ reproduce those with $l = 1$.

This observation requires that all of the atoms occupy the positions 4c, forming layers at $z = {}^1/_4$ and $z = {}^3/_4$. (Layers at $z = 0$ and $z = {}^1/_2$ are ruled out by the fact that positions 4a and 4b could accommodate only two of the five atoms in the molecule.)

There are ten parameters to be evaluated in the determination of the atomic arrangement: x_{NH_4}, y_{NH_4}, x_{Cd}, y_{Cd}, x_I, y_I, x_{II}, y_{II}, x_{III} and y_{III} (the subscripts I, II and III referring to the three non-equivalent sets of chlorine atoms). As the first step in this process sections of the three-dimensional Patterson-Fourier diagram[5] were made for the levels $z = 0$ and $z = {}^1/_2$, as recommended by Harker,[6] with use of the general equation

$$P(x,y,z) = \Sigma_h \Sigma_k \Sigma_l \mid F_{hkl} \mid^2 \cos 2\pi(hx + ky + lz) \quad (1)$$

The calculations could be based on the observed values of intensities of planes ($hk0$) and ($hk1$) alone, because of the intensity regularities, mentioned above, which result from the special values ${}^1/_4$ and ${}^3/_4$ for the z coördinates of all the atoms. The function f^2/Z^2 (f being the atomic scattering power and Z the atomic number) in its dependence on $\sin \theta/\lambda$ has nearly the same values for the atoms Cd, Cl, and N. An averaged function for these atoms was plotted, and summed over l for series of reflections (hkl), with l either even or odd, in order to obtain the factors with which the intensities for reflections ($hk0$) and ($hk1$) were multiplied to give the sums over l in Equation 1. The remaining double summations for $z = 0$ and $z = {}^1/_2$ were then carried out with the aid of the Beevers–Lipson strips,[7] all of the data of Table I being used. The values of $\mid F \mid$ given in the table were obtained from visually estimated intensity values by correction for the Lorentz and polarization factors, the temperature factor being ignored. Contour diagrams representing the results of the calculations are shown as Figs. 1 and 2.

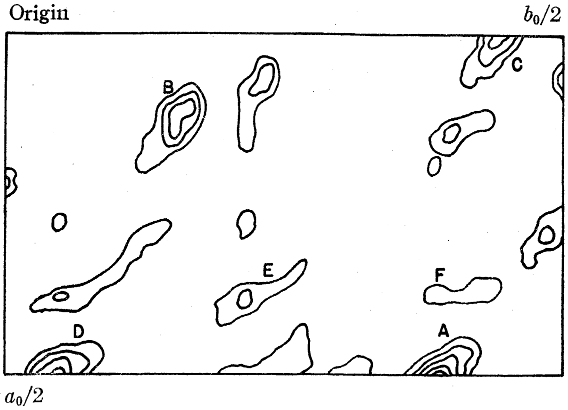

Fig. 1.—Patterson–Harker diagram for the section $z = 0$. The peaks represent the following principal interatomic distances: A, Cd-Cd; B, Cd-Cl_I, Cd-Cl_{III}; C, Cd-Cl_{II} (occurring twice); D, Cd-Cl_{II}, Cd-Cl_I; E, Cd-Cl_I; F, Cd-Cl_{III}.

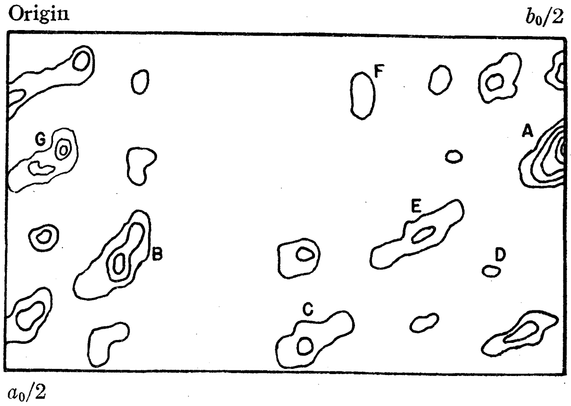

Fig. 2.—Patterson–Harker diagram for the section $z = {}^1/_2$. The peaks represent the following principal interatomic distances: A, Cd-Cd; B, Cd-Cd; C, Cd-Cl_I; Cd-Cl_{II}; E, Cd-Cl_{III}; F, Cd-Cl_I; G, Cd-Cl_{II}; Cd-Cl_{III}.

Peaks in the Patterson–Fourier diagrams represent interatomic distance vectors between pairs of atoms extending from the origin, weighted by the

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[5] A. L. Patterson, *Z. Krist.*, **90**, 517 (1935).

[6] D. Harker, *J. Chem. Phys.*, **4**, 381 (1936).

[7] C. A. Beevers and H. Lipson, *Phil. Mag.*, **17**, 855 (1934); *Proc. Phys. Soc.* (London), **48**, 772 (1936).

TABLE I

Reflections *hk*0, *h*+*k* even. Structure factor: $4\ \Sigma_i f_i \cos hx_i \cos ky_i$

$hk0$	$\frac{1}{4} F_{\text{calcd.}}$	$\frac{1}{4}\lvert F\rvert_{\text{obsd.}}$	$hk0$	$\frac{1}{4} F_{\text{calcd.}}$	$\frac{1}{4}\lvert F\rvert_{\text{obsd.}}$	$hk0$	$\frac{1}{4} F_{\text{calcd.}}$	$\frac{1}{4}\lvert F\rvert_{\text{obsd.}}$	$hk0$	$\frac{1}{4} F_{\text{calcd.}}$	$\frac{1}{4}\lvert F\rvert_{\text{obsd.}}$	$hk0$	$\frac{1}{4} F_{\text{calcd.}}$	$\frac{1}{4}\lvert F\rvert_{\text{obsd.}}$
020	36.9	24.4	190	−11.0	13.1	370	−24.3	30.4	570	−8.4	5.1	7·11·0	−14.5	7.4
040	18.8	15.1	11·1·0	−10.8	7.4	390	46.9	46.1	590	−18.7	18.6	7·13·0	−6.9	....
060	−11.6	14.8	11·3·0	−10.5	....	3·11·0	32.4	39.6	5·11·0	−2.9	2.6	820	−10.1	4.0
080	−21.8	22.1	11·5·0	−6.3	....	3·13·0	13.0	21.8	5·13·0	−12.1	....	840	−8.1	7.7
0·10·0	−4.2	....	11·7·0	−8.7	....	3·15·0	−8.5	7.4	5·15·0	−4.1	6.5	860	−2.0	....
0·12·0	−11.8	8.0	11·9·0	15.0	9.1	3·17·0	−16.3	21.8	620	35.6	33.3	880	7.7	7.7
0·14·0	9.6	8.2	220	−10.2	8.8	420	−21.6	19.5	640	9.2	5.0	8·10·0	7.6	10.5
0·16·0	11.6	14.8	240	−27.2	16.8	440	−10.5	12.2	660	−9.2	15.6	8·12·0	2.9	....
0·18·0	38.2	46.5	260	0.2	....	460	−5.4	....	680	−11.1	14.2	910	−15.1	18.2
200	−23.4	14.0	280	11.8	9.4	480	11.7	14.5	6·10·0	−12.6	16.5	930	−0.7	....
400	−9.8	5.1	2·10·0	13.2	9.4	4·10·0	18.6	13.8	6·12·0	−3.9	....	950	4.0	....
600	37.4	31.8	2·12·0	11.6	13.1	4·12·0	−0.2	....	6·14·0	4.0	....	970	29.9	25.8
800	−15.3	12.2	2·14·0	−19.7	21.1	4·14·0	−4.3	....	710	15.3	12.2	990	23.6	30.9
10·0·0	−13.4	10.5	2·16·0	−8.7	10.5	4·16·0	−20.0	21.8	730	−5.4	....	9·11·0	31.6	41.7
110	23.1	10.0	310	−12.4	12.5	510	14.0	11.1	750	−0.5	....	10·2·0	−16.9	17.9
130	7.1	3.5	330	−19.2	10.4	530	−6.9	....	770	−23.2	25.6	10·4·0	−3.7	....
150	−27.7	17.3	350	13.5	14.8	550	−17.6	26.4	790	−5.4	7.9	10·6·0	1.9	....
170	−17.7	18.4												

Reflections *hk*0, *h*+*k* odd. Structure factor: $4\ \Sigma_i f_i \sin hx_i \sin ky_i$

120	24.8	12.9	2·11·0	−15.7	16.8	450	−26.8	32.5	610	−9.8	7.1	7·14·0	−24.5	31.5
140	23.6	16.0	2·13·0	−16.5	20.0	470	−10.3	6.8	630	−1.5	....	810	9.8	5.4
160	36.4	33.4	2·15·0	−20.0	17.6	490	−5.2	....	650	5.0	....	830	5.8	2.8
180	1.5	....	2·17·0	1.6	....	4·11·0	10.8	15.7	670	6.5	8.0	850	27.1	35.6
1·10·0	−3.8	6.8	320	8.1	17.7	4·13·0	8.8	11.9	690	5.8	8.0	870	22.1	23.8
1·12·0	−24.9	24.8	340	8.2	7.4	4·15·0	19.7	18.2	6·11·0	9.3	8.0	890	4.6	....
1·14·0	−22.9	33.8	360	−5.8	2.0	520	23.6	25.7	6·13·0	2.9	10.5	8·11·0	−9.2	6.3
1·16·0	−13.8	3.7	380	10.2	6.3	540	29.6	32.5	6·15·0	−4.9	....	8·13·0	−32.5	40.2
1·18·0	−10.5	2.8	3·10·0	−11.4	....	560	−13.2	12.2	720	6.5	7.8	920	−6.0	....
210	9.8	6.5	3·12·0	−2.1	....	580	−7.3	....	740	16.0	20.2	940	−2.7	....
230	29.9	19.7	3·14·0	−2.8	....	5·10·0	9.0	10.7	760	22.8	19.7	960	4.6	8.3
250	28.5	17.9	3·16·0	1.1	....	5·12·0	10.7	....	780	15.7	18.9	980	10.0	6.6
270	28.8	18.5	410	11.1	3.2	5·14·0	20.5	16.6	7·10·0	−8.6	7.7	9·10·0	−1.4	5.4
290	5.0	....	430	−37.9	45.5	5·16·0	23.4	29.3	7·12·0	−23.2	23.7			

Reflections *hk*1, *h*+*k* even. Structure factor: $4\ \Sigma_i f_i \sin hx_i \cos ky_i$

$hk1$			$hk1$			$hk1$			$hk1$			$hk1$		
111	27.1	16.2	2·10·1	−15.0	13.3	441	−11.1	11.9	5·15·1	−7.3	11.6	7·11·1	−12.6	....
131	−3.9	5.4	2·12·1	−3.9	....	461	−5.0	....	601	−3.4	....	801	45.4	46.9
151	−3.2	....	2·14·1	3.8	6.1	481	17.7	16.9	621	8.3	6.0	821	17.9	23.5
171	−38.9	37.7	2·16·1	19.2	20.0	4·10·1	21.4	16.8	641	−10.5	3.4	841	−1.2	1.7
191	−23.2	24.6	311	4.9	1.4	4·12·1	6.2	....	661	−3.1	....	861	−10.4	3.7
1·11·1	−28.3	21.1	331	0.1	....	4·14·1	−7.4	....	681	5.5	7.4	881	−12.5	12.3
1·13·1	−10.9	13.1	351	−8.9	7.4	4·16·1	−29.7	24.6	6·10·1	3.2	....	8·10·1	−4.1	....
1·15·1	0.6	8.2	371	5.6	....	511	−8.8	6.5	6·12·1	7.2	....	8·12·1	−10.0	4.8
1·17·1	9.1	4.0	391	−4.9	....	531	−12.5	15.4	6·14·1	−11.2	7.4	911	6.6	....
201	38.3	22.5	3·11·1	9.0	12.2	551	12.2	14.5	711	16.8	20.7	931	1.4	7.1
221	44.9	23.3	3·13·1	−4.6	....	571	17.6	22.9	731	6.8	....	951	−10.6	9.1
241	12.0	4.3	3·15·1	−4.2	....	591	36.3	37.6	751	−24.4	21.9	971	0.6	....
261	−9.8	10.0	401	−27.9	21.0	5·11·1	27.1	36.8	771	−23.0	26.0	991	3.7	....
281	−11.8	10.5	421	−32.5	29.3	5·13·1	13.8	....	791	−27.6	22.0			

Reflections *hk*1, *h*+*k* odd. Structure factor: $4\ \Sigma_i f_i \cos hx_i \sin ky_i$

011	13.4	5.4	1·14·1	−17.6	16.9	3·10·1	14.1	16.8	581	15.3	11.6	781	−1.2	....
031	13.3	7.9	1·16·1	−7.2	....	3·12·1	11.4	7.4	5·10·1	−9.7	....	7·10·1	3.8	....
051	45.6	44.9	211	−27.4	23.9	3·14·1	23.2	21.8	5·12·1	13.4	21.3	7·12·1	−19.5	19.4
071	28.0	29.6	231	−16.8	17.5	3·16·1	27.5	31.2	5·14·1	−14.8	6.5	811	−6.6	....
091	7.6	....	251	−18.9	11.8	411	−2.8	....	611	5.9	7.1	831	−11.4	15.1
0·11·1	−7.1	8.2	271	−4.8	5.7	431	−27.9	27.9	631	20.2	26.4	851	−12.5	8.3
0·13·1	−36.9	41.0	291	8.5	8.3	451	13.9	14.5	651	23.7	32.4	871	−3.9	11.1
0·15·1	7.0	15.7	2·11·1	−4.4	....	471	−3.2	....	671	24.4	26.0	891	−1.2	....
0·17·1	6.3	....	2·13·1	9.1	5.1	491	−1.4	....	691	4.8	....	8·11·1	2.7	11.6
121	2.8	4.0	2·15·1	4.6	6.8	4·11·1	5.6	10.2	6·11·1	−17.1	24.0	921	−18.9	17.8
141	8.5	5.4	2·17·1	15.5	11.7	4·13·1	0.5	....	6·13·1	−20.7	24.8	941	−16.2	10.5
161	20.8	15.2	321	31.2	29.3	4·15·1	14.9	12.5	721	7.2	7.1	961	−25.7	31.6
181	16.9	18.6	341	−37.4	31.8	521	−2.8	4.0	741	7.1	7.4	981	−0.9	....
1·10·1	9.2	16.8	361	17.3	16.9	541	16.8	14.2	761	20.2	19.4	9·10·1	2.8	....
1·12·1	−17.1	23.1	381	−9.3	2.0	561	6.3	3.4						

products of the scattering powers of the atoms. The principal peaks expected are those for Cd–Cd and Cd–Cl. At $z = 0$ the Cd–Cd peak should occur for the two atoms at x_{Cd}, y_{Cd} $^1/_4$ and $^1/_2$ +

$x_{Cd}\ ^1/_2 - y_{Cd}\ ^1/_4$; that is, at the point $^1/_2\ ^1/_2 - 2y_{Cd}$. The most pronounced peak in Fig. 1 is in fact at $^1/_2$, 0.385, corresponding to $y_{Cd} = 0.0575$. The most pronounced peak of Fig. 2, at 0.1667, $^1/_2$, similarly corresponds to $^1/_2 - 2x_{Cd}\ ^1/_2$, and leads to the value $x_{Cd} = 0.1667$. Another Cd–Cd peak, at $2x_{Cd}2y_{Cd}$, also appears on this diagram in the position required by these parameter values.

These values of x_{Cd} and y_{Cd} can be combined with the coördinates of the remaining peaks to obtain values for the coördinates for chlorine atoms. Thus for the level $z = 0$ Cd–Cl or Cd–N peaks are expected at $x_{Cd} - x, y_{Cd} - y$; $^1/_2 + x_{Cd} - x$, $^1/_2 - y_{Cd} - y$; etc. The parameter values obtained in this way are

$$\begin{aligned} x_{I} &= 0.305 & y_{I} &= 0.219 \\ x_{II} &= .164 & y_{II} &= .505 \\ x_{III} &= .025 & y_{III} &= .893 \end{aligned}$$

In addition the ammonium ions can be assigned the parameter values $x_{NH_4} = 0.43$, $y_{NH_4} = 0.82$, inasmuch as these positions are the only ones compatible with a minimum NH_4–Cl distance of about 3.1 Å. These parameter values lead to a structure which is stereochemically satisfactory, as described below.

In order to obtain more accurate values of the parameters a section at $z = {}^1/_4$ of a three-dimensional Bragg–Fourier calculation was carried out, with use as the signs of the F's of those given by the approximate parameter values. The summation over l for the series

$$D(x,y,z) = \Sigma_h\, \Sigma_k\, \Sigma_l\, F_{hkl} \cos 2\pi(hx + ky + lz) \qquad (2)$$

was made in a way similar to that for the Patterson diagrams, namely, by summing the quantity f/Z for series of reflections (hkl) with l even or odd to obtain factors for F_{hk0} and F_{hk1}.

The Bragg–Fourier diagram at $z = {}^1/_4$, shown as Fig. 3, has a very high peak for the cadmium atom, three peaks for the three chlorine atoms, and a small peak for the ammonium ion, in positions corresponding to the following parameter values, which differ by only small amounts from the initial values:

$$\begin{aligned} x_{Cd} &= 0.165 & y_{Cd} &= 0.054 \\ x_{I} &= .284 & y_{I} &= .215 \\ x_{II} &= .167 & y_{II} &= .496 \\ x_{III} &= .026 & y_{III} &= .898 \\ x_{NH_4} &= .43 & y_{NH_4} &= .82 \end{aligned}$$

The agreement between observed and calculated amplitudes of reflection is seen from Table I to be satisfactory. Screening-constant atomic scattering factors[8] were used in the calculation of the F values.

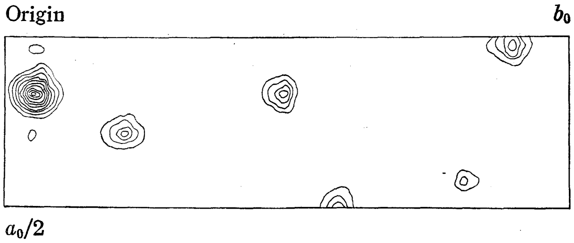

Fig. 3.—Bragg–Fourier diagram for the section $z = {}^1/_4$. The four peaks in the upper part of the diagram represent, from left to right, the atoms Cd, Cl_I, Cl_{II}, and Cl_{III}, and the two peaks below represent Cl_{II} (in part) and NH_4.

Description of the Structure

The structure found for NH_4CdCl_3 is shown in Fig. 4. Each cadmium atom is surrounded by six chlorine atoms, which form a nearly regular octahedron. The Cd–Cl distances have the values 2.60 (2), 2.62, 2.64, and 2.72 (2) Å., the average of these, 2.65 Å., being almost identical with the Cd–Cl distance in $CdCl_2$, 2.66 Å. The variation about the average is probably not real, but the result of small errors in the parameter values. The Cl–Cl distances along octahedral edges have the values 3.53 (2), 3.68 (2), 3.69 (2), 3.73 (2), 3.80 (2), and 3.97 (2) Å. Each octahedron shares two opposed edges with other octahedra to form octahedral strings parallel to the c-axis, as in the rutile structure. These rutile

TABLE II

INTERATOMIC DISTANCES IN NH_4CdCl_3

Atom	Neighbors	Distance Å.	Atom	Neighbors	Distance Å.
Cd	2 Cl_{II}	2.60	Cl_{II}	2 Cd	2.60
	1 Cl_I	2.62		2 NH_4	3.40
	1 Cl_{III}	2.64		1 NH_4	3.47
	2 Cl_{III}	2.72		1 Cl_{III}	3.53
				2 Cl_{II}	3.62
NH_4	4 Cl_I	3.27		2 Cl_I	3.76
	1 Cl_{III}	3.34		2 Cl_{III}	3.80
	2 Cl_{II}	3.40		2 Cl_{II}	3.97
	1 Cl_{II}	3.47		1 Cl_I	4.30
	1 Cl_{III}	3.82		1 Cl_I	4.64
Cl_I	1 Cd	2.62	Cl_{III}	1 Cd	2.64
	4 NH_4	3.27		2 Cd	2.72
	2 Cl_{II}	3.73		1 NH_4	3.34
	2 Cl_{III}	3.76		1 NH_4	3.82
	2 Cl_{III}	3.80		1 Cl_{II}	3.53
	2 Cl_I	3.97		2 Cl_{III}	3.68
	1 Cl_{II}	4.30		2 Cl_{II}	3.69
	2 Cl_I	4.59		2 Cl_I	3.76
	1 Cl_{II}	4.64		2 Cl_I	3.80
				2 Cl_{III}	3.97

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[8] L. Pauling and J. Sherman, *Z. Krist.*, **81**, 1 (1932).

strings are further condensed in pairs, each octahedron sharing two edges with octahedra of the adjacent string. The four shared edges are, as usual for partially ionic crystals, somewhat shorter than the unshared edges.

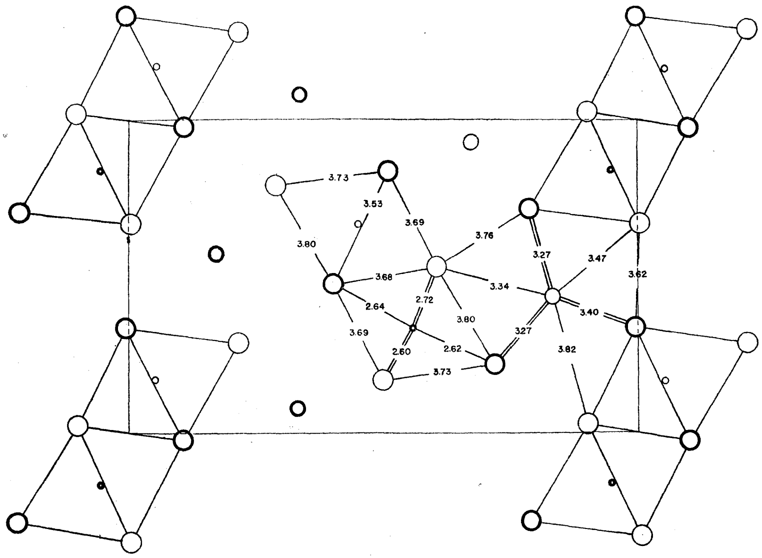

Fig. 4.—The structure of NH_4CdCl_3, projected on the plane (001). Light circles represent atoms at $z = {}^1/_4$ and heavy circles those at $z = {}^3/_4$. Cadmium and chlorine atoms are shown as small and large circles, and ammonium ions as circles of intermediate size.

Each ammonium ion is in contact with nine chlorine atoms, at about 3.27 (2), 3.27 (2), 3.34, 3.40 (2), 3.47, and 3.82 Å. The average of these distances, excluding the largest, is 3.31 Å., which is nearly the same as in NH_4Cl (NH_4–Cl = 3.27 Å. for the high temperature form, with the sodium chloride structure, and 3.34 Å. for the low temperature form, with the cesium chloride structure). The nine chlorine atoms are arranged in the most compact configuration possible for coördination number nine—a triangle of three in the equator, and smaller triangles above and below rotated through 60°. The Cl–Cl distances along the edges of this polyhedron have the values 3.62 (2), 3.69 (2), 3.73 (2), 3.76 (4), 3.80 (2), 4.30 (2), 4.59 (2), and 4.64 (2) Å.

Cleavage along planes of the zone [001] might be expected for the crystal; no cleavage has been reported, however, nor did we observe any in experiments with our small crystals.

The chlorine atoms form bonds to the following numbers:

Cl_I: 1 with Cd, 4 with NH_4
Cl_{II}: 2 with Cd, 3 with NH_4
Cl_{III}: 3 with Cd, 2 with NH_4

These have the total strengths 7/9, 1, and 11/9, respectively; there is, accordingly, some discrepancy with the electrostatic valence rule.[9] It is interesting that the substance crystallizes with this structure rather than a structure such as that of $KMgF_3$, in which the halogen atoms are equivalent, each being common to two octahedra.

The arrangement of the chlorine atoms is compact; as shown in Table II, each chlorine atom has eleven or twelve chlorine atoms as neighbors, at distances between 3.53 and 4.64 Å.

The authors are indebted to the Belgian-American Foundation for the grant of a Fellowship to one of them, permitting this investigation to be carried out.

Summary

A complete structure determination has been made of the orthorhombic crystal NH_4CdCl_3. The unit of structure has the dimensions a_0 = 8.96 ± 0.02 Å., b_0 = 14.87 ± 0.03 Å., c_0 = 3.97 ± 0.01 Å., and contains 4 NH_4CdCl_3. The atomic positions are $xy\ 1/4,\ \frac{1}{2}+x\ \frac{1}{2}-y\ 1/4,\ \frac{1}{2}-x\ \frac{1}{2}+y\ 3/4,\ \overline{xy}\ 3/4$ of the space group $D_{2h}^{16} - Pnam$, with the following parameter values x, y: Cd, 0.165, 0.054; Cl_I, 0.284, 0.215; Cl_{II}, 0.167, 0.496; Cl_{III}, 0.026, 0.898; NH_4, 0.43, 0.82.

The $CdCl_3$ complexes occur in the crystal as infinite polymers, in the form of double rutile strings of $CdCl_6$ octahedra parallel to the c-axis. These complexes are held together by ammonium ions, each of which has nine chlorine atoms coördinated about it. Interatomic distances in the crystal (Table II) are closely related to those in $CdCl_2$ and NH_4Cl.

PASADENA, CALIF. RECEIVED SEPTEMBER 6, 1938

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(9) L. Pauling, THIS JOURNAL, **51**, 1010 (1929).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

The Inversion of Sucrose

BY PAUL M. LEININGER[1] AND MARTIN KILPATRICK

In a paper on electrolyte effects in reactions between a non-electrolyte and the hydrogen ion[2] two typical examples were given, representative of electrolyte effects in (1) reactions showing specific catalysis by the hydrogen ion, and (2) reactions showing acid catalysis in the general sense. This classification has been clarified by experiments in solutions of heavy water,[3] and by Pedersen's analysis of prototropic reactions.[4]

From an examination of the electrolyte effects it appeared that the inversion of sucrose and the hydrolysis of the acetals should be considered purely as catalysis by the hydrogen ion. Evidence of catalytic effects of acid molecules has been advanced by Hammett and Paul,[5] and by Gross, Steiner and Suess.[6] Experiments on the inversion of sucrose in acetate–acetic acid buffer solutions have shown, however, there is no detectable catalytic effect of the molecules of such a weak acid as acetic.[7]

If we are dealing with a case of specific hydrogen-ion catalysis, we can for aqueous solutions postulate the equilibrium

$$S + H_3O^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \left\{ S{\cdot}H_3O \right\}^+ \xrightarrow{k_2} \text{Products} \quad (1)$$

where $k_2 \ll k_{-1}$ and the equilibrium concentration is maintained at all times. The velocity constant is given by

$$k = \frac{k_1}{k_{-1}} k_2 = Kk_2 \quad (2)$$

Now K will vary with the electrolyte concentration, and the resulting change in the concentration of the collision complex will cause a change in the measured velocity constant k. These changes have been observed for the hydrolysis of the acetals and for the inversion of sucrose, but even in dilute solution they seem larger than one would expect, by analogy, from an examination of the change, with electrolyte concentration, of the dissociation constant of anilinium or *o*-chloroanilinium ion.[8,9]

Pedersen determined these two equilibrium constants over a convenient range of temperature, and found no great change in the heat of dissociation (ΔH) with temperature, in contrast to the marked variation of the heat of dissociation with temperature for uncharged acids. By analogy it might be expected that for reactions between a non-electrolyte and an ion, as represented by equation (1), there would be little change with temperature in E_A, the heat of activation computed from the integrated form of the Arrhenius equation

$$E_A = \frac{2.303\, RT_1T_2}{T_1 - T_2} \log \frac{k_{T_1}}{k_{T_2}} \quad (3)$$

where k_{T_1} and k_{T_2} are the velocity constants at temperatures T_1 and T_2, respectively. This seems to be the case for the hydrolysis of diethyl acetal.[2]

An examination of the extensive literature on sucrose inversion (on which some excellent experimental work has been done) yields a number of surprises. For example, in a recent number of THIS JOURNAL we have "The activation energy of 25.7 ± 0.05 kcal. found in the present work on sucrose is in good agreement with 25.83 and 25.8 kcal. obtained by others."[10] The statement ±0.05 kcal. seems hardly justified, since calculation of E_A by equation (3) over the three temperature intervals shows a variation of approximately ±1000 cal. In the same number a communication on the present study[11] calls attention to the fact that the energy of activation varies both with temperature and with concentration of hydrochloric acid. The effect of temperature was reported by Moelwyn-Hughes,[12] who showed that some of the earlier work also revealed a decrease in the activation energy with rise in temperature. The effect of electrolyte concentration on E_A calculated by a method similar to equation (3) has been independently reported by Duboux,[13]

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[1] E. I. du Pont de Nemours and Company Fellow, 1938.

[2] Riesch and Kilpatrick, *J. Phys. Chem.*, **39**, 561 (1935).

[3] For references and discussion see Bonhoeffer, *Trans. Faraday Soc.*, **34**, 252 (1938).

[4] Pedersen, *ibid.*, **34**, 237 (1938).

[5] Hammett and Paul, THIS JOURNAL, **56**, 830 (1934).

[6] Gross, Steiner and Suess, *Trans. Faraday Soc.*, **32**, 883 (1936).

[7] These experiments were carried out in this Laboratory in 1929 by M. L. Kilpatrick.

[8] Pedersen, *Kgl. Danske Videnskab, selskab, Math.-fys. Medd.*, **14**, No. 9 (1937).

[9] Pedersen, *ibid.*, **15**, No. 3 (1937).

[10] Heidt and Purves, THIS JOURNAL, **60**, 1206 (1938).

[11] Leininger and Kilpatrick, *ibid.*, **60**, 1268 (1938).

[12] Moelwyn-Hughes, *Z. physik. Chem.*, **B26**, 281 (1934).

[13] Duboux, *Helv. Chim. Acta*, **21**, 236 (1938).

but Duboux seems unaware of the decrease in energy of activation with increasing temperature reported by Moelwyn-Hughes. Quite recently Pearce and Thomas[14] determined the velocity constants for the inversion of sucrose in 1 molal hydrochloric acid solution in the presence of various salts, and concluded that the heat of activation was practically constant and independent of the nature of the salt. Finally, an examination of the data in the literature indicates that the velocity constant and the energy of activation are also dependent on the initial sucrose concentration.

The present paper includes a report of the work with 0.0584 molar sucrose solutions over the temperature range 0–40°, and with concentrations of hydrochloric acid up to four molar. The results obtained indicate that the literature on the sucrose inversion presents a more understandable picture when one considers the variables, electrolyte and sugar concentration, as well as temperature and concentration of catalyst.

Experimental Part

Sucrose.—Merck best reagent sucrose was used. Several duplicate runs were made with Pfanstiehl special sucrose, but no difference in velocity was observed.

Hydrochloric Acid.—Baker C. P. analyzed hydrochloric acid was used. Here again the same results were obtained with solutions prepared from constant-boiling hydrochloric acid.

Sodium Chloride.—Kahlbaum "zur Analyse mit Garantieschein" grade of sodium chloride was used.

Dilatometers.—At 0° the dilatometer used was that described by Kilpatrick,[15] except for runs lasting over two days, where sealed dilatometers were used. At all other temperatures the dilatometers used were similar to those described by Brönsted, Kilpatrick and Kilpatrick.[16]

Thermostats.—Water-baths regulated to ±0.005° were electrically heated and controlled by relay circuits of radio tube type similar to the one described by Beaver and Beaver.[17] For the experiments at 0°, ice-packed Dewar flasks, kept in a refrigerator room, served as thermostats.

Determination of Temperature.—Temperatures were determined by means of a platinum resistance thermometer, calibrated by the Bureau of Standards, and used in conjunction with a Mueller bridge. Temperature regulation was better than ±0.005° at all temperatures with the possible exception of −0.01° for the long time runs. Although the individual temperatures are given only to one hundredth of a degree, the temperature interval was measured to one thousandth of a degree. The maximum possible error in the temperature interval was 0.01°.

Determination of Concentrations.—The sucrose concentration was known to 0.05%. The hydrochloric acid concentration was obtained by titration of the reacted mixture. The molarity of the hydrochloric acid was thus determined directly for each solution at the temperature at which the experiment had been carried out. The concentration of hydrochloric acid was known to 0.1%. The validity of the method was established by making a duplicate run with a hydrochloric acid solution made up by weight from constant-boiling acid.

Determination of Rate.—Solutions of sucrose and hydrochloric acid were brought to the temperature of the thermostat. A volume of the sucrose solution sufficient to make the resulting mixture 0.0584 molar with respect to sucrose was then added to the hydrochloric acid which had already been placed in the mixing vessel of the dilatometer. After thoroughly mixing, the solution was sealed off and the rate of contraction noted. At the higher temperatures it was necessary to evacuate the solutions before mixing in order to prevent formation of air bubbles during the course of the run. The reader is referred to an earlier paper[15] for the technique employed at 0°. In the case of the acid–salt mixtures, the sucrose was added to a hydrochloric acid solution in which a definite amount of sodium chloride had been dissolved. The velocity constants were evaluated by Guggenheim's method.[18]

Results

The reaction was of the first order over the entire range of temperature and concentration investigated. Scatchard,[19] and Reed and Theriault,[20] analyzing the data of Pennycuick,[21] arrived at similar conclusions.

In Table I are given the values of the observed velocity constant k (the number of moles of sucrose reacting per mole of sucrose per minute) obtained at −0.01°. In this table are also given the values of $k_{H_3O^+} = k/C_{H_3O^+}$ experimentally determined (column 3), and computed as will be described later (column 4).

TABLE I

ELECTROLYTE EFFECT AT −0.01°

HCl (moles/liter)	10^3k, min.$^{-1}$	$10^4k_{H_3O^+}{}^4$ obsd.	$10^4k_{H_3O^+}$, calcd.
0.5900	0.1024	1.736	1.766
1.049	.2450	2.335	2.275
2.207	.9745	4.416	4.306
2.687	1.504	5.595	5.611
3.172	2.295	7.235	7.331
3.714	3.624	9.758	9.885
4.228	5.307	12.55	13.12
4.695	8.110	17.27	16.98
5.239	11.90	22.71	22.91
5.773	18.30	31.71	30.76

In Table II are listed the values of $k_{H_3O^+}$ obtained at temperatures other than zero. The effect of sodium chloride upon $k_{H_3O^+}$ is shown by

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[14] Pearce and Thomas, *J. Phys. Chem.*, **42**, 455 (1938).

[15] Kilpatrick, THIS JOURNAL, **50**, 2891 (1928).

[16] Brönsted, Kilpatrick and Kilpatrick, *ibid.*, **51**, 428 (1929).

[17] Beaver and Beaver, *Ind. Eng. Chem.*, **15**, 359 (1923).

[18] Guggenheim, *Phil. Mag.*, **2**, 538–543 (1926).

[19] Scatchard, THIS JOURNAL, **48**, 2259 (1926).

[20] Reed and Theriault, *J. Phys. Chem.*, **34**, 950 (1931).

[21] Pennycuick, THIS JOURNAL, **48**, 6 (1926).

the experiments marked with an "*a*" in the table; in all cases the addition of the salt caused an increase in $k_{H_3O^+}$, but in no case was the increase as large as that corresponding to the addition of an equal amount of acid.

TABLE II

SUMMARY OF $k_{H_3O^+}$ VALUES

Temp., °C.	No. of expts.	HCl (moles/liter)	$10^3 k_{H_3O^+}$
10.00	1	1.124	1.305
10.00	2	2.141	2.178
10.00	2	2.997	3.365
10.00	2	3.905	5.350
10.00	2	4.592	7.767
10.00	1	1.122	2.019[a]
15.00	1	1.124	2.864
15.00	1	1.493	3.445
15.00	2	2.142	4.698
15.00	1	1.120	4.297[a]
20.00	2	0.9528	5.651
20.00	1	1.123	6.143
20.00	2	1.493	7.271
20.00	2	2.140	9.811
20.00	2	2.999	14.78
20.00	1	1.120	9.127[a]
25.00	1	0.4767	9.420
25.00	4	.9599	11.77
25.00	1	1.123	12.62
25.00	1	1.493	15.05
25.00	3	2.121	20.00
25.00	2	1.116	18.77[a]
30.00	1	0.2506	17.41
30.00	1	.4746	19.30
30.00	3	.6517	20.91
30.00	3	.9457	23.85
30.00	1	1.120	25.65
30.00	1	1.488	30.05
35.00	1	0.4767	37.90
35.00	4	.9519	46.68
35.00	1	.9500	44.00[b]
40.00	2	.2508	67.69
40.00	2	.4741	74.35
40.00	4	.6530	80.16

[a] Solution 1.003 molar with respect to added sodium chloride.

[b] Sucrose concentration reduced to 0.0146 molar.

Where more than one experiment was carried out at a given temperature and acid concentration, the average deviation of $k_{H_3O^+}$ from the mean was computed; the average of the average deviations for these experiments is 0.3%.

In Fig. 1, log $k_{H_3O^+}$ for a given concentration of hydrochloric acid is plotted against the reciprocal of the absolute temperature; the curves reading from top to bottom represent acid concentration of 4.592, 2.999, 2.140, 0.9528 and 0.4767 molar. In addition to our own results, we have plotted results obtained by other workers, as stated in the legend below the figure.

Hitchcock and Dougan[22] also used the dilatometric method to study the rate of inversion of sucrose; for solutions containing two grams of sucrose in 100 cc. of solution, their value of $k_{H_3O^+}$ at 25° differs by only 0.4% from ours at an acid concentration of one molar, but at half molar the difference is 1.9%.

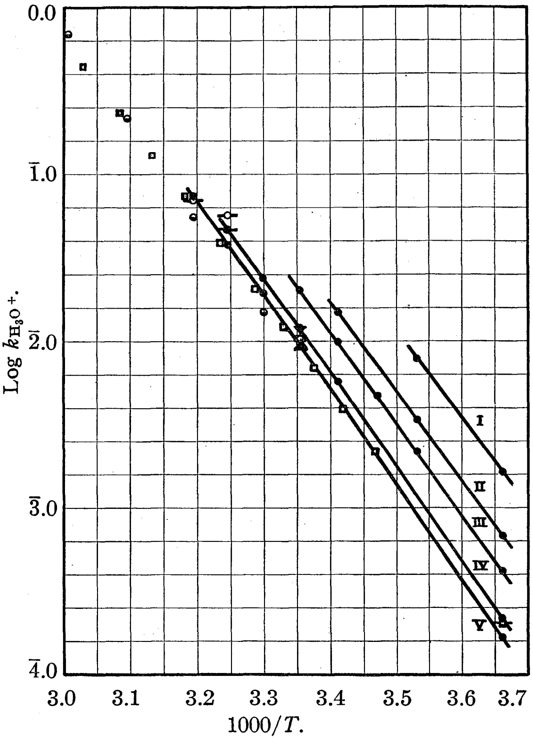

Fig. 1.—Variation of log $k_{H_3O^+}$ with 1000/*T*. Our data sucrose 2 g. per 100 cc. and: I, HCl 4.592 molar; II, HCl 2.999 molar; III, HCl 2.140 molar; IV, HCl 0.9528 molar; V, HCl 0.4767 molar. □, Moelwyn-Hughes,[12] 5% sucrose, HCl 0.19 molar. ◒, Heidt and Purves,[10] 0.01 molar sucrose, HCl 0.00965 molar. -□-, Duboux,[13] sucrose 11.42 g. per 100 cc., HCl 0.4767 molar. ▽, Sturtevant,[23] sucrose 0.1082 molar, HCl 0.5310 molar; sucrose 0.1152 molar, HCl 0.9059 molar. △, Hitchcock and Dougan,[22] sucrose 2 g. per 100 cc., HCl 0.486 molar; sucrose 10 g. per 100 cc., HCl 0.486 molar. -○-, Pennycuick,[21] sucrose 0.5 molar, HCl 0.507 molar and sucrose 0.5 molar, HCl 0.905 molar (at 35°); sucrose 0.5 molar, HCl 0.02 molar (at 40°).

Tables I and II and Fig. 1 show that at any temperature $k_{H_3O^+}$ is a function of the concentration of hydrochloric acid, increasing with increase in the concentration of acid. At a given temperature, over the range of concentration investi-

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[22] Hitchcock and Dougan, *J. Phys. Chem.*, **39**, 1177 (1935).

gated, the effect may be expressed by the equation

$$\log k_{H_3O^+} = \log k^\circ_{H_3O^+} + \beta C \qquad (4)$$

where $k_{H_3O^+}$ represents the velocity constant for molar hydrogen ion in a solution C molar in hydrochloric acid. Figure 2 shows the applicability of equation (4) to our data at −0.01°.

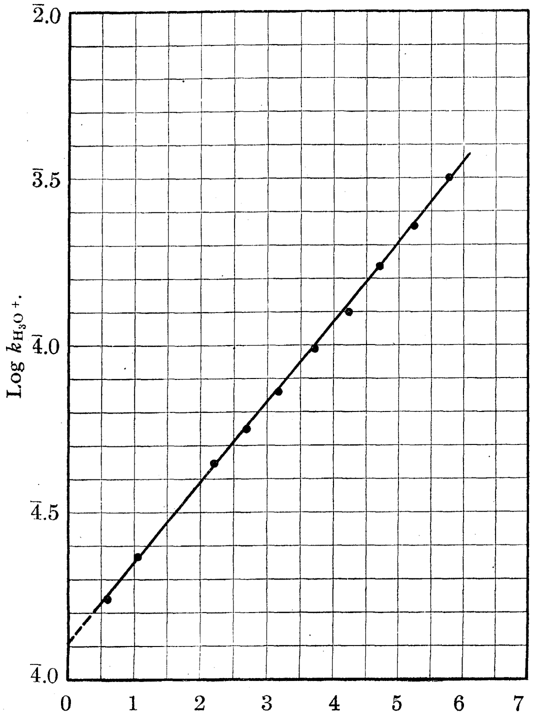


Fig. 2.—Electrolyte effect at −0.01°.

By the method of least squares we obtained the equation

$$\log k_{H_3O^+} = \bar{4}.1057 + 0.2394\ C \text{ (at } -0.01^\circ) \qquad (4a)$$

valid at −0.01°. The values of $k_{H_3O^+}$ (calcd.) given in the fourth column of Table I were computed by equation (4a); the average deviation from the observed value is 2.0%.

Using the polarimetric method, Duboux[13] recently has measured the rate of inversion of sucrose at 0° over a wide range of concentration of hydrochloric acid. His solutions contained 11.42 g. of sucrose in 100 cc. of solution, as compared to our 2.00 g. Upon recomputing his values on the basis of molarity, and applying to the recomputed values the method of least squares, we obtained

$$\log k_{H_3O^+} = \bar{4}.1898 + 0.2392\ C \text{ (Duboux, } 0^\circ) \qquad (4a')$$

The agreement between the two values of β is excellent. The difference in the value of the intercept can be attributed to the difference in the sucrose concentration. That increase in concentration of sucrose causes an increase in $k_{H_3O^+}$ may also be seen in Table II. For a solution 0.95 M in hydrochloric acid, and containing 2 g. of sucrose per 100 cc., $k_{H_3O^+}$ (observed) is 46.68 × 10^{-3} at 35°, while for a solution containing 0.5 g. per 100 cc., $k_{H_3O^+}$ (observed) is 44.00 × 10^{-3}.

The following equations, analogous to (4a), express the effect of acid concentration upon $k_{H_3O^+}$ at the other temperatures investigated.

$$\log k_{H_3O^+} = \bar{4}.8660 + 0.2230\ C \text{ (at 10.00°)} \qquad (4b)$$
$$\log k_{H_3O^+} = \bar{3}.2198 + .2116\ C \text{ (at 15.00°)} \qquad (4c)$$
$$\log k_{H_3O^+} = \bar{3}.5587 + .2045\ C \text{ (at 20.00°)} \qquad (4d)$$
$$\log k_{H_3O^+} = \bar{3}.8793 + .1992\ C \text{ (at 25.00°)} \qquad (4e)$$
$$\log k_{H_3O^+} = \bar{2}.1932 + .1922\ C \text{ (at 30.00°)} \qquad (4f)$$
$$\log k_{H_3O^+} = \bar{2}.4902 + .1846\ C \text{ (at 35.00°)} \qquad (4g)$$
$$\log k_{H_3O^+} = \bar{2}.7857 + .1806\ C \text{ (at 40.00°)} \qquad (4h)$$

These equations were derived from the data given in Table II; they represent the lines obtained by plotting log $k_{H_3O^+}$ against the acid concentration, at the temperature in question.

It was hoped that a quantitative expression for the effect of sucrose concentration upon $k_{H_3O^+}$ might also be formulated from the existing data. While this has not proved possible, there is considerable experimental evidence of the existence of the effect. In addition to the evidence already cited, we mention the following. Hitchcock and Dougan,[22] using the dilatometric method at 25°, noted that at constant acid concentration an increase in the concentration of sucrose caused an increase in $k_{H_3O^+}$. The same thing is shown by a comparison of $k_{H_3O^+}$ obtained by Sturtevant[23] at 25°, using the calorimetric method, with $k_{H_3O^+}$ computed from our equation (4e); by a comparison of the values of $k_{H_3O^+}$ obtained by Heidt and Purves[10] at 30 and 40°, using the copper reduction method, with values computed from our equations (4f) and (4h); by a comparison of the values of $k_{H_3O^+}$ of Pennycuick[21] at 35 and 40°, obtained by the polarimetric method, with values computed from our equations (4g) and (4h); and by a comparison of the values of $k_{H_3O^+}$ of Moelwyn-Hughes,[12] obtained polarimetrically at 15.45 and 19.40°, with our values, after making a correction for the difference in temperature. From all the work examined, with the sole exception of that of Pearce and Thomas,[14] the same conclusion was drawn.

In Table III is given the Arrhenius energy of activation, E_A, computed by means of equation

(23) Sturtevant, This Journal, **59**, 1528 (1937).

TABLE III

ELECTROLYTE EFFECT ON ENERGY OF ACTIVATION

Temp. range, °C.	HCl (moles/liter)	k_{T_2}/k_{T_1}	E_A, cal.
−0.01 to 10.00	1.124	5.506	26,180
− .01 to 10.00	2.141	5.246	25,440
− .01 to 10.00	2.997	5.055	24,870
− .01 to 10.00	3.905	4.872	24,310
− .01 to 10.00	4.592	4.842	24,210[b]
− .01 to 20.00	0.9528	26.20	25,960
− .01 to 20.00	1.123	25.93	25,880
− .01 to 20.00	1.493	25.03	25,600
− .01 to 20.00	2.140	23.64	25,150
− .01 to 20.00	2.999	22.18	24,640
10.00 to 20.00	1.124	4.707	25,550
10.00 to 20.00	2.141	4.505	24,820
10.00 to 20.00	2.998	4.392	24,400
10.00 to 20.00	1.121	4.521	24,880[a]
15.00 to 25.00	1.124	4.406	25,310
15.00 to 25.00	1.493	4.369	25,170
15.00 to 25.00	2.132	4.257	24,730
15.00 to 25.00	1.118	4.368	25,160[a]
20.00 to 30.00	0.9493	4.220	25,420
20.00 to 30.00	1.122	4.175	25,230
20.00 to 30.00	1.491	4.133	25,060
25.00 to 35.00	0.4767	4.023	25,410
25.00 to 35.00	.9559	3.966	25,150
30.00 to 40.00	.2507	3.888	25,610
30.00 to 40.00	.4744	3.852	25,440
30.00 to 40.00	.6524	3.834	25,350

[a] Solution 1.003 molar with respect to sodium chloride.

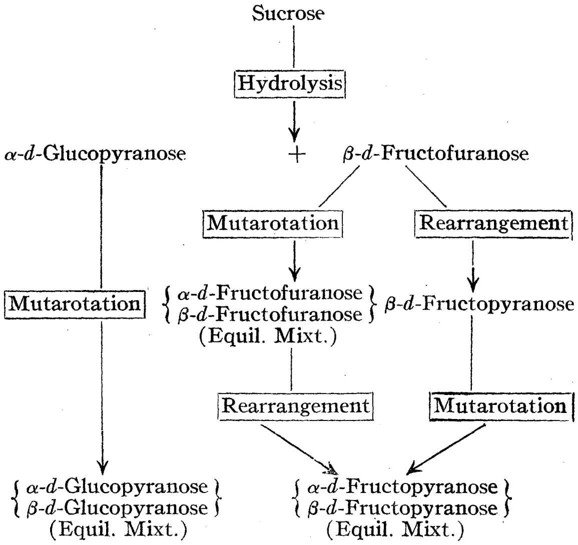
[b] In ref. 11, 4.842 given for hydrochloric acid molarity should be 4.592.

(3) from the values of $k_{H_3O^+}$ listed in Table II, and from values calculated by equation (4a). At this point it is desirable to discuss the probable accuracy of the determination of E_A. For the temperature interval 20 to 30°, errors of 0.3% in the values of $k_{H_3O^+}$, in opposite directions, would result in an error of 104 cal. in E_A at 25°. Errors of 0.1% in the values of the acid concentration, taken in opposite directions, would affect E_A to the extent of 33 cal. Since the effects of possible errors in temperature, time and concentration of sucrose are negligible, the maximum error in E_A determined from velocity constants at temperatures other than −0.01° may be taken as ±150 cal. In similar fashion, a possible error of 2.0% in $k_{H_3O^+}$ at −0.01° yields ±400 cal. for E_A at 5°, and ±250 cal. at 10°.

The two values marked with an "*a*" in the last column of Table III show a diminution of E_A in the presence of sodium chloride; the effect is, however, less than that of an equal amount of acid. Duboux[13] has made similar observations. On the other hand, Pearce and Thomas[14] report no appreciable effect of salt upon E_A. An examination of the results of these authors, however, reveals a distinct trend in the values of E_A in the solutions of barium chloride, which leads us to the conclusion that E_A does decrease with increasing electrolyte concentration.

In view of the change in E_A with electrolyte concentration and temperature reported in Table III, it seems advisable to consider the possibility of reactions other than hydrolysis affecting the measured rate and to reconsider the validity of the dilatometric method.

The following scheme represents the probable reactions involved.



The mutarotation of α-*d*-glucopyranose is approximately fifty times faster than the observed rate under our experimental conditions.[24-26] The mutarotation of β-*d*-fructopyranose is faster than that of α-*d*-glucopyranose.[25,27,28] No rate data are available for hydrochloric acid solutions on the other processes indicated. For enzymes, however, the rate of change of β-*d*-fructofuranose to equilibrium fructose has been shown to be three times faster than the mutarotation of β-*d*-fructopyranose.[29] The possibility of acid decomposition of the equilibrium mixtures of glucose and fructose is ruled out. For the conditions investigated the acid decomposition of the fructose equilibrium mixture is four powers of ten slower

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(24) Hudson, THIS JOURNAL, **29**, 1571 (1907).

(25) Nelson and Beegle, *ibid.*, **41**, 559 (1919).

(26) Brönsted and Guggenheim, *ibid.*, **49**, 2554 (1927).

(27) Riiber and Esp, *Ber.*, **58**, 737 (1925).

(28) Hudson, THIS JOURNAL, **30**, 1564 (1908); *ibid.*, **31**, 66 and 655 (1909).

(29) Bailey and Hopkins, *Biochem. J.*, **27**, 1957 (1933).

than the observed rate.[30] The glucose portion of invert sugar is less readily attacked by acids than the fructose.[31] Although complete rate data are not available for all processes, the fact that the reaction was of the first order in all experiments indicates that the measured reaction is simple and free from complications.

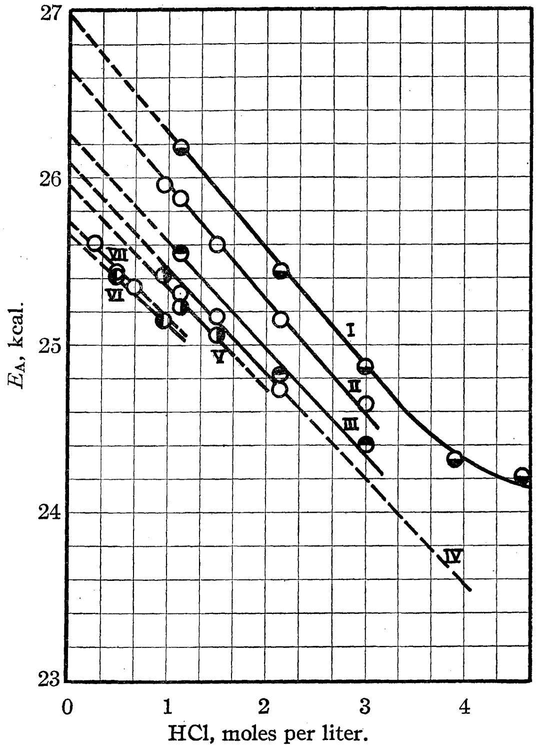

Fig. 3.—Electrolyte effect on energy of activation: I, −0.01 to 10.00°; II, −0.01 to 20.00°; III, 10.00 to 20.00°; IV, 15.00 to 25.00°; V, 20.00 to 30.00°; VI, 25.00 to 35.00°; VII, 30.00 to 40.00°.

In regard to the dilatometric method the volume change for the mutarotation of *α-d*-glucopyranose is approximately 3% of the measured change and in the opposite direction.[26,32] For *β-d*-fructopyranose the volume change is also an expansion amounting to 23% of the measured volume change.[27] Since these processes are rapid the volume change may still be proportional to the percentage of sucrose reacted. The validity of the dilatometric method rests upon the comparison of this method with the polarimetric method[22] and the fact that the dilatometric, polarimetric, calorimetric[23] and copper reduction methods[10] all yield first order constants which are in good agreement when electrolyte and sucrose effects are taken into consideration. Finally, a comparison of the electrolyte effect of hydrochloric acid at 0° (see Table I and equation 4a) obtained by the dilatometric method is in excellent agreement with results obtained by the polarimetric method (see equation 4a′).[13]

In Fig. 3 the value of E_A at the mid-point of the temperature interval is plotted against the concentration of hydrochloric acid. Reading from the top down, the curves represent the effect of acid concentration upon E_A at temperatures of 5, 10, 15, 20, 25, 35 and 30°, respectively. It is evident that E_A decreases with rise in temperature up to 30°, and that E_A decreases with increase in acid concentration. For concentrations not greater than four molar, E_A appears to be a linear function of the acid concentration; at the higher temperatures, however, E_A could not be determined over a wide range of concentration.

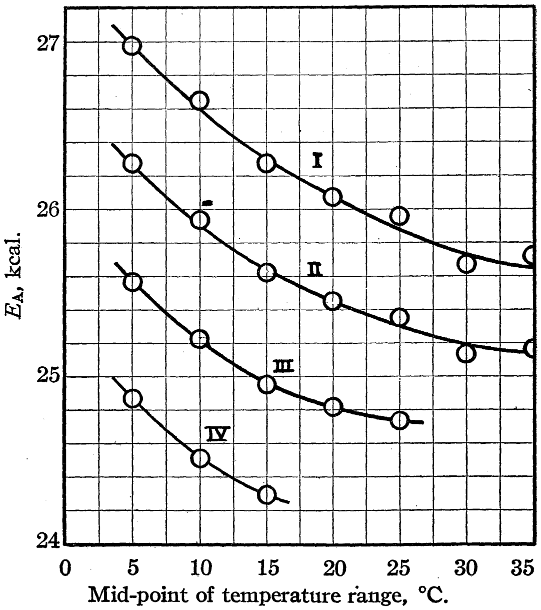

Fig. 4.—Effect of temperature on energy of activation: I, 0 molar HCl; II, 1 molar HCl; III, 2 molar HCl; IV, 3 molar HCl.

Figure 4 and Table IV illustrate the variation of E_A with temperature. The four curves represent E_A at acid concentrations of 0, 1, 2 and 3 molar, respectively, as read off from the lines in Fig. 3.

The graphically determined values of E_A at zero acid concentration were confirmed by computation, by means of equation 3, from the intercepts of equations (4a), (4b), etc. The figure

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(30) Mathews and Jackson, *Bur. Standards J. Research*, **11**, 619 (1933).

(31) Rischbieth, *Ber.*, **20**, 1773 (1887).

(32) Riiber, *ibid.*, **57**, 1599 (1924).

TABLE IV

TEMPERATURE EFFECT ON THE ENERGY OF ACTIVATION

Temp. range, °C.	E_A, cal. 0 molar HCl	1 molar HCl	2 molar HCl	3 molar HCl
−0.01 to 10.00	26,980	26,280	25,570	24,870
− .01 to 20.00	26,650	25,940	25,230	24,510
10.00 to 20.00	26,280	25,620	24,950	24,290
15.00 to 25.00	26,080	25,450	24,820	...
20.00 to 30.00	25,960	25,350	24,740	...
25.00 to 35.00	25,670	25,130	...	...
30.00 to 40.00	25,720	25,160	...	...

shows E_A to decrease with increase in temperature, the rate of change, $\Delta E_A/\Delta T$, being approximately −70 cal. per degree at 10° and smaller at higher temperatures.

It already has been mentioned that a decrease in E_A with increase in temperature was observed previously by Moelwyn-Hughes.[12] His values of E_A are consistently lower than ours for the same temperature and concentration of hydrochloric acid, as may be seen in Fig. 1. Using 5% sucrose solutions, Moelwyn-Hughes found $\Delta E_A/\Delta T$ to be −94 cal. per degree at 33.6°, which is much larger than the rate of change observed by us at this temperature. The early work of Urech,[33] cited by Moelwyn-Hughes in support of his statement of change of E_A with temperature, does not appear to be sufficiently accurate for the purpose in hand. In his analysis of Urech's data, Moelwyn-Hughes averaged values of E_A obtained at different acid concentrations, which is unjustifiable in view of the effect of acid concentration upon E_A. The data of Spohr,[34] also cited by Moelwyn-Hughes, are not convincing proof of the effect of temperature on E_A. Spohr's value of E_A at 32.5° for 0.250 *N* hydrobromic acid is in good agreement with our value for hydrochloric acid. Computation of E_A from the data of Heidt and Purves[10] for the temperature intervals 30–40, 40–50, and 50–59.7° fails to show a consistent effect of temperature.

In addition to the effects upon E_A of temperature, and of concentration of electrolyte, there is probably a slight effect of the sucrose concentration. At a given acid concentration our value of E_A at the mid-point of the 0–25° interval is consistently higher than that of Duboux.[13] The difference between the two values varies from 200 to 900 cal. Duboux's solutions contained 11.42 g. of sucrose per 100 cc., ours, 2 g.

In order to facilitate comparison with data in the literature, we have in Table V given *B* as computed from the equation

$$\log_e k_{H_3O^+} = B - \frac{E_A}{RT} \qquad (5)$$

where $k_{H_3O^+}$ is expressed in sec.$^{-1}$, the values of $k_{H_3O^+}$ employed were obtained from equations (4a), (4b), etc., and E_A was taken from Figure 4.

TABLE V

VARIATION OF *B* WITH TEMPERATURE AND ACID CONCENTRATION

Midpoint of temp. range, °C.	*B* 0 molar HCl	1 molar HCl	2 molar HCl	3 molar HCl
10.00	36.00	35.25	34.56	33.80
15.00	35.45	34.79	34.08	33.40
20.00	35.07	34.44	33.85	...
25.00	34.72	34.20	33.69	...
30.00	34.47	34.02	...	...
35.00	34.33	33.91	...	...

From Table V it appears that *B* decreases both with increase in temperature and with increase in acid concentration. The effect of temperature decreases markedly at the higher temperatures, as does the effect of temperature upon E_A.

Discussion

Inspection of Tables IV and V indicates that the activation energy is the quantity of first importance in the problem, and that the change in activation energy with concentration is the more important effect. From the point of view of the transition state theory,[35–37] the activation energy can be set equal to the increase in heat content, ΔH, for the reaction

$$S + H_3O^+ \longrightarrow \text{Critical complex} \qquad (6)$$

The change in ΔH with change in concentration can then be found by considering the heats of transfer in the following cycle

$$\begin{tikzcd}
\text{Concentration HCl } C_2 & S \arrow[d, "\Delta H_1"] & + & H_3O^+ \arrow[r, "\Delta H''"] \arrow[d, "\Delta H_2"] & X \arrow[d, "\Delta H_3"] \\
\text{Concentration HCl } C_1 & S & + & H_3O^+ \arrow[r, "\Delta H'"] & X
\end{tikzcd} \qquad (7)$$

where $\Delta H'' - \Delta H' = \Delta H_1 + \Delta H_2 - \Delta H_3$

The heat of transfer (ΔH_1) of a mole of sucrose from a solution of concentration $\overline{C}$ in sucrose and C_2 in hydrochloric acid, to a solution $\overline{C}$ in sucrose and C_1 in hydrochloric acid may be considered small in comparison to ΔH_2 and is neglected in

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[33] Urech, *Ber.*, **16**, 762 (1883); **17**, 2165 (1884).

[34] Spohr, *Z. physik. Chem.*, **2**, 194 (1888).

[35] Eyring, *Trans. Faraday Soc.*, **34**, 41 (1938).

[36] Wigner, *ibid.*, **34**, 29 (1938).

[37] Evans and Polanyi, *ibid.*, **34**, 11 (1938).

this calculation. The heat of dilution of H_3O^+ from C_2 to C_1 can be computed from the heat of dilution of hydrochloric acid and potassium chloride on the assumption that the heat of dilution of the chloride ion in hydrochloric acid solutions may be taken as one-half the heat of dilution of potassium chloride for the same change in concentration.

Table VI gives the approximate changes in ΔH_2 per mole at 18°, calculated from the data given by Bichowsky and Rossini.[38]

TABLE VI

COMPARISON OF ΔH_2 AND ΔE_A

C_2 Moles per liter	C_1	Calories per mole ΔH_2	ΔE_A, 20°	ΔE_A, 5°
4	3	300	610[a]	550[a]
3	2	300	620[a]	700
2	1	300	630	710
1	0	500	630	700

[a] Read from Fig. 4.

The value for the heat of transfer (ΔH_3) of a mole of the activated complex between solutions of different hydrochloric acid concentration is dependent on the structure assigned to the activated complex. If we assume that the hydrogen ion makes contact at the oxygen atom joining the two lactone rings of the sucrose molecule,[14] we would have an ion which might be expected to have a heat of dilution intermediate between those of sucrose and hydrogen ion. This would mean that the maximum value of $\Delta H'' - \Delta H'$ would be equal to ΔH_2. The change in E_A for the various intervals compared in Table VI should not exceed the values given for ΔH_2. E_A shows the expected decrease with increasing concentration, but the observed values of ΔE_A are consistently larger than ΔH_2. The heat of dilution of the hydrogen ion is greater at lower temperatures and the values of ΔE_A at 5° show an increase over ΔE_A at 20° except at four molar.

In regard to the effect of sucrose concentration on E_A, calculation of ΔH_1 for solutions of sucrose[39,40] up to 0.5 molar indicates that E_A should decrease by approximately 100 cal. in going from 0.05 to 0.5 molar. Here again the observed effect seems larger than the calculated, though in the right direction.

From these calculations it seems that the change in the energy of activation with electrolyte concentration is understandable on the basis of the transition state theory. The fact that the magnitude of the effect as calculated from the theory is not in agreement with the experimentally determined values may be due to our neglect of the heat of transfer of sucrose (ΔH_1) from one concentration of hydrochloric acid to another. In addition our values for ΔH_2 are based on heats of dilution for aqueous solutions which did not contain sucrose.

A similar picture will result if we do not consider the critical complex at the top of the energy barrier, but consider a preëquilibrium between a collision complex and the reactants, the assumption being made that equilibrium is maintained between the collision complex and the reactants at all times. From equation 2 we have

$$\begin{tikzcd}[column sep=small, row sep=small] \ln k = & \ln K \arrow[d, equal] & + & \ln k_2 \arrow[d, equal] & & \\ & \frac{\Delta S}{R} \arrow[d, dash] & & b \arrow[d, dash] & \cong & \frac{\Delta S^*}{R} \\ & \frac{\Delta H}{RT} & & \frac{\epsilon_A}{RT} & & \end{tikzcd} \qquad (8)$$

where K is the equilibrium constant, ΔH the difference in heat content between the collision complex and reactants, ΔS is the entropy difference, b is a constant, and ϵ_A the activation energy for the unimolecular decomposition of the collision complex. The constant b will include the entropy of activation of the transition state theory.

From the above we have

$$\ln k = \ln C + \frac{\Delta S + \Delta S^*}{R} - \frac{\Delta H + \epsilon_A}{RT} \qquad (9)$$

C being a constant.

At a concentration of acid C_1 we have

$$k_1 = Ce^{(\Delta S_1 + \Delta S_1^*)/R}\, e^{-(\Delta H' + \epsilon_A')/RT} \qquad (10)$$

and at C_2

$$k_2 = Ce^{(\Delta S_2 + \Delta S_2^*)/R}\, e^{-(\Delta H'' + \epsilon_A'')/RT} \qquad (11)$$

The change in the measured energy of activation with change in acid concentration will be

$$(\Delta H'' + \epsilon_A'') - (\Delta H' + \epsilon_A')$$

and our approximate calculations are valid if we assume $\epsilon_A'' = \epsilon_A'$. ϵ_A need not be considered as the true energy of activation, but can be related to it by the equation $\epsilon_1 = \epsilon_A + SRT$ where S is the number of degrees of freedom.

Any attempt at an explanation of the change in B which is associated with the changes in $\Delta S + \Delta S^*$ seems unprofitable until we are able to know something of the order of magnitude of the equilibrium constant K.

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[38] Bichowsky and Rossini "The Thermochemistry of Chemical Substances," Reinhold Publishing Corporation, New York, N. Y., 1936.

[39] "International Critical Tables," Vol. V, p. 161.

[40] Pratt, *J. Franklin Institute*, **185**, 663 (1918).

Experimental studies on various acetals[41] indicate that E_A does not show any great change with temperature or with concentration of electrolytes, but the reactions are too sensitive to hydrogen ion to allow investigation over any wide range of concentration of acid. We plan to extend this study to a reaction of a less complicated substrate than sucrose, which can be studied over a similar range of hydrochloric acid concentration and temperature.

Summary

1. The velocity constant $k_{H_3O^+}$ for the inversion of sucrose has been measured from 0 to 40° over a wide range of hydrochloric acid concentration.
2. Equations for the effect of the electrolyte, hydrochloric acid, on $k_{H_3O^+}$ are given at 5° intervals between 10 and 40° and at $-0.01°$. The effect of electrolyte decreases with increasing temperature.
3. It has been shown that $k_{H_3O^+}$ increases with increasing sucrose concentration.
4. The energy of activation calculated from the Arrhenius equation shows that E_A and B decrease with increasing concentration of hydrochloric acid. This appears to be a general electrolyte effect.
5. The energy of activation also decreases with increasing sucrose concentration.
6. The decrease in E_A and B with increasing temperature has been confirmed.
7. An explanation of these results has been attempted on the basis of the transition state theory and the consideration of a preëquilibrium between reactants and the collision complex.

PHILADELPHIA, PENNA. RECEIVED AUGUST 11, 1938

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[41] Unpublished results, Riesch and Kilpatrick.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

The Action of *t*-Butylmagnesium Chloride with Acetyl Chloride

BY FRANK C. WHITMORE AND W. R. WHEELER

Researches in this Laboratory have shown that ketones of the type $RCOCR_3$ may be obtained by the action of tertiary alkylmagnesium halides and an acid halide.[1] In the present study *t*-butylmagnesium chloride was added to an excess of acetyl chloride in ether solution to determine the by-products.

Pinacolone, the normal product, was obtained in but 17% yield. $(CH_3)_3CMgCl + CH_3COCl \rightarrow (CH_3)_3CCOCH_3 + MgCl_2$. Other products were pinacolyl acetate, ethyl acetate, mesityl oxide, isobutylene, isobutane, carbon monoxide and hexamethylethane.

Pinacolyl alcohol, the product from the reducing action of the Grignard reagent on the ketone, appeared as its acetate in 8% yield.

Ethyl acetate, present to the extent of 9%, based on the acid chloride, was probably formed by interaction of acetyl chloride with the solvent ether rather than by direct reduction of the acid chloride to the primary alcohol.[2] This is confirmed by the formation of only 6.6% of isobutylene. Also, results from this Laboratory[3] have shown that ethyl esters are formed in the reaction of *n*-propyl, *n*-butyl and *n*-amyl Grignard reagents with *t*-butylacetyl chloride, in which cases formation of ethyl alcohol by reduction is excluded. Since acid halides are known to cleave ethers in the presence of anhydrous zinc chloride,[4] an experiment was undertaken which demonstrated that the anhydrous magnesium chloride, formed during the course of the reaction, may act in the same way as zinc chloride.

Several modes of formation are possible for the mesityl oxide, which occurred in 6.6% yield. Karasev[5] observed that *t*-butylmagnesium chloride reacts with ethyl acetate to produce acetone and its condensation products, mesityl oxide and phorone. Kondakow[6] prepared mesityl oxide from isobutylene and acetyl chloride in the presence of anhydrous zinc chloride. Recalling the similarity of zinc and magnesium chlorides in promoting the cleavage of ethers, the latter formation is also possible. In that case the small yield of isobutylene would be explained. Further studies on the mechanism of the forma-

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[1] Whitmore and Badertscher, THIS JOURNAL, **55**, 1559 (1933).

[2] *Cf.* Greenwood, Whitmore and Crooks, *ibid.*, **60**, 2028 (1938).

[3] Whitmore, Whitaker, Mattil and Popkin, *ibid.*, **60**, 2790 (1938).

[4] Norris and Rigby, *ibid.*, **54**, 2088 (1932); Gustus and Stevens, *ibid.*, **54**, 3461 (1932); **55**, 378 (1933).

[5] Karasev, *J. Gen. Chem.*, **7**, 179 (1937); *C. A.*, **31**, 4268 (1937).

[6] Kondakow, *J. Russ. Phys.-Chem. Soc.*, **26**, 12 (1894).

tion of ethyl acetate and of mesityl oxide are in progress.

The trace of hexamethylethane found is the coupling product ordinarily formed in the preparation of the Grignard reagent. A small amount of carbon monoxide was also produced; its formation has been noticed previously in analogous reactions.[7]

The evolution of so large an amount of isobutane as 23.6% was unexpected, and would seem to indicate that both pinacolone and mesityl oxide, totalling 24%, had reacted with the Grignard reagent to form isobutane and the —OMgCl compounds of their enol forms.

Experimental

Preparation of Materials.—The *t*-butylmagnesium chloride was prepared in the usual manner[1] from pure *t*-butyl chloride. The reagent evolved no gas when refluxed in a dry, nitrogen-filled fractionating column.

The acetyl chloride was obtained from Eastman practical grade by careful distillation from dimethylaniline in a 1.5 × 65 cm. fractionating column packed with 3.5 mm. glass helices (Column I).

Reaction of *t*-Butylmagnesium Chloride with Acetyl Chloride.—In a three-liter three-necked flask fitted with a dropping funnel, stirrer and condenser were placed 253 g. (3.2 moles) of acetyl chloride and 640 cc. of dry ether. To this was added, over a twelve-hour period, 2.46 moles of the clear, filtered Grignard reagent in 1010 cc. of solution. A yellow precipitate formed; gas was evolved and collected in carboys filled with salt solution and protected by calcium chloride tubes to prevent the diffusion of water vapor back into the reaction flask. When the addition was complete, the flask was immersed in a salt–ice bath and about one liter of water added with stirring, causing the mixture to become warm and evolve a small amount of gas. The ether layer was separated and the water extracted with three 300-cc. portions of ether. The combined extracts were dried over anhydrous magnesium sulfate and distilled in column I. Some gas was evolved on warming, which was combined with the other gases. Distillation at 742–746 mm. gave the following fractions: nos. 1–7, ether; 8–10, 10.1 g., b. p. 36–61.5°, $n^{20}\text{D}$ 1.3752–1.3868; 11–12, 18.6, 61.5–75.5°, 1.3815–1.3770; 13–14, 7.7, 75.5–85°, 1.3780–1.3827; 15–17, 15.2, 85–104.5°, 1.3920–1.3976; 18–21, 31.3, 104.5–109°, 1.3965–1.3943; 22–23, 15.9, 109–114°, 1.3952–1.3821; 24–26, 34.6, 114–122.5°, 1.3764–1.3852. The remainder of the distillation was carried out at 51 mm. pressure: 27–29, 15.9, 55–60°, 1.4210–1.4157; 30–33, 29.1, 60–64°, 1.4085–1.4040; residue, 46.3 g.

Identification of Products.—No. 9.—Identification of this material was not entirely satisfactory. It contained halogen, and its b. p. 45–50° and $n^{20}\text{D}$ 1.3831 indicate that it was probably impure *t*-butyl chloride, b. p. 50°, $n^{20}\text{D}$ 1.3850.

13.—The b. p. and $n^{20}\text{D}$ corresponded to ethyl acetate. Hydrolysis gave acetic acid, identified by Duclaux numbers, and ethyl alcohol, 3,5-dinitrobenzoate, m. p. 91°.

14–16.—Repeated refraction of these cuts through a 0.55 × 43 cm. helix-packed column (column E) resulted only in the separation of ethyl acetate and pinacolone, and a small amount of hexamethylethane, boiling *ca.* 100°, m. p. 90–94° (sealed tube), insoluble in 93% sulfuric acid.

19.—Identified as pinacolone, 2,4-dinitrophenylhydrazone, m. p. 124.5°.

21–23.—These cuts, washed free of acetic acid using sodium bicarbonate, yielded only pinacolone on redistillation in column E.

25.—The b. p., $n^{20}\text{D}$ and neutral equivalent corresponded to acetic acid.

27–29.—Redistillation through column E gave a fraction of b. p. 128° and $n^{20}\text{D}$ 1.4377 which was identified as mesityl oxide, 2,4-dinitrophenylhydrazone, m. p. 199–200°. Semicarbazide reacted with it to form a solid, m. p. 130.5°, described as one of the possible products.[8]

32–33.—The b. p. and $n^{20}\text{D}$ correspond to pinacolyl acetate. Hydrolysis gave an acid identified as acetic by its Duclaux numbers, and an alcohol boiling at 128°, phenylurethan m. p. 76°, corresponding to pinacolyl alcohol.

Residue.—The material could not be distilled without decomposition even at 5 mm. pressure. Decolorization in acetone solution yielded a reddish oil which could not be crystallized from the usual solvents. It was not investigated further.

Analysis of Gaseous Products.—Analysis was accomplished with the aid of a 0.55 × 36 cm. low temperature column, packed with a single nichrome spiral and the conventional Orsat apparatus. The following products were indicated: isobutane, 33.8 g.; isobutylene, 9.2 g.; carbon monoxide, 0.2 g.

Reaction of Acetyl Chloride with Ether.—One mole of redistilled acetyl chloride, 200 cc. of ether and 120 g. (1.26 moles) of anhydrous magnesium chloride, prepared by the method of Vanino[9] were stirred and refluxed for one hundred hours. The mixture became pasty but no gas was evolved. Water was added to remove the magnesium chloride, the ether layer washed again with a small amount of water and dried over magnesium sulfate. Distillation in a 0.9 × 45 cm. helix-packed column gave about 60 g. of material boiling at 22–31°, indicating that some ethyl chloride was present in ether solution, and four fractions, totaling 8.9 g., boiling 65–83°, $n^{20}\text{D}$ 1.3712–1.3735, which proved to be mainly ethyl acetate; yield 8–10%.

Summary

1. Products formed in the reaction of *t*-butylmagnesium chloride with excess acetyl chloride are isobutane, isobutylene, carbon monoxide, ethyl acetate, pinacolone, pinacolyl acetate and mesityl oxide.

2. Acetyl chloride has been shown to react with diethyl ether in the presence of anhydrous magnesium chloride to form ethyl acetate.

STATE COLLEGE, PENNA. RECEIVED AUGUST 29, 1938

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[7] Schmidlin, *Ber.*, **43**, 1139 (1910). Also unpublished work in this Laboratory by H. M. Crooks, Jr.

[8] Harries and Kaiser, *Ber.*, **32**, 1339 (1899).

[9] Vanino, "Präparative Chemie," 3rd ed., Stuttgart, 1925, p. 439.

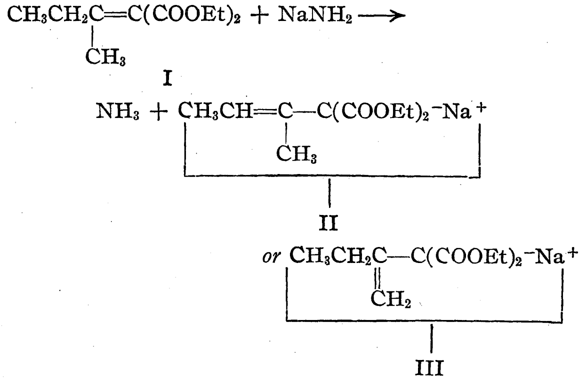
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BRYN MAWR COLLEGE]

The Introduction of Substituted Vinyl Groups. II. (1-Methylpropenyl)-alkylmalonic Esters

BY ARTHUR C. COPE AND EVELYN M. HANCOCK

The preceding paper of this series described a practical indirect method for preparing isopropenylalkylmalonic esters.[1] This communication presents a similar method by means of which 1-methylpropenyl (or symmetrical dimethylvinyl) alkylmalonic esters can be prepared.

The starting point in the syntheses is ethyl (1-methyl-propylidene)-malonate, I, which was obtained by condensing methyl ethyl ketone with malonic ester. On treatment with sodamide, the alkylidene ester gives a sodium derivative, which could be either II or III, since the hydrogen which is lost as ammonia in the reaction might come from either the methylene or the methyl group of I.



$$CH_3CH_2\underset{CH_3}{\underset{|}{C}}{=}C(COOEt)_2 + NaNH_2 \longrightarrow$$

I

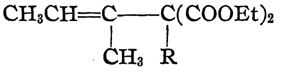
$$NH_3 + \left[CH_3CH{=}\underset{CH_3}{\underset{|}{C}}{-}C(COOEt)_2^{-}Na^{+}\right]$$

II

$$or\ \left[CH_3CH_2\underset{CH_2}{\underset{\|}{C}}{-}C(COOEt)_2^{-}Na^{+}\right]$$

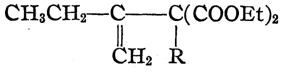
III

The sodium enolate was alkylated with several alkyl halides and dialkyl sulfates. The alkylated esters, which were obtained in good yields, must be either symmetrical dimethylvinyl derivatives, (IV, derived from II), 1-ethylvinyl derivatives (V, derived from III) or mixtures of the two structural types. Formula IV, in addition, permits the existence of two geometric isomers.



$$CH_3CH{=}\underset{CH_3}{\underset{|}{C}}{-}\underset{R}{\underset{|}{C}}(COOEt)_2$$

IV



$$CH_3CH_2{-}\underset{CH_2}{\underset{\|}{C}}{-}\underset{R}{\underset{|}{C}}(COOEt)_2$$

V

The structures of the alkylated esters described in Table I, with the exception of the allyl derivative, were determined by ozonization. Decomposition of the ozonides gave acetaldehyde in quantity and only traces of formaldehyde. The products are, therefore, 1-methylpropenyl esters (formula IV), containing small amounts of the isomeric 1-ethylvinyl substituted esters (formula V).

Two of the esters boiled over three and five degree ranges, respectively, even after careful refractionation. Since the esters were analytically pure, and the structural isomers (V) appear to be present in quite small quantities, the boiling points suggest the presence of both of the possible geometric isomers.

Experimental Part

Ethyl (1-Methylpropylidene)-malonate

Methyl ethyl ketone condenses with malonic ester more slowly and less completely than does acetone under similar conditions.[1] The yield of condensation product does not exceed 20%, although a large proportion of the unreacted malonic ester is recovered.

A mixture of 1 kg. (6.25 moles) of ethyl malonate, 670 g. (9.3 moles) of methyl ethyl ketone, 800 g. of acetic anhydride and 120 g. of zinc chloride was heated under reflux in an oil-bath at 110° for sixty hours. The mixture was cooled, diluted with 800 cc. of benzene and washed with five 500-cc. portions of water. The water washings were extracted with benzene and the product distilled in the same manner as ethyl isopropylidene-malonate.[1] The recovery of ethyl malonate, b. p. 98–100° (22 mm.), plus a small intermediate fraction, was 700 g. (70%), while the yield of condensation product, b. p. 134–136° (22 mm.) was 255 g. (19%). A similar preparation was heated for five days at 100°, after which another 120-g. portion of zinc chloride was added and the mixture heated for seven more days at 100°. The recovery of ethyl malonate plus the intermediate fraction was 612 g. (61%), and the yield of ethyl (1-methylpropylidene)-malonate, b. p. 119–120° (9 mm.), was 260 g. (19%); n^{25}_{D} 1.4479, d^{25}_{25} 1.0108; M_D calcd. 55.85, observed 56.86, exaltation +1.01. *Anal.* Calcd. for $C_{11}H_{18}O_4$: C, 61.64; H, 8.47. Found: C, 61.91; H, 8.49. Duplicate quantitative reductions of 3-g. samples with palladinized charcoal catalyst in ethyl alcohol solution at room temperature and atmospheric pressure were complete in one hour and required 100.2 and 99.5% of the theoretical quantity of hydrogen, respectively. The reduction product was identified as ethyl *s*-butylmalonate by saponification to *s*-butylmalonic acid, m. p. 78–79°,[2] and by conversion to *s*-butyl malonamide with concd. aqueous ammonia;[3] m. p. and mixed m. p. with a known sample 232–233° (uncorr.).

Alkylation of Ethyl (1-Methylpropylidene)-malonate. A. Sodamide Procedure.—The ester was alkylated by a procedure similar to the one used with ethyl isopropylidene-malonate,[1] except that equivalent quantities of ester and

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(1) Cope and Hancock, THIS JOURNAL, **60**, 2644 (1938).

(2) Van Romburgh, *Rec. trav. chim.*, **6**, 152 (1887), gives m. p. 76°.

(3) Dox, THIS JOURNAL, **44**, 1564 (1922).

TABLE I

ETHYL (1-METHYLPROPENYL)-ALKYLMALONATES

Alkyl group	Alkylating agent	Hours refluxed	Yield, %	Boiling point °C.	Boiling point Mm.	$n^{25}{}_D$	$d^{25}{}_{25}$	Molecular refraction Calcd.	Molecular refraction Found	Formula	Carbon,[a] % Calcd.	Carbon,[a] % Found	Hydrogen,[a] % Calcd.	Hydrogen,[a] % Found
Methyl	Dimethyl sulfate	0.25	76	126–127	15	1.4440	1.0076	60.47	60.33	$C_{12}H_{20}O_4$	63.11	62.84	8.84	9.05
Ethyl	Diethylsulfate	.5	70	124–124.5	9	1.4470	0.9989	65.09	64.97	$C_{13}H_{22}O_4$	64.42	64.47	9.16	9.15
Propyl	Propyl bromide	11	65	128–131	9	1.4470	.9863	69.71	69.60	$C_{14}H_{24}O_4$	65.58	65.71	9.42	9.44
Allyl	Allyl bromide	4.5	60	124–129	9	1.4549	1.0016	69.24	69.04	$C_{14}H_{22}O_4$	66.10	65.97	8.73	8.71
Butyl	Butyl bromide	19	67	159–160	22	1.4457	0.9738	74.33	74.17	$C_{15}H_{26}O_4$	66.62	66.67	9.70	9.78

[a] We are indebted to Miss Corris Hofmann for semi-micro combustions.

sodamide were used, rather than an excess of the latter. The properties of five alkyl (1-methylpropenyl)-malonic esters, purified by shaking with concd. ammonia and redistilling through a Widmer column, together with data concerning the preparations, are recorded in Table I.

B. Sodium Ethoxide Procedure.—The ethyl (1-methylpropylidene)-malonate may be alkylated in alcoholic solution, but the yields are poor due to alcoholysis. For example, the following results were obtained in the preparation of ethyl (1-methylpropenyl)-butylmalonate. A solution of 5.75 g. (0.25 mole) of sodium in 200 cc. of absolute alcohol was prepared in a 500-cc. three-necked flask and cooled to −5°. Ethyl (1-methylpropylidene)-malonate, 54 g. (0.25 mole), was added dropwise and the solution stirred for twenty minutes at −5°. Butyl iodide, 56 g. (0.3 mole), was added and the solution quickly heated to boiling. After one and three-quarters hours of refluxing the practically neutral solution was cooled and diluted with water. The ester was extracted with benzene and distilled in vacuum. The yield of crude ester was 61 g., but after shaking with concd. ammonia for two days and redistilling, the yield of pure ester was only 21 g. (31%).

Structures of the Alkylated Esters.—The methyl and ethyl substituted esters (Table I) were reduced quantitatively with palladinized charcoal catalyst, as described above. They required 101 and 99% of the theoretical quantity of hydrogen, respectively, or within experimental error of one mole. The ozonizations were carried out as follows. Solutions of the esters (0.01 mole) in 12 cc. of pentane at −10 to −15° were treated with a rapid stream of ozonized oxygen for one and one-half hours. The solvent was removed in vacuum and the ozonide decomposed with zinc dust and water in the presence of hydroquinone and silver.[4] The mixture was steam distilled rapidly until about 75 cc. had collected. This distillate was transferred to a Claisen flask, and the most volatile portion removed by distilling a volume of 2 cc. into an ice-cooled receiver. Both the original distillate and the residue after redistillation gave positive red and blue ring tests for formaldehyde with resorcinol and gallic acid.[5] The somewhat less sensitive test with resorcinol and sodium hydroxide[6] was negative in each case. The amounts of formaldehyde formed were therefore very small. Further evidence of this fact was obtained by treating the residue from the final distillation with 2,4-dinitrophenylhydrazine reagent. Only traces of an aldehyde were present. The 2 cc. of distillate, however, on treatment with 2,4-dinitrophenylhydrazine and hydrochloric acid in absolute alcohol, gave the 2,4-dinitrophenylhydrazone of acetaldehyde in quantity, m. p. and mixed m. p. 166–168° (corr.).[7] The corresponding derivative of formaldehyde melts at 166° (corr.) but mixtures of the formaldehyde and acetaldehyde derivatives melt 20 to 30° lower.

Similar distillates from the decomposition of the ozonide of a known ester which yields formaldehyde, ethyl isopropenylethylmalonate, gave strong tests for formaldehyde by all of the above methods.

Summary

A method is described by means of which 1-methylpropenyl (or symmetrical dimethylvinyl)-alkylmalonic esters may be prepared from ethyl (1-methylpropylidene)-malonate. The latter ester gives a sodium derivative with sodamide, losing hydrogen from the methylene of the ethyl group rather than from the methyl group. Subsequent alkylation produces the substituted vinyl alkyl malonic esters, $CH_3CH{=}C(CH_3)C(R)(COOEt)_2$.

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(4) *Cf.* Whitmore and Church, *ibid.*, **54**, 3710 (1932).

(5) Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1914, Vol. I, p. 24.

(6) Allen, "Commercial Organic Analysis," Blakiston, Philadelphia, 4th ed., Vol. I, 1912, p. 259.

(7) Campbell, *Analyst*, **61**, 392 (1936).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BRYN MAWR COLLEGE]

The Introduction of Substituted Vinyl Groups. III. (Dialkylvinyl)-alkylcyanoacetic Esters

BY ARTHUR C. COPE AND EVELYN M. HANCOCK

Indirect methods similar to those previously described for introducing isopropenyl and 1-methylpropenyl groups into malonic ester[1] are not equally practical for synthesizing higher (1-alkylvinyl)-alkylmalonic esters. Such syntheses would require as intermediates higher 1-alkylalkylidenemalonic esters, $RCH_2C(R')=C(COOEt)_2$. Esters of the latter type are difficult to prepare because ketones higher in molecular weight than methyl ethyl ketone do not condense easily with malonic ester. Higher ketones do condense readily with cyanoacetic ester to give excellent yields of alkylidene cyanoacetic esters.[2] This paper reports an investigation of the alkylation of these cyanoacetic ester derivatives.

Aralkylidene cyanoacetic esters, which are activated by an aryl group in addition to the nitrile and ester groups, have been alkylated previously.[3] However, an attempt to alkylate an alkylidene derivative not similarly activated by an aryl group, ethyl isopropylidenecyanoacetate, was reported to be unsuccessful.[4] We have found that alkylidenecyanoacetic esters can be alkylated, and that (dialkylvinyl)-alkylcyanoacetic esters are produced in good yields if the conditions of synthesis minimize destruction of the products by alcoholysis.

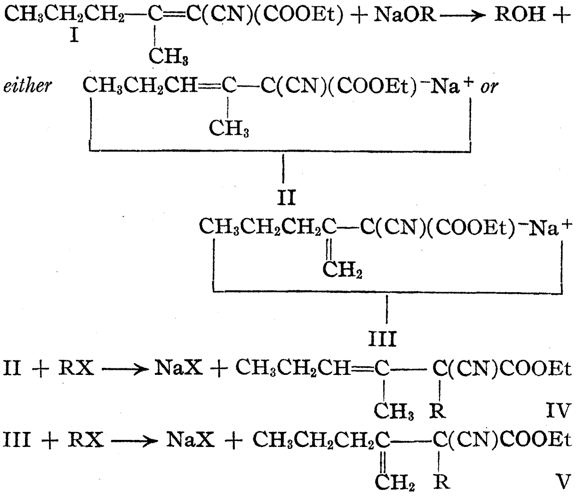
Sodium derivatives can be prepared from the alkylidenecyanoacetic esters by reaction with sodamide, metallic sodium, or sodium alkoxides. Sodamide is the reagent of choice in the malonic ester series,[1] but it produces both cleavage and polymerization of the cyanoacetic esters. The use of powdered sodium in inert solvents causes partial reduction of the unsaturated esters, and partially reduced products are formed when the enolates are alkylated. Sodium alkoxides react with the alkylidene esters to give good yields of the sodium derivatives, which can be alkylated satisfactorily in alcohol solution under proper conditions.

The (dialkylvinyl)-alkylcyanoacetic esters which are produced in the alkylations undergo alcoholysis even more readily than do the corresponding malonic esters, so that the success of their synthesis in alcohol solution is rather surprising. The alkylations of the cyanoacetic esters proceed very rapidly, however, so that the products are in contact with the alcohol and sodium alkoxide for only a short time, and there is little opportunity for alcoholysis.

Yields in the alkylation reactions are poorest in methyl alcohol solution, better in ethyl alcohol, and highest in isopropyl alcohol. This is the order of decreasing effectiveness of the three alcohols in producing alcoholysis in ester–alcohol interchange reactions.[5]

As would be expected, the rapid alkylations obtained with the most active alkylating agents give highest yields. The syntheses of 1-ethylpropenyl and 1-propyl-1-butenyl substituted esters, containing the groups $CH_3CH=C(C_2H_5)$- and $CH_3CH_2CH=C(C_3H_7)$-, gave excellent yields. The yields of 1-methyl-1-alkenyl substituted esters, containing $RCH=C(CH_3)$- groups, were lower regardless of the size of the group R. This is attributed to the hindrance to alcoholysis afforded by the presence of a group larger than methyl in the 1-position of the alkenyl residue in the former esters.

Alkylidenecyanoacetic esters prepared from unsymmetrical ketones can lead to two structural types, as the following equations with the methyl propyl ketone condensation product illustrate.



$$\underset{\text{I}}{CH_3CH_2CH_2{-}\underset{\displaystyle CH_3}{\underset{|}{C}}{=}C(CN)(COOEt)} + NaOR \longrightarrow ROH +$$

$$\textit{either}\quad CH_3CH_2CH{=}\underset{\displaystyle CH_3}{\underset{|}{C}}{-}C(CN)(COOEt)^-Na^+ \quad \textit{or}$$

$$\text{II}$$

$$CH_3CH_2CH_2\underset{\displaystyle CH_2}{\underset{\|}{C}}{-}C(CN)(COOEt)^-Na^+$$

$$\text{III}$$

$$\text{II} + RX \longrightarrow NaX + CH_3CH_2CH{=}\underset{\displaystyle CH_3}{\underset{|}{C}}{-}\underset{\displaystyle R}{\underset{|}{C}}(CN)COOEt \qquad \text{IV}$$

$$\text{III} + RX \longrightarrow NaX + CH_3CH_2CH_2\underset{\displaystyle CH_2}{\underset{\|}{C}}{-}\underset{\displaystyle R}{\underset{|}{C}}(CN)COOEt \qquad \text{V}$$

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(1) (a) Cope and Hancock, THIS JOURNAL, **60**, 2644 (1938); (b) *ibid.*, **60**, 2901 (1938).

(2) *Cf.* Cope, *ibid.*, **59**, 2327 (1937).

(3) Hugh and Kon, *J. Chem. Soc.*, 780 (1930).

(4) Birch and Kon, *ibid.*, **123**, 2443 (1923).

(5) Fehlandt and Adkins, THIS JOURNAL, **57**, 193 (1935); Hatch and Adkins, *ibid.*, **59**, 1694 (1937).

Ozonization of the alkylation products gave propionaldehyde but only traces of formaldehyde, so that formula IV is correct rather than V. The alkylation products of alkylidenecyanoacetic esters derived from four other methyl ketones were ozonized, and the higher aldehydes to be expected on cleavage of molecules having the structures indicated in Table I were formed, while only traces of formaldehyde were produced. Consequently, in this series as well as in the malonic ester series,[1b] the formation of a sodium derivative involves the loss of hydrogen from the methylene of an alkyl group higher than methyl, rather than from the methyl group.

When the various alkylated esters were purified by distillation alone, they were found to contain the corresponding alkylidene esters as impurities. Alkylidenecyanoacetic esters form sodium bisulfite addition compounds,[6] so that it was possible to remove any unalkylated ester present by shaking the crude product with 20% sodium bisulfite solution. Addition of an excess of sodium carbonate solution to the sodium bisulfite extract liberates the alkylidenecyanoacetic esters, which can be recovered in this manner.

Experimental Part

Both methyl and ethyl alkylidenecyanoacetates were alkylated in methyl, ethyl and isopropyl alcohols. Analytically pure esters result only when the alkyl of the ester is the same as that of the alcohol used as a solvent, for otherwise ester interchange results during the alkylation, and mixed esters are produced. Although the mixed esters do not have constant boiling points, they are perfectly satisfactory for use as intermediates in syntheses in which the alkyl of the ester group is removed. The yields of methyl esters obtained in methyl alcohol were poor, and they were prepared in this manner only to obtain pure samples for analyses and physical constants. Methyl esters alkylated in ethyl alcohol usually gave as good yields as did the ethyl esters, however, and both classes gave highest yields when alkylated in isopropyl alcohol.

An additional advantage of using isopropyl alcohol as a solvent is the fact that it permits the use of dialkyl sulfates, particularly diethyl sulfate, as alkylating agents. The dialkyl sulfates are poorly adapted to alkylating esters in ethyl alcohol solution, because of the rapid side reaction which occurs with the alcohol. The hydrogen of the hydroxyl group in isopropyl alcohol is less reactive, so that the competing reaction of the alcohol with the dialkyl sulfate is diminished, and the ester alkylation becomes the principal reaction.

Alkylations in Alcohol Solution.—The ethylation of ethyl (1-methylbutylidene)-cyanoacetate (I) in isopropyl alcohol will be described as a typical example. A solution of 13.8 g. (0.6 mole) of sodium in 600 cc. of dry isopropyl alcohol was prepared in a one-liter three-necked flask. The solution was cooled to 60°, at which temperature sodium isopropoxide started to crystallize out. Ethyl (1-methylbutylidene)-cyanoacetate, 108.6 g. (0.6 mole), was added during four minutes, with stirring. The mixture was cooled in ice during the addition, and the solution was at 25° when the addition was completed. Diethyl sulfate, 94 g. (0.61 mole), was added in one portion and the solution quickly heated to the boiling point. The reaction was vigorous, and after one-half to one hour of refluxing, the solution was neutral to litmus. The mixture was cooled in ice, diluted with 1400 cc. of water, and the ester layer separated. The water layer was extracted four times with benzene, and the combined ester and benzene extracts washed twice with water. Distillation from a modified Claisen flask gave 118 g. of crude ester, b. p. 125–140° (16 mm.). After shaking the crude product for twelve hours with 200 cc. of 20% sodium bisulfite solution and redistilling through a Widmer column, the yield of a mixture of the ethyl and isopropyl esters of ethyl (1-methyl-1-butenyl)-cyanoacetic acid, b. p. 129–133° (14 mm.) was 100 g. (80%, calculated as the ethyl ester). Other alkylations in isopropyl alcohol were performed in a similar manner. When the less active alkyl halides are used in these alkylations, it is not essential to cool the solutions before adding the halides. With the dialkyl sulfates, the reactions are too vigorous unless this precaution is taken. Alkylations in methyl and ethyl alcohols were performed using 700 cc. of the anhydrous alcohols per mole of sodium, and cooling the sodium alkoxide solutions to −5° during the addition of the alkylidene esters. After the esters were added, the solutions were stirred for twenty minutes at −5 to −10° before adding the alkylating agent. The mixtures were then heated rapidly to the boiling point, and the reactions were usually vigorous. Small aliquot portions of those reaction mixtures which did not become neutral were titrated from time to time with standard acid, and refluxed until the alkalinity became constant. The properties of various (dialkylvinyl)-alkylcyanoacetic esters and data concerning the preparations are recorded in Table I.

Sodamide in Inert Solvents.—A sodium derivative was prepared from methyl (1-methylhexylidene)-cyanoacetate by adding 0.5 mole of the ester to an equivalent quantity of sodamide in liquid ammonia solution. On replacing the ammonia with toluene containing a small amount of ether, according to the procedure used in other alkylations with sodamide,[1] a very insoluble sodium derivative was precipitated. Diethyl sulfate was added and the mixture refluxed until it became neutral (two hours), after which the ester was washed and distilled. The low boiling portion of the distillate contained methyl amyl ketone, a cleavage product of the alkylidene ester. The crude ester fraction weighed 21 g., and a large tarry residue remained. The impure product was shaken with sodium bisulfite solution and redistilled. The yield of pure methyl (1-methyl-1-hexenyl)-cyanoacetate, identical with the product described in Table I, was only 14 g. (13%).

Sodium in Inert Solvents.—Powdered sodium was used in several cases for preparing sodium derivatives of the alkylidenecyanoacetic esters. For example, 0.25 mole of methyl (1-propylbutylidene)-cyanoacetate was treated

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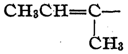
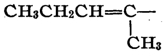
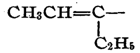
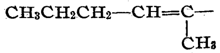
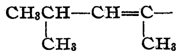
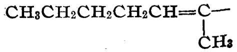
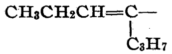
(6) Lapworth and McRae, *J. Chem. Soc.*, 121, 2745 (1922).

TABLE I

SUBSTITUTED VINYLALKYLCYANOACETIC ESTERS

Substituted vinyl group	Alkyl group	Ester	Alkylating agent	Hours refluxed	Yield, %	B. p. (uncorr.) °C.	Mm.	$n^{25}D$	d^{25}_{25}	Molecular refraction Calcd.	Molecular refraction Found	Formula	Nitrogen, % Calcd.	Nitrogen, % Found[a]	Yield of mixed ethyl isopropyl ester, %
1-Methylpropenyl,  $CH_3CH{=}\underset{\displaystyle CH_3}{\underset{\vert}{C}}—$	Ethyl[l]	Ethyl	Ethyl iodide	1.0	55	117–117.5	12	1.4470	0.9665	53.95	54.11	$C_{11}H_{17}O_2N$	7.11	7.16	..
	Propyl	Ethyl	Propyl iodide	0.3	42	120–122.5	9	1.4481	.9560	58.57	58.68	$C_{12}H_{19}O_2N$	6.70	6.78	58
	Butyl	Ethyl	Butyl iodide	2.3	40	134–134.5	9	1.4500	.9478	63.19	63.47	$C_{13}H_{21}O_2N$	6.28	6.39	..
1-Methyl 1-butenyl,  $CH_3CH_2CH{=}\underset{\displaystyle CH_3}{\underset{\vert}{C}}—$	Methyl[l]	Ethyl	Methyl iodide	0.5	68	124–126	16	1.4445	.9589	53.95	54.26	$C_{11}H_{17}O_2N$	7.18	7.02	82[b]
	Ethyl[l]	Ethyl	Ethyl iodide	3.0	63[c]	135–136	17	1.4460	.9530	58.57	58.70	$C_{12}H_{19}O_2N$	6.70	6.71	80[d]
	Propyl	Ethyl	Propyl iodide	1.0	43	128–129	9	1.4480	.9436	63.19	63.50	$C_{13}H_{21}O_2N$	6.28	6.34	70[e]
	Isopropyl	Ethyl	Isopropyl iodide	3.0	42	133–134	13	1.4485	.9482	63.19	63.26	$C_{13}H_{21}O_2N$	6.28	6.30	73[f]
	Allyl	Ethyl	Allyl bromide	1.0	40	130–133	9	1.4602	.9622	62.72	63.16	$C_{13}H_{19}O_2N$	6.34	6.33	55[g]
1-Ethylpropenyl,  $CH_3CH{=}\underset{\displaystyle C_2H_5}{\underset{\vert}{C}}—$	Methyl	Ethyl	Methyl iodide	0.5	87	112–113	8	1.4490	.9703	53.95	54.10	$C_{11}H_{17}O_2N$	7.18	7.20	..
	Ethyl	Ethyl	Ethyl iodide	0.8	70	141–143	22	1.4500	.9637	58.57	58.50	$C_{12}H_{19}O_2N$	6.70	6.57	77[d]
	Propyl	Ethyl	Propyl bromide	1.0	57	132–133.5	10	1.4510	.9541	63.19	63.17	$C_{13}H_{21}O_2N$	6.28	6.33	91
	Isopropyl	Ethyl	Isopropyl iodide	1.5	63	129–130	12	1.4520	.9572	63.19	63.08	$C_{13}H_{21}O_2N$	6.28	6.31	87
1-Methyl-1-pentenyl,  $CH_3CH_2CH_2—CH{=}\underset{\displaystyle CH_3}{\underset{\vert}{C}}—$	Methyl[l]	Ethyl	Methyl iodide	1.0	78	138–139	17	1.4460	.9488	58.57	58.96	$C_{12}H_{19}O_2N$	6.70	6.77	..
	Ethyl[l]	Ethyl	Ethyl iodide	3.5	70	145–146	17	1.4480	.9445	63.19	63.44	$C_{13}H_{21}O_2N$	6.28	6.27	..
1,3-Dimethyl-1-butenyl,  $CH_3\underset{\displaystyle CH_3}{\underset{\vert}{CH}}—CH{=}\underset{\displaystyle CH_3}{\underset{\vert}{C}}—$	Methyl[l]	Methyl	Methyl iodide	2.5	46	130–133	22	1.4475	.9624	53.95	54.39	$C_{11}H_{17}O_2N$	7.18	7.14	..
	Ethyl[l]	Methyl	Ethyl iodide	2.5	32[h]	137–139	22	1.4483	.9561	58.57	58.77	$C_{12}H_{19}O_2N$	6.70	6.59	..
1-Methyl-1-hexenyl,  $CH_3CH_2CH_2CH_2CH{=}\underset{\displaystyle CH_3}{\underset{\vert}{C}}—$	Methyl	Methyl	Methyl iodide	4.0	23[i]	150–152	22	1.4500	.9556	58.57	58.99	$C_{12}H_{19}O_2N$	6.70	6.55	70
	Ethyl	Methyl	Ethyl iodide	4.0	18[j]	158–159	22	1.4524	.9510	63.19	63.54	$C_{13}H_{21}O_2N$	6.28	6.13	..
1-Propyl-1-butenyl,  $CH_3CH_2CH{=}\underset{\displaystyle C_3H_7}{\underset{\vert}{C}}—$	Ethyl[l]	Methyl	Ethyl iodide	3.0	78[k]	150–151.5	22	1.4560	.9596	63.19	63.40	$C_{13}H_{21}O_2N$	6.28	6.35	..

[a] We are indebted to Mr. C. S. Miller for semi-micro Kjeldahl analyses. [b] Dimethyl sulfate gave a 65% yield. [c] Diethyl sulfate gave a 45% yield, ethyl bromide 41%. [d] Using diethyl sulfate. [e] Using propyl bromide. [f] 55% with isopropyl bromide. [g] Using allyl chloride. [h] Yield in ethyl alcohol 83%, calculated as the methyl ester. [i] Yield in ethyl alcohol 77%. [j] Yield in ethyl alcohol 58%. [k] Yield in ethyl alcohol 93%. [l] Ozonized by the procedure described in the Experimental Part.

with 0.25 mole of powdered sodium under 250 cc. of dry ether. The sodium had all dissolved after three hours of refluxing, and the soluble sodium derivative was alkylated with diethyl sulfate approximately as in the similar alkylation of ethyl isopropylidenemalonate.[1a] A 58% yield of methyl (1-propyl-1-butenyl)-ethylcyanoacetate was obtained, b. p. 117–119° (4 mm.); n^{25}_D 1.4489, d^{25}_{25} 0.9482. This ester gave satisfactory nitrogen analyses (calcd. for $C_{13}H_{21}O_2N$: N, 6.28; found: N, 6.38), but the low index of refraction, compared with that of the pure ester prepared in methyl alcohol and described in Table I, indicates the presence of the corresponding reduced ester as an impurity.

Ozonizations.—The esters indicated by footnote *l* in Table I were ozonized by the procedure described previously.[1b] The aldehydes formed on decomposition of the ozonides were converted to the 2,4-dinitrophenylhydrazones as before, and color tests for formaldehyde were made. In each case, a trace of formaldehyde was present, as indicated by positive ring tests with both gallic acid and resorcinol, but in no case was there enough to give the moderately sensitive resorcinol test with sodium hydroxide. As in the previous work, the most volatile portion of each of the distillates was treated with 2,4-dinitrophenylhydrazine and hydrochloric acid in alcohol solution. The derivatives formed were nearly pure as precipitated, and one recrystallization brought them to constant melting point in each case. The respective 1-alkyl-alkenyl esters gave the following aldehydes, as shown by the melting points of their 2,4-dinitrophenylhydrazones and mixed melting points with known samples. The 1-methylpropenyl ester gave acetaldehyde, m. p. and mixed m. p. of the derivative 163–165°. The 1-methyl-1-butenyl esters gave propionaldehyde, m. p. and mixed m. p. of the derivative 153–154°. The 1-methyl-1-pentenyl esters gave butyraldehyde, m. p. and mixed m. p. of the derivative 121–122°. The 1,3-dimethyl-1-butenyl ester gave isobutyraldehyde, m. p. and mixed m. p. of the derivative 181–182°. The 1-methyl-1-hexenyl ester gave valeraldehyde, m. p. and mixed m. p. of the derivative 108–109°.[7] (These melting points are uncorrected.)

Summary

Alkylidenecyanoacetic esters derived from both symmetrical and unsymmetrical ketones give sodium derivatives when treated with sodium alkoxides in alcohol solution. Alkylation of these sodium derivatives with alkyl halides and dialkyl sulfates produces (dialkylvinyl)-alkylcyanoacetic esters, RCH=C(R′)C(R″)(CN)COOR‴. In the formation of a sodium derivative from five alkylidenecyanoacetic esters derived from a series of methyl ketones, hydrogen is lost from the methylene of an alkyl group higher than methyl, rather than from the methyl group. Yields in the alkylation reactions are highest when sodium isopropoxide and isopropyl alcohol are employed, presumably because of the relatively slow alcoholysis of the products in this solvent.

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[7] The valeraldehyde derivatives had a higher melting point than the one previously recorded. All others are in agreement with those reported by Campbell, *Analyst*, **61**, 391 (1936).

BRYN MAWR, PENNA. RECEIVED SEPTEMBER 26, 1938

[CONTRIBUTION FROM THE WILLIAM H. CHANDLER CHEMISTRY LABORATORY, LEHIGH UNIVERSITY]

The Action of Bromine on Nitrothiophene

BY V. S. BABASINIAN

The literature has very little to reveal regarding the behavior of nitrothiophene toward bromine. Casual references to the changes involved merely imply that the halogen attacks the nitro group with avidity, converting the compound to tetrabromothiophene.[1] The reaction was studied more closely in this Laboratory. It was found that in direct contact with the theoretical amount of bromine, nitrothiophene yields mainly tetrabromothiophene, but the product invariably is contaminated with the unattacked nitro compound. On the other hand, when the amount of bromine is reduced to the required minimum for the replacement of a single hydrogen in the thiophene nucleus, brominated intermediates appear in the product along with tetrabromothiophene. The reaction is likewise modified if brominations are effected in neutral or alkaline aqueous suspensions, or in ordinary organic solvents. Small-scale experiments performed under these conditions[2] give every indication that in the direct bromination of nitrothiophene the nitro group offers a degree of resistance to replacement by bromine, permitting the formation of a number of substituted derivatives, and under proper control the reaction pursues a course that can be followed with reasonable certainty.

The author proposes to show that with bromine vapor at room temperature, nitrothiophene

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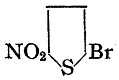
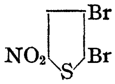
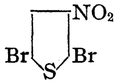
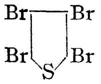
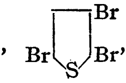
[1] (a) Meyer, "Die Thiophengruppe," Braunschweig, 1888, p. 102; (b) Steinkopf and co-workers, *Ann.*, **512**, 137 (1934).

[2] The author desires to record his gratitude to Messrs. John B. Fishel and Horace F. Ether who performed the preliminary experiments. The analytical data for tetrabromothiophene, given later, were secured by Mr. Ether.

yields four compounds in quantities ample for conclusive identification, and the presence of a fifth derivative of thiophene may be demonstrated by qualitative tests. In the following list the approximate yield of each crude product from 50 g. of nitrothiophene is indicated. The melting points are those of the purified compounds.

—Thiophene	2-Bromo-5-nitro-	2,3-Dibromo-5-nitro-	2,5-Dibromo-3-nitro-	Tetrabromo-
Formula				
Yield, g.	8.5	6.0	0.8[3]	10.0
M. p., °C.	47–48	75.5–76	61	116–117

In the reaction product a fifth derivative of thiophene was isolated in extremely small quantities. Its composition as 2,3,5-tribromothiophene,  is provisionally inferred from a superficial examination of physical properties.

Discussion of Results

The results attained in this bromination justify the assumption that in bromonitrothiophene the substituents occupy positions 2 and 5. They also elucidate the course of the reaction, and offer criteria for the evaluation of the relative stability of intermediates.

The Structure of Bromonitrothiophene.—There are two factors that are likely to control the course of the reaction between bromine and nitrothiophene: namely, (a) the alpha orienting effect of sulfur, and (b) the meta orienting effect of the nitro group. Under the predominating influence of (a) or (b) one would expect the formation of either 2-bromo-5-nitrothiophene or 3-bromo-5-nitrothiophene. If both factors were effective the two isomers might appear as a mixture. It is quite significant that in this reaction approximately 9 g. of an homogeneous bromonitrothiophene was isolated. More important is the fact that the compound produced was in every detail identical with the bromonitrothiophene prepared from 2-bromothiophene by nitration.[4] The formation of the same bromonitrothiophene, whether one brominates *2-nitrothiophene* or nitrates *2-bromothiophene*, points to the conclusion that the product is 2-bromo-5-nitrothiophene.[5] There is no valid reason to doubt the meta orienting capacity of the nitro group. And if under the influence of this factor 3-bromo-5-nitrothiophene was also produced in any quantity, it quickly changed to 2,3-dibromo-5-nitrothiophene because of the available alpha position which an additional bromine could readily occupy.

The Course of the Reaction and Relative Stability.—In the brominated product 2,3-*dibromo-5-nitrothiophene* is also present in moderate quantities. It is natural to assume that this compound was formed by the further bromination of 2-bromo-5-nitrothiophene. Had the reaction followed a normal course, a large percentage of the latter would have produced the former. When the yields of the two products are compared, it will be seen that the amount of 2-bromo-5-nitrothiophene is much larger than that of 2,3-dibromo-5-nitrothiophene. This means that the 2-bromo compound is more resistant to the action of the halogen than the 2,3-dibromo derivative. As the latter accumulates in the reaction product, it is attacked by bromine and ultimately changed to tetrabromothiophene.[6]

From the results it is also possible to determine with reasonable assurance the relative stability of the nitro group toward bromine in these two compounds. That in 2-bromo-5-nitrothiophene this group is not vulnerable may be inferred from the complete absence of 2,5-dibromothiophene in the reaction product. 2,3-Dibromo-5-nitrothiophene shows an altogether different behavior. Had the nitro group been firmly held by the nucleus, further bromination would have resulted in the formation of 2,3,4-tribromo-5-nitrothiophene; but not a trace of this product could be isolated in these experiments. Moreover, if any importance could be attached to evidence gleaned from tests of purely qualitative

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(3) This product could originate only from β-nitrothiophene. Steinkopf and Höpner were able to prove that ordinary nitrothiophene contains about 97.5% of the alpha compound and 2.5% of the beta isomer [*Ann.*, **501**, 176, 182–183 (1933)]. In the course of the present study a partial separation of the two isomers was made by the repeated crystallization of ordinary nitrothiophene from petroleum ether. In one of the bromination experiments a sample of ordinary nitrothiophene was used which had not been separated into the two isomers. Omission of this procedure resulted in a marked increase in the yield of 2,5-dibromo-3-nitrothiophene.

(4) Babasinian, THIS JOURNAL, **57**, 1763 (1935). Compare also ref. 1b, p. 161. The compound produced in this way was provisionally described as 2-bromo-5-nitrothiophene, but no evidence was offered in support of this structure.

(5) *Cf.* von Schweinitz, *Ber.*, **19**, 640, 648 (1886).

(6) 2,5-Dibromo-3-nitrothiophene is not expected to manifest this behavior. Steinkopf and co-workers[1b] (pp. 137 and 161) had pointed out that, unlike 2,3-dibromo-5-nitrothiophene, this compound remains quite stable in an excess of bromine.

nature, 2,3,5-tribromothiophene was formed, at any rate, in detectable quantities. The appearance of this compound and the complete absence of 2,3,4-tribromo-5-nitrothiophene led to the inference that in 2,3-dibromo-5-nitrothiophene the nitro group is too weakly held by the nucleus to resist replacement by the halogen. In consequence, the loosely held group leaves the nucleus to favor the formation of tetrabromothiophene.

Experimental

Fifty grams of nitrothiophene, prepared in the usual way,[7] was spread in a crystallizing dish and supported over 27 cc. of bromine in a covered desiccator. The reaction was allowed to proceed at room temperature for thirty days. In twelve hours over one-half of the bromine had been absorbed and the solid had completely liquefied into a dark red oil. In the following twenty-four hours the oil had in part changed to fine crystals. The final product was a mixture consisting of light red crystals and a yellow oil. Bromine was more rapidly absorbed during the last few days of the allotted period than at the beginning.

Tetrabromothiophene in the Oily Mixture.—The reaction product was chilled and filtered under suction. The precipitate was washed with water, dried, and refluxed with several portions of petroleum ether. The solvent extracted a small quantity of nitrothiophene. The undissolved white residue weighed about 9 g. It was crystallized from hot alcohol and melted at 116–117°.

Anal. Calcd. for C_4Br_4S: S, 8.00; Br, 79.97. Found: S, 7.86; Br, 80.23.

The oily filtrate was neutralized with dilute sodium carbonate, washed with water, and steam-distilled.[8] The distillate was collected in four fractions: Fraction I contained a white solid and an almost colorless oil; II was uniformly oily; III was also uniformly oily; IV distilled slowly as a pure white solid.

Each of the first three fractions was dissolved in ether and dried with calcium chloride. Fraction IV was filtered and dried. Ether was removed from the first three fractions and the oily residues were examined.

2-Bromo-5-nitrothiophene in Fractions I and II.—Fraction I was cooled in ice for a long time and filtered under suction. The crystalline precipitate was brownish-white, yield 7.5 g. It was dissolved in boiling petroleum ether and decolorized with darco. Upon cooling the filtrate yielded snow-white needles which acquired a faint yellow color in air. The recrystallized product melted at 47–48°. The mixed melting point with a pure sample of 2-bromo-5-nitrothiophene was 46–47°.

Anal. Calcd. for $C_4H_2S(NO_2)Br$: S, 15.41; Br, 38.42. Found: S, 15.36; Br, 38.26.

Fraction II was cooled in a freezing mixture and filtered. The solid proved to be 2-bromo-5-nitrothiophene.

2,3-Dibromo-5-nitrothiophene in Fraction III.—Fraction III was cooled and filtered. The precipitate yielded 3.5 g. of bright yellow crystals which melted at 74–75°. A petroleum ether solution, after treatment with darco, yielded white crystals which acquired a faint yellow coating when exposed to air. The compound is moderately volatile with steam. The distilled solid is pure white, while the clear aqueous residue in the distillation flask retains the faint yellow color. After recrystallization from petroleum ether the steam-distilled solid remained almost white in a brown desiccator for several weeks. It melted at 75.5–76°.[9]

Anal. Calcd. for $C_4HS(NO_2)Br_2$: S, 11.17; Br, 55.70. Found: S, 11.04; Br, 55.80.

Fraction IV Yields Tetrabromothiophene, 2,3-Dibromo-5-nitrothiophene, and a Trace of Lower-melting Crystals.—The solid obtained as Fraction IV weighed 9.5 g. It was crystallized from a large volume of methanol. The nitrogen-free crystals melting at 113–114° proved to be tetrabromothiophene. After concentration the alcoholic filtrate yielded 2.5 g. of 2,3-dibromo-5-nitrothiophene. Upon further concentration the mother liquor was found to contain a trace of a white solid which melted at 62–67°.

The isolation of compounds in the oily filtrates was accomplished by distillation *in vacuo* at constant pressure. Serious decomposition could be reduced to a negligible minimum if the process was carried out slowly, below 130°.

Oily filtrates from Fractions I, II and III were distilled under a pressure of 5 mm. and collected at the following temperature ranges: A, at or below 105° (trace of solid or oil); B, at 109–110° (mainly solid); C, at 112–115° (oil); D, at 118–123° (mainly solid); E, at 123–128° (solid and oil). Distillates containing mixtures of oil and solid were cooled and filtered. The precipitate was freed from impurities by the usual methods. Oils, or oily filtrates, were dissolved in solvents and cooled; when the solution failed to form crystals, the solvent was evaporated and the oil was refractionated. Purified products could be obtained only in small quantities. When melting points and qualitative tests furnished fair indications of identity with previously analyzed compounds, results were checked by determinations of mixed melting points.

Distillate A was composed mainly of unattacked *nitrothiophene.*

Distillate B yielded *2-bromo-5-nitrothiophene.*

Distillate C produced a compound melting at 28–32° in quantities too small for complete purification. This is probably *2,3,5-tribromothiophene*[1a] (p. 79).

Distillate D contained almost exclusively *2,3-dibromo-5-nitrothiophene.*

Distillate E was found to be a mixture of *tetrabromothiophene, 2,3-dibromo-5-nitrothiophene,* and *2,5-dibromo-3-nitrothiophene.* For the isolation of these compounds the distillate was cooled and filtered. The solid was dissolved in methanol and purified with darco. From the clear solution bright yellow crystals of 2,3-dibromo-5-nitrothiophene were obtained.

The oily filtrate was dissolved in boiling alcohol. Upon

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(7) Babasinian, THIS JOURNAL, **50**, 2749 (1928).

(8) A dark brown semi-solid remained in the distillation flask. Weight, after drying, about 10 g. Insoluble in most ordinary solvents. Boiling acetone removed from it a dark red heavy oil leaving an insoluble brown powder which burned very slowly over a direct flame. The oil and the brown powder were not examined further.

(9) There can be no doubt that the white product, showing this melting point, is 2,3-dibromo-5-nitrothiophene. Steinkopf and coworkers describe it as a bright yellow solid and give its melting point as 75° (ref. 1b, p. 156).

cooling crystals were obtained which had the characteristics of tetrabromothiophene. The mother liquor was carefully concentrated. When cooled in a freezing mixture, white, shiny crystals were formed which melted at 55–65°; weight less than 1 g. It was recrystallized from petroleum ether, then distilled with steam and the solid distillate was again crystallized from the same solvent. The final product melted at 61°. Analysis showed that the compound was 2,5-dibromo-3-nitrothiophene.[10]

Anal. Calcd. for $C_4HS(NO_2)Br_2$: S, 11.17; Br, 55.70. Found: S, 10.90; Br, 56.16.

Summary

In the vapor phase and at room temperature a limited quantity of bromine converts ordinary nitrothiophene into 2-bromo-5-nitrothiophene, 2,3-dibromo-5-nitrothiophene, 2,5-dibromo-3-nitrothiophene and tetrabromothiophene.

Qualitative tests also indicate the formation in traces of one other brominated derivative of thiophene.

The reaction confirms the heretofore assumed structural formula of bromonitrothiophene.

The reaction leads to the inference that in 2-nitrothiophene the nitro group resists replacement by bromine during the entry of the first atom of halogen into the thiophene nucleus; but this group is considerably loosened after the entry of the second bromine atom.

BETHLEHEM, PENNA. RECEIVED SEPTEMBER 12, 1938

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[10] The same compound had been produced by the direct bromination of 3-nitrothiophene,[1b] p. 161.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF TRINITY COLLEGE]

Ternary Systems. V. Phthalic Acid, Magnesium Phthalate and Water. VI. Magnesium Phthalate, Lithium Phthalate and Water

BY STERLING B. SMITH AND EDWARD C. ELY[1]

Introduction

A number of phase rule studies of ternary systems involving phthalates and acid phthalates, particularly of the alkalies, have been made in this Laboratory. It is for the purpose of gaining further information regarding the solubilities of these salts that this investigation has been undertaken.

Experimental Part

Materials and Methods.—The phthalic acid used was prepared by crystallizing from aqueous solution sublimed phthalic anhydride obtained from the Eastman Kodak Company.

Magnesium phthalate was prepared by adding to an aqueous solution of phthalic acid an excess of magnesium carbonate, A. R. The solution was boiled to drive off carbon dioxide and filtered hot to remove the insoluble magnesium carbonate. The filtrate was evaporated to a small volume and allowed to stand several days while the magnesium phthalate crystallized out. The salt was filtered on a Büchner funnel and allowed to dry in the air. The composition of this salt was found by analysis to be $2MgC_8H_4O_4 \cdot 11H_2O$. Air dried samples heated to constant weight in an electric oven at 120° lost weight corresponding to 34.72, 34.60, 34.58, 34.45, 34.27 and 34.23% of water. The theoretical value for the per cent. of water in $2MgC_8H_4O_4 \cdot 11H_2O$ is 34.47%.

Lithium phthalate, $2Li_2C_8H_4O_4 \cdot 3H_2O$, was prepared as described in a previous publication.[2]

Magnesium acid phthalate, while not a component of either of these systems, appears as one of the solid phases and is used in the preparation of mixtures for analysis. It was prepared by adding slightly more than one-half the equivalent weight of magnesium carbonate to an aqueous solution containing the equivalent weight of phthalic acid, boiling off the carbon dioxide and evaporating to crystallization.

Solubilities were determined by analyzing solutions obtained by rotating mixtures of the three components in an electrically controlled thermostat for a minimum of twenty-four hours. In making up the mixtures, as far as possible the salts were used which exist as solid phases after equilibrium has been reached. At 0° the temperature was maintained constant by the use of ice and a small amount of salt. Temperature variations were within ±0.1°. When equilibrium was attained, the mixtures were allowed to settle and samples for analysis removed from the clear supernatant liquid by means of a pipet. When necessary to ensure a clear solution, a small plug of cotton or glass wool was inserted in a short piece of rubber tubing and slipped over the end of the pipet. Due to the viscosity of many of these solutions, density determinations were not attempted.

The composition of the solid phases was determined by the analysis of wet residues according to Schreinemakers.[3]

In the system phthalic acid, magnesium phthalate and water, phthalic acid was determined by titration with standard alkali. Magnesium phthalate was determined by precipitation of the magnesium as magnesium am-

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[1] The material for this paper was taken from a thesis of Mr. Edward C. Ely presented to the Graduate Committee of Trinity College in partial fulfilment of the requirements for the Master of Science degree. Original manuscript received February 15, 1938.

[2] Smith, Sturm and Ely, THIS JOURNAL, **57**, 2406 (1935).

[3] Schreinemakers, *Z. physik. Chem.*, **11**, 76 (1893).

monium phosphate followed by ignition to the pyrophosphate. Water was determined by difference.

In the system magnesium phthalate, lithium phthalate and water, water was determined as loss in weight when a sample was heated to constant weight in a platinum dish in an electric oven at 180°. Magnesium phthalate was determined in the same sample by the pyrophosphate method and lithium phthalate determined by difference. Solutions saturated with both lithium phthalate and magnesium phthalate were so viscous and so dense that a week was required for the solid phase to settle. Even then these solutions were slightly turbid after passing through glass wool. No improvement was found after centrifuging. Solubility determinations, therefore, in this system near its univariant point may be off as much as 0.5%.

Experimental Results.—Isotherms at 0, 25 and 50° have been completed for the system phthalic acid, magnesium phthalate and water. Compound formation takes place at all three temperatures. The solubility isotherms, therefore, consist of three intersecting curves representing isothermally univariant equilibrium between the solutions and one solid phase, and two isothermally invariant points where two solid phases are in equilibrium with the solution.

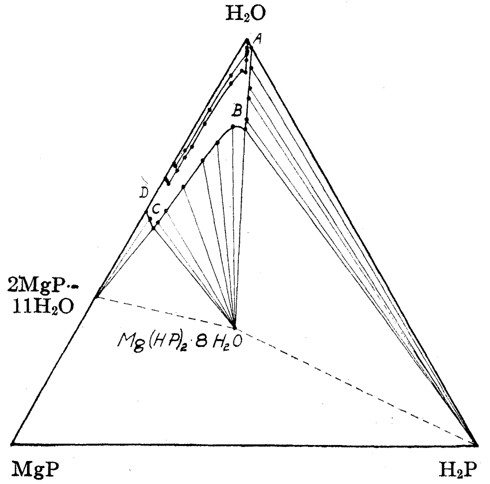

Fig. 1.—Temperatures, 0, 25, 50°.

One isotherm at 25° has been completed for the system magnesium phthalate, lithium phthalate and water. A second isotherm at 50° was undertaken but due to the extreme viscosity of the solutions at the higher concentrations, no conclusive results were obtained near the invariant point and further experiments abandoned. The 25° isotherm shows no evidence of compound formation. The isotherm consists of two intersecting curves representing isothermally univariant equilibrium between the solutions and one solid phase, and one isothermally invariant point at which the solution is in equilibrium with two solid phases. The portion of the 50° isotherm which is reported is similar. It is possible that compound formation or solid solution may occur in that region where unsatisfactory non-reproducible results were obtained.

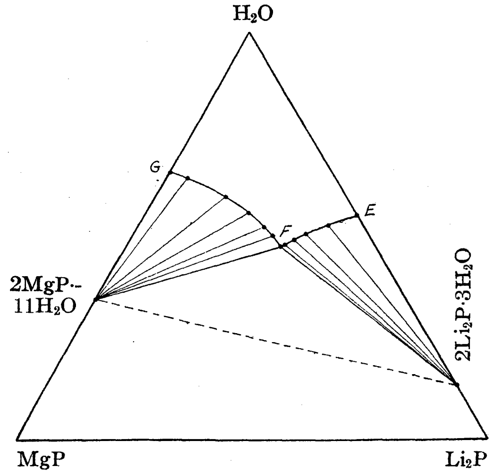

Fig. 2.—Temperature, 25°.

Experimental results are given in Tables I and II. The symbol "P" is used here as in previous work to designate the phthalate radical, $C_8H_4O_4$.

TABLE I

SOLUBILITY DATA: THE SYSTEM H_2P, MgP, H_2O

Point in Fig.	Solution		Wet residues		Solid phases
	% H_2P	% MgP	% H_2P	% MgP	
			Temperature, 0°		
A	0.29	None	...	...	H_2P
	1.00	0.99	83.34	...	H_2P
B	1.58	1.93	66.55	8.32	H_2P; $Mg(HP)_2 \cdot 8H_2O$
	1.58	1.95	53.17	18.52	H_2P; $Mg(HP)_2 \cdot 8H_2O$
	1.59	1.95	46.41	28.57	H_2P; $Mg(HP)_2 \cdot 8H_2O$
	1.06	7.69	29.43	34.47	$Mg(HP)_2 \cdot 8H_2O$
	.76	16.20	28.80	34.71	$Mg(HP)_2 \cdot 8H_2O$
	.47	26.58	27.30	36.09	$Mg(HP)_2 \cdot 8H_2O$
C	.39	30.76	15.05	48.66	$Mg(HP)_2 \cdot 8H_2O$; $2MgP \cdot 11H_2O$
	.39	30.80	23.43	43.34	$Mg(HP)_2 \cdot 8H_2O$; $2MgP \cdot 11H_2O$
D	None	30.63	...	...	$2MgP \cdot 11H_2O$
			Temperature, 25°		
A	0.69	None	...	...	H_2P
	1.69	1.27	79.12	0.28	H_2P
	2.70	2.66	81.91	0.56	H_2P
B	3.61	4.16	48.66	20.50	H_2P; $Mg(HP)_2 \cdot 8H_2O$
	3.62	4.18	29.64	28.56	H_2P; $Mg(HP)_2 \cdot 8H_2O$
	3.60	4.14	58.50	9.98	H_2P; $Mg(HP)_2 \cdot 8H_2O$
	3.23	4.71	24.96	28.39	$Mg(HP)_2 \cdot 8H_2O$
	2.33	8.92	28.12	31.48	$Mg(HP)_2 \cdot 8H_2O$
	1.79	19.17	23.07	31.97	$Mg(HP)_2 \cdot 8H_2O$
	1.72	20.46	22.74	32.54	$Mg(HP)_2 \cdot 8H_2O$
	1.60	22.75	25.70	33.87	$Mg(HP)_2 \cdot 8H_2O$
	1.54	23.49	29.61	35.95	$Mg(HP)_2 \cdot 8H_2O$
	1.36	27.49	...	...	$Mg(HP)_2 \cdot 8H_2O$
	1.30	30.98	27.03	36.72	$Mg(HP)_2 \cdot 8H_2O$
	1.21	32.26	26.86	36.18	$Mg(HP)_2 \cdot 8H_2O$

TABLE I (*Concluded*)

Point in Fig.	Solution		Wet residues		Solid phases
	% H_2P	% MgP	% H_2P	% MgP	
C	1.16	34.42	27.32	39.32	$Mg(HP)_2 \cdot 8H_2O$; $2MgP \cdot 11H_2O$
	1.17	34.38	10.05	55.37	$Mg(HP)_2 \cdot 8H_2O$; $2MgP \cdot 11H_2O$
	1.03	34.26	0.85	58.39	$2MgP \cdot 11H_2O$
	0.47	34.16	.56	60.80	$2MgP \cdot 11H_2O$
D	None	34.11	...	...	$2MgP \cdot 11H_2O$
			Temperature, 50°		
A	1.72	None	...	...	H_2P
	4.13	2.85	95.22	...	H_2P
	6.15	5.36	...	...	H_2P
	7.43	6.95	...	...	H_2P
	9.47	9.95	74.86	3.20	H_2P
B	10.18	11.22	49.49	22.21	H_2P; $Mg(HP)_2 \cdot 8H_2O$
	10.23	11.16	52.68	19.79	H_2P; $Mg(HP)_2 \cdot 8H_2O$
	10.23	11.20	33.98	29.33	H_2P; $Mg(HP)_2 \cdot 8H_2O$
	7.95	13.68	29.61	34.15	$Mg(HP)_2 \cdot 8H_2O$
	6.56	18.72	...	...	$Mg(HP)_2 \cdot 8H_2O$
	5.52	24.20	27.92	35.73	$Mg(HP)_2 \cdot 8H_2O$
	4.64	31.51	26.07	35.85	$Mg(HP)_2 \cdot 8H_2O$
	3.88	38.25	28.22	38.11	$Mg(HP)_2 \cdot 8H_2O$
	3.67	41.19	...	...	$Mg(HP)_2 \cdot 8H_2O$
C	3.54	42.85	16.31	49.81	$Mg(HP)_2 \cdot 8H_2O$; $2MgP \cdot 11H_2O$
	3.56	42.75	15.32	48.39	$Mg(HP)_2 \cdot 8H_2O$; $2MgP \cdot 11H_2O$
	3.49	42.79	14.88	49.39	$Mg(HP)_2 \cdot 8H_2O$; $2MgP \cdot 11H_2O$
	3.12	42.71	0.75	60.43	$2MgP \cdot 11H_2O$
D	None	42.28	...	...	$2MgP \cdot 11H_2O$

TABLE II

SOLUBILITY DATA: THE SYSTEM MgP, Li_2P, H_2O

Point in Fig.	Solution		Wet residues		Solid phases
	% Li_2P	% MgP	% Li_2P	% MgP	
			Temperature, 25°		
E	45.24	None	...	...	$2Li_2P \cdot 3H_2O$
	41.12	7.52	78.94	2.39	$2Li_2P \cdot 3H_2O$
	36.72	12.98	80.93	2.40	$2Li_2P \cdot 3H_2O$
	34.50	16.39	81.47	2.66	$2Li_2P \cdot 3H_2O$
	33.05	19.27	74.92	5.13	$2Li_2P \cdot 3H_2O$
F	32.50	19.98	34.51	34.49	$2Li_2P \cdot 3H_2O$; $2MgP \cdot 11H_2O$
	32.50	19.97	35.51	33.65	$2Li_2P \cdot 3H_2O$; $2MgP \cdot 11H_2O$
	32.51	19.96	17.70	47.85	$2Li_2P \cdot 3H_2O$; $2MgP \cdot 11H_2O$
	29.53	20.43	7.67	54.70	$2MgP \cdot 11H_2O$
	26.88	20.96	7.14	54.28	$2MgP \cdot 11H_2O$
	21.78	22.40	6.25	55.58	$2MgP \cdot 11H_2O$
	19.63	23.06	4.25	55.43	$2MgP \cdot 11H_2O$
	14.86	25.31	3.88	56.37	$2MgP \cdot 11H_2O$
	4.55	31.09	1.12	58.71	$2MgP \cdot 11H_2O$
G	None	34.14	...	...	$2MgP \cdot 11H_2O$

Temperature, 50°

Solution		Solid phases
% Li_2P	% MgP	
46.01	None	$2Li_2P \cdot 3H_2O$
41.76	6.97	$2Li_2P \cdot 3H_2O$
35.22	18.32	$2Li_2P \cdot 3H_2O$
31.05	26.06	$2Li_2P \cdot 3H_2O$
...	...	......
...	...	......
...	...	......
17.49	34.75	$2MgP \cdot 11H_2O$
11.78	36.10	$2MgP \cdot 11H_2O$
3.18	40.31	$2MgP \cdot 11H_2O$
None	42.28	$2MgP \cdot 11H_2O$

The Acid Salt.—The composition of the acid salt, $Mg(HP)_2 \cdot 8H_2O$, was determined by the extrapolation of tie lines which intersect at a point in the isotherms representing a composition which agrees very closely with this. The algebraic extrapolation of the tie lines as shown by Hill and Ricci[4] gives values for the composition which agree closely with the theoretical value of 28.91% water. The maximum deviation in this case was 0.90% with an average deviation of 0.10%. When samples of the hydrated acid salt were dried in an electric oven for twenty-four hours at 110°, percentages of water were found ranging from 28.71 to 29.12. Analyses of the hydrated acid salt for magnesium phthalate and phthalic acid gave an average value for water by difference of 29.08%. The octahydrate was kept in a desiccator over anhydrous magnesium acid phthalate for a prolonged period without loss in weight, giving no evidence of a lower hydrate.

The acid salt, $Mg(HP)_2 \cdot 8H_2O$, is congruently soluble only at 50°, for the three temperatures studied.

Summary

1. The solubility relations in the ternary system phthalic acid, magnesium phthalate and water at 0, 25 and 50° have been determined.

2. Compound formation has been found to take place in this system at all of these temperatures.

3. The composition of this compound has been shown to be $MgC_8H_4O_4 \cdot H_2C_8H_4O_4 \cdot 8H_2O$.

4. This acid salt is crystallizable from aqueous solution at temperatures of 50° and above.

5. When crystallized from water solution at room temperature, magnesium phthalate has the formula, $2MgC_8H_4O_4 \cdot 11H_2O$.

6. An isotherm showing the solubility relations in the ternary system magnesium phthalate, lithium phthalate and water at 25° has been completed. A 50° isotherm is incomplete.

7. No evidence of double salt formation in this system has been established.

HARTFORD, CONNECTICUT RECEIVED OCTOBER 14, 1938

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[4] Hill and Ricci, THIS JOURNAL, **53**, 4306 (1931).

[CONTRIBUTION FROM THE MOORE LABORATORY OF CHEMISTRY, AMHERST COLLEGE]

Heats of Adsorption of Gases on Chromic Oxide at Low Temperatures*

BY RALPH A. BEEBE AND DENNIS A. DOWDEN

As a result of numerous researches on the adsorption of gases on catalytically active solid surfaces, van der Waals and activated adsorptions have become clearly recognized as separate and distinct types. In many instances it has been shown that a gas may be held in both states of adsorption upon the same solid surface. Frequently the two types occur in more or less well separated temperature ranges, the activated type being characteristic of the higher temperature. In certain cases, however, the critical increment of the activated adsorption is sufficiently low so that the temperature range of this process overlaps that of the low temperature van der Waals adsorption.

In the present investigation heats of adsorption, in the low temperature region, have been measured calorimetrically using the six gases, argon, hydrogen, deuterium, carbon monoxide, nitrogen, and oxygen on a reduced chromic oxide surface. The order of magnitude of the heats indicates that all these gases, with the single exception of argon, are in part held in a state of activated adsorption as well as in the van der Waals state even at the low temperature of −183°. Moreover, in the experiments with carbon monoxide, nitrogen, and oxygen, the complex form of the time–temperature curves on a partially covered surface has led us to the conclusion that the adsorbed gas changes over on the surface from an initial van der Waals state to a final state of activated adsorption.

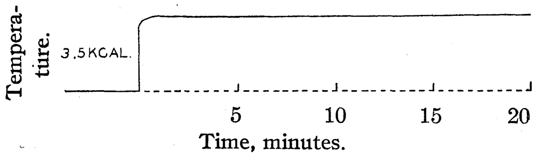

Fig. 1.—Time–temperature curve for argon at −183°.

The catalytic activity of chromic oxide at −183° for the reaction $H_2 + D_2 \rightleftarrows 2HD$[1] leads to the conclusion that the adsorption of hydrogen and of deuterium on that adsorbent is, in part at least, of the activated form. Special interest is therefore attached to the heats of adsorption of the hydrogen isotopes which give independent evidence for the activated adsorption of these gases at −183°. The present work confirms the results of a previous investigation by Beebe and Orfield[2] using hydrogen alone.

Experimental

Apparatus.—A detailed description of the vacuum jacketed calorimeter used in this work has been given in an earlier publication. The calorimeter, which had a total heat capacity of 4.839 cal. at −183° and contained 11.95 g. of chromic oxide, was used without any dismantling or alteration after the heat measurements with hydrogen previously described.[2] The thermocouple wires were led into the calorimeter by means of tungsten bridges sealed through the Pyrex glass. The whole calorimeter vessel including the tungsten bridges was immersed in a suitable bath for constant temperature. For the temperatures −183, −195, and 0°, respectively, baths of liquid oxygen, liquid nitrogen, and an ice–water mixture were used. In the experiments designated in Table II for hydrogen and deuterium, and in all the other work except the first carbon monoxide series, a small quantity (about 0.2 cc.) of helium was admitted to the inside of the calorimeter. This produced a residual pressure of approximately 0.1 mm., and served to improve the conditions for effective heat distribution.

Especially in the hydrogen and deuterium measurements, very careful attention was given to experimental details such as the temperature and duration of outgassing, and the protection of the external leads of the thermocouple from chance fluctuations in room temperature. As a result, it was possible to read the differential heats with greater precision than in the earlier work, and the results were remarkably reproducible in successive series of measurements for all corresponding increments of gas added to the surface.

In Fig. 1 is given a typical time–temperature curve for argon at −183°. The rapid rise to maximum temperature following the admission of the gas, and the almost negligible rate of cooling after the temperature rise, both indicate that the calorimetric conditions were very satisfactory, and the temperature recorded by the thermocouple was truly the average temperature of the whole metal calorimeter with negligible heat lag due to poor thermal distribution. This type of curve, which was obtained under all conditions in the measurements with argon as well as with the isotopes of hydrogen,[3] will be referred to as a *normal* time–temperature curve in comparison to curves of *abnormal* type resulting from the more complex nature of the adsorption processes in the cases of the other gases studied at −183°.

(*) Supported by a grant from the Penrose Fund of the American Philosophical Society.

[1] Gould, Bleakney and Taylor, *J. Chem. Phys.*, **2**, 362 (1934).

[2] Beebe and Orfield, THIS JOURNAL, **59**, 1627 (1937).

[3] Owing to a misunderstanding, the time–temperature curve in Fig. 2 of the paper by Beebe and Orfield was inverted when printed. The downward break in the curve as printed actually represents a rise in temperature.

Because of the much greater rate of heat loss from the metal calorimeter by radiation at the higher temperature, the rate of cooling after the liberation of the heat of adsorption was very much more rapid at 0° than at −183°. However, owing to the rapid rate of adsorption and consequent quick rise to maximum temperature, the heat at 0° could be determined from the time–temperature curves with a fair degree of accuracy. It is noteworthy, however, that this calorimetric method is more satisfactory at the lower temperature.

Materials.—The hydrogen was prepared from electrolytic tank hydrogen by first passing over hot copper and then through a trap filled with glass wool and immersed in liquid air.

Deuterium was produced by electrolysis of 99% deuterium oxide with careful provision for the exclusion of gaseous impurities during the electrolysis and the transfer of the gas.

The method of preparation of carbon monoxide has been described previously.[4] Analysis showed that it contained at least 98% of carbon monoxide and no oxygen.

Pure oxygen was obtained by heating potassium permanganate crystals *in vacuo*.

The nitrogen was obtained from tank nitrogen by mixing with 5% of electrolytic hydrogen, passing the mixed gases over a mixture of copper and copper oxide granules at 400°, and removing the water vapor by means of a calcium chloride tube and liquid air trap.

The argon gas purchased from the Air Reduction Sales Company was spectroscopically pure.

The chromic oxide was the same "unglowed" sample used in the earlier experiments.[2] Following each series of heat measurements, the surface was outgassed for three hours at 400°, except in the case of oxygen. For the removal of the latter gas, the final three-hour period of outgassing was preceded by a one-hour period of reduction in a hydrogen atmosphere. During this reduction the hydrogen was removed and replaced several times to eliminate the water vapor produced.

Results

The Adsorption Isotherms at −183°.—In Fig. 2 are plotted the isotherms from data obtained in the course of the heat measurements at −183°. Hydrogen, deuterium, and carbon monoxide were adsorbed instantaneously (in less than two minutes) with no residual pressure up to 20, 28, and 120 cc., respectively. Argon, nitrogen, and oxygen produced small residual pressures even for the initial increments of gas admitted. In no case was the amount of gas, unadsorbed after two minutes, more than 4% of the total increment admitted. In all cases in which there was residual unadsorbed gas the pressure underwent a slow decrease which was usually complete in twenty minutes. The pressures plotted in Fig. 2 were read twenty minutes after admission of the gas increments. The amount of gas adsorbed in the interval between two and twenty minutes after admission was never more than 2% of the total increment adsorbed, and in most cases much less than that. It was therefore disregarded and the amount of gas adsorbed after two minutes was used in the calculation of the differential heats.

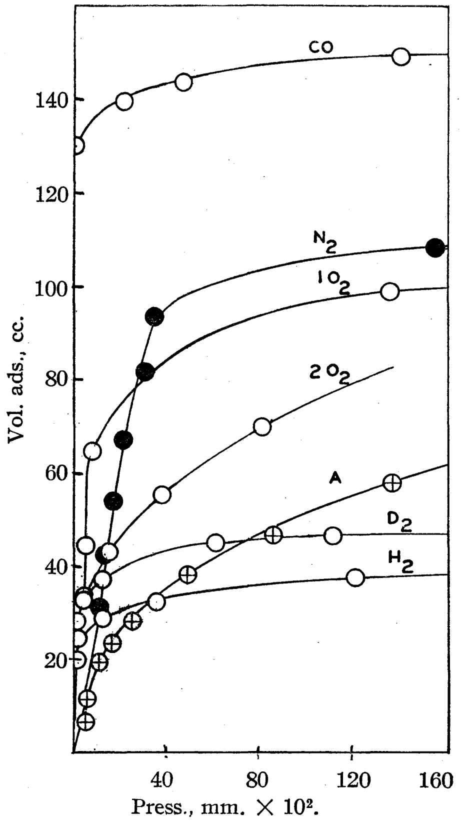

Fig. 2.—Adsorption isotherms on 11.95 g. of Cr_2O_3 at −183°.

With the exception of oxygen, the isotherms were remarkably reproducible. The curves shown in Fig. 2 for carbon monoxide and nitrogen are composites of four series with the former and two with the latter. Only one series was measured with argon. The isotherms for hydrogen and deuterium in Fig. 2 represent data from four series with deuterium and three with hydrogen. These measurements with the hydrogen isotopes were performed before any of the other gases were admitted to the chromic oxide surface. The order of experiments was D_2, D_2, H_2, D_2, H_2, H_2, D_2. For simplicity, only a few representative points have been plotted, but for the scale used, other points not plotted would fall on the isothermal lines without any apparent deviation. It is therefore definitely established that deu-

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(4) Beebe and Wildner, THIS JOURNAL, **56**, 642 (1934).

terium is more firmly held than hydrogen on a chromic oxide surface at −183°.

Analysis showed that the adsorbed carbon monoxide could be removed unchanged by evacuation at 400°, the desorbed gas containing no carbon dioxide. No attempt was made to analyze the other gases after desorption but the reproducibility of the isotherms as well as the differential heat curves, for all the gases studied with the exception of oxygen, provide strong evidence that the three-hour evacuation at 400° was sufficient to remove the adsorbed gases completely without changing the state of the chromic oxide surface. The adsorbed film of oxygen could be removed only as water vapor after reduction in hydrogen. This treatment resulted in a change in the activity of the surface as shown by the failure of the isotherms and heat curves to coincide in the successive series of measurement for oxygen. No experiments with oxygen were attempted until all the other work had been completed. Hence only in the case of the first oxygen series was the surface the same as that employed for the other gases.

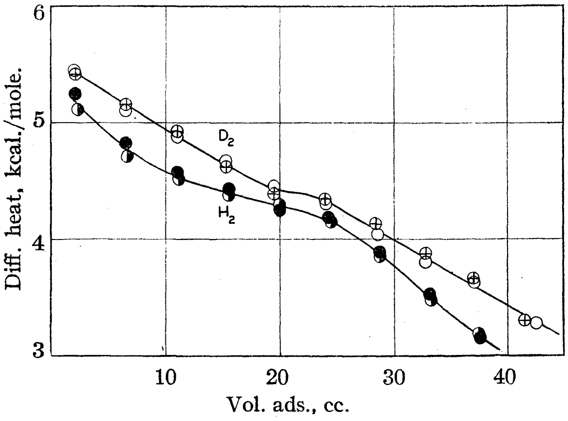

Fig. 3.—Series 1, H_2 ●; Series 2, H_2 ◑; Series 1, D_2 ⊕; Series 2, D_2 ○.

The Heats of Adsorption at −183°, Argon, Hydrogen, and Deuterium.—The results for the single series of differential heat measurements with argon are given in the lower curve in Fig. 8. Because of the magnitude of the differential heats which fall between 4.2 and 2.7 kcal./mole and because of the normal form of the time–temperature curves (Fig. 1) it is concluded that the process for argon at −183° is a simple van der Waals adsorption.

In all, four series of differential heat measurements were made with deuterium and three with hydrogen. The results of two series with each isotope are shown in Fig. 3. Details for typical series are also given in Table I. It is apparent that the heats are definitely higher with the heavier isotope for all corresponding portions of the chromic oxide surface.

TABLE I

Total vol. ads. cc.		Diff. heat kcal./mole		Resid. press., cm. Hg × 10^3	
H_2	D_2	H_2	D_2	H_2	D_2
2.20	2.14	5.11	5.43	....	...
6.55	6.51	4.82	5.14	....	...
11.00	10.93	4.57	4.91	....	...
15.52	15.25	4.44	4.62	....	...
19.91	19.59	4.31	4.39	0.32	...
24.31	24.00	4.18	4.33	1.67	...
28.74	28.40	3.89	4.14	11.30	0.45
33.16	32.78	3.53	3.87	32.61	2.55
37.57	37.14	3.16	3.64	115.50	9.43
	42.5		3.30		32.50

The integral heats, obtained by a process of summation of the differential heats for the increments comprising the first 37.2 cc. of each isotope adsorbed, are listed in Table II (Series 1–7). The integral heats evolved when 37.2 cc. of gas was admitted at one time were also measured in one experiment for each hydrogen isotope. The results are given in Table II (Series 8 and 9). It is interesting that the values obtained by direct admission of the whole 37.2 cc. are higher than those found by a summation of the differential heats. We believe that this difference is a real one and not due to experimental error. A similar discrepancy has been observed by Magnus and his co-workers[5] in the case of sulfur dioxide on charcoal, and these authors have suggested an explanation based on the assumption of slow establishment of equilibrium in the crevices of the adsorbent. It is probable that a similar

TABLE II

Series no.	Gas adsorbed	Integral heat, kcal./mole (37.2 cc. ads.)	
1	D_2		4.79
2	D_2		4.76
3[a]	H_2	4.27	
4[a]	D_2		4.77
5	H_2	4.45	
6	H_2	4.47	
7	D_2		4.81
	Av.	4.40	4.78
8	D_2		5.12
9	H_2	4.81	

[a] Helium present.

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[5] Magnus, Giebenhain and Velde, *Z. physik. Chem.*, **150A**, 285 (1930).

explanation is applicable in the present instance, In any case, it appears to be established that for the interval 0 to 37.2 cc. adsorbed, the integral heat of adsorption of deuterium exceeded that of hydrogen by approximately 0.35 kcal. per mole.

The Heats of Adsorption at −183°, Carbon Monoxide, Nitrogen, and Oxygen.—Unlike the gases already discussed, carbon monoxide, nitrogen, and oxygen failed to produce normal time–temperature curves under all conditions. This anomalous behavior is illustrated in the case of carbon monoxide by the curves in Fig. 4. Curves I, II, and III are the time–temperature curves obtained with approximately equal increments of about 4.5 cc. of the gas on a surface to which had been added already 0, 55, and 112 cc., respectively, *i. e.*, these curves were obtained from measurements on a bare surface, a partly covered surface, and a nearly saturated surface.

A normal type of curve was obtained when no carbon monoxide was previously adsorbed (Curve I); however, with successive increments of the gas the rise to maximum temperature became less and less sharp, and then began to divide into a rapid and a slow stage (Curve II) until finally the slow stage had assumed such a low rate that it could scarcely be detected in the twenty-minute period of observation (Curve III). Except when the experiments were interrupted overnight (see below), all the other time–temperature curves observed in the series of measurements fitted in form to their intermediate positions in the series. In all the carbon monoxide increments up to 120 cc. adsorbed, *all the gas disappeared from the gas phase within one minute after admission.*

From these observations we are forced to conclude that the adsorption of carbon monoxide on chromic oxide at −183° consists of two distinct and separate processes which we shall call Process A and Process B. Process A is rapid for all states of the surface and gives a heat of approximately 4 kcal.; Process B is rapid for a bare surface but becomes progressively slower for successive increments until it is too slow to observe. Process B yields an additional heat of about 8 kcal., bringing the total heat up to 12 kcal. For reasons given later under Discussion we believe Process A is a van der Waals adsorption, and that the final result of Process B is a state of activated adsorption. If this is true, the heat values 4 and 12 kcal. represent differential heats of van der Waals and of activated adsorption, respectively, and have therefore been so designated in Fig. 5. Furthermore, because of the slow evolution of heat long after all the gas had disappeared from the gas phase, it seems probable that the gas, initially adsorbed by van der Waals forces, subsequently underwent a change into the activated state without leaving the surface.

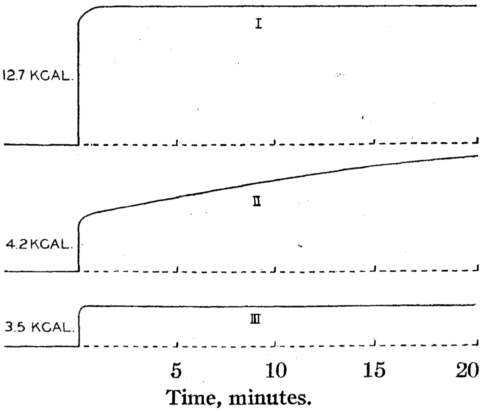

Fig. 4.—Time–temperature curves for CO at −183°.

The data listed in Fig. 5[6] indicate that there is a decrease in the differential heats of activated adsorption with increasing surface covered suggesting a variation in surface activity.[7] However, we do not feel certain that this has been demonstrated conclusively because of the difficulty in estimating the total heat rise, especially in the region 30–80 cc. adsorbed.

The heat experiments with nitrogen and oxygen produced the same division into Processes A and B. As in the case of carbon monoxide, the heat of Process A was about 4 kcal. for both these gases. The heats of activated adsorption were, however, about 8 kcal. for nitrogen and 20–27

(6) From the experimental observations on a relatively bare surface, it is possible to estimate the differential heats of the activated adsorption only. On a nearly covered surface where Process A occurs exclusively, only van der Waals heats are measured. On partially covered surfaces (Curve II, Fig. 4), however, it is possible to determine both the heat of van der Waals absorption from the initial rapid heat evolution, and the heat of activated adsorption from the total heat evolved. For this reason heat data for both types of adsorption are given for the region 40–80 cc. adsorbed. The heat of activated adsorption could be determined with fair accuracy for the initial increments up to a total of 30 cc. Beyond that point it became increasingly difficult to estimate the total heat evolution because of the decreasing rate of Process B with each successive increment. Beginning at about 40 cc. adsorption, it was possible to estimate the initial sharp rise due to van der Waals adsorption. Beyond 55 cc. the results could be determined more accurately because Process A was more sharply differentiated for the later increments.

(7) It is possible that the activated adsorption of carbon monoxide, oxygen, and nitrogen is non-selective as it has been shown to be with hydrogen (see below). In that case, the true differential heats would decrease more rapidly with successive increments than in the experimental values given in Fig. 5.

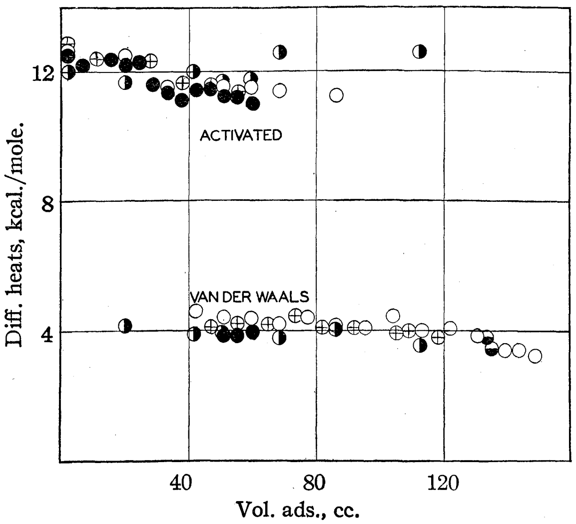

Fig. 5.—CO on Cr_2O_3: Series 1, 2, and 3 at −183° ⊕, ○, and ●; after outgassing at −183° ◒; Series 1 at −195° ◑.

kcal. for oxygen. Typical time–temperature curves are given in Figs. 6 and 7 for initial, intermediate, and final increments of each gas. The differential heats for both activated and van der Waals adsorption are shown in Figs. 8 and 9.

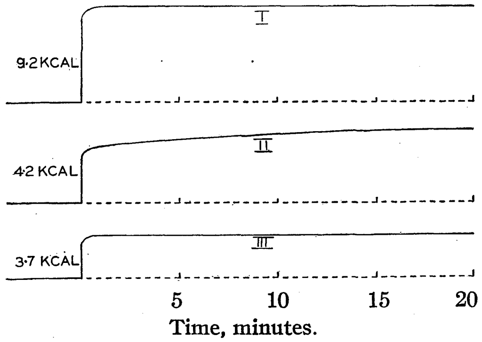

Fig. 6.—Time–temperature curves for nitrogen at −183°.

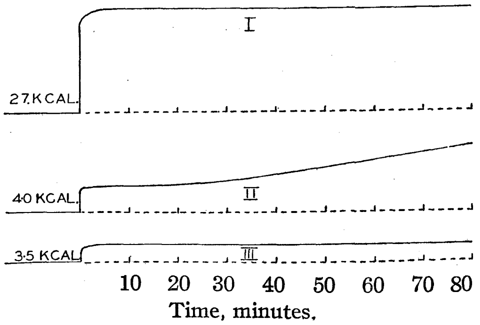

Fig. 7.—Time–temperature curves for oxygen at −183°.

Owing to the change in activity of the chromic oxide surface in the three oxygen experiments, the differential heat values were not reproducible. Series 1, 2, and 3 produced initial heats of 27, 21, and 25.5 kcal., respectively. It is noteworthy that the same order of activity for the three series is indicated by the adsorption isotherms from Series 1 and 2 in Fig. 2. Unfortunately, Series 3 was not carried far enough to determine the position of the isotherm.

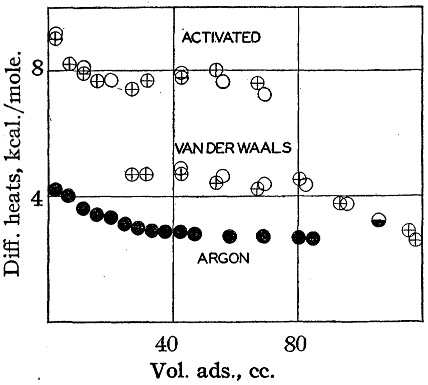

Fig. 8.—N_2 and argon at −183°: Series 1, N_2 ⊕; Series 2, N_2 ○; N_2 after outgassing at −183° ◒; argon ●.

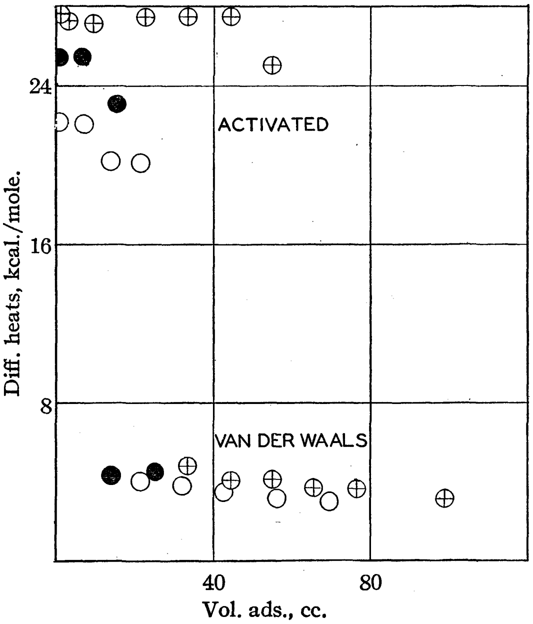

Fig. 9.—O_2 on Cr_2O_3 at −183°: Series 1 ⊕; Series 2 ○; Series 3 ●.

Following several of the series of heat measurements, the chromic oxide surface was outgassed for one hour at −183°. The differential heats were measured for increments subsequently added to the surface. As might have been expected, the form of the time–temperature curves and the magnitude of the heats both indicated van der Waals adsorption exclusively. The data for two such experiments with carbon monoxide and one with nitrogen are given in Figs. 5 and 8. A similar result was obtained in previous work in this Laboratory with carbon monoxide on copper at −183°.[8] These experiments demonstrate the reversibility of the van der Waals process at −183°, as well as the irreversible nature of the activated adsorption.

Carbon Monoxide on an Oxygen Covered Surface, and Oxygen on a Carbon Monoxide Covered Surface at −183°.—An investigation was made of the heat liberated by the addition of carbon monoxide to an oxygen covered surface at −183°.[9] Following oxygen Series 3 at −183°, the unadsorbed oxygen and presumably most of the van der Waals adsorbed oxygen were removed by evacuation for one hour at the same temperature. It is estimated that 25 cc. of activated adsorbed oxygen remained. The differential heats for carbon monoxide on this surface were then determined. The time–temperature curves for intermediate increments in the series had the abnormal form observed with carbon monoxide on an initially bare surface, indicating the presence of the rapid Process A, van der Waals adsorption, followed by a slow Process B, activated adsorption. The results of this experiment are given in Table III.

TABLE III

HEATS OF ADSORPTION AT −183°

Vol. of increment ads., cc.	Resid. press., mm. × 10^2	Diff. heat of ads., kcal./mole van der Waals	Activated	Total vol. ads., cc.
		CO on O_2 Covered Surface		
2.24	2.2	..	12.84	2.24
3.67	not meas.	..	12.38	5.87
3.39	7.1	..	11.41	9.29
3.75	12.9	..	11.41	17.51
4.34	32.0	4.50	9.67	30.65
4.36	74.3	4.21	...	44.11
4.42	102.5	4.31	...	48.54
4.38	117.9	3.98	...	66.64
		O_2 on CO Covered Surface		
1.84	..	..	12.73	1.84
2.26	..	..	11.59	4.10
4.32	77.0	3.20	...	8.42

Another series of heat measurements was conducted for oxygen on a carbon monoxide covered surface at −183°. In this experiment the surface was prepared by adding carbon monoxide at −183° until there was a residual pressure, and then outgassing for one hour at that temperature, leaving a surface film of approximately 100 cc. of carbon monoxide adsorbed in the activated state. The differential heats then obtained upon admission of successive increments of oxygen are given in Table III. The time–temperature curves were normal, giving no evidence for a slow process. The magnitude of the heats indicates an activated adsorption for the initial increments with a van der Waals adsorption of the final increment added.

A comparison of our data in Table III, with the results of the experiments with a single gas on an initially bare surface, reveals the following facts: (1) the presence of 25 cc. of adsorbed oxygen reduces the volume of carbon monoxide adsorbed in the activated state from 113 to 40 cc. (at 1 mm. residual pressure) but causes no great change in the heat of activated adsorption which is approximately 12 kcal. whether the surface was initially bare or oxygen-covered; (2) 100 cc. of adsorbed carbon monoxide brings about a very great decrease in the volume of oxygen adsorbed in the activated form from 25 to 4 cc.; moreover, the heat of the activated adsorption of oxygen is reduced from 25 kcal. on the initially bare surface to 13 kcal. on the carbon monoxide covered surface.

The complexity of the experimental conditions especially when two gases are present simultaneously on the chromic oxide surface which itself contains two different kinds of atoms makes an explanation of the above observations rather precarious. An explanation appears to be possible if we assume that: (1) the activated adsorption of oxygen occurs on the surface chromium atoms only; (2) the activated adsorption of the carbon monoxide occurs chiefly on the oxygen atoms of the chromic oxide but to some extent on the most active chromium atoms. However, we prefer not to present such an explanation until further experimental results are available.

Heat of Adsorption of Carbon Monoxide at −195°; the Energy of Activation of Process B.—In order to find the temperature coefficient of the rate of Process B, heat measurements were made in one series for carbon monoxide at −195°. The results were analogous to those at −183°

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[8] Beebe, Low and Goldwasser, THIS JOURNAL, 58, 2196 (1936).

[9] Because it was impossible to reproduce exactly the state of activity of the surface after oxygen was once admitted, it is important to know the order in which the experiments were conducted. After the oxygen measurements were begun, the order of experiments was, oxygen Series 1 and 2 at −183°, oxygen Series 3 and carbon monoxide on an oxygen covered surface at −183°, oxygen on a carbon monoxide covered surface at −183°, and oxygen on a plain surface at 0°.

except that Process B was slower for corresponding surface covered. As a result it was possible to differentiate Processes A and B earlier in the series (20 cc. adsorbed). Process B persisted further in the series making it possible to estimate the heats of activated adsorption up to 112 cc. adsorbed. The differential heats are given in Fig. 5. This persistence of Process B at −195° for larger amounts adsorbed than at −183° was possibly due to the higher total adsorptive capacity of the chromic oxide at the lower temperature. The adsorptive capacity beyond 112 cc. was not determined because the supply of liquid nitrogen ran out at that point.

From the rates of heat evolution at −195 and −183°, it was possible to estimate the rates of Process B at those two temperatures. From these data the energy of activation of the process was calculated. For surfaces on which the amounts already adsorbed before admission of the increment were 40, 50, 60, and 70 cc., respectively, the corresponding activation energies were 180, 300, 420, and 690 cal.

Heats of Adsorption at 0°.—The adsorption of argon and of the isotopes of hydrogen was negligibly small at 0° in the low pressure range studied, and the adsorptive capacity of the chromic oxide for carbon monoxide, oxygen, and nitrogen was much less at 0 than at −183°. The differential heats were determined for each of the latter three gases. The results for carbon monoxide and oxygen are given in Table IV. Only two increments of nitrogen of 1.88 cc. each were adsorbed. These had residual pressures of 1 and 1.7 mm., respectively, and each produced heats of 18.1 kcal.

At 0° the time–temperature curves were normal in type with all three gases giving no evidence for the two Processes A and B found at −183°. It is probable that van der Waals adsorption (Process A) was absent, and that the rate of the activated adsorption (Process B), which was slow after the initial increments at −183°, was too rapid to observe on any part of the surface at the higher temperature.

TABLE IV

HEATS OF ADSORPTION ON CHROMIC OXIDE AT 0°

Vol. of increment ads., cc.	Resid. press., mm. × 10^2	Diff. heat of ads., kcal./mole	Total vol. ads., cc.
	Carbon Monoxide		
2.22	1.3	15.2	2.22
2.28	1.4	14.1	4.50
2.20	3.1	13.8	12.90
2.21	3.9	13.2	19.60
2.33	6.2	12.5	26.0
2.21	16.2	12.3	35.0
2.17	40.6	12.0	44.0
2.13	104.1	10.7	52.8
2.00	297.5	9.9	61.4
	Oxygen		
1.59	..	50.0	1.59
1.01	..	49.6	2.60
1.05	..	50.1	3.63
0.98	..	46.9	4.65
1.11	..	48.4	5.89
1.02	..	44.2	6.83
1.09	..	43.3	14.47
0.83	23.0	17.6	27.42

Discussion

Hydrogen and Deuterium at −183°.—The most important conclusion to be drawn from the work on the hydrogen isotopes is that the heats are altogether too high to be accounted for by van der Waals forces alone, and the process must be in large part of the activated type. The significance of the heat measurements, in connection with the catalytic activity of chromic oxide at −183° observed by Gould, Bleakney, and Taylor,[1] has been discussed in detail by Beebe and Orfield.[2] The discussion given by them for hydrogen may be applied equally well to the present data with deuterium.

According to Urey and his co-workers,[10] the heats of vaporization of hydrogen and deuterium are, respectively, 183 and 276 cal. per mole. We find the higher heat of adsorption for the heavier isotope. It should not be inferred from this, however, that only van der Waals forces are in operation at −183°.

In a study of the dissociation pressures of potassium deuteride and hydride in the temperature range 270 to 360°, Sollers and Crenshaw[11] have found that potassium holds hydrogen more strongly than deuterium, but a detailed study of their data leads them to suggest that at low temperatures the hydride may have the higher dissociation pressure. This would be in accordance with the results of the present investigation on chromic oxide shown in Fig. 2, and exactly the reverse of the case of hydrogen and deuterium adsorption on copper previously studied in this Laboratory.[12]

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(10) Scott, Brickwedde, Urey and Wahl, *J. Chem. Phys.*, **2**, 454 (1934).

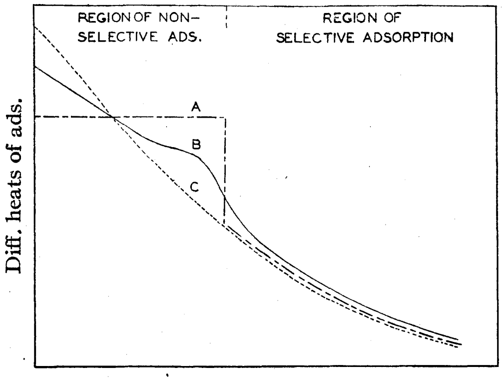
(11) Sollers and Crenshaw, THIS JOURNAL, **59**, 2015 (1937).

(12) Beebe, Low, Wildner and Goldwasser, *ibid.*, **57**, 2527 (1935).

The difference in the shapes of the two differential heat curves in Fig. 3 seemed at first perplexing, but can be explained, we believe, in the following manner. It has been demonstrated[13] that the adsorption of the initial increments of hydrogen on chromic oxide at −183° is non-selective,[14,15] occurring on those portions of the surface with which it first comes in contact.[2] If this non-selectivity of the process were complete the heat values would be constant for the whole region studied because they would really represent integral heats of adsorption for successive layers.[4] If, on the other hand, the adsorption were non-selective for a part of the surface but selective for the remainder, then a discontinuous curve like Curve A in Fig. 10 would be expected provided the true distribution of energies on the surface is represented by Curve C. It is easy to see that the experimentally determined curve for hydrogen is of the form of Curve B which lies between Curves A and C. It is further noteworthy that the region of non-selective adsorption cannot go much beyond 20 cc. adsorbed because from here on there is a residual gas pressure, as shown in Table I, indicating equilibrium conditions under which non-selective adsorption would be impossible.

The fact that the horizontal step in the heat curves, which is so definite for hydrogen, is almost absent in the deuterium data, suggests that the phenomenon of non-selective adsorption is much less marked for the heavier isotope. Now non-selective adsorption occurs when the rate of adsorption is great compared to the rate of diffusion of the gas; this causes the gas to be adsorbed on those successive layers of the adsorbent with which it first comes in contact. The slower rate of diffusion of deuterium should give more time for the non-selective process to occur. Since, however, it is the hydrogen adsorption which is the more non-selective of the two, it seems evident that the rate of adsorption of the lighter isotope must be the greater by a ratio considerably more than enough to compensate for the $\sqrt{2}$ diffusion factor. Of course the rates cannot be compared by direct measurement because the adsorption of either isotope is complete in less than one minute after admission to the adsorbent surface.

Pace and Taylor[16] found no difference for hydrogen and deuterium in the rates of the activated adsorption process on chromic oxide at 218° and one atmosphere pressure. It is not surprising that the present investigation, carried out at −183° and very low pressures, should yield results which differ from those of the above authors. Moreover, because of the very low value of T used in the exponential $e^{-E/RT}$, a small difference in the activation energies for the two isotopes would be sufficient to account for a relatively large difference in the rates of adsorption.



Volume adsorbed.

Fig. 10.

Carbon Monoxide, Nitrogen, and Oxygen at −183°.—Evidence has been presented under Results to show that on a partially covered surface at −183° the adsorption of carbon monoxide, nitrogen, and oxygen consists of two processes which have been called Process A and Process B. Analysis of the experimental data shows that Process A is rapid under all conditions and is nonspecific in nature, yielding a heat of about 4 kcal. regardless of the nature of the gas adsorbed[17] or of the state of the adsorbing surface. We believe that these observations justify the assumption that Process A is a van der Waals adsorption exclusively. Process B differs from Process A in two important respects: (1) the heats of adsorption are much higher than in Process A and are specific to the gas used and to the condition of the chromic oxide surface; and (2) the rate of adsorption varies greatly as a function of the amount of gas already on the surface. The first of the above characteristics of Process B eliminates the possibility that it is a van der Waals process,[18] and

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(13) This was done with a calorimeter similar to that described by Beebe [*Trans. Faraday Soc.*, **28**, 761 (1932)]. Using this instrument at −183°, it was found that the form of the time–temperature curve obtained upon admission of hydrogen was greatly influenced by the position of the thermocouple. This was interpreted to indicate non-selective adsorption by the same reasoning as that used by Beebe in the case of carbon monoxide on copper at 0°.

(14) Russell and Ghering, THIS JOURNAL, **57**, 2544 (1935).

(15) This phenomenon has been called "non-uniform" in previous publications from this Laboratory. We believe, however, that the term "non-selective" used by Russell and Ghering, describes the process more accurately; we shall therefore use it in the future.

(16) Pace and Taylor, *J. Chem. Phys.*, **2**, 578 (1934).

(17) The three gases carbon monoxide, nitrogen, and oxygen and in addition argon have boiling points which all fall within the twelve-degree range from −183 to −195° and as a consequence we should expect them to have approximately the same heats of vaporization. It is therefore not surprising that the heats of van der Waals adsorption which result from changes of a physical nature are found experimentally to be nearly the same for all four gases.

(18) Barrer, *Proc. Roy. Soc.* (London), **161A**, 476 (1937), has calculated from the isotherms at low temperatures the heats of adsorption of nitrogen, argon, and hydrogen on graphite and has suggested that the higher values obtained for the initial increments of gas adsorbed may be attributed to the van der Waals adsorption of the molecules in cracks sufficiently narrow to permit both walls to influence the adsorption. For crevices with plane and nearly parallel sides, the heat of adsorption would be approximately double the value for a plane surface. Moreover, the calculations of DeBoer and Custers, *Z. physik. Chem.*, **25B**, 225 (1934), showed, for adsorption in hemispherical pockets, tubes, and cells, maximum energies of four, six, and eight times, respectively, the energies on a plane surface. The high initial heats of 8 kcal. observed by us in the case of nitrogen conceivably might be explained on the basis of the calculations of DeBoer and Custers. However, the higher heats of 12 and 27 kcal. with carbon monoxide and oxygen could scarcely be

we must conclude that the final result of Process B is a state of activated adsorption.[19]

From the experimental evidence, however, it is difficult to decide with certainty whether the rate controlling factor in Process B is one of activated adsorption or of activated surface diffusion. As we shall see, the choice between these alternatives depends upon the accessibility of the adsorbing surfaces to the incoming gas. We shall use the case of carbon monoxide in this discussion, although it also applies to nitrogen and oxygen.

We have already assumed that the chromic oxide surface is capable of both van der Waals and activated adsorption. Let us make certain further assumptions:

1. The van der Waals adsorption requires zero activation energy, and it is easy for a van der Waals adsorbed molecule to be desorbed and begin a surface migration.
2. The activated adsorption requires a small finite activation energy which increases with successive increments from an initial negligibly small value to a relatively large value as the surface becomes more completely covered.[20] Desorption occurs with great difficulty for molecules held on the surface in the activated state.
3. All the surface, whether internal or external, is easily accessible either by direct gaseous diffusion or by a very rapid surface migration of the van der Waals adsorbed carbon monoxide to the internal part of the surface.

On the basis of these assumptions the time required for the activated adsorption would be the rate controlling factor. The adsorption of the first carbon monoxide increment admitted to a bare chromic oxide surface would be in part van der Waals and in part activated depending upon whether the chance collisions of the carbon monoxide molecules with the surface brought them first into contact with points of low or high surface energy. But the molecules held by van der Waals forces would soon move to adjacent active points, with the net effect that the gas would disappear immediately from the gas phase and the time–temperature curve would show a quick rise in temperature giving a heat of 12 kcal. (Curve I, Fig. 4). After the initial increments had been added, the most active surface points would become covered so that there would be none left capable of immediate activated adsorption. As a result, the next increment added would be first adsorbed by van der Waals forces but these adsorbed molecules would then migrate rapidly on the surface to points capable of activated adsorption but requiring a finite activation energy so that this activated process would be slower. The time–temperature curve (Curve II, Fig. 4) would then be divided, with a quick rise corresponding to a rapid van der Waals adsorption of 4 kcal. of heat and the slow rise due to Process B, the activated adsorption, producing a heat of about 12 kcal. This activated adsorption process would of course become progressively slower as the degree of activity of remaining uncovered surface points became less and less. Finally, when all points capable of activated adsorption were covered, the slow Process B would be eliminated and only van der Waals adsorption would occur on the remaining surface, resulting in the normal type of curve (Curve III, Fig. 4) with a heat of 4 kcal. On the basis of this theory the experimentally determined activation energies for Process B, which ranged from 180 to 690 cal. for the interval 40–70 cc., would be the energies of activation of the activated adsorption.

On the other hand, we may arrive at an alternative explanation of Process B by changing assumptions 2 and 3 above as follows:

2. The activated adsorption requires a negligibly small activation energy on all parts of the surface, adsorption occurring immediately once a gas molecule comes into contact with an active surface point.
3. Only the external part of the surface is readily accessible to the gas,[21] a finite time being

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accounted for in that way. In addition to this the large variation in the heats of Process B with the three gases makes it very probable that it is not a van der Waals process.

(19) The absence of any slow Process B at −183° in the curves for hydrogen and deuterium seems, at first, to be anomalous, especially when we consider that there is evidence that the adsorption of these gases is activated in part at least. If we assume, however, that the activated adsorption for the isotopes of hydrogen requires an even smaller energy of activation than does that for carbon monoxide, nitrogen, or oxygen, we may predict that, at an even lower temperature, the rate of Process B might be sufficiently slow to differentiate it from Process A.

(20) The decreasing differential heats with successive increments (Fig. 5) indicate variable surface activity. At −183°, even small differences in the activity of the surface points, and consequently in the activation energies required for adsorption, would suffice to account for relatively large differences in the rates of adsorption on different portions of the surface. This is true because of the small value of T used in the exponential $e^{-E/RT}$.

(21) During the preparation of the adsorbent, the removal of water molecules from the hydrated chromic oxide gel must have produced a relatively large percentage of internal surface on the walls of cracks or capillaries penetrating the granules. The point at issue is whether these cracks or capillaries are of sufficient width so that the carbon monoxide molecules can reach their walls with ease or whether a considerable length of time might be required. In other words, is the internal surface "internal" to a carbon monoxide molecule?

required for the surface migration of carbon monoxide molecules, initially adsorbed on the external surface, down the faces of the cracks or capillaries into the internal surface of the chromic oxide.

We may then explain the time–temperature curves for partially covered surfaces (Curve II, Fig. 4) as indicating an initial van der Waals adsorption on the easily accessible external surface followed by a slow surface migration to the points located in the internal surface which are capable of activated adsorption. The decreasing rate of Process B with successive increments of gas added to the surface would then be attributed to the increasing periods of time required for the surface diffusion of the adsorbed molecules into the more and more difficultly accessible areas of the internal surface. In other words, the rate controlling factor would be an activated diffusion, and the experimental values 180 to 690 cal. would be the activation energies for this diffusion process.[22]

It is of course possible that both activated adsorption and activated diffusion have some influence on the rate of the slow process observed. Regardless of the mechanism,[23] the important point, which must be emphasized, is that we have definite evidence that there are two distinct types of adsorption on the same partially covered chromic oxide surface at −183°, and that the gas initially held by van der Waals forces changed over, *on the surface,* into the activated state.

The Effect of Temperature on the Adsorption.—In comparing the results at −183° with those at 0° using carbon monoxide, nitrogen, and oxygen, respectively, on the chromic oxide, it is apparent that the amount of each of these gases adsorbed is considerably less at the higher temperature. This is not surprising in the case of the carbon monoxide and that of the nitrogen because the adsorption of these gases is a reversible process, a large fraction of the gas adsorbed at −183° being desorbed when the temperature is raised to 0°. This would mean simply that certain surface points capable of holding carbon monoxide or nitrogen at −183° are no longer able to do so at 0°. The adsorption of oxygen, on the other hand, is irreversible, and oxygen once adsorbed in the activated state is removable only by reduction in a hydrogen atmosphere at about 400°. It is not easy to see, therefore, why the volume adsorbed at 0° should not be at least as great as that adsorbed at −183°. We suggest the possibility that pairs of oxygen atoms may be held in an activated state on each chromium atom of the surface at −183° but that single atoms of the oxygen are held on each chromium atom at 0°. This postulated difference in the nature of the adsorption complexes at the two temperatures would also account for the observed change in the heat of adsorption from 25 kcal. at −183° to 50 kcal. at 0°.[24] The marked difference in the heats of adsorption of nitrogen at the two temperatures seems to indicate that, with this gas also, there must be a great difference in the nature of the binding forces in operation at the two temperatures. In contrast with the data for oxygen and nitrogen, the heats of activated adsorption of carbon monoxide are very nearly the same at −183 and 0°, indicating that there is little difference in the nature of the binding at the two temperatures.

Anomalous Effect Caused by Interruption of a Series of Heat Measurements.—In the measurements with carbon monoxide at −183° the successive increments usually were admitted at intervals of approximately one hour. When the series was interrupted overnight, say for a period of fifteen hours, with the surface partially covered, the first time–temperature curve recorded the next morning was always anomalous in two respects: (1) the slow Process B was almost completely absent; and (2) the heat of the rapid Process A was measurably higher (about 0.2 kcal.) than that for the preceding increment, or of the next increment following after a one-hour period. In other words, when the adsorption had been carried to the stage at which the next time–temperature curve would be like Curve II in Fig. 4 if the series were not interrupted, the curve actually obtained after an overnight interruption was more nearly of the form of Curve III, Fig. 4, and the heat of Process A was 4.4 instead of 4.2 kcal. The second time–temperature curve recorded in the morning was free from these anomalous characteristics, giving a heat of 4.2 kcal. for Process A and having the slow rise in temperature indicating the recurrence of Process B. This anomalous behavior was always observed whenever a carbon monoxide series in the intermediate stage was interrupted overnight.

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[22] Lennard-Jones [*Trans. Faraday Soc.,* **28,** 333 (1932)] has calculated an activation energy of this order of magnitude for the surface diffusion of argon on potassium chloride at −183°.

[23] In this discussion we have assumed that the van der Waals and activated adsorption occur exclusively on different surface points. It is possible, however, that the *same* points may be capable of both types of adsorption, and this possibility already has been suggested by Lennard-Jones.[22] On the latter assumption, Process B might represent the change of a molecule, held to a given point by van der Waals forces, over into the activated state on the *same* point. There is nothing in our observations to justify the elimination of this possibility which would, of course, be unfavorable to the theory of activated diffusion as the rate controlling factor in Process B.

[24] This high heat of reaction at 0° is of the same order of magnitude as the heat of the stoichiometric reaction between oxygen and chromic oxide to form chromium trioxide (36.2 kcal. per mole of oxygen). It seems probable, therefore, that the surface reaction is somewhat similar to the stoichiometric one in this case.

The same was always true for the oxygen and nitrogen adsorption experiments.

We believe this anomaly can be explained as follows. Suppose there are surface points on which the carbon monoxide molecules are held by forces of the van der Waals type, but with a binding energy slightly greater than the average van der Waals binding, and suppose that as a result of this greater binding force a considerable time is required for the desorption of molecules from these points, which we shall call X-points. These X-points would become covered in the early increments and owing to the greater difficulty of desorption they would then remain covered during the admission of later increments at the stage represented by Curve II, Fig. 4, so long as the series of measurements was continued without interruption. On the other hand, upon standing overnight, the X-points would be left vacant by the slow process of desorption, the desorbed molecules being subsequently adsorbed on points capable of activated adsorption. The first increment admitted in the morning would then be adsorbed on the X-points, with a heat of 4.4 kcal., which is 0.2 kcal. in excess of the normal 4.2 kcal. Moreover, because of the difficulty of desorption from the X-points, Process B, resulting from a shift over to the state of activated adsorption, would be practically eliminated. However, for the next increment following after the normal one-hour interval, with the X-points covered, the normal heat of 4.2 kcal. would be obtained and the normal rate of Process B would be observed.

Conclusion.—We wish to emphasize the novel application of the calorimetric method in the present investigation. Using charcoal at 20° as an adsorbent, Lendle[25] has measured the heat evolved during the slow activated adsorption on charcoal of oxygen *from the gas phase*, a process which could also be followed by observing the slow disappearance of unadsorbed gas. Barry and Barrett[26] have made a similar calorimetric study in the case of the adsorption of water vapor on gold. In the experiments with carbon monoxide on chromic oxide at $-183°$, there was no residual unadsorbed gas after the first minute, and the slow evolution of heat could be attributed only to a change *on the surface* from the van der Waals to the activated state.[27] Because all the gas disappeared almost instantaneously, the calorimetric method offered the only means of observing the presence of the slow process. It will be interesting to find out how general is this activated adsorption via an initial van der Waals process. Calorimetric work at $-183°$ now in progress in this Laboratory shows that the adsorption of oxygen on iron synthetic ammonia catalyst follows the same complex mechanism, the time–temperature curves being of the same general form as Curve II, Fig. 7. The details of this work will be published at a later date.

Summary

1. The heats of adsorption of argon, hydrogen, deuterium, carbon monoxide, nitrogen, and oxygen, on reduced chromic oxide, have been determined calorimetrically in the low temperature region.

2. The magnitude of the heats indicates that all these gases except argon are adsorbed in part in the activated state even at $-183°$.

3. The form of the time–temperature curves on a partially covered surface at $-183°$ indicates that with carbon monoxide, nitrogen, and oxygen the adsorption is complex, the gases initially adsorbed in the van der Waals state undergoing a slow change on the surface over into a state of activated adsorption.

4. From the heat measurements with carbon monoxide at -183 and $-195°$ the activation energy of the above slow surface change has been estimated at 180 to 690 cal./mole. It is suggested that the rate controlling process in this slow change may be (1) a slow activated adsorption, or (2) a slow surface diffusion.

5. The effects of carbon monoxide on the heat of oxygen adsorption and of oxygen on the heat of carbon monoxide adsorption have been investigated experimentally.

6. The heats of adsorption of carbon monoxide, nitrogen, and oxygen have been measured at 0° as well as at $-183°$, and the results at the two temperatures have been compared.

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(25) Lendle, *Z. physik. Chem.*, **172A**, 77 (1935).

(26) Barry and Barrett, THIS JOURNAL, **55**, 3088 (1933).

(27) In accounting for certain anomalies observed in their study of the effect of pressure on the rate of adsorption of hydrogen on chromic oxide at about 200°, Burwell and Taylor [THIS JOURNAL, **58**, 697 (1936)] were led to postulate a similar mechanism, "the slow process being a reaction between surface atoms which receive the necessary activation energy and hydrogen molecules adsorbed by van der Waals forces."

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Acid Amides as Hypnotics. I. Acylureas[1]

BY F. F. BLICKE AND A. P. CENTOLELLA[2]

The introduction of an acyl group such as diethylbromoacetyl or allylisopropylacetyl into urea converts the latter into an excellent hypnotic. Publications which illustrate the manner in which hypnotic activity varies with the nature of the acyl group are very few in number.

TABLE I

SUBSTITUTED MALONIC ESTERS, MALONIC ACIDS, ACETIC ACIDS AND ACETYL CHLORIDES

		Malonic ester		Malonic acid[a]						Acetic acid		Acetyl chloride	
		B. p., °C.	Mm.	M. p., °C.	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found	B. p., °C.	Mm.	B. p., °C.	Mm.
1	Propyl-β-phenylethyl	190–195	14	123–124	$C_{14}H_{18}O_4$	67.16	66.97	7.25	7.32	195–200	20	164–169	19
2	Isopropyl-β-phenylethyl	204–206	24	129–130	$C_{14}H_{18}O_4$	67.16	66.90	7.25	7.33	198–204	35	160–165	21
3	Allyl-β-phenylethyl	205–208	20	128–129	$C_{14}H_{16}O_4$	67.71	67.44	6.50	6.55	196–199	22	205–210	15
4	Isobutyl-β-phenylethyl	205–208	20	136–137	$C_{15}H_{20}O_4$	68.14	68.16	7.46	7.27	200–203	20	216–222	18
5	β-Cyclohexylethyl-β′-phenylethyl	255–260	30	134–135	$C_{19}H_{26}O_4$	71.64	71.36	8.24	8.24	245–250	19	220–225	25
6	Ethyl-γ-phenylpropyl	195–200	18	148–149	$C_{14}H_{18}O_4$	67.16	67.25	7.25	7.14	193–196	18	217–220	30
7	Ethyl-δ-phenylbutyl	216–220	22	114–115	$C_{15}H_{20}O_4$	68.14	68.33	7.46	7.57	227–230	50	190–194	22
8	Ethyl-ε-phenylamyl	230–235	25	106–107	$C_{16}H_{22}O_4$	69.02	69.23	7.97	7.98	213–219	20	199–204	20
9	Ethyl-ζ-phenylhexyl	227–233	18	67–68	$C_{17}H_{24}O_4$	69.83	69.56	8.28	8.19	218–222	17	206–210	21
10	Ethylcinnamyl	215–220	30	133–134	$C_{14}H_{16}O_4$	67.71	67.77	6.50	6.38	215–220	35	184–190	20

[a] The malonic acids were recrystallized from benzene.

TABLE II

SUBSTITUTED ACETYLUREAS

	Acetylurea[a]	M. p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
1	N-Methyl-diethyl	93–95	$C_8H_{16}O_2N_2$	16.26	16.06
2	Ethyl-propyl	200–201	$C_8H_{16}O_2N_2$	16.26	16.19
3	N-Methyl-ethyl-butyl	77–78	$C_{10}H_{20}O_2N_2$	13.98	13.78
4	Ethyl-butyl-α-bromo	84–85	$C_9H_{17}O_2N_2Br$	(30.10	30.17 Br)
5	Ethyl-amyl	138–139	$C_{10}H_{20}O_2N_2$	13.98	13.91
6	Ethyl-hexyl	126–127	$C_{11}H_{22}O_2N_2$	13.06	12.70
7	Ethyl-β-cyclohexylethyl	176–177	$C_{13}H_{24}O_2N_2$	11.66	11.71
8	Di-β-cyclohexylethyl	175–176	$C_{19}H_{34}O_2N_2$	8.68	8.77
9	β-Phenylethyl	174–175	$C_{11}H_{14}O_2N_2$	13.59	13.86
10	Ethyl-benzyl	141–142	$C_{12}H_{16}O_2N_2$	12.72	13.01
11	Ethyl-β-phenylethyl	152–153	$C_{13}H_{18}O_2N_2$	11.96	11.77
12	Di-β-phenylethyl	149–150	$C_{19}H_{22}O_2N_2$	9.15	9.25
13	Propyl-β-phenylethyl	148–150	$C_{14}H_{20}O_2N_2$	11.28	11.20
14	Isopropyl-β-phenylethyl	157–158	$C_{14}H_{20}O_2N_2$	11.28	11.47
15	Allyl-β-phenylethyl	115–116	$C_{14}H_{18}O_2N_2$	11.38	11.48
16	Butyl-β-phenylethyl	117–118	$C_{15}H_{22}O_2N_2$	10.68	10.70
17	Isobutyl-β-phenylethyl	149–150	$C_{15}H_{22}O_2N_2$	10.68	10.75
18	β-Cyclohexylethyl-β′-phenylethyl	148–149	$C_{19}H_{28}O_2N_2$	8.85	8.89
19	Ethyl-γ-phenylpropyl	143–145	$C_{14}H_{20}O_2N_2$	11.28	11.68
20	Ethyl-δ-phenylbutyl	137–138	$C_{15}H_{22}O_2N_2$	10.68	10.83
21	Ethyl-ε-phenylamyl	120–121	$C_{16}H_{24}O_2N_2$	10.10	10.35
22	Ethyl-ζ-phenylhexyl	122–123	$C_{17}H_{26}O_2N_2$	9.65	9.89
23	Ethylcinnamyl	139–140	$C_{14}H_{18}O_2N_2$	11.38	11.37

[a] The compounds were recrystallized in the following manner: compounds 8, 14, 18, 20, 21 and 22 from petroleum ether (90–100°); compound 7 from alcohol; compounds 3, 4, 11 and 16 from dilute alcohol; compounds 2, 5, 6, 9 and 12 from acetone; compound 13 from 50% acetone; compounds 10, 17 and 19 from a mixture of one part acetone and two parts petroleum ether; compounds 15 and 23 from a mixture of one part acetone and nine parts petroleum ether.

In this paper we have described a number of disubstituted acetylureas, $R_2CH\text{-}CO\text{-}NH\text{-}CO\text{-}NH_2$ (Table II), which were examined pharmacologically by Mr. J. W. Nelson and Dr. G. F.

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[1] This paper represents part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by A. P. Centolella in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

[2] The Upjohn Company Fellow.

Cartland in The Upjohn Company Laboratories.[3] It was quite surprising to find that none of these ureas were effective to any great degree when injected intraperitoneally into white rats although, in a second paper, it will be shown that some of the corresponding acetamides are strong hypnotics.

The ureas were obtained by the following general method: conversion of malonic ester into the required disubstituted derivative, $R_2C(CO-OC_2H_5)_2$, hydrolysis of the ester, elimination of carbon dioxide with the formation of a disubstituted acetic acid, $R_2CH—COOH$, preparation of the corresponding acetyl chloride and treatment of the latter with urea or methylurea.[4]

The new intermediates are described in Table I.

Experimental Part

The procedures are illustrated in the case of allyl-β-phenylethylacetylurea.

To sodium ethylate, prepared from 1000 cc. of absolute alcohol and 46 g. of sodium, there was added, slowly, 320 g. of malonic ester. After one hour the mixture was stirred and refluxed and 370 g. of β-phenylethyl bromide added during the course of two hours. The mixture was stirred and refluxed for two hours longer, most of the alcohol removed by distillation and 500 cc. of water added to the cold residue. The ester layer was separated and the aqueous layer extracted six times with 75-cc. portions of ether; yield of β-phenylethylmalonic ester 424 g. or 80% of the calcd. amount; b. p. 182–185° (12 mm.).[5]

In a manner similar to that described above, allyl-β-phenylethylmalonic ester was prepared from sodium ethylate, obtained from 300 cc. of alcohol and 13.8 g. of sodium, 159 g. of β-phenylethylmalonic ester and 73.2 g. of allyl bromide; yield 159 g. or 88% of the calcd. amount.

A mixture of 80 g. of potassium hydroxide, 250 cc. of 70% alcohol and 101 g. of the disubstituted malonic ester was refluxed for twenty-four hours, most of the alcohol removed, 250 cc. of water added and then about 140 cc. of hydrochloric acid added to the cold mixture. The crude acid separated from the acidic mixture as an oil but soon solidified; yield 78 g. or 94% of the calcd. amount.

Fifteen grams of the allyl-β-phenylethylmalonic acid was heated in an oil-bath at 180° until most of the carbon dioxide had been evolved and then heated at 150–160° for six hours; yield 10.7 g. or 86% of the calcd. amount.

A mixture of 28 g. of the acetic acid and 45 g. of commercial thionyl chloride was heated for two hours on a steam-bath after the initial vigorous reaction had subsided and the excess thionyl chloride then removed; the yield of acid chloride was 21 g. or 70% of the calcd. amount.

Nine grams of allyl-β-phenylethylacetyl chloride and 9.6 g. of dry urea were heated in an oil-bath at 125°. As soon as the material had melted the temperature was dropped to 110–115°. After six hours the product was cooled and rubbed in a mortar with enough 10% sodium carbonate solution to keep the mixture alkaline. The solid material was filtered, washed with water and recrystallized; yield 8.9 g. or 90% of the calcd. amount.

Summary

A number of new disubstituted malonic esters, malonic acids, acetic acids, acetyl chlorides and acetylureas have been described.

No strong hypnotics were found among the disubstituted acetylureas, $R_2CH—CO—NH—CO—NH_2$, studied.

ANN ARBOR, MICHIGAN RECEIVED OCTOBER 10, 1938

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[3] Their results will be published by them in detail in another journal.

[4] Davis and Blanchard, THIS JOURNAL, **51**, 1797 (1929).

[5] Dolique [*Ann. chim.*, [10] **15**, 447 (1931)] reported 184–185° at 15 mm.

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Acid Amides as Hypnotics. II. Acetamides[1]

BY F. F. BLICKE AND A. P. CENTOLELLA[2]

It has been known for a long time that certain representatives of three types of acid amides—substituted acetamides, acylureas and cyclic amides such as substituted barbituric acids and hydantoins—exhibit strong hypnotic activity.

During late years, due to the popularity of barbituric acid compounds, the study of the acetamide type has been neglected except for the publications of Volwiler and Tabern[3] and of Junkmann.[4]

Most of the acetamides, described hitherto as compounds which possess hypnotic action, are trisubstituted derivatives such as diethylallylacetamide. Since, in general, trisubstituted acetamides are more difficult to obtain than the disubstituted compounds we have prepared a considerable number of the latter in order to determine their activity as hypnotics.

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[1] This paper represents part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by A. P. Centolella in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

[2] The Upjohn Company Fellow.

[3] Volwiler and Tabern, THIS JOURNAL, **58**, 1353 (1936).

[4] Junkmann, *Arch. exptl. Path. Pharmakol.*, **186**, 552 (1937).

TABLE I

SUBSTITUTED ACETAMIDES

The amides were recrystallized in the following manner: compound 4 was recrystallized from water; compounds 2, 5, 9, 10, 14, 16, 17, 18, 21 and 25 from petroleum ether (90–100°); compounds 6, 11, 12 and 20 from dilute alcohol; compounds 13, 15 and 22 from 50% acetone and compound 19 from acetone.

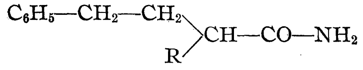
	Acetamide	M. p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
1	Diethylthio	80–81	$C_6H_{13}NS$	(24.45	24.50 S)
2	N-Methyldiethyl	79–80	$C_7H_{15}ON$	10.84	10.76
3	N-Butyldiethyl	34–35	$C_{10}H_{21}ON$	8.15	8.00
4	Ethylbutyl	106–107[a]	......	..	..
5	N-Methylethylbutyl	69–70	$C_9H_{19}ON$	8.93	9.07
6	N-Ethylethylbutyl	58–59	$C_{10}H_{21}ON$	8.18	7.94
7	N-β-Hydroxyethylethylbutyl	47–49[b]	$C_{10}H_{21}O_2N$	7.48	7.25
8	N-Butylethylbutyl	Oil[c]	$C_{12}H_{25}ON$	7.03	6.77
9	Ethylamyl	102–103[d]	$C_9H_{19}ON$	8.99	8.91
10	Ethylhexyl	106–107	$C_{10}H_{21}ON$	8.18	8.06
11	Ethyl-β-cyclohexylethyl	134–135	$C_{12}H_{23}ON$	7.10	7.09
12	N-Methylethyl-β-cyclohexylethyl	111–112	$C_{13}H_{25}ON$	6.63	6.65
13	N-Ethylethyl-β-cyclohexylethyl	96–97	$C_{14}H_{27}ON$	6.21	6.07
14	N-β-Hydroxyethylethyl-β′-cyclohexylethyl	90–91	$C_{14}H_{27}O_2N$	5.82	5.80
15	N-Butylethyl-β-cyclohexylethyl	61–62	$C_{16}H_{31}ON$	5.53	5.39
16	Di-β-cyclohexylethyl	173–174	$C_{18}H_{33}ON$	5.01	5.07
17	N-Methyldi-β-cyclohexylethyl	164–165	$C_{19}H_{35}ON$	4.78	4.80
18	N-Ethyldi-β-cyclohexylethyl	137–138	$C_{20}H_{37}ON$	4.56	4.78
19	Butyl-β-cyclohexylethyl	140–141	$C_{14}H_{27}ON$	6.21	6.26
20	N-Methylbutyl-β-cyclohexylethyl	110–111	$C_{15}H_{29}ON$	5.85	5.55
21	N-Ethylbutyl-β-cyclohexylethyl	94–95	$C_{16}H_{31}ON$	5.53	5.64
22	N-β-Hydroxyethylbutyl-β′-cyclohexylethyl	92–93	$C_{16}H_{31}O_2N$	5.20	5.13
23	N-(Diethylacetyl)-morpholine	Oil[e]	$C_{10}H_{19}O_2N$	7.56	7.21
24	N-(Ethylbutylacetyl)-morpholine	Oil[f]	$C_{12}H_{23}O_2N$	6.57	6.32
25	N,N′-*bis*-(Diethylacetyl)-ethylenediamine	230–231	$C_{14}H_{26}O_2N_2$	10.95	10.70

[a] Raper [*J. Chem. Soc.*, **91**, 1837 (1907)] reported 101–102°. [b] B. p. 199–200° at 15 mm. [c] B. p. 177–178° at 5 mm. [d] Volwiler and Tabern [THIS JOURNAL, **58**, 1353 (1936)] found 96°. [e] B. p. 159–160° at 9 mm. [f] B. p. 185–186° at 9 mm.

In Table I of this paper there have been described di-*n*-alkyl- and *n*-alkyl-β-cyclohexylethylacetamides and, in some instances, corresponding N-alkyl and N-hydroxyalkyl derivatives. The evaluation of all of our compounds, from the pharmacological standpoint, has been carried out by Mr. J. W. Nelson and Dr. G. F. Cartland in The Upjohn Company Laboratories and the data obtained will be published by them in another journal. However, it may be stated that the following amides in Table I have been shown to be very effective hypnotics when injected intraperitoneally into white rats: diethylthio-, ethylbutyl-, N-methylethylbutyl-, ethylamyl-, ethylhexyl- and N-β-hydroxyethylethyl-β′-cyclohexylethylacetamide.

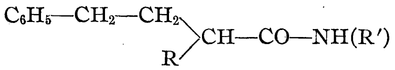
Especially interesting is the relatively high activity of diethylthioacetamide; in fact, it is the strongest hypnotic in the group (Table I) and is approximately five times as potent as diethylacetamide. However, the therapeutic index (minimum lethal dose/minimum hypnotic dose) of both diethylthioacetamide and diethylacetamide is low, 1.2 in each instance.

The disubstituted acetamides, described in Table II, are of three types. In type I, one substituent is represented by the β-phenylethyl group, the other, R, by ethyl, propyl, isopropyl, allyl, butyl, isobutyl, β-cyclohexylethyl or β-phenylethyl. In this group the ethyl, propyl, isopropyl, allyl and isobutyl compounds are strong hypnotics.



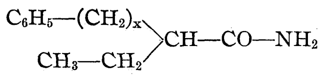
$$\left.\begin{matrix}C_6H_5{-}CH_2{-}CH_2\\ R\end{matrix}\right\rangle CH{-}CO{-}NH_2$$

I



$$\left.\begin{matrix}C_6H_5{-}CH_2{-}CH_2\\ R\end{matrix}\right\rangle CH{-}CO{-}NH(R')$$

II



$$\left.\begin{matrix}C_6H_5{-}(CH_2)_x\\ CH_3{-}CH_2\end{matrix}\right\rangle CH{-}CO{-}NH_2$$

III

A second type, II, represents compounds of type I in which a substituent, R′, has been in-

TABLE II

SUBSTITUTED ACETAMIDES

The amides were recrystallized in the following manner: compound 2 from water; compounds 8, 9, 10, 11, 12, 15, 16, 20, 22, 24, 25, 26 and 27 from petroleum ether (90–100°); compounds 18, 19 and 21 from dilute alcohol; compound 17 from acetone; compound 13 from 50% acetone; compounds 5 and 23 from a mixture of one part acetone and two parts petroleum ether (90–100°); compounds 1, 4, 6, 7, 10 and 14 from a mixture of one part acetone and nine parts petroleum ether.

	Acetamide	M. p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
1	Ethylbenzyl	117–118	$C_{11}H_{15}ON$	7.90	8.00
2	Ethyl-β-phenylethyl	105–106[a]	$C_{12}H_{17}ON$	7.32	7.30
3	N-Methylethyl-β-phenylethyl	98–99	$C_{13}H_{19}ON$	6.83	6.93
4	N-Ethylethyl-β-phenylethyl	72–73	$C_{14}H_{21}ON$	6.39	6.56
5	Di-β-phenylethyl	162–163	$C_{18}H_{21}ON$	5.53	5.42
6	N-Methyldi-β-phenylethyl	124–125	$C_{19}H_{23}ON$	5.24	5.15
7	N-Butyldi-β-phenylethyl	86–87	$C_{22}H_{29}ON$	4.43	4.29
8	β-Cyclohexylethyl-β′-phenylethyl	170–171	$C_{18}H_{27}ON$	5.14	5.41
9	Propyl-β-phenylethyl	109–110	$C_{13}H_{19}ON$	6.81	6.78
10	N-Methylpropyl-β-phenylethyl	93–94	$C_{14}H_{21}ON$	6.39	6.33
11	N-Ethylpropyl-β-phenylethyl	84–85	$C_{15}H_{23}ON$	6.00	6.08
12	N-β-Hydroxyethylpropyl-β′-phenylethyl	74–75	$C_{15}H_{23}O_2N$	5.63	5.70
13	N-Butylpropyl-β-phenylethyl	69–70	$C_{17}H_{27}ON$	5.36	5.23
14	Isopropyl-β-phenylethyl	121–122	$C_{13}H_{19}ON$	6.81	6.85
15	N-β-Hydroxyethylisopropyl-β′-phenylethyl	83–84	$C_{15}H_{23}O_2N$	5.63	5.55
16	Allyl-β-phenylethyl	90–91	$C_{13}H_{17}ON$	6.89	7.13
17	Butyl-β-phenylethyl	124–125	$C_{14}H_{21}ON$	6.40	6.56
18	N-Methylbutyl-β-phenylethyl	108–109	$C_{15}H_{23}ON$	6.00	5.75
19	N-Ethylbutyl-β-phenylethyl	71–72	$C_{16}H_{25}ON$	5.67	5.85
20	N-β-Hydroxyethylbutyl-β′-phenylethyl	66–67	$C_{16}H_{25}O_2N$	5.36	5.25
21	N-Butylbutyl-β-phenylethyl	59–60	$C_{18}H_{29}ON$	5.28	5.01
22	Isobutyl-β-phenylethyl	89–90	$C_{14}H_{21}ON$	6.40	6.61
23	Ethyl-γ-phenylpropyl	118–119	$C_{13}H_{19}ON$	6.81	6.82
24	Ethyl-δ-phenylbutyl	107–108	$C_{14}N_{21}ON$	6.40	6.43
25	Ethyl-ε-phenylamyl	98–99	$C_{15}H_{23}ON$	6.01	6.12
26	Ethyl-ζ-phenylhexyl	113–114	$C_{16}H_{25}ON$	5.67	5.75
27	Ethylcinnamyl	94–96	$C_{13}H_{17}ON$	6.89	6.72

[a] Levy [*Compt. rend.*, **194**, 175 (1932)] found 104° but did not record an analysis.

troduced into the amide group; R′ = methyl, ethyl, butyl or β-hydroxyethyl. Three compounds in this series proved to be strong hypnotics: N-ethylethyl-β-phenylethylacetamide, N-ethylpropyl-β-phenylethylacetamide and N-β-hydroxyethylpropyl-β′-phenylethylacetamide.

Six compounds of the general formula III were prepared in which $x = 1, 2, 3, 4, 5$ and 6. Two of these compounds are strong hypnotics, namely, ethyl-β-phenylethylacetamide and ethyl-ε-phenylamylacetamide.

Experimental Part

The amides were obtained by interaction of the disubstituted acetyl chloride with ammonia or the required amine. The new acid chlorides and their general method of preparation were described previously.[5]

Allyl-β-phenylethylacetamide was obtained in 87% yield when 4.5 g. of allyl-β-phenylethylacetyl chloride was added slowly, with vigorous stirring, to 20 cc. of ammonia water which was cooled with ice.

To prepare N,N′-bis-(diethylacetyl)-ethylenediamine 20 cc. of a 66% aqueous solution of ethylenediamine was stirred, cooled and 2.6 g. of diethylacetyl chloride added dropwise. The precipitate was filtered, washed with water, dried and recrystallized four times from petroleum ether; yield 2.4 g. or 95% of the calcd. amount.

No attempt was made to discover a satisfactory procedure for the preparation of diethylthioacetamide. However, sufficient material for our purpose was obtained when 22 g. of phosphorus pentasulfide and 23 g. of diethylacetamide were mixed intimately, 175 cc. of benzene added and the mixture refluxed for five minutes. The warm benzene was decanted from the pasty residue and the latter extracted with three 25-cc. portions of hot benzene. The solvent was removed from the combined benzene solutions and the gummy, yellow residue recrystallized from petroleum ether (90–100°).

Summary

A number of new dialkyl-, alkyl-β-cyclohexylethyl- and alkyl-β-phenylethylacetamides have been described. In some instances N-alkyl derivatives were prepared.

Some of the amides have been found to be strong hypnotics.

ANN ARBOR, MICHIGAN

RECEIVED OCTOBER 10, 1938

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[5] Blicke and Centolella, THIS JOURNAL, **60**, 2923 (1938).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. XLVII.* The Reduction Products of Estrone

BY RUSSELL E. MARKER AND EWALD ROHRMANN

In paper XLII[1] of this series the isolation and properties of two isomeric estranediols from human non-pregnancy urine were described. These diols were designated tentatively as diol-A, melting at 242° and diol-B, melting at 204°. Oxidation of these diols yielded different diketones, indicating that the two diols must differ at least in regard to the configuration at C_5 or C_{10}. It is not surprising that one of these diols isolated from the non-pregnancy urine was identical with an estranediol first obtained by Dirscherl[2] by the catalytic hydrogenation of estrone.

By the catalytic hydrogenation of estrone in an acid medium Dirscherl obtained two estranediols, one melting at 206° and the other at 155°. In addition to these he obtained two monohydroxy estrane compounds which apparently were formed by the elimination of the hydroxyl group at C_3. In his work no attempt to establish the configuration of the hydroxyl groups was made.

In an attempt to obtain more information concerning the configuration of the estranediols we have carried out the hydrogenation of α-estradiol in acid medium. This reaction yielded a diol melting at 204° which was found to be identical with the diol obtained by Dirscherl from the catalytic hydrogenation of estrone. This diol must therefore possess the α-configuration at C_{17}. In addition to this diol a compound of the composition $C_{18}H_{30}O_2 \cdot C_{18}H_{30}O$ melting at 175° was obtained. This substance appears to be a molecular compound. Upon oxidation with chromic acid at room temperature, it yielded a diketone melting at 170° which was identical with the diketone obtained by the oxidation of α-estranediol.

The α-estradiol used in the hydrogenation experiment was prepared in good yield by the aluminum isopropylate reduction of estrone. The compound was separated from the β-estradiol by means of its insoluble digitonide.[3]

In the catalytic hydrogenation of estrone and α-estradiol we have obtained no positive evidence of the formation of the estranediol melting at 242° obtained from human non-pregnancy urine.[1] This fact suggests that whereas catalytic hydrogenation of estrone produces compounds having the same configuration at C_5 and C_{10}, the reductive processes taking place in the body during the utilization of estrone may result in the formation of estranediols differing in their configurations at these asymmetric centers.

Experimental Part

Reduction of Estrone with Aluminum Isopropylate.—A mixture of 1 g. of estrone, 70 cc. of dry isopropyl alcohol and 1 g. of aluminum isopropylate was refluxed on a steam-bath for five hours. Approximately 50 cc. of the mixture was then slowly distilled off over a period of five hours. One gram of potassium hydroxide in 30 cc. of hot methanol was then added to the hot residue and the mixture allowed to stand for thirty minutes. The mixture was then poured into water and acidified with hydrochloric acid. The acidic mixture was extracted with ether and the ether extract was washed with water. The ether was removed, the crystalline residue dissolved in 15 cc. of hot 80% alcohol, and a boiling solution of 2 g. of digitonin in 80 cc. of 95% alcohol and 20 cc. of water was added. The resulting solution was cooled and allowed to stand for six hours. The white crystals of the digitonide which separated were filtered and washed with a little 95% alcohol. The dried crystalline digitonide weighed 1.5 g.

The digitonide was dissolved in 15 cc. of hot pyridine and the resulting solution heated on the steam-bath for twenty-five minutes. The hot solution was then poured into 200 cc. of ether and 15 cc. of methanol and the white precipitate was filtered and washed with ether. The filtrate was washed first with dilute hydrochloric acid and then with water. The ethereal solution was evaporated on the steam-bath and the crystalline residue after crystallization from acetone melted at 174°. This product gave no depression in melting point when mixed with an authentic sample of α-estradiol.

The filtrate from the digitonide separation was evaporated to a volume of 25 cc., 200 cc. of ether added, and the mixture thoroughly shaken. The mixture was filtered and the residue washed with ether containing 5% methanol. The filtrate was evaporated to dryness and the residue was crystallized from acetone to give β-estradiol melting at 215° (uncorr.).

Reduction of α-Estradiol.—To a solution of 1 g. of α-estradiol, m. p. 175°, dissolved in 100 cc. of absolute alcohol containing 1 cc. of concentrated hydrochloric acid, was added 500 mg. of platinum oxide catalyst. This was shaken with hydrogen at about five pounds (0.3 atm.) pressure and room temperature for five hours. The mixture was filtered and the filtrate poured into 300 cc. of water. The resulting mixture was extracted with ether and the ether extract washed first with sodium hydroxide

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(*) Paper XLVI, THIS JOURNAL, **60**, 2442 (1938).

(1) Marker, Rohrmann, Lawson and Wittle, THIS JOURNAL, **60**, 1901 (1938).

(2) Dirscherl, *Z. physiol. Chem.*, **239**, 53 (1936).

(3) Wintersteiner, THIS JOURNAL, **59**, 765 (1937).

solution and then with water. The ether was evaporated and the residual alcohol removed by heating *in vacuo*. The sirupy residue was dissolved in acetone and allowed to crystallize at 0°. The white crystals which separated were recrystallized from acetone to give a product melting at 204°. This gave no depression in melting point with an authentic sample of estranediol obtained by the hydrogenation of estrone.

The filtrate remaining after removal of the high melting diol was evaporated to a volume of about 4 cc. and allowed to crystallize at 0°. The white crystals were recrystallized from acetone to give needles melting at 175°. This gave a depression of 18° when mixed with a sample of estranediol-3,17α.

Anal. Calcd. for $C_{18}H_{30}O_2 \cdot C_{18}H_{30}O$: C, 79.9; H, 11.2. Found: C, 79.8; H, 11.0.

To a solution of 50 mg. of the molecular compound, m. p. 175°, in 15 cc. of glacial acetic acid was added a solution of 200 mg. of chromic oxide in 10 cc. of glacial acetic acid and 2 cc. of water. The resulting solution was allowed to stand at room temperature for forty minutes. The mixture was then poured into 200 cc. of water and the resulting mixture extracted with ether. The ether extract was washed with sodium carbonate solution and finally with water. The ether was evaporated and the crystalline residue distilled in high vacuum, the fraction distilling at 130–160° being collected. This fraction was crystallized from aqueous methanol to give crystals melting at 170° which gave no depression in melting point when mixed with the diketone (m. p. 170°) obtained by the oxidation of estranediol-3,17α.

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.8; H, 9.5. Found: C, 78.9; H, 9.9.

Summary

Estrone has been reduced with aluminum isopropylate to give α- and β-estradiols. α-Estradiol upon catalytic hydrogenation yielded estranediol-3,17α, and a molecular compound $C_{18}H_{30}O_2 \cdot C_{18}H_{30}O$. Oxidation of both compounds yielded estranedione.

STATE COLLEGE, PENNA. RECEIVED OCTOBER 7, 1938

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. XLVIII.* Isolation of Androsterone and Pregnanol-3-α from Human Pregnancy Urine

BY RUSSELL E. MARKER AND ELMER J. LAWSON

Recently a new theory of the biogenesis of the steroidal hormones was proposed.[1] This theory assumes that the cortical hormones (C_{21} and C_{19}) and the sex hormones (C_{21}, C_{19} and C_{18}) arise, not from cholesterol, but from a precursor (I) which may be cortin itself, constructed possibly from sugar units, by reductive processes possibly involving ascorbic acid in the suprarenal glands. While dehydrative and hydrolytic processes are involved, there is no necessity in this theory to assume that any of the steroidal hormones are formed by oxidations. Examples of transformations of the type we postulated in the organism have been found recently. Steiger and Reichstein[2] have shown that their substance J, and a new stereoisomer, O, are not, as was thought at the time of the appearance of Paper XL,[1] 3,11,20-triols, but are instead 3,17,20-triols. When triol-J is heated with alcoholic sulfuric acid, dehydration occurs with the formation of *allo*-pregnanol-3β-one-20. This type of dehydration coupled with the reduction of the carbonyl grouping at C_{20} is supposed to account for the degradation of the dihydroxyacetone residue to give ultimately a $CH_3—\overset{|}{C}H—OH$ (α) residue at C_{17}. It should be noted that while dehydration may remove the hydroxyl group either at C_{17} or C_{21} to give after reduction $C_{17,20}$ or $C_{20,21}$ glycols, the formation of $C_{17,21}$ glycols is not possible, and these should not be found in urines or glandular extracts.

Again, recent work by Mason[3] has shown that Kendall's compound E (Reichstein's Fa, Wintersteiner's F) is converted by the action of calcium hydroxide into adrenosterone. This reaction is simply a hydrolytic process, constituting in fact the reversal of an ordinary aldol condensation. Thus it is not necessary to employ an oxidative mechanism to account for the formation of the C_{19} steroids from the C_{21} steroids. The possibility of the oxidation of steroids in the suprarenals is also very remote in view of the presence of the highly reducing ascorbic acid. Certainly, no oxidation vigorous enough to rupture ordinary —C—C— bonds or oxidize methylene groups is likely to occur, or need be postulated.

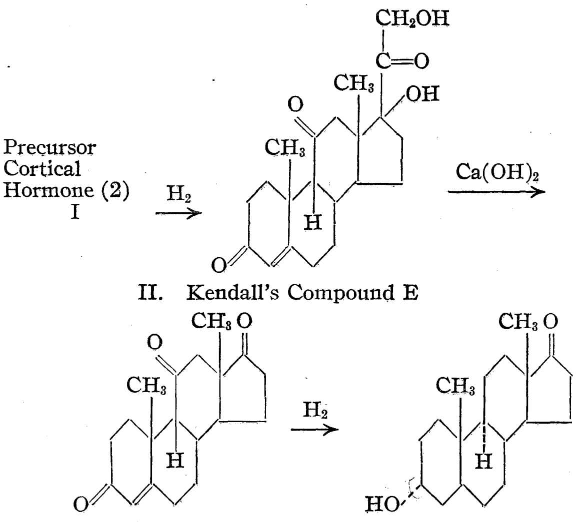
An essential feature of the theory is the as-

(*) Paper XLVII, THIS JOURNAL, **60**, 2927 (1938).

[1] Marker, *ibid.*, **60**, 1725 (1938).

[2] Steiger and Reichstein, *Helv. Chim. Acta*, **21**, 546 (1938).

[3] Mason, *Proc. Staff Meet. Mayo Clinic*, **13**, 235 (1938).



II. Kendall's Compound E

III. Adrenosterone

IV. Androsterone

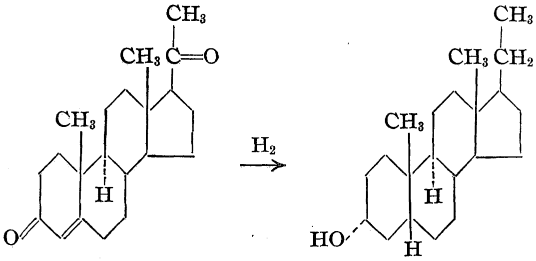
Fig. I

sumption that carbonyl groups adjacent to tertiary carbon atoms can be reduced to methylene groups *in vivo* as well as *in vitro*. This type of reduction has been observed in the laboratory in the case of the reduction of 7-keto-cholesteryl chloride to α-cholestyl chloride[4] and in the case of the reduction of uranetrione[5] to pregnanediol and uranediol. It is further assumed that while this reaction involves no inversion of the tertiary hydrogen at C_{17}, the tertiary hydrogen atom at C_9 is inverted from the β- to the α-type. Evidence for the occurrence of this type of reduction can be adduced from the isolation from urines of uranediol[6] and uranolone[7] which contain no oxygen atoms at C_{20}, and from cortical extracts by Steiger and Reichstein[2] of the compounds J, O and K, which contain no oxygen atoms at C_{11}. There is no reasonable doubt that the parent structure of J, O and K is that of *allo*-pregnane since all these have been converted to androstanedione-3,17. The question of the configuration at C_9 of the parent ring system of the other cortical derivatives having oxygen atoms at C_{11} is, as both Steiger and Reichstein[8] and one of us[1] have indicated, not definitely settled. The attempted correlation of corticosterone and digoxigenin[9,9a] has not shed any further light on this problem; indeed the non-identity of the Δ^4,3,11-diketocholenic acids obtained might be used as an argument to indicate that cortical derivatives are of the *allo*-urane type.

Further support for our theory of the biogenesis of the steroidal hormones has now been found in the isolation of pregnanol-3-α and androsterone from human pregnancy urine.

We have reported previously the fractionation of semicarbazones of ketones from human pregnancy urine. At the time that work was carried out a semicarbazone fraction of intermediate solubility was obtained which was assumed to be impure *allo*-pregnanol-3α-one-20 semicarbazone. An investigation of this fraction, however, has shown it to be androsterone, as proved by mixed melting points and its conversion to androstanedione. We believe that the occurrence of androsterone in human pregnancy urine and of estrone in stallions' urine indicates that these hormones are derived ultimately from sources other than the gonads, namely, from the suprarenal steroids by degradations of the type we have discussed previously. Thus, androsterone (IV) could arise from adrenosterone (III) as indicated in Fig. 1. To conceive of the androsterone as being derived from progesterone would involve a side-chain oxidation of a type more vigorous than is likely to occur in the glands.

The isolation of pregnanol-3-α, which we have prepared from pregnanol-3α-one-20,[10] was accomplished by precipitating the 3-β-OH sterols with digitonin and fractionating the 3-α-OH sterols by means of chromatographic adsorption and high vacuum distillation. The pregnanol-3-α, after isolation as its acetate which is not very soluble in cold methanol, showed no depression in melting point with an authentic sample. With the exception of cholesterol and equistanol, this is the first mono-oxygenated steroid isolated from glandular extracts or urines.



V. Progesterone

VI. Pregnanol-3

Fig. II.

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[4] Marker, Kamm, Fleming, Popkin and Wittle, THIS JOURNAL, **59**, 619 (1937).

[5] Marker, Kamm, Oakwood, Wittle and Lawson, *ibid.*, **60**, 1061 (1938); Marker, Wittle and Oakwood, *ibid.*, **60**, 1567 (1938).

[6] Marker, Rohrmann and Wittle, *ibid.*, **60**, 1561 (1938).

[7] Marker, Lawson, Wittle and Crooks, *ibid.*, **60**, 1559 (1938).

[8] Steiger and Reichstein, *Helv. Chim. Acta*, **21**, 161 (1938).

[9] Steiger and Reichstein, *ibid.*, **21**, 828 (1938).

[9a] Since this paper was submitted for publication, Mason and Hoehn [THIS JOURNAL, **60**, 2824 (1938)] have shown that the diketocholenic acid derived from digoxigenin is Δ^4,3,12-diketocholenic acid.

[10] Marker and Lawson, *ibid.*, **60**, 2438 (1938).

It undoubtedly arises from progesterone by reductive processes such as we have discussed, and its presence in urines must be considered valuable evidence in support of the proposed theory.

Experimental Part

In the crystallization of the semicarbazones of the ketonic fraction of human pregnancy urine sterols, the more insoluble semicarbazone was that of *epi-allo*-pregnanolone. From the mother liquors of this was obtained the more soluble semicarbazone of *epi*-pregnanolone. A fraction of intermediate solubility between these two semicarbazones was crystallized from ethanol six times to a decomposition point of 255°. This semicarbazone became very insoluble as it became purer, thus resembling the semicarbazone of *epi-allo*-pregnanolone, and for that reason it was not further investigated until the present time. The yield was 1.5 g. from 150,000 liters of human pregnancy urine.

Androsterone from Human Pregnancy Urine.—To a solution of 500 mg. of the above semicarbazone in 25 cc. of ethanol was added a solution of 2.5 cc. of concd. sulfuric acid in 5 cc. of water, and the mixture was refluxed for one hour. Water was added and the mixture extracted with ether. The residue after evaporation of the ether was sublimed in a high vacuum at 135–150° and then crystallized from dilute methanol to give a product melting at 176°. It gave no depression in melting point when mixed with an authentic sample of androsterone, but depressed the melting point of *epi-allo*-pregnanolone to 140–145°.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.6; H, 10.4; mol. wt., 290. Found: C, 78.8; H, 10.5; mol. wt. (Rast), 283.

Oxidation of Androsterone to Androstanedione.—Twenty milligrams of androsterone isolated from human pregnancy urine was dissolved in 5 cc. of acetic acid and a solution of 7 mg. of chromic oxide in 2 cc. of 90% acetic acid was added. After standing for one hour at room temperature, water was added and the product extracted with ether. After removal of the solvent the residue was sublimed in high vacuum at 120° and then crystallized from dilute methanol to give androstanedione, m. p. 128°, which did not depress in melting point when mixed with an authentic sample.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.1; H, 9.8. Found: C, 79.0; H, 9.9.

Isolation of Pregnanol-3-α from Human Pregnancy Urine.—The sterol fraction from 40,000 liters of human pregnancy urine after hydrolysis by alkali, removal of the pregnanediol and *allo*-pregnanediol by crystallization from acetone, and the ketones by Girard's reagent, was dissolved in 500 cc. of ether. To this was added 5 liters of ligroin and the ether removed by distillation. The mixture was cooled and the ligroin layer decanted from the tar which separated. The tarry residue was dissolved in 2 liters of ethyl alcohol and 200 g. of digitonin in 8 liters of hot alcohol was added. It was allowed to stand overnight and the digitonide was filtered and washed well with cold alcohol. The filtrate was concentrated to about 500 cc. and 5 liters of ether was added. It was again filtered from digitonin and the filtrate was evaporated to dryness *in vacuo*. This treatment removed all sterols having hydroxyl groups of the beta configuration.

The residue was dissolved in 250 cc. of pyridine and 200 g. of succinic anhydride was added. After heating for one hour on a steam-bath, ice was added and the succinate extracted with a large volume of ether. The pyridine was removed by washing with dilute hydrochloric acid and the ethereal layer was then extracted with sodium carbonate solution and a 2% solution of sodium hydroxide. The aqueous layers were combined, acidified and then extracted with ether. The solvent was removed and the residue saponified by refluxing with alcoholic potassium hydroxide solution. This carbinol fraction was extracted with ether and the solvent evaporated to dryness. On standing for several months some crystalline material appeared. It was treated with sufficient ether (cold) to filter. Upon washing with cold ether 23 g. of crystalline substance was obtained. The filtrate gave no precipitate when treated with a solution of alcoholic digitonin. The solvent was removed from the filtrate and the residue (115 g.) was dissolved in 2 liters of dry benzene. It was treated chromatographically with 800 cc. of aluminum oxide in 24-mm. diameter tubes. The absorbed material was washed with one liter of dry benzene, then with 5 liters of dry ether. Evaporation of the ether wash gave 12 g. of residue, which was sublimed *in vacuo* and the fraction distilling up to 120° collected. Upon washing with acetone this sublimate crystallized. It was converted into its acetate by boiling for half an hour with acetic anhydride. The acetate was crystallized several times from methanol, but could not be completely purified. After hydrolysis with alcoholic potassium hydroxide the sterol was dissolved in benzene, passed through a tube of aluminum oxide and washed out by ether and acetone. The eliminated material was crystallized from dilute methanol to a constant melting point of 146°. The product when mixed with *epi*-pregnanol-3 gave no depression in melting point. The amount of purified product was 26 mg., although much larger amounts are present.

Anal. Calcd. for $C_{21}H_{36}O$: C, 82.8; H, 11.8. Found: C, 82.5; H, 11.6.

Work on the identification of the *epi*-sterols from the other fractions is in progress at present and will be reported in THIS JOURNAL when the chemical structure of the products has been ascertained.

We wish to thank Dr. Oliver Kamm and Parke, Davis and Co. for their generous help and assistance in various phases of this work.

Summary

The theory of the biogenesis of the steroidal hormones is discussed, and additional supporting evidence cited. The isolation of androsterone and pregnanol-3-α from human pregnancy urine is described.

STATE COLLEGE, PENNA. RECEIVED OCTOBER 7, 1938

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. XLIX.* Isolation of Pregnanediols from Bull's Urine

BY RUSSELL E. MARKER, EUGENE L. WITTLE AND ELMER J. LAWSON

In a recent paper[1] from this Laboratory it was suggested that the parent male, female and cortical hormones arise from a common precursor, and that in the course of utilization of these hormones they are excreted as reduction products. For example, while the three isomeric pregnanediols, pregnanediol-3(α),20(α), *allo*-pregnanediol-3(α),-20(α) and *allo*-pregnanediol-3(β),20(α), which are the reduction products of progesterone, have been isolated from the urines of pregnant women, mares and cows,[2] they have been found to be absent or present only in traces in the urines of stallions[3] and non-pregnant women.[4] However, we have now found that bull's urine contains large amounts of the pregnanediols. The table below shows the approximate quantities of the pregnanediols present in various urines. Evidently bull's urine is the richest source of the pregnanediols yet investigated.

	Approximate quantities isolated, mg. per gallon of urine		
	Pregnanediol-3(α),-20(α)	*allo*-Pregnanediol-3(α),-20(α)	*allo*-Pregnanediol-3(β),-20(α)
Human pregnancy	50	25	6
Human non-pregnancy	8	4	.
Human male	.	.	.
Mare pregnancy	50	25	6
Cow pregnancy	25	15	3
Stallion	none	none	none
Bull	100	50	12

Thus there are now at least three instances of the apparently anomalous occurrence of steroids in urines, namely, the presence of estrone in stallion's urine,[5,6] of androsterone[7] in human pregnancy urine and of the pregnanediols in bull's urine. At present it seems that these results can best be explained by assuming, in accordance with the theory set forth recently,[1] that these compounds originate from cortical derivatives. In this connection it should be noted that cortical extracts have been found to have both estrogenic and progestational activity,[8,9] and recently Beall and Reichstein[10] have isolated progesterone and *allo*-pregnanol-3(β)-one-20 from this source. Also, Reichstein[11] recently has announced the isolation from cortical extracts of 21-hydroxyprogesterone. While it might be argued, since Reichstein's extracts are obtained from the suprarenals of both bulls and cows, that the progesterone he isolated was derived only from cows, the isolation of the pregnanediols from bull's urine nullifies this argument. Whether these pregnanediols come from the testes or the suprarenals is not yet known, but it is evident, since the bull has no ovaries, that progesterone is formed in other glands. If the pregnanediols from bull's urine are formed from cortical derivatives, it appears that either progesterone or Δ^4-pregnenol-20(α)-one-3 is an intermediate step in the reductive processes involved. Should the latter prove to be the case, it might suggest that Δ^4-pregnenol-20(α)-one-3 functions as a male hormone in the bull. There seems to be no doubt but that the occurrence of the pregnanediols is normal for the bull since the urine investigated was collected from sixteen bulls, and inordinately large amounts would have had to have been excreted if these steroids arose as the result of some disfunction in one of the bulls.

Besides the isomeric pregnanediols, a considerable amount of equistanol has also been found in bull's urine. Equistanol is present in the urines of mares, stallions, cows and bulls, but not in humans. On the other hand, human urine contains comparable amounts of cholesterol but only traces are present in the urines of mares, cows, bulls and stallions.

The mode of isolation of these steroids was essentially the same as that employed in other similar investigations reported from this Laboratory. The urine collected from sixteen mature bulls was hydrolyzed with hydrochloric acid, extracted with butanol and then hydrolyzed by alkali. It was filtered and extracted to yield an ether insoluble solid, and a sirupy concentrate. The former, after acetylation, yielded pregnanediol-3(α),20-

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(*) Paper XLVIII, THIS JOURNAL, **60**, 2928 (1938).

(1) Marker, THIS JOURNAL, **60**, 1725 (1938).

(2) Marker, *ibid.*, **60**, 2442 (1938).

(3) Marker, Lawson, Rohrmann and Wittle, *ibid.*, **60**, 1555 (1938).

(4) Marker, Rohrmann, Lawson and Wittle, *ibid.*, **60**, 1901 (1938).

(5) Deulofeu and Ferrari, *Z. physiol. Chem.*, **226**, 192 (1934).

(6) Haussler, *Helv. Chim. Acta*, **17**, 531 (1934).

(7) Marker and Lawson, Sterols. XLVII, THIS JOURNAL, **60**, 2927 (1938).

(8) Engehart, *Klin. Wochr.*, **9**, 2114 (1930).

(9) Callow and Parkes, *J. Physiol.*, **87**, 28P (1936).

(10) Beall and Reichstein, *Nature*, **142**, 479 (1938).

(11) Reichstein, *Helv. Chim. Acta.*, **21**, 1197 (1938).

(α) diacetate, and a mother liquor which gave *allo*-pregnanediol-3(α),20(α) on hydrolysis. The sirupy concentrate after Girard's reagent and acid-succinate separations yielded a carbinol fraction which was treated with digitonin solution. The digitonide mixture gave, after decomposition, *allo*-pregnanediol-3(β),20(α), and β-equistanol. The results of our investigation of the other fractions obtained will be submitted soon for publication.

The authors wish to thank Dr. Oliver Kamm and Parke, Davis & Co. for their generous assistance in various phases of this work.

Experimental Part

The bull's urine used in this investigation was collected from 16 mature bulls. After hydrolyzing the urine by boiling with 10% hydrochloric acid for thirty minutes, a precipitate which formed was collected and the filtrate thoroughly extracted with butanol. The solvent was removed by vacuum distillation to a sirup and the latter dissolved in a large volume of ether and filtered from some solid material. The ether was evaporated to give 4500 cc. of sirup.[12]

The concentrate was dissolved in 10 liters of ether and shaken with sodium carbonate and sodium hydroxide solution to remove phenolic and acidic materials. The ether was evaporated and the residue steam distilled with an excess of aqueous potassium hydroxide (20 pounds (9.1 kg.) of potassium hydroxide per 1000 gallons (3800 liters) of urine extract) until no more volatile organic material came over. The mixture was cooled to room temperature, filtered and the residue washed well with water and ice cold ether. The filtrate was extracted well with ether and the solvent removed. The ether insoluble precipitate amounted to 175 mg. per gallon.

Pregnanediol-3(α),20(α) and *allo*-Pregnanediol-3(α), 20(α).—The precipitate obtained as described above was refluxed for one hour with 7 volumes of acetic anhydride, the solution cooled to 0°, and filtered. The crystalline acetate was recrystallized from methanol to give a pure product melting at 180°. The yield was 100 mg. per gallon. Mixed with pregnanediol-3(α),20(α)-diacetate, this acetate gave no depression in melting point.

Anal. Calcd. for $C_{25}H_{40}O_4$: C, 74.2; H, 10.0. Found: C, 73.9; H, 10.0.

Hydrolysis of this pregnanediol-3(α),20(α) diacetate with alcoholic potassium hydroxide gave pregnanediol-3(α),20(α) melting at 240°. It gave no depression in melting point when mixed with an authentic sample.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.8; H, 11.3. Found: C, 78.6; H, 11.1.

The acetic anhydride mother liquors were evaporated to dryness and the residue hydrolyzed with alcoholic potassium hydroxide solution. Dilution of the solution with water gave a solid which was collected, washed well with water, and recrystallized from alcohol to a melting point of 243°. This was *allo*-pregnanediol-3(α),20(α) since it depressed to 215° with pregnanediol-3(α),20(α) but gave no depression with *allo*-pregnanediol-3(α),20(α). The yield was approximately 50 mg. per gallon of urine.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.8; H, 11.3. Found: C, 78.5; H, 11.2.

The diacetate prepared in the usual manner was crystallized from methanol. It melted at 141° and did not depress with an authentic sample of *allo*-pregnanediol-3(α),-20(α) diacetate.

Anal. Calcd. for $C_{25}H_{40}O_4$: C, 74.2; H, 10.0. Found: C, 74.0; H, 9.9.

The β-Steroids in Bull Urine.—The ether washings of the crude pregnanediols and the ether extract of the aqueous filtrate were combined and evaporated to a sirup. The sirup was dried by distilling 1 liter of benzene from it. The tarry residue was dissolved in 1 liter of alcohol and refluxed thirty minutes with 30 g. of Girard's reagent. The solution was diluted with ether and ice, the layers separated, and the aqueous layer extracted with ether. The aqueous layer was acidified with hydrochloric acid and heated on a steam-bath. The ketonic oil was extracted with ether and set aside for an examination now in progress.

The ethereal extract from the Girard's separation was evaporated to a sirup which was dried as before by distilling benzene from it. The residue was heated for one hour with 300 cc. of pyridine and 240 g. of succinic anhydride and then poured on ice. Ether was added and the pyridine removed by shaking with hydrochloric acid. The acid succinate mixture was then removed from the ethereal solution by shaking with sodium carbonate solution. The ethereal solution which contained hydrocarbons was reserved for a separate investigation now in progress. The carbonate solution was acidified, extracted with ether and after removal of the ether, hydrolyzed with an excess of alcoholic potassium hydroxide. The carbinol mixture was extracted with ether, and the solvent removed. The residue was dissolved in hot alcohol and an excess of a hot 2% alcoholic digitonin solution (200 mg. of digitonin per gallon of urine) was added. After standing overnight the digitonide was filtered and washed with cold alcohol. The filtrate was evaporated to 200 cc. and 5 liters of ether added. The suspension was filtered to remove the digitonin and soluble digitonides. The digitonin–digitonide mixture was combined giving 245 mg. per gallon of urine. The filtrate which contained sterols of the *epi*-OH configuration was reserved for a separate investigation now in progress.

The digitonides were dried and heated with 5 volumes of pyridine on a steam-bath for one hour. This was poured into ether, filtered, and the digitonin washed well with ether. The ethereal filtrate was freed of pyridine by shaking with hydrochloric acid solution, the solvent removed, and the residue dissolved in a small amount of benzene. On standing overnight a crystalline crop deposited. This was collected and recrystallized from methanol and acetone to give *allo*-pregnanediol-3(β),-20(α), m. p. 215°. When mixed with *allo*-pregnanediol-3(β),20(α), it gave no depression in melting point. Mixed with uranediol it depressed the melting point to 185°.

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[12] We wish to thank the Parke, Davis & Co. for performing the above collection, hydrolysis and extraction at their laboratories and supplying us with the ethereal concentrate.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.8; H, 11.3. Found: C, 78.6; H, 11.2.

Upon refluxing with acetic anhydride it gave a diacetate melting at 168° which gave no depression in melting point when mixed with the diacetate of *allo*-pregnanediol-3(β),20(α). This compound was present in bull urine to the extent of 12 mg. per gallon.

The benzene was removed from the filtrate of the *allo*-pregnanediol-3(β),20(α) and the residue sublimed in high vacuum collecting a fraction distilling at 120–150°. This was crystallized from ethyl alcohol and methyl alcohol to a melting point of 137°. The product was saturated to bromine and when mixed with β-equistanol isolated from stallion, cow pregnancy, and mare pregnancy urine it gave no depression in melting point.

Upon refluxing with acetic anhydride it gave an acetate melting at 126° which did not depress the melting point of β-equistanol acetate. Equistanol was present in bull's urine to the extent of 8 mg. per gallon. As in the case of stallions, mares and cows pregnancy urine, the amount of cholesterol present was very small when compared to that in human urine. An investigation of the other steroid fractions will be reported in This Journal in the near future.

Summary

Pregnanediol-3(α),20(α), *allo*-pregnanediol-3(α),20(α), *allo*-pregnanediol-3(β),20(α) were isolated from bull's urine in quantities about twice or more than that of human pregnancy urine. Equistanol also was isolated but very little cholesterol was found.

State College, Penna.

Received October 17, 1938

[Contribution from the Department of Chemistry, West Virginia University]

β-Alkoxy Ethyl Esters of Chlorocarbonic and Carbamic Acids

By H. G. Ashburn, A. R. Collett and C. L. Lazzell

In order to study the relative narcotic powers of a series of carbamic acid esters containing an ethereal oxygen in the alcohol group, we have prepared a series of twelve esters of chlorocarbonic acid, ten of which are new, and from them their corresponding carbamic acid esters, eleven of which are new.

β-Alkoxyethanols.—The β-alkoxyethanols were prepared by treating ethylene oxide with the desired alcohol in the presence of a small amount of sulfuric acid as a catalyst,[1,2] except in the cases of the tertiary butoxy and tertiary amoxy ethanols for which aluminum fluosilicate was used as a catalyst.[3,4]

β-Alkoxyethyl Chlorocarbonates.—The chlorocarbonates were prepared by the action of phosgene upon the various β-alkoxyethanols.[5] A calculated excess of liquid phosgene was placed in a 500-cc. round-bottomed flask clamped in a freezing mixture. A reflux condenser, through which a freezing mixture was passed, was then attached. The alcohol was added drop by drop, the mixture being stirred mechanically, until all was added, and the reaction mixture allowed to come to room temperature gradually. The flask was opened and allowed to remain open for a day, at room temperature, in order to evaporate the excess phosgene. The mixture was poured into ice water, the ester separated and dried over anhydrous calcium chloride. It was then distilled *in vacuo* at 1–20 mm. pressure. The tertiary butoxy and tertiary amoxy chlorocarbonates could not be prepared by this reaction. *bis*-Ethylene chlorocarbonate was obtained in both cases.

The analyses were made in a few cases by digesting the sample with 10% sodium hydroxide, then titrating against standard silver nitrate, using potassium chromate as an indicator. In all cases the chlorocarbonates were converted into their respective carbamates and analyzed for nitrogen by the Kjeldahl method. Refractive indices were determined by means of an Abbe refractometer and surface tension values obtained by means of a du Nouy tensiometer at 25°. The Harkins correction for the ring method was applied. The yields are based upon the amount of the glycol ether used. Table I shows the boiling points, under reduced pressure, the refractive indices, surface tensions (corrected), yields, and the densities of the chlorocarbonates.

β-Alkoxyethyl Carbamates.—The carbamates were prepared from the corresponding chlorocarbonates by treating them with aqueous ammonia. The carbamates, with the exception of the β-methoxy, β-ethoxy- and β-isopropoxyethyl carbamates were purified by distillation *in vacuo*. These three were purified by crystallization from propylene chloride. The yield is based on the chlorocarbonate used. In Table II the yield, melting point or boiling point, and the analyses for the carbamates are given.

Narcotic Properties

Emerson and Abreu[6] have found that the β-ethoxyethyl carbamate is less active and less toxic than urethan. They also found that the propoxy and isopropoxy derivatives are roughly equivalent to urethan in narcotic activity and toxicity and

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[1] Ashburn, Collett and Lazzell, This Journal, **57**, 1862 (1935).

[2] German Patent 580,075, July 5, 1933; *C. A.*, **27**, 4814 (1933).

[3] Ashburn, Collett and Lazzell, This Journal, **58**, 1549 (1936).

[4] French Patent 39,773, Feb. 17, 1931; *C. A.*, **26**, 4826 (1932).

[5] Dumas and Péligot, *Ann. chim.*, [2] **58**, 52 (1835); *Ann.*, **15**, 1–60 (1835); *Ann.*, **10**, 284 (1834); Hentschel, *Ber.*, **18**, 1177 (1885).

[6] From a report by Emerson and Abreu working in the Pharmacological Laboratory of the University of California Medical School, San Francisco, California.

TABLE I

β-ALKOXYCHLOROCARBONATES ($ROCH_2CH_2OCOCl$)

Alkyl group	Yield, %	B. p. °C.	Mm.	$d^{25}_{abs.}$	n^{25}_D	γ_{25}	Chlorine, % Calcd.	Chlorine, % Found	
CH_3—[a]	93	58.7	13.0	1.1905	1.4163	30.86	...	...	...
C_2H_5—[a]	77	67.2	14.0	1.1341	1.4169	29.45	...	...	...
$CH_3(CH_2)_2$—	81	78.3	13.0	1.0879	1.4193	28.55	21.32	20.77	20.48
$(CH_3)_2CH$—	85	71.5	12.0	1.0820	1.4156	27.09	...	...	...
$(CH_3)(CH_2)_3$—	91	93.0–93.5	14.0	1.0696	1.4241	28.64	19.66	19.78	19.80
$(CH_3)_2CHCH_2$—	59	84.0–85.0	12.0	1.0657	1.4205	27.18	...	...	...
$(C_2H_5)(CH_3)CH$—	83	83.0–84.0	14.0	1.0404	1.4180	25.73	...	...	...
$(CH_3)(CH_2)_4$—	83	104.3	12.0	1.0508	1.4275	28.67	18.44	18.74	18.59
$(CH_3)_2CH(CH_2)_2$—	91	95.0–96.0	10.0	1.0565	1.4268	27.63	...	...	...
$(C_2H_5)(CH_3)CHCH_2$—	87	102.0	14.0	1.0700	1.4272	29.00	...	...	...
$(C_2H_5)_2CH$—	72	87.0–87.5	8.5	1.0619	1.4261	27.54	...	...	...
$(n\text{-}C_3H_7)(CH_3)CH$—	90	91.8	9.5	1.0750	1.4262	27.90	...	...	...

[a] The β-methoxy and β-ethoxy ethyl chlorocarbonates are marketed by the Eastman Kodak Company, which gives their boiling points as 54–60° at 13 mm., and 55–65° at 15 mm., respectively.

TABLE II

β-ALKOXYETHYL CARBAMATES ($ROCH_2CH_2OCONH_2$)

Alkyl groups	Yield, %	M. p. °C.	B. p. °C.	Mm.	Nitrogen, % Calcd.	Nitrogen, % Obtained	
CH_3—	13.3	46.8	...	...	11.86	11.65	11.81
C_2H_5—[a]	39.0	62.2	...	...	10.52	10.21	10.46
$CH_3(CH_2)_2$—	12.7	..	132.2–132.5	7.0	9.65	9.94	9.54
$(CH_3)_2CH$—	66.6	53.0	...	...	9.65	9.55	9.83
$CH_3(CH_2)_3$—	63.5	..	132.2–132.4	2.5	8.69	8.57	8.59
$(CH_3)_2CHCH_2$—	23.2	..	133.0–134.0	5.0	8.69	8.85	8.85
$(C_2H_5)(CH_3)CH$—	34.0	..	135.4	3.0	8.69	8.33	8.32
$(CH_3)(CH_2)_4$—	43.0	..	142.2	3.0	8.00	7.96	7.88
$(CH_3)_2CH(CH_2)_2$—	29.8	..	131.4	1.5	8.00	7.47	7.79
$(C_2H_5)(CH_3)CHCH_2$—	11.9	..	129.0–130.0	2.0	8.00	7.87	8.28
$(C_2H_5)_2CH$—	63.5	..	133.0–134.0	2.5	8.00	8.06	7.73
$(n\text{-}C_3H_7)(CH_3)CH$—	26.6	..	137.0–138.0	3.5	8.00	8.31	7.75

[a] Recorded in the literature as 62° (I. G. Farbenind. S. G. E. P. 309,108 (1928); *Chem. Zentr.*, **100**, II, 650 (1929), and is marketed by the Eastman Kodak Company which gives the melting point of its product as 61–62°.

that the isomers of butoxy and amoxy derivatives are more active and more toxic than urethan.

Summary

Ten new β-alkoxyethyl esters of chlorocarbonic acid and eleven new β-alkoxyethyl esters of carbamic acid have been prepared and some of their physical constants determined.

MORGANTOWN, W. VA.

RECEIVED AUGUST 20, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

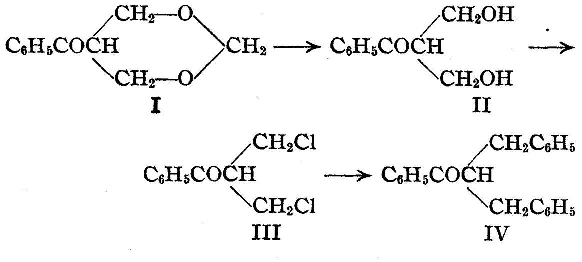
The Condensation of Paraformaldehyde with Aromatic Ketones

BY REYNOLD C. FUSON, W. E. ROSS AND C. H. MCKEEVER[1]

The condensation of simple aliphatic ketones has been studied thoroughly and can be caused to proceed in a controllable manner to give relatively simple products. With aromatic ketones, however, the reaction appears to take place only with difficulty. For example, the interaction of formaldehyde and acetophenone in the presence of various alkaline catalysts has been reported to give only complex products.[2] Using potassium carbonate as the catalyst Manta[3] converted propiophenone to a dimethylol derivative in which the carbonyl group had been reduced to a carbinol group. With isobutyrophenone Manta obtained a still more complex product. In Manta's experiments the reaction mixtures were heated.

We have found that simpler products are obtained if the reaction is carried out at room temperature and allowed to continue for a longer period. When acetophenone was treated with paraformaldehyde in methanol in the presence of potassium carbonate a high yield was obtained of a compound which proved to be the formal of the dimethylol derivative (I).

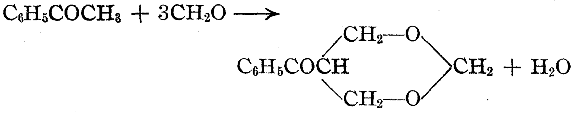
The structure of the formal was proved by the following transformations.



Treatment with concentrated hydrochloric acid converted it to the dichloro ketone (III) and formaldehyde. The latter was identified by formation of the β-naphthol derivative, di-β-naphtholmethane. The structure of the dichloro ketone was established by converting it into dibenzylacetophenone (IV) by the Friedel-Crafts method. An authentic specimen of this compound, made from acetophenone and benzyl chloride by the method of Nef,[4] proved to be identical.

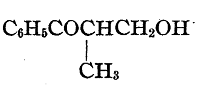
The formal was hydrolyzed by treatment with concentrated sulfuric acid but the dimethylol derivative (II) could not be isolated.

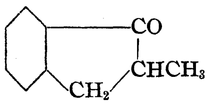
The foregoing facts indicate that the reaction between acetophenone and paraformaldehyde is represented by the equation

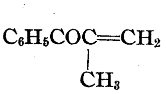


Although the ratio of aldehyde to ketone was varied considerably, the formal was always the chief product. This is remarkable because acetal formation generally does not take place in alkaline media. It is somewhat strange also that none of the early workers in the field have reported this reaction. However, the result is not entirely novel. In 1937, Gilbert, Morgan and Griffith[5] obtained a formal by treating methyl ethyl ketone with formaldehyde in the presence of sodium hydroxide.

Propiophenone reacted slowly with paraformaldehyde to give β-benzoylpropyl alcohol (V) which shows no tendency to undergo spontaneous dehydration. For example, it forms the corresponding urethan when treated with phenyl isocyanate.


V


VI


VII

Dehydration was effected, however, by the action of concentrated sulfuric acid. The product proved to be α-methylhydrindone (VI) and not the expected isopropenyl ketone (VII). Bromine brought about substitution giving α-bromo-α-methylhydrindone. The melting point of this derivative corresponds with that given by Salway and Kipping[6] for α-bromo-α-methylhydrindone. Confirmatory evidence for the structure of the α-methylhydrindone was obtained by oxidation which converted it to *o*-phthalic acid.

This ring closure involves the cyclodehydration

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[1] Röhm and Haas Research Assistant.

[2] Van Marle and Tollens, *Ber.*, **36**, 1351 (1903); Tollens, *ibid.*, **37**, 1435 (1904); Schäfer and Tollens, *ibid.*, **39**, 2181 (1906).

[3] Manta, *J. prakt. Chem.*, **142**, 11 (1935).

[4] Nef, *Ann.*, **310**, 316 (1900).

[5] Gilbert, Morgan and Griffith, *J. Chem. Soc.*, 841 (1937).

[6] Salway and Kipping, *J. Chem. Soc.*, **95**, 166 (1909).

of a 2-aroyl-1-alkanol and is a novel method of synthesis of 2-alkyl-1-indanones.

Experimental

The Action of Formaldehyde on Acetophenone.—A mixture of 45 g. of paraformaldehyde, 180 g. of acetophenone, 2 g. of potassium carbonate and 300 cc. of methyl alcohol was shaken for seven days at room temperature and poured into a liter of water. The mixture was acidified with hydrochloric acid and extracted with four 100-cc. portions of benzene. The combined benzene extracts were washed three times with water. The solvent was evaporated and the residue distilled under diminished pressure. Sixty-four grams of acetophenone was recovered. Eighty-five grams of the formal of 2-benzoyltrimethylene glycol was obtained; b. p. 124–126° (3 mm.). The residue remaining in the flask was a heavy viscous resin. The formal reduced Benedict's solution and gave a silver mirror with Tollens' reagent.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.71; H, 6.29. Found: C, 68.91; H, 6.5.

The Action of Hydrochloric Acid on the Formal.—Five grams of the formal was shaken with 50 cc. of concentrated hydrochloric acid at room temperature for twenty-four hours. The mixture was then allowed to stand until the oil had solidified completely. The solid was collected on a filter, the filtrate was diluted to 150 cc. and to it were added 7.5 g. of β-naphthol and 30 cc. of ethyl alcohol. The mixture was boiled for five minutes and allowed to cool. The crystals which formed weighed 6 g. After recrystallization from dilute ethyl alcohol the compound melted at 190–191°, with darkening at 180°. It was evidently di-β-naphtholmethane.

The yield of the solid chloro compound—1,3-dichloro-2-benzoylpropane—was 5 g.; m. p. 56–57°.

Anal. Calcd. for $C_{10}H_{10}OCl_2$: C, 55.3; H, 4.6; Cl, 32.67. Found: C, 55.73; H, 4.55; Cl, 32.97.

Condensation of 1,3-Dichloro-2-benzoylpropane with Benzene.—To a solution of 10 g. of the dichloride in 200 cc. of dry benzene was added all at once 8 g. of anhydrous aluminum chloride. The mixture was shaken overnight and decomposed with ice. The oily product obtained by benzene extraction solidified after several hours and was recrystallized from 80% ethyl alcohol; m. p. 78°. A mixed melting point determination showed the compound to be α,α-dibenzylacetophenone.

The Action of Sulfuric Acid on the Formal of 2-Benzoyltrimethylene Glycol.—Ten grams of the formal was poured into 50 cc. of concentrated sulfuric acid, with stirring. The mixture became warm and the odor of formaldehyde was discernible. After standing for ten minutes, it was poured into 500 cc. of water. By extracting this mixture with ether there was obtained a pungent lachrymatory oil. Distillation gave a small amount of yellow liquid; b. p. 101–105° (3 mm.). The residue set to a resin which was insoluble in alcohol and acetone. The distillate also resinified when allowed to stand.

The Reaction of Propiophenone with Formaldehyde.—A mixture of 40 g. of propiophenone, 9 g. of paraformaldehyde, 4 g. of potassium carbonate and 200 cc. of methyl alcohol was shaken at room temperature for four days. It was then poured into a liter of water. The resulting mixture was acidified with hydrochloric acid and extracted with three 60-cc. portions of benzene. The combined benzene extracts were washed three times with water and the solvent evaporated. By distillation of the residue there was obtained 32 g. of propiophenone and 8 g. of an oil boiling at 143–145° (5 mm.). The residue was negligible.

The 32 g. of recovered propiophenone was shaken for seven days with a mixture of 7.5 g. of paraformaldehyde, 2 g. of potassium carbonate and 100 cc. of methyl alcohol. From this run 16 g. of the oil was obtained. It was 2-benzoylpropyl alcohol.

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.12; H, 7.37. Found: C, 73.31; H, 7.58.

The phenylurethan (from 80% methyl alcohol) melted at 86–87°.

Anal. Calcd. for $C_{17}H_{17}O_3N$: N, 4.94. Found: N, 5.2.

α-Methylhydrindone.—Ten grams of the keto alcohol was poured into 50 cc. of cold sulfuric acid, with stirring. The stirring was continued for two hours and the mixture was poured into 500 cc. of water. Extraction with ether gave 6 g. of α-methylhydrindone; b. p. 88–90° (3 mm.).

Anal. Calcd. for $C_{10}H_{10}O$: C, 82.15; H, 6.9. Found: C, 82.22; H, 7.2.

Oxidation with dilute nitric acid gave a high yield of *o*-phthalic acid.

α-Bromo-α-methylhydrindone.—To a solution of 1 cc. of the α-methylhydrindone in 10 cc. of carbon tetrachloride was added from a pipet a solution of bromine in carbon tetrachloride. The addition was continued until a slight color persisted. Approximately 11 cc. of a solution containing 0.05 g. of bromine per cubic centimeter was added. The reaction was accompanied by copious evolution of hydrogen bromide. The solvent was evaporated and the residual oil solidified after being allowed to stand for several days. The bromohydrindone crystallized from dilute alcohol in large, colorless plates; m. p. 72–73°.

Summary

The condensation of paraformaldehyde with acetophenone has been carried out in methanol with potassium carbonate as the catalyst. An excellent yield is obtained of the formal (I) of the dimethylol derivative.

Similar treatment of propiophenone gives the monomethylol derivative (V). When dehydrated this compound is transformed into α-methylhydrindone (VI).

URBANA, ILLINOIS RECEIVED SEPTEMBER 30, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF AGRICULTURE, UNIVERSITY OF WISCONSIN]

The Effect of Acids on Carotenoids[1]

BY FORREST WARD QUACKENBUSH, HARRY STEENBOCK AND WILLIAM HAROLD PETERSON

The action of acids on carotenoids has become a matter of practical importance as well as scientific interest in recent years. The ensiling of legumes with mineral acids, *e. g.*, mixtures of hydrochloric–sulfuric (the A. I. V. process) and phosphoric, has produced a silage which often appears to have not only all the carotene of the green alfalfa but in some cases more carotene than is found in the original herbage.[2–4] Such results naturally have raised doubts regarding the validity of the data and have indicated the need of more information regarding the character of the pigments contained in the so-called carotene fraction.

The work described in this paper shows that several carotene-like pigments are produced by the action of acids on green forage, that these pigments have no vitamin A value, and that they may to some extent be secreted into milk.

Experimental

Effect of Mineral Acid on the Apparent Carotene Content of Alfalfa.—The samples (forage or silage) were extracted with hot alcohol, the extract was saponified with alcoholic potassium hydroxide, and the carotenoids were obtained by shaking with several portions of benzine (Skellysolve B, b. p. 65–75°). The united extracts were washed with water and the non-carotene pigments (xanthophyll, etc.) removed by extracting with an equal volume of 85% ethanol in four successive portions. The residual carotene and the extracted xanthophyll were determined spectrophotometrically. The results agreed satisfactorily with the values obtained by the method of Willstätter and Stoll.[5]

Typical analytical data (Table I) showed increases in the carotene values in alfalfa which had been treated with mineral acids. It was observed that while the carotenoid pigments from fresh green alfalfa separated sharply between benzine and 85% ethanol, those from acidified alfalfa did not. With fresh alfalfa the alcohol was practically colorless after three extractions of the benzine solution but with silage or acidified fresh alfalfa even the fourth extract was highly colored. Continued extraction did not result in a sharper separation, and the use of higher concentrations of alcohol gave only slightly better results. The immediate cause of these analytical difficulties became clear when the carotene fractions were subjected to chromatographic analysis.

TABLE I

INCREASE IN "CAROTENE" FRACTION FROM ALFALFA AFTER TREATMENT WITH MINERAL ACIDS

	Sample and treatment	Carotenoids (gamma/g. dry tissue) Carotene	Xanthophyll
1	Green alfalfa	126	225
2	A. I. V. silage from above alfalfa	184	190
3	Green alfalfa	193	368
4	Green alfalfa acidified before extraction	261	134
5	A. I. V. silage from above alfalfa	302	298

Chromatographic Separation of the Carotene-like Pigments.—In the first experiments magnesium oxide (Merck U. S. P. X, heavy) was used to make the chromatographic column. The benzine solution was evaporated to dryness in a vacuum and the residue taken up with a small volume of benzine. The concentrated solution was poured on the adsorbent and the column washed with benzine to a maximum separation of the bands.

Three sharp bands made their appearance from the carotene fraction of green alfalfa. These were identified by their relative positions in the chromatogram, by their spectral absorption, and by their phasic distribution between benzine and 85% ethanol as due to α-carotene, β-carotene and lutein, respectively. β-Carotene preponderated in quantity. Acidified forage gave a fourth band almost as wide as that of β-carotene. It occupied a position in the column so close to lutein that, even after long washing, the two almost merged. The upper portion of the new band was dull red and the lower portion yellow-orange. To effect their separation the column was removed, and divided; the pigments were eluted with ether, transferred to benzine, and readsorbed on fresh magnesium oxide. By repeating this fractionation several times, small quantities of red and yellow pigments, which appeared to be free from each other, were obtained. In benzine the yellow pigment exhibited sharp maximal spectral absorption at 448 and 477 mμ. The red pigment showed no distinct maxima, but a general absorption throughout the range between these two regions.

A search was made for a more satisfactory method for separating the pigments and calcium carbonate, magnesium carbonate and aluminum oxide were found to be better than magnesium oxide. Benzene, ether, and carbon disulfide gave no better results than benzine. However, good separation was obtained in a magnesium oxide column by washing with benzine containing a small quantity of absolute alcohol. The pigments in the carotene

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[1] Published with the approval of the director of the Wisconsin Agricultural Experiment Station.

[2] Virtanen, *Biochem. Z.*, **258**, 251 (1933).

[3] Peterson, Bohstedt, Bird and Beeson, *J. Dairy Science*, **18**, 63 (1935).

[4] Peterson, Bird and Beeson, *ibid.*, **20**, 611 (1937); Shinn, Kane, Wiseman and Cary, *J. Biol. Chem.*, **119**, lxxxix (1937).

[5] Willstätter and Stoll, "Untersuchungen über Chlorophyll. Methoden und Ergebnisse," Verlag von Julius Springer, Berlin; Wiseman and Kane, *J. Biol. Chem.*, **114**, cviii (1936).

fraction from silage separated into six major bands in addition to those of γ- and β-carotene. There were also some minor bands but these contained insufficient pigment for characterization. For convenience the six major bands were given the alphabetical designations, A to F.

The method finally adopted for separating the pigments was as follows. The benzine solution was forced into a uniformly packed column of magnesium oxide by means of air or nitrogen under a pressure of 1 to 1.5 atmospheres. The chromatogram was washed with benzine until the carotene bands had separated from the other pigments. Washing was then continued with a mixture of absolute ethanol (1% by volume) in benzine until bands A, B, and C had clearly separated and the carotene bands had passed out of the column. By increasing the alcohol to 2%, bands, D, E, and F were separated and bands, A, B, and C were eluted consecutively. Bands D, E, and F were eluted by increasing the concentration of alcohol, first to 3% and then to 5%. When the several eluates were collected and their extinction coefficients measured (475 mμ), it was found that less than 10% of the total pigment had been lost. A diagram of a typical chromatogram obtained with the carotene fraction from A. I. V. alfalfa silage is shown in Fig. 1.

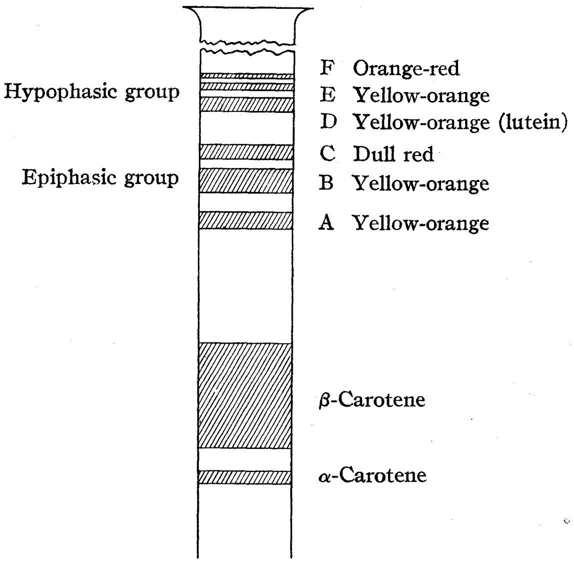

Fig. 1.—Diagram of a magnesium oxide chromatogram showing the chief carotenoid bands obtained from A. I. V. alfalfa silage.

Properties of the Pigments.—Besides occupying different positions in the chromatogram, the six pigments exhibited dissimilarities in color, spectral absorption, and phasic distribution. In the magnesium oxide column, pigments A, B, D, and E were a deep yellow, pigment C a dull brick-red, and pigment F an orange-red. In dilute benzene solution pigments A, B, D, and E were greenish-yellow and pigments C and F were reddish.

Pigments A, B, D, and E gave absorption bands which were essentially identical in form and in position of their maxima; all conformed to published data for lutein. Pigment C gave an abnormally wide absorption band which was highest in the region between 448 and 476 mμ (in benzine) but without any distinct maximum. On the other hand pigment F exhibited two distinct, though not sharp, maximal absorption bands. The absorption values of the pigments in three different solvents are given in Table II.

TABLE II

REGION OF MAXIMAL SPECTRAL ABSORPTION OF THE SIX PIGMENTS FROM ALFALFA SILAGE

Pigment	Solvent CS_2	$CHCl_3$	Benzine
A	475–476 506	457 486–487	447 477
B	475–476 506	457 486–487	447–448 477
C	480–504	457–486	448–476
D	475–476 506	456–457 486–487	447–448 477
E	476 506	457 487	447–448 476–477
F	477–484 502–509	457–464 486–491	449–453 478–481

The phasic distribution of the six pigments was especially significant. Pigments A, B, and C were distinctly epiphasic, while D, E, and F were hypophasic to the same degree. Their percentage distribution as shown in Table III was obtained by shaking the benzine solutions of the individual pigments, in similar concentrations (having equal extinction coefficients), with equal volumes of 85% ethanol.

TABLE III

PHASIC DISTRIBUTION OF THE PIGMENTS BETWEEN BENZINE AND 85% ETHANOL

(Expressed in per cent. of total)

	Isolated from silage		Obtained from lutein by acid treatment	
Pigment	Benzine	85% EtOH	Benzine	85% EtOH
A	81	19	79	21
B	84	16	79	21
C	81	19	^{a}	^{a}
D	22	78	21	79
E	23	77	22	78
F	22	78	..	..

[a] Only a trace; insufficient for measurements.

In the hope of obtaining the epiphasic pigments in crystalline condition, the carotene fraction from 10 kg. of acidified alfalfa was fractionated chromatographically. The resulting benzine–alcohol eluates of pigments A, B, and C were concentrated to small volumes and allowed to stand in a refrigerator for several weeks. Although these solutions were many times more concentrated than a saturated solution of β-carotene, the pigments failed to crystallize. Attempts to crystallize them from ethanol, benzene plus methanol, and carbon disulfide were likewise unsuccessful.

Origin of the Pigments.—The apparent increase in the carotene content of alfalfa silage prepared with mineral acids was accompanied by a decrease in xanthophyll (Table I). This suggested that the new pigments were formed from the xanthophyll pigments by the action of acids. When the crude xanthophyll fraction from untreated alfalfa was refluxed with acid as is done in extracting silage, the solution was almost completely decolorized. When an acidified solution of the crude xanthophyll, 0.1 *N* hydrochloric acid in 85% ethanol, was held at 45–50° overnight, its extinction coefficient decreased 25%. When this solution was made slightly alkaline with potassium hydroxide (in 85% ethanol) and shaken with benzine 65% of the pigment passed into the benzine phase. A control sample of crude xanthophyll lost none of its color when subjected to the same treatment except for the addition of acid, and only 17% of the pigment passed into the benzine phase.

To determine the effect of acid on lutein, pure lutein was prepared from fresh green alfalfa by two successive adsorptions on magnesium oxide from alcohol–benzine mixtures. The second eluate produced typical lutein crystals. When these were dissolved in 85% ethanol, the resulting solution showed a value $E^{1\ \mathrm{cm.}}_{475} = 4.0$. This is equivalent approximately to 0.20 mg. of lutein per cc. Ten-cc. portions of this solution were set aside at 45–50° in the dark, for fourteen hours, after the addition of various acids. The solutions were then made slightly alkaline with potassium hydroxide, and each was adjusted to a volume of 20 cc. with 85% ethanol, and shaken with 20 cc. of benzine. When equilibrium was attained, the percentage distribution between the two solvents was determined spectrophotometrically. That the stronger acids produced marked changes in the solubility of the pigment was shown by the values obtained for the benzine phase (Table IV). The values for the 85% ethanol phase represent the difference between these figures and 100.

TABLE IV

EFFECT OF VARIOUS ACIDS UPON LUTEIN

Sample	Normality and kind of acid	% of pigment remaining after treatment	% of remaining pigment found in the benzine phase	Chromatographic distribution of pigments after treatment (Total pigment remaining = 100% in each case)			
				A	B	D	E
1	None	100	20			100	
2	*N*/40 acetic	80	24	10	Trace	90	
3	*N*/40 lactic	98	38	28	5	62	5
4	*N*/40 oxalic	98	71	69	17	7	7
5	*N*/40 H_2SO_4	75	70	56	36	6[a]	
6	*N*/80 HCl	57	65	60	18	16[a]	
7	*N*/40 HCl	65	69	60	25	11[a]	
8	*N*/20 HCl	65	71	51	32	12[a]	
9	*N*/5 HCl	31	72	6	74	Trace	Trace

[a] Pigments from bands D and E combined.

The chromatogram yielded not less than three and in some cases five well-defined bands which in their position and appearance resembled strikingly the bands obtained from silage. Treatment with acetic acid produced bands A, B, and D. All other acids produced one additional band, E, and in two cases a fifth band, C. Lutein subjected to all the manipulations except acidification retained its chromatographic behavior unchanged.

The individual pigments were collected quantitatively as they were eluted from the chromatogram. The extinction coefficient and solution volume were then measured for each fraction. From these data the percentage of each pigment in the sample was calculated (Table IV). Care was taken to maintain a fairly constant volume of eluate, and to make the spectrophotometric readings with solution depths which would give log I/I_0 values very close to 0.50. Close agreement was then obtained between the values for total pigment before and after separation.

The phasic distribution and spectral absorption of pigments A, B, D, and E obtained from lutein were found to be identical with those of the corresponding pigments found in silage (Tables II and III).

Pigment D proved to be residual lutein. When the various D-fractions from all of the samples were combined and analyzed chromatographically, the pigment remained almost quantitatively in a single band; other pigments appeared only in traces. When a sample of lutein was mixed with the purified pigment D, and a chromatogram prepared, again a single band appeared. However, when pure lutein was mixed with any of the other three purified pigments, *viz.*, A, B, and E, two bands appeared in the chromatogram. Analyzed separately each produced a single band.

From the various data which have been presented it is concluded that pigments A, B, and E are derived from lutein by the action of acids. The origin of pigments C and F has not as yet been clearly ascertained.

Occurrence and Distribution of the Acid-derived Pigments.—When it was found that the acid-derived pigments could be extracted from freshly acidified alfalfa, the question arose as to whether they were products of ensiling or artifacts formed during extraction under acid conditions. To determine this a sample of alfalfa silage was made slightly alkaline with potassium hydroxide before extraction and its carotenoids were compared with those extracted from silage in the usual way, *i. e.*, without alkalization. The epiphasic fractions from these two extracts were found to contain equal quantities of total pigment, and the chromatograms from both fractions contained the eight bands previously described (Fig. 1).

It is evident from the results presented in Table IV that mineral acids are more effective than lactic or acetic acid in converting lutein to pigments A and B. It might be predicted that a carotene fraction from silage produced by a natural lactic acid fermentation would contain a relatively higher percentage of true carotene than that from silage prepared with mineral acids. This was found to be the case (Table V). Only 57% of the pigment in the carotene fraction from the A. I. V. silage was found in the carotene

TABLE V

RELATIVE PROPORTIONS OF THE CAROTENOID PIGMENTS IN ALFALFA FORAGE FOLLOWING VARIOUS TREATMENTS OF IDENTICAL MATERIAL

Sample	Percentage distribution: Epiphasic pigments				Hypophasic	Recovery after chromatographic separation, %
	Carotene	A	B	C	D + E + F	
Oven-dried alfalfa	85	..	..	..	15 (D only)	...
A. I. V. alfalfa silage—total pigments	38	7	14	4	37	90
A. I. V. alfalfa silage—carotene fraction	57	9	19	5	10	100
Molasses alfalfa silage—total pigments	50	4	7[a]		39	96
Molasses alfalfa silage—carotene fraction	75	5	9[a]		11	101

[a] Pigment from bands B and C combined.

bands of the chromatogram as compared with 75% for the naturally fermented silage.

Since silages constitute a considerable part of the ration of the dairy cow, it is important to know whether the acid-derived pigments are present in butter fat produced on such rations. Four samples of butter fat which have been analyzed contained such pigments. Gillam and Heilbron[6] have reported that the chief carotenoids in butter fat are carotene, kryptoxanthin and lycopene. The presence of kryptoxanthin was confirmed, but lycopene was not detected in our samples.

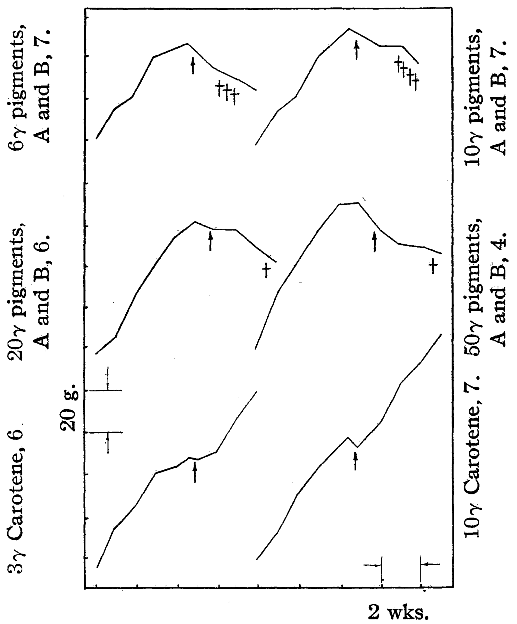

Fig. 2.—Growth curves of rats which received β-carotene and pigments A and B.

Biological Assay of the Epiphasic Pigments, A and B.—The epiphasic pigments, A and B, were tested for vitamin A activity before our technique for chromatographic fractionation had been fully developed. The tests were made on a mixture of the two pigments in which pigment A was present in somewhat larger amounts than pigment B. The assays were executed essentially according to the technique of Baumann and Steenbock.[7] The control rats were fed pure β-carotene separated chromatographically from extracts of fresh green alfalfa. To facilitate convenient dosage the pigments were incorporated in Wesson oil by evaporating their concentrated benzine solutions with the oil under reduced pressure. Resumption of growth, cure of ophthalmia, and the production of normal vaginal smears were employed as criteria of vitamin A activity. The β-carotene was fed at levels of 3 and 10 gamma daily. The mixture of pigments A and B was fed at levels equivalent to 6, 10, 20 and 50 gamma of β-carotene based on the extinction coefficients of their solutions. While the feeding experiments were in progress the oil solutions were checked for deterioration from time to time by spectrophotometric methods.

The data show clearly that the epiphasic pigments, A and B, could not function as precursors of vitamin A (Fig. 2). While the daily administration of 3 gamma of β-carotene restored growth and normal oestrus and cured the ophthalmia completely, even the highest dosage with pigments A and B, equivalent to 50 gamma of β-carotene, failed to restore even normal oestrus.

Discussion

When the separation of the non-carotene pigments into six distinct bands was first observed, its significance was viewed with some suspicion. It was well known that certain extraneous substances can affect the distribution of pigments in a chromatogram. Furthermore, it has been reported[8] that carotenes may undergo profound changes during chromatographic adsorption. However, the possibility that the pigments were of chromatographic origin is not supported by the experimental evidence. The non-carotene portion of the chromatogram from silage was unlike that from fresh alfalfa. When the chromatogram from alfalfa was washed with benzine–alcohol mixtures, bands A, B, and C failed to make their appearance; practically all of the pigment remained in band D. Also, after the initial separation, each of the new pigments gave a single characteristic band when chromatographed by itself. And, finally, besides differing in their chromatographic behavior, the individual pigments showed other differences in physical properties, *e. g.*, solubility and in some cases spectral absorption.

It is probable that Kuhn, *et al.*,[9] dealt with a mixture of pigments A, B, D, and E when they treated lutein with oxalic acid. The severity of their treatment was not markedly different from ours, for while they used a lower concentration of acid they employed a higher temperature. Although they did not differentiate their resultant pigment from lutein in its chromatographic behavior or spectral absorption, it was distinctly more epiphasic than lutein. We likewise did not succeed at once in separating our pigments from lutein chromatographically although we used a number of adsorbents and solvents. It was only later through a fortunate choice of mixtures of solvents that we were able to effect a good separation.

It is evident that the pigments derived from lutein are the chief cause of the abnormal caro-

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[6] Gillam and Heilbron, *Biochem. J.*, **29**, 834 (1935).

[7] Baumann and Steenbock, *Science*, **76**, 417 (1932).

[8] Gillam and El Ridi, *Biochem. J.*, **30**, 1735 (1936).

[9] Kuhn, Winterstein and Lederer, *Z. physiol. Chem.*, **197**, 141 (1931).

tene values reported for A. I. V. silage. The extent to which the apparent carotene values differ from the true values is dependent on such factors as strength of acid used, lutein content of the forage, temperature of the silage and period of ensiling. While the usual method of analysis may give carotene figures that are nearly twice the true values for A. I. V. silage, too high results are also obtained in the analysis of silages made by normal fermentation processes. The need for a more reliable method of determining carotene in these silages is obvious.

Chromatographic data on butter indicate the presence of the same pigments as those found in silage. Although the amount of these new pigments has not been determined, their presence points to the need of more information regarding the value of acid-preserved silages for increasing the vitamin A potency of milk.

Summary

Five new carotenoids, designated as pigments A, B, C, E, and F, have been obtained from alfalfa silage and from acidified fresh alfalfa. They were not present in untreated forage. Dilute solutions of A, B, and E in benzine were greenish-yellow and those of C and F were reddish.

The pigments were partially fractionated by their phasic distribution between benzine and 85% ethanol; A, B, and C were epiphasic, E and F were hypophasic. Quantitative separation was effected by use of the magnesium oxide chromatogram and elution with benzine-alcohol mixtures. The bands of A, B, and C formed below that of lutein; those of E and F above it. The pigments were eluted from the column in the alphabetical order given by gradually increasing the percentage of alcohol in the solvent. Spectral absorption of the pigments was markedly less valuable for differentiation than chromatographic behavior. Absorption curves of A, B, and E were essentially the same as those of lutein; those of C and F showed no well-defined maxima.

A high order of solubility in the usual carotenoid solvents was shown by A, B, and C. Attempts to effect their crystallization were not successful.

A, B, and E were produced from lutein in large amounts by treatment with either 0.025 hydrochloric or sulfuric acid, and in smaller amounts with 0.025 *N* lactic and acetic acids. The stronger acids favored the production of B; weaker acids the production of A. The origin of C and F was not clearly established.

Inasmuch as the usual methods of carotene analysis fail to differentiate between carotene and pigments A, B, and C, values obtained by these methods on silages, especially those prepared with mineral acids, are obviously too high.

When fed to vitamin A deficient rats, A and B exhibited no biological activity. Both pigments were found in butters produced by cows on A. I. V. silage.

MADISON, WIS. RECEIVED AUGUST 27, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

Researches on Pyrimidines. CLIX. Synthesis of 6-Benzyl- and 5-Benzyluracils[1]

BY TREAT B. JOHNSON AND JOSEPH C. AMBELANG[2]

One conclusion predictable from an examination of the skeleton structure of the pyrimidine cycle as represented by formula II, is the existence of two interdependent zones of chemical activity which envelop the pyrimidine molecule. Each of these zones is characterized by its encompassment of a specific organic structure. Zone "A" includes the unsaturated amidine portion of the pyrimidine cycle, while zone "B" incloses the cyclic allyl structure of the molecule. Any alteration or tautomeric change in the specific, unsaturated structure embraced by one zone necessarily leads to a corresponding change in the constitution of the grouping in the other, and also its chemical reactivity. In other words, we are dealing with a dual system of reactions in our study and development of pyrimidine chemistry and if tautomeric structures be accepted for these unsaturated cyclic groupings in the different zones, as theory provides, positions 1 and 3 included in zone "A" and positions 4 and 6 in zone "B," respectively, are identical.

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(1) Constructed from a portion of a dissertation presented by Joseph C. Ambelang, in June, 1938, to the Graduate Faculty of Yale University in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

(2) Sterling Professorship of Chemistry Research Assistant 1938–1939.

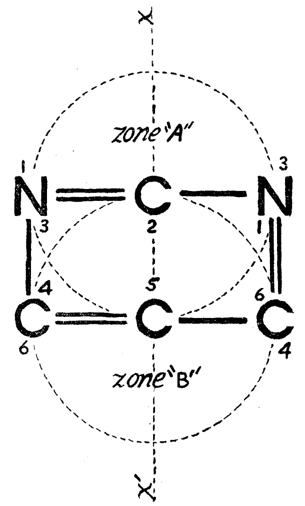
These conclusions lead to the recognition of an unique symmetry of the pyrimidine cycle characterized by an axis of symmetry (x-x') passing through the two permanent numerical positions of the ring, namely, 2 and 5. It is an interesting fact that in the pyrimidine portion of the constitutional formula of the vitamin B_1 molecule (thiamine), this axis of symmetry (x-x') prevails, and constitutes a chain of four carbon atoms as represented in formula I. This chain includes the two permanent positions of the pyrimidine moiety (2 and 5).

$$C—\overset{2}{C}\cdots\cdots\cdots\cdots\overset{5}{C}—C$$

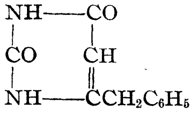
I

It might be predicted, therefore, on the basis of this knowledge and reasoning that the reactivity of a substituent grouping in position 5 of the pyrimidine ring would be dependent on, or influenced in some degree by, the character of the group or radical attached to the carbon in position 2. Such a postulation has already been supported by experimental data. In fact, we already have a knowledge of chemical reactions applicable to pyrimidine compounds, which are specific for the two zones of influence, "A" and "B," and permit us to confine our attack to either zone independently, without involving the grouping characteristic of the other. This dual system of reactions has also been revealed by researches on the chemistry of purines.[3]

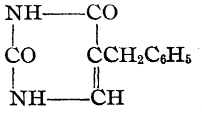
In the light of our previous knowledge from researches in this Laboratory, and under guidance of the above speculations, it became of great interest to the authors to learn more about structural differences influencing the degree of reactivity of organic groupings functioning in the pyrimidine ring and occupying particularly positions 5 and 6 or 5 and 4 in zone "B" (formula II) of the pyrimidine molecule. It was, therefore, decided to incorporate a new series into our researches, and to synthesize first for study the two isomeric benzyluracils, namely, 6-benzyluracil and 5-benzyluracil as represented by formulas III and IV, respectively. Neither compound has been described previously in the literature. The methods of synthesis and a description of several intermediates and new derivatives are presented in the experimental part of this paper. In a future publication the authors will discuss some interesting results obtained by catalytic reduction of these two isomeric uracil derivatives III and IV.



II



III



IV

Experimental Part

Preparation of 2-Thio-6-benzyluracil

$$\overline{NH—CS—NH—C(C_7H_7){=}CH—CO}$$

Method 1.—Ten grams (0.05 mole) of ethyl phenylacetylacetate (ethyl γ-phenylacetoacetate) was mixed intimately with 3.7 g. (0.05 mole) of thiourea and 10 drops of concentrated hydrochloric acid. After standing for one week in a stoppered flask, the suspension was transferred to an open dish and dried *in vacuo* over concentrated sulfuric acid. The desiccated product was then refluxed for two hours with 9 g. of potassium hydroxide in 33 g. of absolute alcohol and the solution finally concentrated at 100°, until encrustation appeared. On acidifying with hydrochloric acid this pyrimidine separated as an oil which soon solidified. It was purified by crystallization from 95% alcohol and melted at 222–223°. The yield was only 9% of the theoretical. This method of synthesis has been applied previously by Sonn and Litten[4] but with no mention of yields obtained. They assigned a melting point of 216–219° to the compound. No attempt was made by them to desulfurize the pyrimidine. This reaction very probably involves first the formation of the intermediate ureide $C_6H_5CH_2COCH_2CONHCSNH_2$, which is then closed up to the pyrimidine by the action of the alkali.

Method 2.—Thiourea (52 g.) and ethyl phenylacetylacetate (140 g.) were dissolved in a cooled solution of sodium ethylate (0.68 mole of sodium in 495 g. of absolute alcohol) and the mixture heated on a steam-bath for four hours. The excess of alcohol was then removed by evaporation and the residue dissolved in 125 cc. of water. Acidification of the cooled solution with hydrochloric acid led to the precipitation of the desired thiopyrimidine in a

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(3) Consult Gilman's "Organic Chemistry," Vol. II, Chapter 11, "Chemistry of Pyrimidines, Purines and Nucleic Acids," by T. B. Johnson, John Wiley and Sons, Inc., New York, N. Y., 1938.

(4) Sonn and Litten, *Ber.*, **66**, 1518 (1933).

yield of 37%. It was purified by crystallization from 95% alcohol and melted at 222–223°. This pyrimidine is soluble in aqueous ammonia and hot glacial acetic acid; moderately soluble in hot alcohol and acetone, slightly soluble in water and insoluble in benzene, ether, chloroform, and carbon bisulfide.

Anal. Calcd. for $C_{11}H_{10}ON_2S$: N, 12.84. Found: N, 12.85, 12.95.

$NH—C(SC_2H_5)=N—C(C_7H_7)=CH—CO$, **2-Ethyl-thio-6-benzyl-4-oxypyrimidine.**—A solution of 9 g. of pseudo-ethylisothiourea hydrobromide in 10 cc. of water was mixed with 10 g. of ethyl phenylacetylacetate, and to the mixture was added 5.5 g. of potassium hydroxide dissolved in 8 cc. of water. After standing at ordinary temperature overnight the solution was acidified with acetic acid when the above mercaptopyrimidine separated in a yield of 28%. It was purified by crystallization from methyl alcohol and melted at 128–129°. This compound is soluble in ethyl alcohol, glacial acetic acid, acetone, benzene, chloroform and boiling carbon bisulfide; moderately soluble in ether, and insoluble in aqueous ammonia.

Anal. Calcd. for $C_{13}H_{14}ON_2S$: N, 11.38. Found: N, 11.52, 11.56.

6-Benzyluracil, $NH—CO—NH—C(C_7H_7)=CH—CO$. —This pyrimidine is prepared easily as follows: (1) by digestion of 2-thio-6-benzyluracil with 10% chloroacetic acid; and (2) by hydrolysis of the corresponding 2-ethylthio derivative with hydrochloric acid. The pyrimidine was purified by crystallization from glacial acetic acid or 95% alcohol and melted at 261–262°. It is soluble in warm acetic acid and in aqueous ammonia; moderately soluble in acetone, hot alcohol; slightly soluble in hot water, and insoluble in ether, benzene, chloroform and carbon bisulfide.

Anal. Calcd. for $C_{11}H_{10}O_2N_2$: C, 65.32; H, 4.98; N, 13.86. Found: C, 65.16, 65.34; H, 4.98, 4.90; N, 13.80, 13.85.

$NH—CO—NH—C(C_7H_7)=CBr—CO$, **6-Benzyl-5-bromouracil.**—6-Benzyluracil is attacked by bromine in glacial acetic acid at 40–50° with substitution in the pyrimidine ring giving this monobromo substitution product. The compound was purified easily by crystallization from glacial acetic acid and melted at 230–232°. The pyrimidine is soluble in warm glacial acetic acid, acetone, and aqueous ammonia, and insoluble in water, ether, benzene, and chloroform.

Anal. Calcd. for $C_{11}H_9O_2N_2Br$: N, 9.97. Found: N, 9.97, 10.00.

That the bromine is substituted in the pyrimidine ring and not in the aromatic nucleus of the benzyl group substituted in position-6 was shown as follows: 1 g. of the bromopyrimidine was oxidized by refluxing it in hot water with barium permanganate (0.0059 mole) and barium hydroxide. After complete discoloration of the permanganate the alkaline solution was filtered, and then concentrated to a volume of 20 cc. and cooled. On acidifying with hydrochloric acid colorless benzoic acid deposited and melted, after crystallization from hot water, at 121–122°.

Chlorination of 6-Benzyluracil in Methyl Alcohol

$NH—CO—NH—C(OCH_3)(C_7H_7)—C(Cl_2)—CO$,[5] **Formation of 2,4-Diketo-6-benzyl-6-methoxy-5,5-dichlorohexahydropyrimidine.**—Chlorine gas was passed into an ice-cooled suspension of 0.5 g. of 6-benzyluracil in 30 cc. of methyl alcohol until the pyrimidine dissolved. The cold reaction mixture was then exposed to a blast of air to remove the alcohol and excess of chlorine and the residue allowed to dry. We obtained 0.6 g. of the above hexahydropyrimidine, which was purified by crystallization from methyl alcohol, or a mixture of chloroform and carbon tetrachloride. It melted at 157–159° with decomposition. This pyrimidine is soluble in glacial acetic acid, acetone, ether, and chloroform; and slightly soluble in warm benzene, hot water, and insoluble in petroleum ether.

Anal. Calcd. for $C_{12}H_{12}O_3N_2Cl_2$: N, 9.24. Found: N, 9.20, 9.17.

This pyrimidine is not changed by exposure to pyridine. Two grams was dissolved in 20 cc. of pyridine and the solution allowed to stand for one week. It had assumed a greenish fluorescence. After volatilizing the pyridine a sirup was obtained which deposited crystals on treatment with water. This solid was identified as the original hexahydropyrimidine, and after crystallization from dilute methyl alcohol melted at 160–162°.

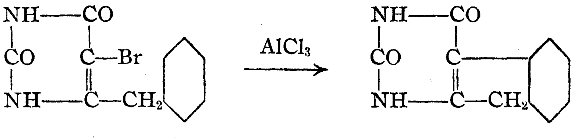
Anal. Calcd. for $C_{12}H_{12}O_3N_2Cl_2$: C, 47.54; H, 3.99; N, 9.24. Found: C 47.62; H, 3.64; N, 9.57.

$NH—CO—NH—C(C_7H_7)=C(Cl)—CO$, **Action of Hydrobromic Acid on the above Hexahydropyrimidine. Formation of 6-Benzyl-5-chlorouracil.**—This change is brought about by digesting the hexahydropyrimidine (1 g.) in glacial acetic acid (25 cc.) with constant boiling hydrobromic acid (2 cc.). After boiling for two hours the acid solution was poured into water when the above chlorouracil derivative separated. It was purified by crystallization from dilute acetic acid and melted at 266–267°.

Anal. Calcd. for $C_{11}H_9O_2N_2Cl$: N, 11.84. Found: N, 12.02.

This same chloropyrimidine is formed in poor yield by passing chlorine gas into a suspension of 6-benzyluracil in 10% acetic acid.

Attempted Cyclization of 6-Benzyl-5-bromouracil:



one and five-tenths grams of 6-benzyl-5-bromouracil and 1.5 g. of aluminum chloride were dissolved by stirring in 50 cc. of nitrobenzene. After standing for four hours at room temperature and two hours at 50° the solution was then poured into ice water. The nitrobenzene was removed by steam distillation and the insoluble residue left behind purified by crystallization from dilute acetic acid. We recovered 1.4 g. of the unaltered bromopyrimidine melting at 232–233°.

Preparation of $C_6H_5CH_2CH_2COOC_2H_5$, Ethyl Hydrocinnamate.—A quantitative yield of this ester was pre-

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[5] See Johnson and Sprague, THIS JOURNAL, **60**, 1622 (1938).

pared for our research by reduction of ethyl cinnamate in the presence of Raney nickel catalyst.[6] Eighty grams of the cinnamic ester was diluted with ethyl alcohol to a volume of 100 cc., the mixture transferred to a copper liner of an autoclave, and after addition of 3 g. of the nickel catalyst was subjected to 120 atmospheres of hydrogen at room temperature. After twenty minutes of shaking the observed drop in pressure corresponded to the absorption of 0.5 mole of hydrogen. The purified ester boiled at 104–105° at 3 mm. and at 245° under atmospheric pressure.

Formation of the Sodium Salt of Ethyl-formyl 3-Phenylpropionate.[7]—A mixture of 178 g. (1 mole) of ethyl hydrocinnamate and 81 g. (1.1 mole) of ethyl formate was added slowly over a period of twenty hours to 23 g. of sodium wire suspended in 500 cc. of anhydrous ether. The excess of ether was then distilled off *in vacuo* at room temperature and the crude salt of the resulting formyl derivative used for the following reaction.

Formation of $\mathrm{NH{-}CS{-}NH{-}CH{=}C(C_7H_7){-}CO}$, **2-Thio-5-benzyluracil.**—The crude sodium salt from the preceding preparation and 50 g. of pulverized thiourea were added to 350 g. of absolute alcohol and the mixture then refluxed at 100° for four hours. The excess of alcohol was then evaporated, the crude reaction product dissolved in 500 cc. of cold water and the aqueous solution acidified with hydrochloric acid. Sixty-eight grams of the above pyrimidine separated. It was purified by crystallization from ethyl alcohol and melted at 210–211°. This pyrimidine is soluble in aqueous ammonia, glacial acetic acid, and acetone, moderately soluble in hot ethyl alcohol; slightly soluble in hot water and insoluble in ether, chloroform and benzene.

Anal. Calcd. for $C_{11}H_{10}ON_2S$: N, 12.84. Found: N, 12.83, 12.76.

5-Benzyluracil, $\mathrm{NH{-}CO{-}NH{-}CH{-}C(C_7H_7){-}CO_2}$.—This pyrimidine is formed by digesting the above 2-thiopyrimidine with 10% chloroacetic acid. It was purified by crystallization from glacial acetic acid and melted at 294–295°. The pyrimidine is soluble in aqueous ammonia, slightly soluble in dioxane, acetone, ethyl alcohol and hot water, and insoluble in chloroform, ether and benzene.

Anal. Calcd. for $C_{11}H_{10}O_2N_2$: C, 65.32, H, 4.98; N, 13.86. Found: C, 65.18, 65.61; H, 4.90, 4.95; N, 13.77, 13.82.

$\mathrm{NH{-}CO{-}NH{-}CH(OCH)_3{-}C(Cl)(C_7H_7){-}CO}$, **2,4-Diketo-6-methoxy-5-benzyl-5-chlorohexahydropyrimidine.**—Chlorine gas was bubbled into an ice-cooled suspension of 5-benzyluracil (1 g.) in methyl alcohol (50 cc.) until the pyrimidine practically dissolved. The alcohol solution was then exposed to a blast of air to remove the excess of solvent and chlorine gas when we obtained 1 g. of this hexahydropyrimidine. It was purified by crystallization from methyl alcohol. This pyrimidine showed a characteristic double melting point, melting first at 217–218°, then solidifying and melting finally at 232–234°. It was soluble in acetone and glacial acetic acid, and insoluble in ether and benzene.

Anal. Calcd. for $C_{12}H_{13}O_3N_2Cl$: N, 10.34. Found: N, 10.59, 10.70.

When this pyrimidine was digested with hydrobromic acid in glacial acetic acid it was converted into 5-benzyluracil melting at 292–294°.

Summary

1. 2-Thio-6-benzyluracil and 2-thio-5-benzyluracil have been synthesized.

2. These two isomeric pyrimidines are desulfurized by digestion with chloroacetic acid giving smoothly 6-benzyluracil and 5-benzyluracil.

3. 6-Benzyluracil is attacked by bromine in glacial acetic acid solution with formation of the corresponding 5-bromo derivative.

4. Both 6-benzyl- and 5-benzyluracil are attacked normally by chlorine in wood alcohol giving hexahydropyrimidines. The chlorination is confined entirely to zone "B" of the pyrimidine molecule.

NEW HAVEN, CONN.

RECEIVED OCTOBER 4, 1938

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(6) Adkins, *Ind. Eng. Chem., Anal. Ed.*, **4**, 342 (1932); Covert and Adkins, THIS JOURNAL, **54**, 4116 (1932).

(7) Phalnikar and Nargund, *J. Univ. Bombay*, **4**, 106 (1935); *Chem. Zentr.*, **107**, I, 4556 (1936).

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF CORNELL UNIVERSITY]

Colloid Chemistry of Leaf and Flower Pigments. II. Qualitative Analysis of Leaf Pigments[1]

BY WILDER D. BANCROFT AND JOHN E. RUTZLER, JR.

In spite of all the work that has been done on plant pigments, nobody seems to have worked out any quick and easy method of identifying qualitatively the types of pigments occurring in leaves and flowers. The late Mrs. Onslow[2] says that no such thing is possible.

Even if Mrs. Onslow's pessimistic view were right—which we do not admit—we believe that a poor system of qualitative analysis would be better than none at all. Our experience convinces us that such a system will bring to light many interesting facts that have been overlooked in the past. Nobody knew, for instance, that leuco-anthocyanins are present in the leaves of the sugar maple in July but not in May. A careful study of this system will show whether flavone-like substances are or are not the precursors of leuco-anthocyanins in this plant. We[3] have been using our system of qualitative analysis successfully in determining the precursors of anthocyanins in specific cases.

It is for these and other reasons that we are presenting a preliminary system of qualitative analysis of leaf pigments. We do not know the limits of accuracy and there are cases in which the proposed scheme does not function well owing to excessive adsorption. It has worked well for us so far, and we are presenting it for consideration and criticism. Most of the data were available in the literature and we have merely arranged and checked them. We have been using the method for over three years and have found it helpful.

Unless otherwise stated all leaves are used fresh and are shredded by hand, although the scheme of analysis also works when dry leaves are employed. Such terms as carotenes, xanthophylls, flavones, anthocyanins, anthocyanidins and leuco-anthocyanins, are used generically and refer to any or all of the pigments grouped under any one head and not necessarily to any single pigment. It would probably be wiser to extract in some cases in an oxygen-free atmosphere and in the dark, but these precautions were not taken and may be considered as future refinements, which may be of importance when studying the flavones and leuco-anthocyanins.

Recommended Method of Qualitative Analysis

1. **Tests for flavones, leuco-anthocyanins, anthocyanins and anthocyanidins** are made by treating the shredded leaves with a 2–10% solution of formic acid, extracting by heating in boiling water if no pink or red color appears in the cold extract after from six to twenty-four hours. The solution may be colorless, pale yellow, red or pink. If colorless or pale yellow, no anthocyanins or anthocyanidins are present. Addition of aqueous ammonia or aqueous caustic soda causes a marked deepening of the yellow color if flavones are present. If the stronger formic acid causes a visible decomposition of the chlorophyll, this must be taken into account.

In a few cases with yellow autumn leaves, notably with those of the dogwood before it turns pink, the formic acid solution is yellow and the color does not deepen appreciably on adding ammonia. If enough ether is added to make a second liquid layer, the yellow goes to a considerable extent, sometimes completely, into the ether layer. This means that flavones are present at most in small amounts. The yellow color is due chiefly to what Tswett[4] calls "water-soluble yellow pigments of unknown constitution." Since the organic chemists have not yet determined how many of these there are or what their special properties are, it is impossible at present to differentiate them.

A pink or red color in the formic acid solution denotes anthocyanins, anthocyanidins or both, either accompanied or unaccompanied by flavones. If the solution is colorless with cold extraction and pink, red or brownish-red when extracted hot, practically all of the pink or red pigment was present in the leaf as leuco-anthocyanins. In such a case it is more satisfactory to heat the shredded leaves on the water-bath in a 5–10% sulfuric acid solution. With a strong acid, hydrolysis takes place rapidly and it is only necessary to heat for fifteen minutes to an hour to get a good test. In cases of doubt it is desirable to add butyl alcohol to the cooled solution. The red pigment concentrates in the butyl alcohol layer and becomes conspicuous.

To determine the presence of anthocyanins and anthocyanidins in the pink formic acid solution, add isoamyl alcohol to the pink solution and dilute gradually with water. If the isoamyl alcohol extracts practically all the pink color from dilute acid solution, the pigments are anthocyanidins and not anthocyanins. This case occurs rarely except when one has broken down a leuco-anthocyanin. If the isoamyl alcohol extracts practically no pink color, the pigments are anthocyanins. If both layers become pink, continued extraction with isoamyl alcohol may be done until one or the other of the layers becomes practically colorless. Willstätter and Everest[5] recommend

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[1] Original manuscript received December 13, 1935.

[2] Onslow, "The Anthocyanin Pigments of Plants," 1925, p. 49.

[3] Bancroft and Rutzler, THIS JOURNAL, **60**, 2738 (1938).

[4] Palmer, "Carotinoids and Related Pigments," 1922, p. 63.

[5] Willstätter and Everest, *Ann.*, **401**, 207 (1913).

washing the amyl alcohol layer with dilute sulfuric acid.

To determine flavones in the presence of anthocyanins, shake the pink formic acid solution with ether. Remove the practically colorless ether layer and add aqueous ammonia or caustic soda to it. A yellow color in the water layer denotes the presence of flavones. Anthocyanidins do not interfere with this test, and leuco-anthocyanins do not go into the ether layer. If the ether layer is yellow and the color goes only partly into the water layer on adding aqueous ammonia or caustic soda, Tswett's "water-soluble yellow pigments of unknown constitution" must be present along with flavones.

If the amyl alcohol test for anthocyanidins is negative, the amyl alcohol layer may be removed and tested for flavones with aqueous ammonia or aqueous caustic soda. Anthocyanidins interfere with this test.

Anthocyanins are glycosides and anthocyanidins are the corresponding sugar-free pigments. So far as we now know, anthocyanidins occur only very rarely as such in plants. A test for them is desirable, partly because it is not uncommon for chemists accidentally to convert anthocyanins into anthocyanidins in the laboratory, and partly because anthocyanidins may occur more often than we now realize in autumn leaves whose red color is due to decomposition of leuco-anthocyanins.

2. **Tests for carotenes and xanthophylls** can be made more rapidly if the leaves are air-dried or vacuum-dried. It is safer, but not necessary, to use the leaves that have been extracted with the formic acid solution, because that eliminates any possible confusion over flavones and water-soluble yellows. Treat air-dried leaves with a low-boiling petroleum ether or with a so-called heptane, 90–100°. A little chlorophyll dissolves, so a greenish-yellow denotes presence of carotenes or xanthophylls or both. The green can be removed, if desired, by letting the solution stand in contact with aqueous hydrochloric acid. Add 90–95% methyl alcohol to the petroleum ether or heptane solution. Xanthophylls go into the methyl alcohol layer and carotenes stay in the upper layer. If both are present, the extraction should be continued until one or the other layer becomes practically colorless.

3. **Tests for chlorophyll** in red, yellow and brown leaves can be made by treating them, after or before extraction with formic acid and with heptane, with a methyl alcohol solution or with a 50–50 mixture of methyl and isoamyl alcohols. A green color, which disappears on adding aqueous hydrochloric acid, denotes presence of chlorophyll. The disappearance of the chlorophyll is a time reaction and does not occur instantaneously. Since chlorophyll goes readily into benzene and anthocyanin does not, the two can be separated qualitatively by shaking with benzene.

Simplified Method of Analysis

A quicker, simpler and less accurate method of qualitative analysis is to extract the leaves with methyl alcohol which takes out practically everything. Make up an ether–water system such that the two liquid layers are about equal in volume. Add some of the methyl alcohol extract. A green color in the ether layer denotes chlorophyll. This green will disappear gradually on adding hydrochloric acid, more slowly after adding ammonia. It is safer not to draw final conclusions in regard to yellow pigments until the chlorophyll has disappeared pretty completely. To the ether–water mixture containing some of the methyl alcohol extract, add aqueous hydrochloric acid solution. A pink color in the water layer indicates anthocyanins or anthocyanidins. Remove the ether layer and add aqueous ammonia to it. A yellow color in the water layer shows the presence of flavones. A yellow color exclusively or chiefly in the ether layer indicates the so-called water-soluble yellow pigments.

Remove the ether layer, add "heptane" to it and evaporate off the ether. Add 90–95% methyl alcohol. A yellow color in the heptane denotes carotenes and a yellow color in the water layer shows xanthophylls, subject always to possible errors due to the presence of water-soluble yellow pigments.

Positive results by this method are reliable. Negative results should be checked if there is any reason to doubt them. Methyl alcohol usually will extract anthocyanins readily, but we have seen a red cactus blossom which was scarcely touched by methyl alcohol and gave up its pigment readily to a formic acid solution. Acetic acid has very little effect on the flavones in the jonquil. Since methyl alcohol increases the mutual solubility of ether and water, a large amount of methyl alcohol may introduce complications, while smaller amounts of methyl alcohol may mean correspondingly smaller amounts of pigment to be tested.

Discussion

Both these methods work with from a fraction of a leaf upward. Any group of pigments that cannot be determined in an extract from six leaves can be ignored for all ordinary purposes, though there may be especial reasons for determining such pigments as flavins. For substances like these, special methods must be and have been developed.

By using an approximately constant weight of leaves in approximately the same state of dryness and a constant amount of solution, the methods can be made semi-precise. It was possible to show one year that leuco-anthocyanins were present in the leaves of the sugar maple in Ithaca in July and not in the leaves of the Norway maple. It was also shown that the green leaves of the copper beech, which had been red earlier in the season, contained relatively large amounts of leuco-anthocyanins in July, small amounts early in September and an almost negligible amount toward the end of September. A more exhaustive study of this system ought to give some definite information as to the precursors of leuco-anthocyanins. We do not know now whether flavones are or are not possible precursors of the leuco-anthocyanins and we do not know anything about the reds that appear in young leaves in tropical forests.

Summary

It is possible to identify many leaf and flower pigments by suitable treatment with methyl alcohol, butyl alcohol, amyl alcohol and ether in acid and alkaline solutions.

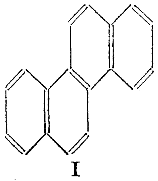
Ithaca, New York Received October 26, 1938

[Contribution from the Chemical Laboratory of The Ohio State University]

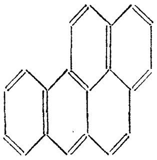
A New Synthesis of Chrysene Derivatives

By Melvin S. Newman

The desirability of preparing methyl derivatives of all of the five polycyclic aromatic hydrocarbons of the formula $C_{18}H_{12}$ has been pointed out previously.[1] Of these, derivatives of 1,2-benzanthracene have received the greatest attention. With the recent synthesis of 8-methyl-1,2-benzanthracene[2] all of the monomethyl derivatives of 1,2-benzanthracene have been made available for the study of the effect of structure on cancer-producing activity.[3] Of the other members of this class of hydrocarbons chrysene, I, offered a most promising field for research not only because of the similarity of its carbon skeleton to that of the steroids but also because the active carcinogenic agent in coal tar, 3,4-benzpyrene, II,[4] may be considered as a chrysene substituted in positions 4 and 5.



I



II

Of the known methods for the synthesis of chrysene and its derivatives[5] none seemed adequate for the preparation of various methyl- and dimethylchrysenes desired for biological testing. The work herein reported was undertaken in an effort to find a general method suitable for the preparation of variously substituted derivatives of chrysene.

The successful synthesis proceeds from benzalacetophenone by well-known reactions to α,γ-diphenylbutyric acid.

$$C_6H_5COCH{=}CHC_6H_5 + HCN \longrightarrow$$
$$C_6H_5COCH_2CH(CN)C_6H_5 \xrightarrow[H_2SO_4]{CH_3OH}$$
$$C_6H_5COCH_2CH(COOCH_3)C_6H_5 \xrightarrow{H_2O}$$
$$C_6H_5COCH_2CH(COOH)C_6H_5 \xrightarrow[HCl]{Zn—Hg}$$
$$C_6H_5CH_2CH_2CH(COOH)C_6H_5$$

The acid chloride of α,γ-diphenylbutyric acid was cyclized in benzene solution by aluminum chloride to 1-keto-2-phenyl-1,2,3,4-tetrahydronaphthalene III (87% yield) and the remaining steps in the synthesis are indicated below. This part of the synthesis consists essentially of an extension of the phenanthrene synthesis of Cook.[6]

Although one might expect the ketone III to be somewhat hindered, the Reformatsky reaction proceeded vigorously and the yield of the acid IV varied from 60 to 68%. The double bond is placed in the ring instead of the alternate position of conjugation with the carboxyl group because of the failure to isolate III from the products of ozonization. Surprisingly, low pressure catalytic reduction of this acid, its sodium salt, or its methyl ester using palladium or platinum catalysts failed almost completely. Invariably the acid was recovered for the most part unchanged. Reduction in excellent yield was finally effected by the action of 2% sodium amalgam on an aqueous alcoholic solution of the sodium salt, *using acid which had been recovered from unsuccessful attempts at catalytic hydrogenation.* When freshly prepared pure acid was used, *no reduction took place.* While an exhaustive search into the reason for this phenomenon was not made, the effect was noted in several different runs. If an alcoholic solution of the pure acid were shaken with Adams platinum catalyst and hydrogen and then recovered, this acid could be reduced by sodium amalgam. It may be that

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[1] Newman and Joshel, This Journal, **60**, 485 (1938).

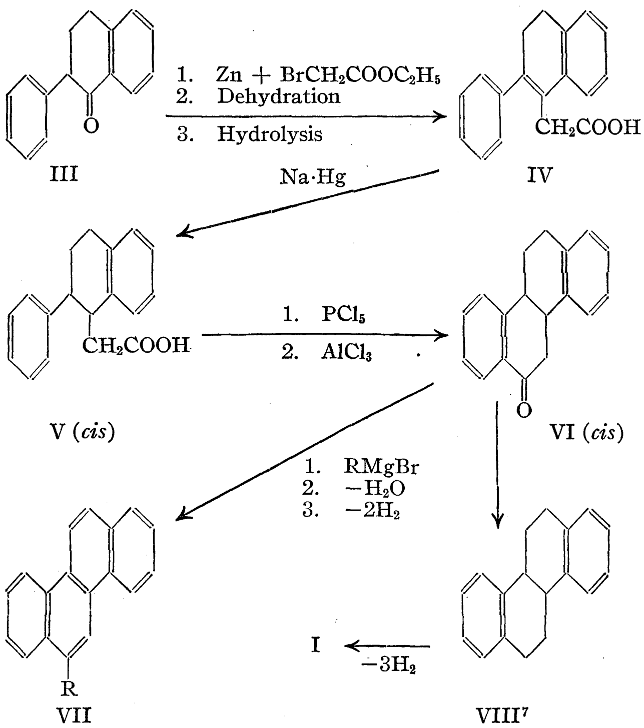
[2] Cook and Robinson, *J. Chem. Soc.*, 505 (1938).

[3] For the most recent report on the activity of methyl-1,2-benzanthracenes see Shear, *Am. J. Cancer*, **33**, 499 (1938); Fieser, *ibid.*, **34**, 37 (1938).

[4] Cook, Hewett and Hieger, *J. Chem. Soc.*, 395 (1933).

[5] Fieser, "The Chemistry of Natural Products Related to Phenanthrene," Rheinhold Publishing Corporation, New York, N. Y., 1936 or 1937, p. 22.

[6] Cook, Hewett and Lawrence, *J. Chem. Soc.*, 71 (1936).



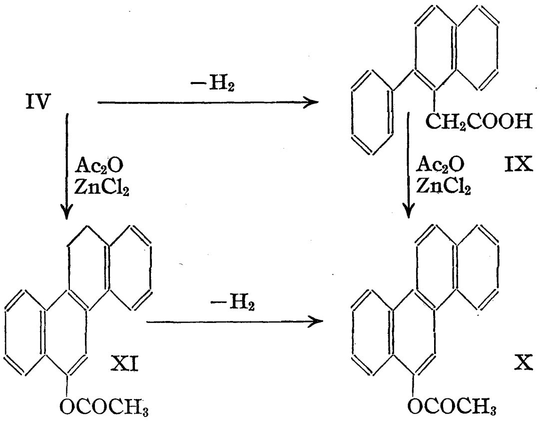
some colloidal platinum is the cause of the results noted for in a patent[8] it is claimed that spongy metals or alloys act as a catalyst for the reaction of sodium amalgam with aqueous solutions. The reduction proceeded in excellent yield to give a mixture of two racemates, one of which easily was isolated pure in 62% yield by fractional crystallization. The remainder of the reduced acids consisted of a difficultly separable mixture.[9]

The ketone VI was prepared in 81% yield by an intramolecular Friedel–Crafts condensation of the chloride of V. Upon Clemmensen reduction the known *cis* 5,6,11,12,13,14-hexahydrochrysene,[7] m. p. 76.8–77.8°, corr., was obtained. This fact forms the basis for assigning the *cis* structure to the acid V and the ketone VI. The formation of chrysene by heating this hydrocarbon with selenium[7] was confirmed. By treating the ketone VI with the appropriate Grignard reagent, followed by dehydration and dehydrogenation, both 6-methylchrysene,[10] m. p. 161.0–161.4°, and 6-ethylchrysene,[11] m. p. 126.4–126.8°, were prepared in 82 and 50% yields, respectively.

Upon oxidation, 6-methylchrysene gave a mixture of products from which a small yield of 6-methyl-11,12-chrysenequinone, m. p. 210–212°, dec., was obtained. This structure is assigned on the basis of the fact that the quinone readily formed a yellow phenazine derivative, m. p. 220–221°, with *o*-phenylenediamine. For comparison the phenazine derivative of chrysenequinone, m. p. 215–216°, was prepared, the mixed melting point being depressed over 20°, whereas a mixed melting point of the two quinones showed no depression.

An interesting variation leading to the formation of the acetates of 6-chrysenol and 11,12-dihydro-6-chrysenol is indicated below.

The dehydrogenation of the unsaturated acid IV to IX by heating with sulfur proceeded in 79% yield and the cyclization by a new application of the procedure of Fieser and Hershberg[12] yielded the acetate of 6-chrysenol, X, in 80% yield. The yields in the alternate procedure were 87% for the acetylative cyclization and 50% for the dehydrogenation. On hydrolysis, X and XI were converted into 6-chrysenol,[13] m. p. 248–250° with decomposition, and 11,12-dihydro-6-chrysenol, m. p. 156.2–156.6°, respectively. The former yielded chrysenequinone on oxidation and 6-methoxychrysene,[14] m. p. 127.2–127.8°, on methylation.



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(7) Ramage and Robinson, *J. Chem. Soc.*, 607 (1933).

(8) German patent 652,549 (1937).

(9) The author is indebted to Dr. E. B. Hershberg for reducing a small sample in a high pressure hydrogenator using copper chromite. The mixture of reduced acids produced by this reduction was very similar to that mixture produced by sodium amalgam reduction.

(10) Sen-Gupta, *Current Sci.*, **5**, 295 (1936), reported the synthesis of 6-methylchrysene and gave its melting point as 152–153°. Because of the melting point recorded, it seems likely that some other hydrocarbon—possibly 3-methyl-1,2-benzanthracene, m. p. 155°, synthesized by Cook, *J. Chem. Soc.*, 1087 (1930)—was at hand.

(11) Funke and Müller, *J. prakt. Chem.*, **144**, 242 (1936), give the melting point of 6-ethylchrysene as 126°.

(12) Fieser and Hershberg, THIS JOURNAL, **59**, 1028 (1937).

(13) Kern, U. S. Patent 1,996,475; *C. A.*, **29**, 3356[1] (1935), gives the melting point of 6-chrysenol as 240–242°.

(14) French Patent 794,534 (1936); *C. A.*, **30**, 5238[6] (1936), gives the melting point of 6-methoxychrysene (called 2-methoxychrysene) as 126°.

Experimental[15]

α-Phenyl-β-benzoylpropionitrile.—Conditions were found which make possible the preparation of this intermediate in much less time than recommended.[16] A solution of 108 g. of potassium cyanide in 200 cc. of water was added under the surface to a solution at 55° of 135 g. of benzalacetophenone in 700 cc. of alcohol. The addition was made over a period of five minutes with continual shaking. After five minutes, the contents were warmed to 60°, the flask was wrapped with several towels and allowed to stand undisturbed for ninety to one hundred minutes, the temperature being maintained at 60° by the heat of reaction. After cooling the crystals were collected by filtration and washed colorless with cold 50% alcohol. The yield was 146 g. (95%) of material melting at 124.4 to 126°.

α,γ-Diphenylbutyric Acid.—The above nitrile was converted into methyl α-phenyl-β-benzoylpropionate[17] and hence to the free acid by alkaline hydrolysis.

In a typical reduction[18] the product obtained from 120 g. of α-phenyl-β-benzoylpropionic acid was distilled at 3 mm. The fraction, 101 g., boiling at 199–203° was dissolved in 250 cc. of warm petroleum ether (b. p. 65–110°) and on cooling 91 g. of white crystals, m. p. 68–71°, was obtained. From the mother liquor only 2 g. more of good product crystallized, making the yield 82%. On one recrystallization the melting point rose to 72–3°[19] with little loss. In an experiment in which the entire crude product at each stage was used directly for the next step, there was obtained 128 g. (62%) of α,γ-diphenylbutyric acid, m. p. 72–73°, from 183 g. of benzalacetophenone. Separate attempts were made to hydrolyze and reduce α-phenyl-β-benzoylpropionitrile, and methyl α-phenyl-β-benzoylpropionate in one step using the Clemmensen procedure but the yield of reduced acid was small, a considerable amount of both starting materials being recovered.

1-Keto-2-phenyl-1,2,3,4-tetrahydronaphthalene, III.—In the best of several experiments 91 g. of α,γ-diphenylbutyric acid was converted into the acid chloride with 83 g. of phosphorus pentachloride. After removing all volatile phosphorus compounds on the water pump at 100°, the pale yellow oil was dissolved in 380 cc. of thiophene-free benzene and 53 g. of aluminum chloride was added during one-half hour (external cooling). After stirring for three hours at room temperature, the deep red reaction mixture was heated to 40° several times during the next seven hours, cooled, and poured on ice and hydrochloric acid. The benzene was removed by steam and the organic matter collected and dissolved in 300 cc. of alcohol. The first crop of pale buff crystals was distilled, b. p. 182–183 at 2.5–3 mm. The product in the mother liquors was also distilled and the combined distillates yielded a total of 73.0 g. (87%) of white plates, m. p. 76–77°. If the entire reaction product were distilled before a preliminary crystallization the yield was reduced from 5 to 10%. On standing the ketone frequently took on a pink tinge. A sample recrystallized for analysis melted at 76.2–77.0°.

*Anal.** Calcd. for $C_{16}H_{14}O$: C, 86.45; H, 6.34. Found: C, 86.11; H, 6.61.

The **semicarbazone** melted with decomposition at 250–251.4° after sintering at 245°.

*Anal.** Calcd. for $C_{17}H_{17}ON_3$: N, 15.04. Found: N, 15.18.

3,4-Dihydro-2-phenyl-1-naphthaleneacetic Acid, IV.—In a typical experiment, a mixture of 10 g. each of ketone and granulated zinc, 16 g. of ethyl bromoacetate, 40 cc. of dry thiophene-free benzene, and a pinch of the copper salt of the enol form of ethyl acetoacetate was heated until reaction commenced, after which the heat of reaction was sufficient to reflux the solvent. In larger runs cooling was necessary. After ten minutes, the mixture was heated on the steam-bath for thirty minutes. The cooled reaction mixture was poured into dilute hydrochloric acid and the organic matter collected in the benzene layer. After removing the solvent, the product was dehydrated by heating with a small crystal of iodine at 210–215° for thirty minutes under 100 mm. pressure, following which a pale yellow viscous oil, b. p. 180–200° at 3 mm., was distilled. The distillate was saponified with alcoholic potassium hydroxide. By crystallization and recrystallization from benzene there was obtained 8.1 g. (68%) of the acid IV as dense colorless prisms which contained benzene of crystallization removed by drying at 100°. The melting point was 155–156° and a portion was crystallized from benzene and alcohol to a constant melting point of 156.2–156.8°.

Anal.† Calcd. for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 82.17; H, 5.98.

A carbon tetrachloride solution of the acid readily decolorized bromine.

An ozonolysis, for which the author is indebted to Dr. Shinowara, was carried out in acetic acid. The neutral portion of the products of ozonolysis yielded only intractable oils from which no semicarbazone could be obtained. The acid fraction consisted mainly of starting unsaturated acid, m. p. 152–156°.

***cis*-2-Phenyl-1,2,3,4-tetrahydro-1-naphthaleneacetic Acid, V.**—Attempts were made to reduce IV using both platinum and palladium catalysts in acetic acid and in 95% alcohol. There was no further absorption of hydrogen after the catalyst was reduced. The entire crude acid as recovered from the solvent had a melting range of 20° but on one crystallization from benzene, over 65% was recovered with a good melting range, 152–156°, not depressed by the authentic acid. No better results were obtained using the methyl ester in alcohol solution or the sodium salt in aqueous solution. Further unsuccessful attempts at reduction involved the Clemmensen reduction and boiling with phosphorus and hydriodic acid. In a typical reduction with sodium amalgam, 4.90 g. of acid IV was dissolved in 20 cc. of 95% alcohol (distilled over potassium hydroxide), and an equivalent amount of sodium hydroxide in 200 cc. of water was added, followed by 360 g. of 2% sodium amalgam (made by dropping mercury on molten sodium under sulfur-free xylene). After standing for three days at 35–40°, the solution was heated to 100° to dissolve the insoluble sodium salt which had crys-

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(15) All melting points corrected. Analyses marked * by H. S. Clark, † by K. Eder, University of Chicago.

(16) *Org. Syntheses*, **10**, 80 (1930), John Wiley and Sons, New York, N. Y.

(17) Kohler, Peterson and Bickel, This Journal, **56**, 2000 (1934).

(18) Martin, *ibid.*, **58**, 1438 (1936).

(19) Compare Kohler and Kimball, *ibid.*, **55**, 4632 (1933).

tallized. The acids precipitated on acidification were crystallized from 80 cc. of benzene. The first crop melted at 170–172° and the next two crops somewhat lower. On recrystallization from alcohol a total of 3.06 g. (62%) of white needles, m. p. 171–172°, was obtained. A portion recrystallized for analysis melted at 172.0–172.8°.

Anal.† Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.26; H, 6.74.

The acids in the mother liquors were saturated as shown by a failure to decolorize bromine in carbon tetrachloride. These acids undoubtedly formed a mixture of the two racemates.

***cis*-6-Keto-5,6,11,12,13,14-hexahydrochrysene, VI.**—In the best experiment, 4.29 g. of acid V was warmed with 3.5 g. of phosphorus pentachloride for one hour after which phosphorus compounds were removed under reduced pressure on the water-bath at less than 90°. The pale yellow acid chloride was dissolved in 30 cc. of dry sulfur-free benzene and 2.18 g. of powdered aluminum chloride added in portions. The reaction mixture warmed up and took on a green color. After three hours at 30–50°, the mixture was poured into dilute hydrochloric acid and the benzene layer separated and washed successively with hydrochloric acid, sodium hydroxide, water, and saturated sodium chloride solution. After removing the benzene the product crystallized from alcohol. In all 3.23 g. (81%) of ketone which crystallized in dense prisms, m. p. 74.4–76.4°, was obtained. A sample recrystallized for analysis melted at 75.8–76.8° and formed colorless prisms.

Anal.† Calcd. for $C_{18}H_{16}O$: C, 87.06; H, 6.50. Found: C, 86.53, 87.53; H, 6.74, 6.58.

The semicarbazone formed very small crystals from pyridine–alcohol, m. p. 255–258°, dec., after sintering at 251°.

Anal.† Calcd. for $C_{19}H_{19}ON_3$: N, 13.76. Found: N, 13.74.

***cis*-5,6,11,12,13,14-Hexahydrochrysene, VIII.**—By a modified[18] Clemmensen reduction, from 1.0 g. of *cis*-ketone, VI, there was obtained 0.52 g. (55%) of hexahydrochrysene, m. p. 74.4–75.8°. After two recrystallizations from alcohol, thick white plates, m. p. 76.8–77.8°, were obtained. Ramage and Robinson[7] give the melting point for *cis*-hexahydrochrysene as 75°. A mixture of VI and VIII melted at 61–66°.

6-Methylchrysene, VII (R = CH_3).—To a solution of 0.461 g. of VI in 3 cc. of ether and 3 cc. of benzene was added 2 cc. of 2.7 *M* methylmagnesium bromide in ether. A white complex separated immediately but soon dissolved. After thirty minutes of refluxing, the reaction mixture was decomposed with dilute hydrochloric acid and the organic material heated at 220° for ten minutes to effect dehydration. The residue was heated with 0.120 g. of sulfur at 230° for twenty minutes during which time hydrogen sulfide was evolved copiously. Distillation at 3 mm. yielded a yellow distillate which immediately solidified. By crystallization from benzene there was obtained a total of 0.368 g. (82%) of **6-methylchrysene**, m. p. 160.2–161.2°. Recrystallization from benzene–alcohol resulted in colorless stout needles, m. p. 161.0–161.4°. **The picrate,** from benzene–alcohol, formed bright orange needles, m. p. 170.0–170.6°.

Anal.† Calcd. for $C_{19}H_{14}$: C, 94.18; H, 5.82. Found: C, 94.15; H, 5.95. Calcd. for $C_{25}H_{17}O_7N_3$: N, 8.91. Found: N, 8.96.

6-Methylchrysene-11,12-quinone.—6-Methylchrysene (0.32 g.) was oxidized by boiling with 1 g. of sodium dichromate and 10 cc. of acetic acid for five hours. The red oxidation product was recrystallized until its behavior on melting remained constant. The product obtained in very small amount formed beautiful bright red needles which, when the temperature of the melting point bath was raised slowly, darkened slightly above 200° and melted with much decomposition at 210–212°. The temperature of decomposition was higher, the faster the rate of heating and on rapid heating it melted at 218–220°. The decomposition point was not affected by mixing the sample with authentic chrysenequinone, m. p. 242–242.6°. The color of the solution of 6-methylchrysenequinone in cold concentrated sulfuric acid was blue-violet and not quite as pronounced as the deep blue color of chrysenequinone under the same conditions.

Anal.† Calcd. for $C_{19}H_{12}O_2$: C, 83.81; H, 4.44. Found: C, 83.75; H, 4.74.

Chrysophenazine and 5-Methylchrysophenazine.[20]—Condensation products of chrysenequinone and 6-methylchrysenequinone with *o*-phenylenediamine in alcohol–acetic acid were obtained easily. After recrystallization from pyridine–alcohol **chrysophenazine** formed long silky yellow needles, m. p. 215–216°.

*Anal.** Calcd. for $C_{24}H_{14}N_2$: N, 8.48. Found: N, 8.40.

5-Methylchrysophenazine formed small yellow needles, m. p. 220–221°, and a mixed melting point with the above was depressed 20°.

Anal.† Calcd. for $C_{25}H_{16}N_2$: N, 8.14. Found: N, 8.45.

6-Ethylchrysene, VII, (R = C_2H_5).—In a manner entirely analogous to that used in the preparation of 6-methylchrysene there was obtained from 0.765 g. of VI, 0.378 g. of 6-ethylchrysene, m. p. 124–125°. On recrystallization from benzene–alcohol colorless needles, m. p. 126.4–126.8°, were obtained. A solution in warm concentrated sulfuric acid had a blue-violet color as mentioned by Funke.[11] The picrate, bright orange needles, m. p. 136.2–136.8°, was prepared in and recrystallized from benzene–alcohol.

*Anal.** Calcd. for $C_{26}H_{19}O_7N_3$: N, 8.66. Found: N, 8.64, 8.65.

2-Phenyl-1-naphthaleneacetic Acid, XI.—A mixture of 2.64 g. of IV and 0.32 g. of sulfur was heated at 220–225° for ninety minutes. Hydrogen sulfide was evolved copiously for the first twenty minutes but if the reaction were stopped at this point the yield was greatly decreased. The slightly colored reaction product was crystallized from benzene yielding a total of 2.07 g. (79%) of the desired acid IX as colorless prisms, m. p. 192–193°.

*Anal.** Calcd. for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 81.99; H, 5.52.

6-Chrysenyl Acetate, X.—A solution of 1.60 g. of IX and a small amount of anhydrous zinc chloride in 8 cc. of

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(20) *Chemical Abstracts* numbering.

acetic anhydride and 8 cc. of acetic acid[12] was refluxed for one hour, cooled, and diluted with water. On further cooling there crystallized in colorless needles 1.39 g. (80%) of **6-chrysenyl acetate**, m. p. 157–158°. A sample recrystallized for analysis melted at 158.6–159.2°.

Anal.† Calcd. for $C_{20}H_{14}O_2$: C, 83.89; H, 4.93. Found: C, 83.58; H, 5.02.

6-Chrysenol.—The acetate was converted into 6-chrysenol by heating with alcoholic potassium hydroxide for five minutes. The cooled yellow solution was diluted with dilute hydrochloric acid, whereupon the color almost disappeared. Soon 6-chrysenol separated in almost colorless needles in quantitative yield. Upon recrystallization from acetone–benzene, 6-chrysenol[13] formed colorless needles, m. p. 248–250°, with decomposition. Darkening and sintering took place as low as 240°. Upon oxidation with sodium dichromate in acetic acid, 6-chrysenol was converted in theoretical yield to chrysenequinone.

*Anal.** Calcd. for $C_{18}H_{12}O$: C, 88.50; H, 4.95. Found: C, 88.61, 88.75; H, 5.13, 5.26.

6-Methoxychrysene.—An aqueous methyl alcoholic solution of 0.515 g. of 6-chrysenol containing 1 cc. of 50% potassium hydroxide was treated with two 0.5-cc. portions of dimethyl sulfate. After a time pale yellow crystals separated. The reaction mixture was warmed, diluted with water, and cooled in an ice-bath. By crystallization of the reaction product from benzene–alcohol there was obtained 0.464 g. (85%) of white needles, m. p. 125–127°. A sample recrystallized from benzene–alcohol melted at 127.2–127.8°.[14]

*Anal.** Calcd. for $C_{19}H_{14}O$: C, 88.35; H, 5.46. Found: C, 88.16; H, 5.48.

11,12-Dihydro-6-chrysenyl Acetate, XI.—Under conditions similar to those used in the preparation of 6-chrysenyl acetate, X, 3.00 g. of IV was cyclized to yield 2.80 g. (87%) of XI, m. p. 94–96°. A sample recrystallized from alcohol melted at 95.6–96.2°.

Anal.† Calcd. for $C_{20}H_{16}O_2$: C, 83.31; H, 5.59. Found: C, 83.31; H, 5.96.

Under conditions identical to those used in the dehydrogenation of IV to IX, **11,12-dihydrochrysenyl acetate** was converted in 50% yield into **6-chrysenyl acetate.**

11,12-Dihydro-6-chrysenol.—By saponification with alcoholic potassium hydroxide for one hour, 0.342 g. (80%) of 11,12-dihydro-6-chrysenol, m. p. 155.6–156.4°, was obtained from 0.50 g. of XI. A sample recrystallized for analysis from alcohol formed colorless elongated prisms, m. p. 156.2–156.6°.

*Anal.** Calcd. for $C_{18}H_{14}O$: C, 87.77; H, 5.73. Found: C, 87.67, 88.15; H, 5.72, 5.85.

An attempt at methylation resulted in the formation of an uninviting brown viscous oil.

Fluorescence in Ultraviolet Light.—The following compounds exhibited vivid blue fluorescence when viewed in ultraviolet light: 2-phenyl-3,4-dihydro-1-naphthaleneacetic acid, *cis*-6-keto-5,6,11,12,13,14-hexahydrochrysene, *cis*-5,6,11,12,13,14-hexahydrochrysene, 6-methylchrysene, 6-chrysenol, and 6-methoxychrysene.

Summary

A new synthesis for hydrocarbons containing the chrysene nucleus is described. The starting material is benzalacetophenone which is converted by well-known reactions into α,γ-diphenylbutyric acid. This acid is cyclized to 1-keto-2-phenyl-1,2,3,4-tetrahydronaphthalene. By the Reformatsky reaction, followed by dehydration and saponification, this ketone is converted into 3,4-dihydro-2-phenyl-1-naphthaleneacetic acid which on reduction with sodium amalgam yields *cis*-2-phenyl-1,2,3,4-tetrahydro-1-naphthaleneacetic acid. Upon cyclization this acid yields *cis*-6-keto-5,6,11,12,13,14-hexahydrochrysene from which, by reaction with methyl- and ethylmagnesium bromides, followed by dehydration and dehydrogenation, there is obtained, respectively, 6-methyl- and 6-ethylchrysene. 6-Methylchrysene on oxidation yields 6-methylchrysene-11,12-quinone.

By dehydrogenation with sulfur, 3,4-dihydro-2-phenyl-1-naphthaleneacetic acid is converted into 2-phenyl-1-naphthaleneacetic acid from which is formed 6-chrysenyl acetate by acetylative cyclization. The latter is hydrolyzed to 6-chrysenol, in turn methylated to 6-methoxychrysene. On acetylative cyclization 3,4-dihydro-2-phenyl-1-naphthaleneacetic acid yields 11,12-dihydro-6-chrysenyl acetate which is hydrolyzed to 11,12-dihydro-6-chrysenol and is dehydrogenated to 6-chrysenyl acetate.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE PENNSYLVANIA STATE COLLEGE]

Hydrogen Fluoride as a Condensing Agent. II. The Alkylation of Benzene by Olefins

BY J. H. SIMONS AND S. ARCHER

In a previous communication[1] we announced the successful alkylation of benzene using hydrogen fluoride as the condensing agent. The first successful alkylation of aromatic compounds by olefins was reported by Balsohn in 1879.[2] Since that time acidic substances such as sulfuric acid,[3] phosphoric acid,[4] and phosphorus pentoxide[5] have been used to effect such condensations. Hydrogen fluoride has been used as a promoter with boron fluoride in the alkylation of paraffins by olefins.[6]

Ipatieff[3] stated that in the case of the condensation reaction catalyzed by sulfuric acid, there were three competing reactions. These were, first, alkylation of the aromatic hydrocarbon, second, polymerization of the olefin, and, third, the reaction of the unsaturated compound with the acid to form an ester. Since it has been shown that hydrogen fluoride polymerizes olefins,[7] and also adds to double bonds,[8] we believe that similar side reactions also can take place in the case of alkylation catalyzed by hydrogen fluoride. However, under the conditions employed, no evidence was found for any reaction except alkylation. If polymerization or addition of hydrogen fluoride occurred, they were in relatively small amounts.

The reaction mixture after removal of the acid and subsequent drying, was always clear and almost colorless. Fractionation proceeded smoothly and efficiently in all cases, and no compounds boiling at temperatures between those of benzene and the alkylbenzenes were found. The olefins used were propylene, isobutene, pentene-2, trimethylethylene, and cyclohexene. All, except propylene, were prepared by dehydration of the proper alcohol. The alkylbenzenes formed were characterized by means of physical constants and by conversion to the monoacetamino derivative as described by Ipatieff and Schmerling.[9]

Experimental

General Method.—One to five mols of relatively dry hydrogen fluoride was distilled from the container through a water-cooled copper coil into a copper flask in an ice-bath. Two to five mols of benzene was then added and a rubber stopper inserted. This stopper carried an inlet and an outlet tube of copper and a copper stirrer provided with a mercury seal. One-half to one mol of olefin was then added slowly with stirring. The stirring was continued for three to five hours usually at 0°, but sometimes the reaction was allowed to warm to room temperature. The mixture was poured onto ice and neutralized with sodium carbonate. After washing the benzene layer with sodium carbonate solution, it was separated, dried with potassium carbonate or magnesium sulfate, and distilled. The product was then redistilled and a portion converted into the acetamino derivative. The yields and certain physical properties of the products are given in Table I.

Conclusions.—As indicated in a previous communication, hydrogen fluoride has been found to be useful as an agent for the alkylation of benzene by olefins. Although the reactions were performed using sufficient hydrogen fluoride to give two liquid layers, the reaction probably takes place in the hydrocarbon layer. The amount of hydrogen fluoride could be varied within wide limits without affecting the results, and other experiments which have been performed in this laboratory indicate that the reactions proceed rapidly with only sufficient hydrogen fluoride to form a saturated solution in the hydrocarbon.

As no great care was taken to ensure high yields and as the reactions were not studied to find the conditions for maximum yield, the yields obtained were surprisingly high. These probably could be increased to practically the theoretical by using greater care and larger reaction mixtures.

Extreme precautions to ensure anhydrous conditions were not taken. In some cases the reaction mixtures were exposed to moist laboratory air for considerable periods of time without affecting the results. Aqueous solutions of hy-

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(1) Simons and Archer, THIS JOURNAL, **60**, 986 (1938).

(2) Balsohn, *Bull. soc. chim.*, [2] **31**, 539 (1879).

(3) Ipatieff, Corson and Pines, THIS JOURNAL, **58**, 919 (1936).

(4) Ipatieff, Pines and Komarewsky, *Ind. Eng. Chem.*, **28**, 222 (1936).

(5) Truffault, *Compt. rend.*, **202**, 1286 (1936).

(6) Ipatieff and Grosse, THIS JOURNAL, **57**, 1616 (1935).

(7) Fredenhagen, *Z. physik. Chem.*, **A164**, 176 (1933).

(8) Grosse and Linn, *J. Org. Chem.*, **3**, 26 (1938).

(9) Ipatieff and Schmerling, THIS JOURNAL, **59**, 1056 (1937).

TABLE I

ALKYLATION OF BENZENE BY OLEFINS USING HYDROGEN FLUORIDE

Olefin	Product	Yield, %	B. p., °C.	Press., mm.	n^{20}	M. p., acetamino deriv., °C.
Propylene	Monoisopropylbenzene	84	149–150	730	1.4913–6	105–105.5
Isobutene	Mono-*t*-butylbenzene	44	166.5–168	728	1.4921	168–169.5
	Di-*t*-butylbenzene	41	77–78[a]			
Pentene-2[b]	Phenylpentane[c]	47	79–80	17	1.4883	119–120
Trimethylethylene	Mono-*t*-amylbenzene	21	71–72	12	...	140–142
	Di-*t*-amylbenzene	60	262–265	740	...	
Cyclohexene	Cyclohexylbenzene	62	234.5 7–8[a]	737	...	129–131

[a] Melting point. [b] Prepared from redistilled *s*-amyl alcohol: b. p. 117° (742 mm.), n^{20} 1.4083. The olefin boiled at 35.4° (742 mm.), n^{20} 1.3809. [c] This is probably a mixture of beta and gamma phenylpentanes. (n. b.) Propylene also reacted with naphthalene to give monoisopropylnaphthalene and probably a di- and triisopropylnaphthalene in good yields.

drofluoric acid undoubtedly can be used for some reactions.

Summary

Hydrogen fluoride has been found to be a very useful agent for the alkylation of benzene by olefins. Propylene, isobutane, pentene-2, trimethylethylene, and cyclohexene were used. Very good yields were obtained.

STATE COLLEGE, PENNA. RECEIVED SEPTEMBER 1, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE PENNSYLVANIA STATE COLLEGE]

Hydrogen Fluoride as a Condensing Agent. III. Alkylation of Aromatics with Aliphatic Halides

BY J. H. SIMONS AND S. ARCHER

In a previous communication[1] we have indicated the use of hydrogen fluoride to promote the reaction between benzene and alkyl halides. A more detailed account of reactions between aromatic compounds and alkyl halides can now be reported.

The use of aluminum chloride and other metallic halides to catalyze condensations between alkyl halides and aromatic compounds is very well known.[2] However, a search of the literature failed to reveal any instance wherein sulfuric or other acidic catalysts have effected such a condensation. It is worthy of note, therefore, that hydrogen fluoride can promote such a condensation.

When tertiary chlorides are used, only extremely mild conditions are required. The reaction proceeds smoothly at 0° and at atmospheric pressure. When secondary halides are employed, higher temperatures are necessary to bring about a reaction. At 25° a small amount of propylated benzenes was formed from the reaction between isopropyl chloride and benzene. Primary halides did not react detectably at either 0 or 25°. At higher temperatures, however, *n*-propyl bromide does react readily with benzene.

In addition to alkylation two other reactions might be expected. When metallic halides are used in reactions involving aromatic compounds, condensation of the rings occurs and resins and tars are formed. In these reactions using hydrogen fluoride no such residues were found. In another experiment reported from this Laboratory,[3] it was found that either *t*-butyl chloride or *t*-amyl chloride, when treated with hydrogen fluoride, produced a complicated mixture of higher boiling compounds. Fortunately in the presence of the aromatic compound in excess these reactions took place to a negligible extent if at all.

The halides used were isopropyl chloride, *t*-butyl chloride, *t*-amyl chloride and *n*-propyl bromide.

[1] Simons and Archer, THIS JOURNAL, **60**, 986 (1938).

[2] N. O. Calloway, *Chem. Rev.*, **17**, 327 (1935).

[3] Simons, Fleming, Whitmore and Bissinger, THIS JOURNAL, **60**, 2267 (1938).

TABLE I

ALKYLATION OF AROMATICS BY ALIPHATIC HALIDES USING HYDROGEN FLUORIDE

Halide	Product	Yield, %	B. p., °C.	Press., mm.	n^{20}	M. p. of acetamino deriv., °C.
n-Propyl[a] bromide	Propylbenzene[b]	48	150–153	740	....	...
Isopropyl chloride	Polyisopropylbenzene[c]	..	155–175	740	....	166
t-Butyl chloride	Mono-*t*-butylbenzene	10	167–170	740	1.4908	169–170
	Di-*t*-butylbenzene	60	77–78[d]			
t-Amyl chloride	Mono-*t*-amylbenzene	41.5	71– 74	12		139–140.5
	Di-*t*-amylbenzene	21.5	127–130	12		
t-Butyl chloride	*p*-*t*-Butyltoluene[e]	75	72–72.5	12	1.4919	163.5–164.5[f]
			188	740		
t-Butyl chloride	Mono-*t*-butylnaphthalene[g]	46	142–143	14		
	Di-*t*-butylnaphthalene[h]	8	148[d]			
	Di-*t*-butylnaphthalene	28	80–81[d]			

[a] This reaction was run in a copper bomb at 80°. [b] This was a mixture of 88% isopropylbenzene and 12% normal propylbenzene determined from the melting point 80–92° of a sulfonamide derivative. The technique of this identification is given in the following paper of this series. [c] This reaction proceeded very slowly at 25°; only a small amount of product was obtained, which distilled over a considerable range. The acetamino derivative was made of the highest boiling portion which is probably a polysubstituted benzene. [d] Melting point. [e] The aromatic used was toluene. [f] This is the melting point of *p*-*t*-butylbenzoic acid made from the product by oxidation with (1:2) nitric acid. Its determined neutral equivalent was 179, calcd. 178. [g] The aromatic used was naphthalene. It was dissolved in carbon tetrachloride for the reaction. [h] Two isomeric di-*t*-butylnaphthalenes were obtained. See Gump, THIS JOURNAL, **53**, 380 (1931).

The aromatic compounds employed were benzene, toluene and naphthalene.

Experimental

General Method.—The method used was similar to that reported in the second paper of this series.[4] The reactions, however, usually required two to three times as long. Hydrogen chloride was evolved in the reactions using chlorides and this was tested for in the escaping gases with a bead of silver nitrate solution. The reactions were stopped when this test was negative. Table I gives the collected results of the experiments.

Conclusion.—Hydrogen fluoride has been found to be an unusually effective agent to promote the reaction between alkyl halides and aromatic compounds. The reaction has been found to be most rapid with tertiary halides and least rapid with primary halides. The yields are relatively high although no effort has been made to obtain high yields and no study has been made of the best conditions for the reactions. The yields probably could be greatly improved. The amount of hydrogen fluoride necessary is probably greater than when olefins are used but only because some of it is lost in the escaping gas. Great care for the exclusion of moisture was not taken and small amounts of water apparently do not prevent the reaction.

Hydrogen fluoride has several advantages over the use of metallic halides for these reactions. Polymerization of the aromatic compounds is avoided and this results not only in higher yield but also in greater ease of separation and purification of the products. For aromatic compounds such as naphthalene that are solid at temperatures at which most of the reactions take place, a very convenient solvent (carbon tetrachloride) can be used with no apparent reaction between it and the other reagents. This solvent cannot be employed when aluminum chloride is used instead of hydrogen fluoride.

Summary

Hydrogen fluoride has been found to be an effective agent to promote the reaction between alkyl halides and aromatic compounds. The halides used were *n*-propyl bromide, isopropyl chloride, *t*-butyl chloride and *t*-amyl chloride, and the aromatic compounds were benzene, toluene and naphthalene.

STATE COLLEGE, PENNA. RECEIVED SEPTEMBER 1, 1938

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(4) Simons and Archer, THIS JOURNAL., **60**, 2952 (1938).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE PENNSYLVANIA STATE COLLEGE]

Hydrogen Fluoride as a Condensing Agent. IV. The Reaction of Cyclopropane with Benzene

BY J. H. SIMONS, S. ARCHER AND ELIZABETH ADAMS

In the two previous papers in this series[1] it was shown that hydrogen fluoride was an efficient agent to promote the reaction between either olefins and aliphatic halides and aromatic compounds.

Of considerable interest is the reaction of cyclopropane and benzene. Ipatieff and Grosse[2] carried out this reaction using aluminum chloride and found that only the normal propylbenzenes were formed. We have used hydrogen fluoride to cause the same reaction and have found a similar result, *i. e.*, the normal compound is the only product.

It is believed that cyclopropane does not isomerize to form propylene before alkylation.[2] A possible mechanism to account for the formation of the normal rather than the iso compound may be given. The cyclopropane molecule, being under strain, will be the center of an abnormal electromagnetic field, as is indicated by its magnetic susceptibility.[3] This may cause it to add a proton to form a hypothetical and transitory propyl ion. The additional strain may cause the ring to break and irrespective of where it breaks a normal propyl positive ion will be formed. The reaction of this ion with benzene will produce normal propylbenzene and a proton.

In the reaction between paraffins and olefins catalyzed by boron trifluoride with hydrogen fluoride as a promoter, Grosse and Linn[4] assumed that the initial step in the mechanism was the addition of the acid to the double bond, followed by the removal of hydrogen fluoride as the alkyl fluoride condensed with the saturated hydrocarbon. A similar mechanism may be postulated for the reaction between olefins and aromatics, as catalyzed by hydrogen fluoride. However, the suggested course of reaction does not adequately explain the reactions of cyclopropane. When this hydrocarbon reacts with hydrogen fluoride, *n*-propyl fluoride is predominantly formed, along with a small but significant amount of isopropyl fluoride. If it is the alkyl fluoride that reacts with the aromatic hydrocarbon, then one should expect both the normal and the iso compound to be formed when cyclopropane reacts with benzene. Yet it has been shown that no isopropylbenzenes are found in the reaction products. It is therefore assumed that the organic reactions catalyzed by hydrogen fluoride proceed through some ionic mechanism similar to those postulated by Whitmore for polymerizations and rearrangements.

Experimental

Sulfonamide Method of Identification.—In order to evaluate the composition of a possible mixture of normal and isopropylbenzene, a method employing the melting points of the sulfonamide derivatives was employed.

The sulfonamides were usually prepared in triplicate. A 3-g. sample was shaken with twice its volume of concd. sulfuric acid until the hydrocarbon dissolved completely. A saturated salt solution was added to precipitate the sulfonic acid and the latter was washed free of sulfuric acid with more of the salt solution. After drying at 110°, the sulfonic acid was treated with 8 to 10 g. of phosphorus pentachloride; and the mixture was then heated on the steam-bath for four hours. At the end of this time, the mass was poured into water, extracted with ether, washed with water and dried over sodium sulfate. Ammonia was passed onto the sulfonyl chloride for one hour. The ammonium chloride was filtered off and the solution dried again over sodium sulfate. The ether was evaporated and a melting point taken without recrystallization: m. p. of *n*-propyl sulfonamide, 102.5°; m. p. of isopropyl sulfonamide, 98°; m. p. of 57:43 mixture of iso and normal, respectively, 73°. The latter was the lowest point on the melting point curve. Mixtures of varying percentages of each were made and the melting points taken. From the data, a temperature–composition diagram was constructed. From this diagram, the percentage of both components in a mixture of the two can be determined.

Cyclopropane and Benzene.—The technique was similar to that described for reactions between olefins and benzene.[1] Fractionation gave the following

Compound	B. p., °C.	n^{20}	Yields, %
Monopropylbenzene	154–157	1.4920	42
Dipropylbenzene	97–98 (16 mm.)	1.4928	20
Tripropylbenzene	130–131 (14 mm.)	1.4950	3

The sulfonamide of the monopropylbenzene melted at 99–105°, 99–105.2°. A mixed melting point with the corresponding derivative of pure isopropylbenzene was 80–92°. Thus cyclopropane gave the only normal propyl benzenes.

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(1) Simons and Archer, THIS JOURNAL, **60**, 2952 and 2953 (1938).

(2) Ipatieff and Grosse, *J. Org. Chem.*, **2**, 447 (1937).

(3) Farquharson and Sastri, *Trans. Faraday Soc.*, **33**, 1474 (1937).

(4) Grosse and Linn, *J. Org. Chem.*, **3**, 26 (1938).

Summary

Cyclopropane has been found to react with benzene catalyzed by hydrogen fluoride to give normal propylbenzenes in good yield. A possible mechanism for the reaction is postulated.

STATE COLLEGE, PENNA. RECEIVED SEPTEMBER 1, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE PENNSYLVANIA STATE COLLEGE]

Hydrogen Fluoride as a Condensing Agent. V. Reactions of Compounds Containing Oxygen and Reactions of Tertiary Halides with Olefins

BY J. H. SIMONS, S. ARCHER, AND H. J. PASSINO

In the preceding papers of this series[1] the usefulness of hydrogen fluoride has been shown as a condensing agent for reactions between aromatic compounds and either unsaturated compounds or halides. That this reagent will promote many other reactions can now be shown. It appears that it catalyzes the same reactions that acidic reagents such as sulfuric acid catalyze and also the reactions that metallic halides such as aluminum chloride or boron trifluoride catalyze. For some reactions it is not only more convenient technically but also produces higher yields. There are reactions that hydrogen fluoride promotes that have not been reported using other reagents. One of these is a reaction between an aliphatic halide and an olefin. Two examples of this reaction are reported here in preliminary form. These are the reactions of tertiary butyl chloride with trimethylethylene and with cyclohexene.

The reactions of compounds containing oxygen are somewhat different from reactions of compounds that do not. Due to the peculiar properties of hydrogen fluoride, one cannot predict its effect in these reactions. To show the usefulness of hydrogen fluoride for them an account of the following reactions is included. Tertiary butyl alcohol has been caused to react with benzene to form tertiary butyl benzene, tertiary butyl chloride has reacted with phenol to form tertiary butyl phenol, and tertiary butyl chloride has been made to react with ethyl furoate. For these reactions larger quantities of hydrogen fluoride are required.

Many other types of reactions undoubtedly can be performed by means of hydrogen fluoride but the variety that has now been accomplished shows the general usefulness of this reagent in organic reactions. The reasons for its apparent uniqueness probably can be found in its physical and chemical properties. These have been summarized by Simons.[2] Despite its apparent weakness in aqueous solutions, it is a very powerful acidic substance. This property of donating protons makes it a useful reagent for organic reactions such as polymerizations and rearrangements in which a positive organic ion is the intermediate. The fact that the other halogen halides are insoluble in it accounts for the reactions in which a halogen halide is eliminated. Its unusual ability to form addition compounds, which is so evident in its numerous complex inorganic compounds, probably accounts for its usefulness in reactions involving aromatic compounds. A complex intermediate similar to those postulated for reactions using aluminum chloride may be the active agent. It is certainly much more soluble in benzene than would be expected from its high dielectric constant. It is readily eliminated during the course of many organic reactions in which not more than one fluorine atom is attached to the same carbon atom, not because the carbon fluoride bond is weak but because the energy of formation of hydrogen fluoride is so very high.

Experimental

The same techniques were used as previously described[1] with the following exceptions. Tertiary butyl alcohol was added at one time as it clogged the delivery tube if added slowly. Ethyl furoate was used in solution in carbon tetrachloride. Much larger quantities of hydrogen fluoride were required in reactions involving oxygen containing compounds, and the reactions required a longer time. The reaction of ethyl furoate required about one hundred and fifty hours.

Tertiary Butyl Chloride and Trimethylethylene.—Distillation of the reaction products gave a constant boiling fraction of refractive index 1.4279–1.4315. It boiled 63–65° at 19 mm. This product was definitely an olefin with physical properties corresponding to the expected nonenes. The remainder of the material boiled over a continuous range of temperatures both above and below the constant boiling fraction. Apparently many products

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[1] Simons and Archer, THIS JOURNAL, **60**, 2952 and 2953 (1938); Simons, Archer and Adams, *ibid.*, **60**, 2955 (1938).

[2] Simons, *Chem. Rev.*, **8**, 213 (1931).

TABLE I

CONDENSATION REACTIONS USING HYDROGEN FLUORIDE INVOLVING OXYGEN CONTAINING COMPOUNDS

Alkyl compounds	Aromatic compound	Product	Yield, %	B. p., °C.
t-Butyl alcohol	Benzene	Mono-*t*-butylbenzene	3	165
		Di-*t*-butylbenzene	8	78–78.5[a]
t-Butyl chloride	Phenol	*p*-*t*-Butylphenol	85	234–238[b]
t-Butyl chloride	Ethyl furoate	Ethyl 5-*t*-butylfuroate	54	116–117 (16 mm.)[c]

[a] Melting point. A mixed melting point with known *p*-di-*t*-butylbenzene was 77–78°. [b] The *p*-*t*-butylphenol melted at 97–98°, *p*-toluenesulfonate of it melted at 108–109°. [c] n^{20} 1.4749, the ester on saponification gave 5-*t*-butylfuroic acid which melted at 105–105.5°.

are formed, and this reaction requires further study. The constant boiling fraction represents about 18% yield.

Tertiary Butyl Chloride and Cyclohexene.—Distillation of the reaction products gave a fraction boiling 40–42° under a pressure of 18 mm. and at 141.5–142° at 739 mm. The refractive index of this fraction was 1.4578. It decolorized bromine water and gave only a very weak chloride ion test. Since neither boiling point nor refractive index checks whatsoever with di- or triisobutylene, and since it appears to be an olefin, it is very probable that polymerization has occurred between the tertiary butyl chloride and the cyclohexene to give either a tertiary butyl cyclohexene or a substituted cyclohexyl ethylene.

The yield of this fraction was 31% of the theoretical. A triisobutylene fraction of less than 10% was also obtained.

Conclusions.—The general usefulness of hydrogen fluoride as a reagent in organic reactions has now been well established. The technique of its use is somewhat different than that of other similar reagents but its utility seems to be much greater than any of them. There are reactions such as that between an olefin and a tertiary chloride which it promotes that have not been previously reported.

Summary

Hydrogen fluoride has been found useful to catalyze reactions between tertiary butyl chloride and both trimethylethylene and cyclohexene. It also has been found to catalyze reactions involving oxygen containing compounds. Tertiary butyl alcohol has been caused to react with benzene, tertiary butyl chloride formed tertiary butylphenol upon reaction with phenol, and ethyl 5-*t*-butylfuroate was formed from tertiary butyl chloride and ethyl furoate.

An explanation for the general utility of hydrogen fluoride in organic reactions is sought in its chemical and physical properties.

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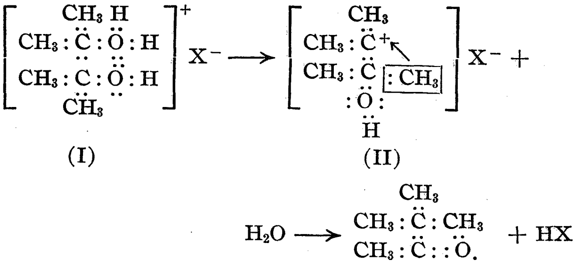
[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

The Pinacol–Pinacolone Rearrangement: the Preparation and Rearrangement of Tetramethylethylene Bromohydrin

BY GEORGE W. AYERS, JR.[1]

The Stieglitz mechanism[2] of the pinacol–pinacolone rearrangement assumes that an intermediate oxonium salt (I) loses water to leave a nucleus[3] (II) in which one of the carbon atoms possesses only three pairs of electrons. This "fault" in the molecule is then repaired by the migration of a negative methyl group, with its full complement of electrons, from the adjacent carbon atom to the electron deficient carbon atom



$$\left[\begin{array}{c} \mathrm{CH_3}\ \ \mathrm{H} \\ \mathrm{CH_3}:\ddot{\mathrm{C}}:\ddot{\mathrm{O}}:\mathrm{H} \\ \mathrm{CH_3}:\mathrm{C}:\ddot{\mathrm{O}}:\mathrm{H} \\ \mathrm{CH_3} \end{array}\right]^{+} \mathrm{X}^{-} \longrightarrow \left[\begin{array}{c} \mathrm{CH_3} \\ \mathrm{CH_3}:\ddot{\mathrm{C}}^{+}\nwarrow \\ \mathrm{CH_3}:\ddot{\mathrm{C}}\ \boxed{:\mathrm{CH_3}} \\ :\ddot{\mathrm{O}}: \\ \ddot{\mathrm{H}} \end{array}\right] \mathrm{X}^{-} +$$

(I) (II)

$$\mathrm{H_2O} \longrightarrow \begin{array}{c} \mathrm{CH_3} \\ \mathrm{CH_3}:\ddot{\mathrm{C}}:\mathrm{CH_3} \\ \mathrm{CH_3}:\ddot{\mathrm{C}}::\ddot{\mathrm{O}}. \end{array} + \mathrm{HX}$$

(III)

This rearrangement, in which one carbon atom is completely reduced and another completely oxi-

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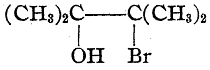
[1] Under the supervision of the late Dr. Julius Stieglitz. This paper is a portion of the thesis presented by the author to the Graduate School of the University of Chicago for the degree of Doctor of Philosophy in December, 1931.

[2] (a) Stieglitz, *Am. Chem. J.*, **39**, 29, 166 (1908); (b) Derby, *ibid.*, **39**, 437 (1908); (c) McCracken, *ibid.*, **39**, 437, 586 (1908); (d) Migita, *Bull. Chem. Soc. Japan*, **3**, 308 (1928); (e) R. B. Cooper, Doctor's Dissertation, University of Chicago, 1930; (f) K. H. Adams, Doctor's Dissertation, University of Chicago, 1932; (g) Stieglitz, Cooper and Ayers, *Trans. Ill. State Acad. Sci.*, **25**, 173 (1933); for a review of previous work see Gilman, "Organic Chemistry, An Advanced Treatise," Vol. I, 1938, p. 720, and Porter, "Molecular Rearrangements," 1928, p. 85.

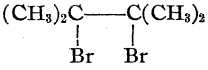
[3] See Whitmore, THIS JOURNAL, **54**, 3274 (1932).

dized, is a manifestation of the tendency of compounds in an intermediate stage of oxidation or reduction to revert, through migrations of electrons, to a state of complete oxidation or reduction. As a corollary of this mechanism it should be possible to bring about the rearrangement of halohydrins by elimination of halide ion, to the corresponding ketone. Adams observed that tetramethylethylene chlorohydrin did not decompose at 150°, and that only at 175°, in benzene solution, did any noticeable decomposition take place. Since halide ion can be separated more easily from an alkyl bromide than from the corresponding chloride, it was of interest to ascertain whether rearrangement of tetramethylethylene bromohydrin (IV) can be induced by heating. This hitherto unknown compound was found to lose hydrogen bromide, even at 100°, to yield pinacolone. The corresponding iodohydrin[1] was stable only in solution; the solid, which resisted purification, decomposed spontaneously to pinacolone and other products.



$$\begin{array}{cc}(CH_3)_2C\text{——} & C(CH_3)_2\\ | & |\\ OH & Br\end{array}$$

(IV)



$$\begin{array}{cc}(CH_3)_2C\text{——} & C(CH_3)_2\\ | & |\\ Br & Br\end{array}$$

(V)

The preparation of tetramethylethylene bromohydrin (IV) from anhydrous pinacol and gaseous hydrogen bromide provided several interesting observations. Dependent on dilution, nature of the solvent and rate of addition of hydrogen bromide, a variety of products could be isolated. In the absence of solvent a mixture of bromohydrin (IV) and dibromide (V) was obtained. In anhydrous ether, primarily, a mixture of pinacol hydrobromides was formed, which, upon continued passage of hydrogen bromide, was converted to bromohydrin (IV). Further reaction with hydrogen bromide brought about formation of dibromide (V). In chloroform, the same reagents caused precipitation of a white crystalline compound, the composition of which corresponded to (I), in which X^- is bromide. This hydrobromide was unstable, losing water from the solid state within a few hours, and passed over into the bromohydrin (IV). The corresponding hydrochloride was made in a similar manner by Harries,[4] who observed that it decomposed at 55° but failed to identify the products. Finally, in ligroin or carbon tetrachloride there was formed a crystalline compound, stable for several weeks at room temperature, which had a composition corresponding to dipinacol hydrobromide, $[(C_6H_{14}O_2)_2H]Br$. Formation of a dimolecular product indicated that pinacol itself might be dimolecular in certain solvents, and this was found to be the case in benzene. This dipinacol hydrobromide can also be separated from the mixture of hydrobromides formed in anhydrous ether, since pinacol hydrobromide (I) is converted to bromohydrin (IV) which volatilizes, leaving the pure dimolecular compound.

The pure bromohydrin (IV) is quite unstable, decomposing slightly even on standing overnight in the refrigerator. In an open tube at 110° it rearranges to pinacolone. When mixed with dry sodium bicarbonate, to remove any trace of catalyzing acid formed by decomposition, the bromohydrin (IV) showed evidence of decomposition even at 100°. After extremely thorough drying of a benzene solution of the bromohydrin, the latter rearranged to pinacolone when the solution was heated at 100° for six hours. Rearrangement to pinacolone also took place when an ether solution of the bromohydrin was shaken with aqueous solutions of silver nitrate or sodium thiosulfate, or with silver oxide.

The properties of pinacol hydrobromide (I) (X = Br) lend support to the Stieglitz mechanism of the pinacol rearrangement. Under the ordinary conditions of the acid catalyzed rearrangement in aqueous solution the small amount of pinacol hydrohalide must be in the form of the highly ionized oxonium salt (I). In water the oxonium and halide ions are separated by so many intervening water molecules that the "fault" occurring in the molecule (II) when water is split off can be adjusted only by rearrangement to pinacolone. On the other hand, in the crystalline hydrobromide, the bromide ions are within atomic distances of the oxonium ions, and can, when water is lost by the latter, slip to the positively charged carbon atom, with formation of the bromohydrin (IV).

Experimental

Anhydrous Pinacol.—Pinacol hydrate was prepared according to "Organic Syntheses."[5] The best yields were obtained when most of the acetone was added before the reaction started. Dehydration[6,2f] was effected

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[4] Harries, *Ann.*, **383**, 183 (1911).

[5] "Org. Syntheses," Vol. V, 1926, p. 87; Coll. Vol. I, 1932, p. 448.

[6] Städeler, *Ann.*, **111**, 281 (1859); Linnemann, *Ann. Suppl.*, **3**, 377 (1865); Risseghem, *Bull. soc. chim. Belg.*, **30**, 8 (1921); King and Stewart, *Proc. Trans. Nova Scot. Inst. Sci.*, **17**, 262 (1930).

as follows. The hydrate, in a large round-bottomed flask, was heated with an oil-bath to 110°; suction was then applied with a water-pump until evaporation of water stopped. The flask was returned to atmospheric pressure, the bath temperature raised by 10° and the previous operation was repeated. The same series of operations was repeated until a high-boiling liquid started to condense on the walls of the flask. The pinacol was then distilled at atmospheric pressure and the fraction boiling at 170–175° collected as anhydrous pinacol, yield, *ca.* 30%. About 50% of the charge was recovered from the condensate formed in dehydration or as partially hydrated pinacol in the fore-run of the distillation.

The water-white product solidified upon standing, and could be used for most purposes without further treatment. Absolutely anhydrous pinacol, m. p. 38°, b. p. 172°,[7] was obtained by redistillation at atmospheric pressure.

Tetramethylethylene Bromohydrin.—A rapid stream of hydrogen bromide was passed continuously through a solution of 25 g. of anhydrous pinacol in 375 cc. of anhydrous ether. The white precipitate which started to form in one minute settled as a faintly yellow, viscous liquid. After twenty-five minutes the whole mixture became homogeneous and was washed immediately with four portions of distilled water and dried over sodium sulfate. The filtered solution was concentrated, either under reduced pressure or by evaporation in a gentle stream of air, to a pasty crystalline mass. This was dried in a desiccator on porous plate, over calcium chloride and paraffin; yield, 21–27% (8–10.4 g.). The melting point of the impure bromohydrin varied with different preparations from 66 to 71°. The purest samples were obtained in small preparations with low yields. The crude bromohydrin was recrystallized from ligroin in the same manner that it was originally isolated from ether solution. It was thus obtained as a fluffy white crystalline powder, which, after drying over calcium chloride and paraffin, melted at 70.5°. Large pure crystals of the same melting point were obtained as a sublimate from impure samples of the bromohydrin, which had been stored in the refrigerator.

Anal. Calcd. for $C_6H_{13}OBr$: Br, 44.13. Found: Br, 44.22, 44.24.

The solid bromohydrin is extremely volatile, with a camphoraceous odor and lachrymatory properties. If it contains traces of water it develops brown specks, on standing overnight, with lowering of the melting point. However, perfectly dry samples can be preserved for some time.

Pinacol Hydrobromide, $C_6H_{14}O_2{\cdot}HBr$.—Gaseous hydrogen bromide was passed into an ice-cold solution of 5 g. of anhydrous pinacol in eight volumes of chloroform. The solution remained clear for some time, when it suddenly solidified. Hydrogen bromide was passed through for an additional minute; the mixture was filtered with suction, washed once with chloroform and sucked dry. The crystals were pressed on porous plate and dried over calcium chloride and paraffin.

Anal. Titration with 0.09632 *N* KOH. Calcd. for $C_6H_{14}O_2{\cdot}HBr$: HBr, 40.65. Found: HBr, 40.88.

Pinacol hydrobromide is a colorless, crystalline solid, soluble in water and fuming in moist air. A sample, kept in a desiccator on porous plate, over calcium chloride and paraffin, for two days, disappeared to leave only a trace of material which contained only 35.9% of hydrogen bromide. That it had been converted to bromohydrin (IV) was evident from the odor of the latter and the absence of hydrogen bromide.

Dipinacol Hydrobromide, $(C_6H_{14}O_2)_2{\cdot}HBr$. **(A).**—A solution of 5 g. of anhydrous pinacol in 125 cc. of ligroin (30–50°) was treated with hydrogen bromide until precipitation was complete. The sticky white product was washed four times with ligroin and dried overnight on a porous plate over sulfuric acid and paraffin.

(B).—A solution of 5 g. of anhydrous pinacol in 75 cc. of carbon tetrachloride was treated with hydrogen bromide until the primarily formed oily layer, after becoming extremely viscous, changed to a granular solid. The solid was washed four times with carbon tetrachloride, pressed on porous plate and dried overnight over calcium chloride and paraffin.

Anal. Titration with 0.4363 *N* KOH, phenolphthalein indicator. Calcd. for $(C_6H_{14}O_2)_2{\cdot}HBr$: HBr, 25.5. Found: HBr, A, 25.3; B, 25.4.

Freshly precipitated dipinacol hydrobromide is granular, changing, on standing, to well-defined crystals, m. p. 52–54°. Under anhydrous conditions it is stable, showing no change in composition after two weeks. It dissolves instantly in water, and deliquesces in the air to form a solution of the components.

Dipinacol hydrobromide was also isolated from the mixture of hydrobromides formed, as a viscous liquid, in the first stage of the preparation of the bromohydrin (IV). On standing for several days in a desiccator, over calcium chloride and paraffin, the true hydrobromide became converted to bromohydrin (IV), which sublimed to leave pure dipinacol hydrobromide.

Molecular Weight of Anhydrous Pinacol.—The molecular weight was determined cryoscopically in benzene.

Expt.	Weight of pinacol	Weight of benzene	ΔT	Molecular weight Found	Calcd. $(C_6H_{14}O_2)_2$
1	24.138	526.4	0.960°	245	236
2	23.201	554.4	0.927°	231	236

Thermal Rearrangement of Tetramethylethylene Bromohydrin.—Equal volumes (10 cc.) of a solution of 1.12 parts of bromohydrin in 10 parts of benzene, previously dried over sodium sulfate for eighteen days in the refrigerator, were sealed in four Pyrex tubes and heated for six hours, two at 100° and two at 150°. All were then acid to methyl orange and gave copious precipitates with Nessler's solution, indicating pinacolone formation. More voluminous precipitates were obtained from the tubes heated at 150° than from those at 100°, indicating more nearly complete rearrangement at the higher temperature.

An analytical sample (1 g.) of the bromohydrin decomposed when heated in an open glass tube in a bath at 110°. This experiment was repeated with a sample that had been mixed with four parts of sodium bicarbonate, and ketone formation was demonstrated with Nessler's solution.

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(7) "Int. Crit. Tables," Vol. I, 1926, p. 204, gives m. p. 38° and b. p. 172.8°.

Rearrangement of Tetramethylethylene Bromohydrin by Chemical Reagents.—Portions of a solution of bromohydrin in absolute ether were treated with aqueous solutions of (1) silver nitrate and (2) sodium thiosulfate and (3) an aqueous suspension of silver oxide. After treatments (1) and (3) gave precipitates of silver bromide, excess sodium chloride solution was added and the precipitates were removed by filtration. In treatment (2) the ether was decanted from the turbid aqueous layer. All three then gave copious precipitates with Nessler's solution. A fourth sample, untreated otherwise, gave no precipitate with this reagent, nor did an aqueous solution of pinacol hydrate, which had been previously treated, as above, with silver nitrate and sodium chloride.

Summary

1. Depending on the reaction conditions, the action of gaseous hydrogen bromide on anhydrous pinacol leads to tetramethylethylene bromohydrin, tetramethylethylene dibromide, pinacol hydrobromide or dipinacol hydrobromide. Pinacol hydrobromide is the intermediate in bromohydrin formation, as well as the postulated intermediate in the hydrobromic acid-catalyzed rearrangement of pinacol to pinacolone.

2. Tetramethylethylene bromohydrin rearranges to pinacolone on heating or on treatment, at room temperature, with halide abstracting reagents. This lends support to the Stieglitz mechanism of the pinacol–pinacolone rearrangement.

CHICAGO, ILLINOIS RECEIVED JULY 13, 1938

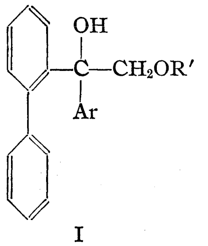
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Synthesis of Phenanthrene Derivatives. I. 9-Phenyl- and 9-*p*-Tolylphenanthrene

BY CHARLES K. BRADSHER AND ALLAN K. SCHNEIDER

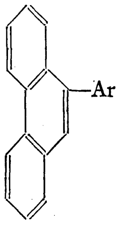
With the exception of the elaborate Pschorr[1] synthesis, all of the methods usually employed for the synthesis of phenanthrene derivatives have a common disadvantage. They involve one step in which hydrophenanthrenes are dehydrogenated at high temperatures by the action of sulfur, selenium or platinum. Frequently a desired phenanthrene derivative is incapable of surviving such a treatment, and it was in the hope of providing a means for the synthesis of such derivatives that this research was undertaken.

A new cyclization reaction has been discovered giving promise of accomplishing this end. When compounds of type I were treated with mineral acids they lost the elements corresponding to one molecule of water and one molecule of methyl alcohol or phenol to form the corresponding 9-arylphenanthrene (II).



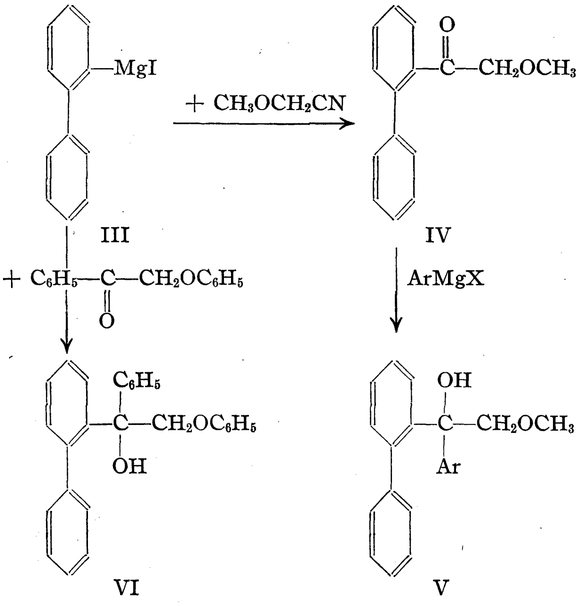
I

(R' = CH_3 or C_6H_5)



II

The carbinols used were prepared by two methods.



In the first, 2-xenylmagnesium iodide (III) was treated with methoxyacetonitrile. Upon hydrolysis the reaction product gave 2-(ω-methoxyaceto)-biphenyl (IV). This upon treatment with phenyl- or *p*-tolylmagnesium bromide gave the corresponding carbinol (V).

In the second method, ω-phenoxyacetophenone was treated with 2-xenylmagnesium iodide (III) to form 1-phenyl-1-(2-xenyl)-2-phenoxyethanol-1 (VI).

When treated with concentrated sulfuric acid

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(1) Pschorr, *Ber.*, **29**, 496 (1896).

the methoxyethanols (V) underwent cyclization to give the corresponding hydrocarbons, 9-phenyl- and 9-*p*-tolylphenanthrene. The phenoxyethanol (VI) lost only the elements of water when treated with concentrated sulfuric acid. The structure of this new compound has not been determined. When VI was refluxed for twenty-two hours with constant-boiling hydrobromic acid, 9-phenylphenanthrene was obtained in good yield. This hydrocarbon has been prepared previously by Koelsch,[2] by Bergmann[3] and by Weizmann.[4] The 9-*p*-tolylphenanthrene is a new hydrocarbon and was found to melt slightly lower than the corresponding phenyl compound.

Further work is in progress on the development of this synthesis.

The authors are indebted to the Monsanto Chemical Company for a gift of 2-aminobiphenyl.

Experimental

2-(ω-Methoxy)-acetobiphenyl (IV).—A Grignard reagent was prepared in an atmosphere of nitrogen by the action of 2.7 g. of magnesium turnings on 28 g. of 2-iodobiphenyl[5] in 100 cc. of anhydrous ether. When the formation of the reagent was complete, about two-thirds of the ether was distilled from the reaction mixture. A solution of 7.1 g. of methoxyacetonitrile[6] in 100 cc. of dry benzene was added and the mixture refluxed for fifteen hours. At the conclusion of this period the magnesium salt was decomposed by the addition of a mixture of ammonium hydroxide and ammonium chloride solution. The ether-benzene layer was separated and extracted with 0.1 *N* hydrochloric acid. Concentrated hydrochloric acid was then added and the mixture refluxed for two hours. The ketone was taken up in ether, dried and distilled. The product was a slightly yellow oil, b. p. 159–162° (4 mm.); yield, 13.3 g. (60%).

Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.61; H, 6.24. Found: C, 79.92; H, 6.35.

1-Phenyl-1-(2-biphenyl)-2-methoxyethanol-1 (V).—A solution of 4 g. (0.018 mole) of 2-(ω-methoxy)-acetobiphenyl in 20 cc. of dry ether was added to 0.03 mole of phenylmagnesium bromide and the mixture refluxed for thirty minutes. A solution of ammonium chloride was then added and the ether layer separated and dried. After removal of the ether under reduced pressure there remained about 3 cc. of a red-brown oil. No effort was made to purify this material further.

9-Phenylphenanthrene.—Approximately 0.75 cc. of the above carbinol was dissolved at room temperature in 5 cc. of concentrated sulfuric acid. After thirty minutes the dark brown sirup was poured on 25 g. of ice. The hydrocarbon was extracted with ether and isolated by vacuum sublimation. A small amount of a white substance was obtained which, twice recrystallized, melted at 104–105°.

Anal. Calcd. for $C_{20}H_{14}$: C, 94.49; H, 5.51. Found: C, 94.24; H, 5.59.

The picrate crystallized as orange-red needles, m. p. 114°. It decomposed on attempted recrystallization. Upon decomposition of the picrate in ether with dilute ammonium hydroxide the hydrocarbon was recovered; m. p. 104–105°.

1-*p*-Tolyl-1-(2-biphenyl)-2-methoxyethanol-1 was made in the same manner as the corresponding phenylcarbinol, using *p*-tolylmagnesium bromide. The resulting light brown oil was not purified.

9-*p*-Tolylphenanthrene.—Three cubic centimeters of the oil obtained above was mixed with 8 cc. of concentrated sulfuric acid and allowed to stand for thirty minutes. The remainder of the procedure was identical with that used for the preparation of the phenylphenanthrene. Large, rhombic, transparent crystals were obtained from ether–petroleum ether, m. p. 90–91°.

Anal. Calcd. for $C_{12}H_{16}$: C, 94.03; H, 5.97. Found: C, 94.14; H, 6.06.

A picrate was made in the usual manner. Fine orange-red needles precipitated after an hour in an ice–salt bath. These melted at 126–127°.

1-Phenyl-1-(2-biphenyl)-2-phenoxyethanol-1 (VI).—A Grignard reagent was prepared from 20 g. of 2-iodobiphenyl. To this was added a solution of 15.2 g. of ω-phenoxyacetophenone[7] in 50 cc. of dry benzene. The mixture was refluxed for one hour and then decomposed with a 20% solution of ammonium chloride. After removal of the solvents under reduced pressure the carbinol was crystallized from ether–petroleum ether. Irregular white crystals, m. p. 93–95°, were obtained. The yield was 17.1 g. (65% of the theoretical). An analytical sample prepared by repeated crystallization melted at 94–95°.

Anal. Calcd. for $C_{26}H_{22}O_2$: C, 85.24; H, 6.01. Found: C, 85.06; H, 6.10.

Reaction of VI with Sulfuric Acid.—One gram of the above carbinol was suspended in 7 cc. of concentrated sulfuric acid and the mixture heated at about 100° until the oil formed at first had resolidified. The mixture was poured on ice and the product collected and crystallized from acetic acid as white prisms with m. p. 148–149°. The yield was 0.3 g. Twice recrystallized the product melted at 150–152°.

Anal. Calcd. for $C_{26}H_{20}O$: C, 89.65; H, 5.75. Found: C, 89.54; H, 5.96.

Cyclization of VI with Hydrobromic Acid.—To a boiling solution of 3.4 g. of VI in 20 cc. of acetic acid, 10 cc. of constant boiling hydrobromic acid was added. The mixture was refluxed for twenty hours, poured into water and taken up in ether. The phenol was extracted with dilute alkali and the ethereal solution evaporated. The residue, once recrystallized from ethyl alcohol, melted at 103–104° and was shown to be **9-phenylphenanthrene** by a mixed melting point determination; yield, 2 g. (84%).

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(2) Koelsch, THIS JOURNAL, **56**, 480 (1934).

(3) Bergmann and Bergmann, *ibid.*, **59**, 1443 (1937).

(4) Weizmann, Bergmann and Berlin, *ibid.*, **60**, 1331 (1938).

(5) Cook, *J. Chem. Soc.*, 1087 (1930).

(6) Scarrow and Allen, *Org. Syntheses*, **13**, 56 (1933).

(7) Möhlau, *Ber.*, **15**, 2497 (1882).

Summary

Two phenanthrene hydrocarbons, 9-phenyl- and 9-*p*-tolylphenanthrene, have been prepared from 2-iodobiphenyl by a synthesis involving a new type of ring closure.

URBANA, ILLINOIS RECEIVED SEPTEMBER 26, 1938

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Studies in the Phenanthrene Series. XXII. Derivatives of Dibenzisoquinoline and Naphthisoquinoline[1]

BY ERICH MOSETTIG AND EVERETTE L. MAY[2]

In previous communications from this Laboratory we described the synthesis of a number of hydrogenated and N-methylated benzofuroquinolines[3] and naphthoquinolines,[4] which we hoped might exhibit an analgesic effect because of their superficial structural similarity to morphine. These compounds, however, proved to be either very weak analgesics or were entirely ineffective.[5] Since morphine may be interpreted as an isoquinoline derivative, a higher analgesic effectiveness—within the series of tetracyclic compounds consisting of three isocyclic rings and one nitrogen-containing ring—may be expected of phenanthrene derivatives in which the nitrogen is located in β-position to one of the benzene nuclei, *i. e.*, of compounds that include in their structure the isoquinoline system.

Apparently, the most practicable methods for preparing isoquinoline derivatives are those in which compounds of the general type R—C—C—N— are employed as starting materials. In various attempts to prepare compounds of this type we found that the phenanthrene derivatives $C_{14}H_9$-$CHOCH_3CH_2NH_2$ (IV, V) were relatively easily accessible by the method of Rosenmund,[6] which was later somewhat modified by Mannich and coworkers.[7] We employed in the second step of this preparation—the reduction of the corresponding nitro ether—platinum oxide as catalyst successfully, and alcohol as solvent. Attempts to cyclize the formyl derivatives of IV and V and the benzoyl derivative of V, according to Mannich and coworkers,[7] in order to obtain isoquinoline derivatives, by simultaneous loss of water and methanol, were unsuccessful, in spite of manifold experimental variations in respect to solvent and condensing agent. The resulting reaction mixtures consisted of colored, tarry, or partly charred products.

Equally unsuccessful were the attempts to cyclize the formyl derivatives of the β-phenanthryl ethyl amines VII and VIII to dihydroisoquinoline derivatives by the Bischler–Napieralski method. Also in this series of experiments we employed many variations such as those devised by Pictet, by Decker, and by Späth.[8] After several practically unsuccessful attempts to prepare the ethylamine derivatives (VI, VII, VIII) by the Hofmann or Curtius degradation of β-phenanthrylpropionic acids,[9] we finally obtained these amines, according to the method of Slotta and Szyszka,[10] by electrolytic reduction of the corresponding nitrostyrene derivatives (I, II, III). The 3-derivative (VII) was also prepared by chlorination of 3-(2-amino-1-hydroxyethyl)-phenanthrene and subsequent catalytic dechlorination.

By cyclizing the formaldehyde condensation products of VI and VIII with dilute aqueous hydrochloric acid according to the method of Decker and Becker,[11] we obtained the expected tetrahydroisoquinoline derivatives (IX, X)[12] in satisfactory yields. The cyclization apparently proceeded in both series (2 and 9) only in one di-

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[1] The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, the University of Virginia, and the University of Michigan. Paper XXI, THIS JOURNAL, **60**, 2464 (1938).

[2] Mallinckrodt Research Fellow, 1937–1938, E. R. Squibb and Sons Research Fellow, 1938–.

[3] Mosettig and Robinson, THIS JOURNAL, **57**, 902 (1935).

[4] (a) Mosettig and Krueger, *ibid.*, **58**, 1311 (1936); (b) Continued in "Studies in the Phenanthrene Series, XIX," Mosettig and Krueger, *J. Org. Chem.*, in press.

[5] Eddy, *J. Pharmacol.*, **58**, 159 (1936), and unpublished results.

[6] Rosenmund, *Ber.*, **46**, 1034 (1913).

[7] Mannich and Walther, *Arch. Pharm.*, **265**, 1 (1927); Mannich and Falber, *ibid.*, **267**, 601 (1929).

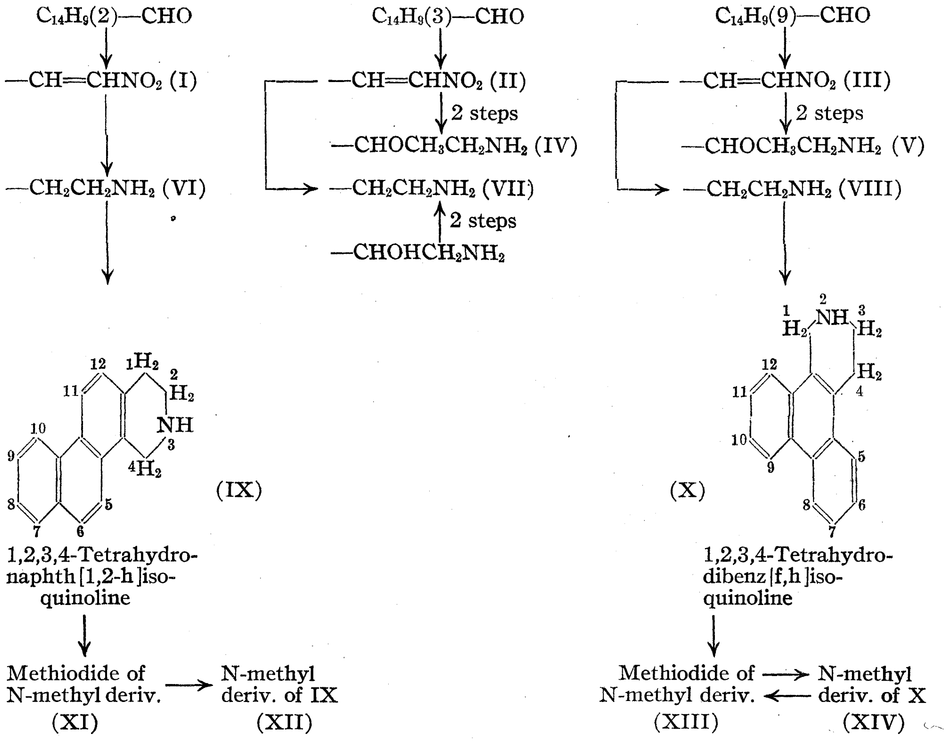
[8] Bischler and Napieralski, *Ber.*, **26**, 1903 (1893); Pictet and Kay, *ibid.*, **42**, 1973 (1909); Decker, Kropp, Hayer and Becker, *Ann.*, **395**, 299 (1913); Späth, Berger and Kuntara, *Ber.*, **63**, 134 (1930).

[9] See van de Kamp, Burger and Mosettig, THIS JOURNAL, **60**, 1321 (1938).

[10] Slotta and Szyszka, *J. prakt. Chem.*, [2] **137**, 339 (1933).

[11] Decker and Becker, *Ann.*, **395**, 342 (1913).

[12] The orientation, numbering, and names of the heterocyclic compounds included in this paper have been recommended to us by Dr. Capell through the kindness of Dr. Crane. *Cf.* Patterson, THIS JOURNAL, **50**, 3083 (1928).



rection. No tetrahydroisoquinoline ring closure could be accomplished in the 3-series, with the formaldehyde condensation product of VII. Under the conditions employed in the 2- and 9-series only hydrolysis took place, the whole starting material, the β-phenanthrylethylamine VII, being recovered unchanged. Forcing the reaction (concentrated hydrochloric acid, longer reaction time) led to amorphous hydrochlorides of a brown, muddy color which resisted all attempts of purification. 3-Methyl-1,2,3,4-tetrahydronaphth-[1,2-h]isoquinoline (XII) and 2-methyl-1,2,3,4-tetrahydrodibenz[f,h]isoquinoline (XIV) were prepared readily and in good yields by converting IX and X to the quaternary methiodides XI and XIII and subsequently decomposing the latter by heating in a vacuum.

There hardly can be any doubt concerning the structure of X, since the alternative ring closure from position 9 to position 8 of phenanthrene would necessarily result in a seven-membered nitrogen-containing ring. For the isoquinoline derivative, obtained from the formaldehyde condensation product of VI, we advance for reasons of analogy the structural formula IX, since, to our knowledge, all cyclizations of side chains as —C—C—C, —C—C—C—C, and —N—C—C—C— attached to position 2 of phenanthrene take place in position 1.[4b]

We also attempted to cyclize the formaldehyde condensation products of the amino ethers IV and V, respectively, according to the method of Decker and Becker,[11] but no cyclization took place and IV and V were recovered unchanged from the reaction mixture.

Because of present lack of material only 2-methyl-1,2,3,4-tetrahydrodibenz[f,h]isoquinoline XIV was investigated pharmacologically by Dr. Eddy at the University of Michigan.[13] Noteworthy, besides the marked analgesic effect of this substance (M. E. D. 20 mg./kg. cat), is its great hypnotic effect (M. E. D. 5 mg./kg. cat) which unfortunately is accompanied by an equally marked emetic effect when the substance is administered orally.

Experimental

3-(2-Nitrovinyl)-phenanthrene[14] (II).—To a solution of 10 g. of 3-phenanthrene aldehyde[15] in 375 cc. of alcohol was added 6.3 g. of nitromethane. The mixture was cooled (0–5°) and an ice cold solution of 5 g. of potassium hydroxide in 100 cc. of alcohol was dropped in with mechanical stirring during half an hour (the temperature was not allowed to rise above 15°). The precipitate (potassium salt of the condensation product) was brought into solution with ice water, and the nearly clear solution was poured slowly into 200 cc. of 10% hydrochloric acid which had

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(13) Eddy, unpublished results.

(14) See Rosenmund, *Ber.*, **43**, 3412 (1910); Lange and Hambourger, THIS JOURNAL, **53**, 3865 (1931).

(15) Mosettig and van de Kamp, *ibid.*, **55**, 2995 (1933).

been cooled previously to 10°. The yellow, finely divided crystalline solid was collected, washed with water, and recrystallized from benzene; yellow needles, m. p. 180–180.5° (corr.), yield 90%.

Anal. Calcd. for $C_{16}H_{11}O_2N$: C, 77.10; H, 4.45. Found: C, 77.19; H, 4.06.

2-(2-Nitrovinyl)-phenanthrene (I).—This compound was prepared like the 3-isomer, but, owing to the lesser solubility of the phenanthrene-2-aldehyde, more solvent was necessary (5 g. of aldehyde in 350 cc. of alcohol). It showed a tendency to precipitate at first, in an amorphous state, when poured into the hydrochloric acid. It is decidedly more soluble in benzene than the 3-isomer and was purified by crystallization from benzene–petroleum ether as yellow needles, m. p. 134.5–137° (corr.), yield 80%.

Anal. Calcd. for $C_{16}H_{11}O_2N$: C, 77.10; H, 4.45. Found: C, 76.80; H, 4.18.

9-(2-Nitrovinyl)-phenanthrene (III).—The preparation was carried out as above, but more solvent was required (5 g. of aldehyde in 420 cc. of alcohol). The nitrostyrene derivative was recrystallized from benzene–petroleum ether: yellow needles, m. p. 173–173.5° (corr.), yield 95%.

Anal. Calcd. for $C_{16}H_{11}O_2N$: C, 77.10; H, 4.45. Found: C, 77.50; H, 4.66.

This compound has been prepared recently in essentially the same manner by Reichert and Wegner,[16] who report the m. p. 173°.

9-(1-Methoxy-2-nitroethyl)-phenanthrene.—To an ice cold (0–5°) suspension of 5.0 g. of finely divided III in 125 cc. of methanol was added, under mechanical stirring, 33 cc. of a sodium methoxide solution prepared from 4.5 g. of sodium and 100 cc. of methanol. A clear solution was obtained in about one-half hour. It was decanted from a small amount of unchanged starting material and acidified with 5 cc. of glacial acetic acid. The solution was evaporated in a water-pump vacuum to dryness at a temperature as low as possible, 500 cc. of water was added to the residue, and the resulting pale yellow precipitate was filtered, washed with water, and recrystallized from ethyl alcohol: pale yellow plates, m. p. 134–134.5° (corr.), yield nearly quantitative.

Anal. Calcd. for $C_{17}H_{15}O_3N$: OCH_3, 11.02. Found: OCH_3, 10.59.

3-(1-Methoxy-2-nitroethyl)-phenanthrene.—This compound was prepared like the 9-isomer, except that the reaction mixture was kept at 0 to −5° for two hours. The purification of the final precipitate (from water) offered some difficulties. It was dissolved in warm alcohol and gradually cooled to room temperature, whereby some oily material was deposited. The solution was decanted, and on further cooling more oil precipitated. The solution was again decanted until finally a clear solution resulted, from which, on standing overnight, pale yellow crystals separated. They were recrystallized from alcohol: pale yellow circular plates, m. p. 102–104° (corr.), yield 55%.

Anal. Calcd. for $C_{17}H_{15}O_3N$: OCH_3, 11.02. Found: OCH_3, 10.67.

3-(1-Methoxy-2-aminoethyl)-phenanthrene (IV).—Four grams of the corresponding nitro ether and 0.15 g. of platinum oxide suspended in 200 cc. of alcohol absorbed the required amount of hydrogen in twenty to thirty hours. The resulting clear, colorless solution was filtered from the catalyst and evaporated to dryness in a vacuum. The oily base was dissolved in alcoholic hydrogen chloride and the hydrochloride was precipitated with ether. It crystallized from alcohol–ether in short colorless needles of m. p. 232–233° (dec.), yield 85%.

Anal. Calcd. for $C_{17}H_{18}ONCl$: Cl, 12.32. Found: Cl, 12.03.

9-(1-Methoxy-2-aminoethyl)-phenanthrene (V).—This compound was prepared like the 3-isomer. Its hydrochloride crystallized from alcohol–ether in colorless needles, m. p. 252–253° (dec.), yield 95%.

Anal. Calcd. for $C_{17}H_{18}ONCl$: Cl, 12.32. Found: Cl, 12.09.

Picrate, m. p. 215–217° (dec.).

Anal. Calcd. for $C_{23}H_{20}O_8N_4$: N, 11.66. Found: N, 11.73.

Formyl Derivative.—To an ethereal solution of V (prepared from 3 g. of hydrochloride) was added 0.6 g. of anhydrous formic acid. The crystalline formate was filtered and heated in a metal bath at 150° for about thirty minutes. The resulting brown oil turned to a crystalline brittle mass on cooling. It was dissolved in a little benzene and precipitated with petroleum ether; colorless leaflets, m. p. 138–140° (corr.), yield 70%.

Anal. Calcd. for $C_{18}H_{17}O_2N$: N, 5.01. Found: N, 4.90.

Benzoyl Derivative.—A mixture of V (prepared from 1 g. of hydrochloride), 0.6 g. of benzoyl chloride, and 4 cc. of 0.5 *N* sodium hydroxide solution was cooled and shaken. The crystalline mass that formed within a few minutes was filtered and washed with water. It crystallized from methanol–water in white leaflets of m. p. 147.5–148.5° (corr.), yield 80%.

Anal. Calcd. for $C_{24}H_{21}O_2N$: C, 81.09; H, 5.96. Found: C, 80.72; H, 5.92.

3-(2-Aminoethyl)-phenanthrene (VII).—The electrolytic reduction was carried out in an apparatus which was essentially the same as that described by Slotta and Szyszka.[10] A suspension of 7 g. of very pure 3-(2-nitrovinyl)-phenanthrene in a mixture of 50 cc. of alcohol, 80 cc. of glacial acetic acid, and 12 cc. of concentrated hydrochloric acid was introduced into the cathode compartment containing a prepared lead electrode of 60 sq. cm., while the anode compartment, containing a cooling spiral, was filled to the same level with 20% sulfuric acid. The current was kept at 3.5 amperes for three hours, at 4.5 amperes for two hours, and at 5 amperes for about five hours, temperature between 50 and 60°. The resulting clear solution at the cathode was decanted and evaporated nearly to dryness in a vacuum. The brown oily residue was dissolved in water and the solution was made alkaline and extracted with ether. The oil obtained from the ethereal solution was distilled slowly at 120–130° at a pressure of about 0.1 mm. The oily distillate was dissolved in a small volume of ether and allowed to stand in the cold for a few hours. A small amount of crystalline material (probably of higher molecular weight) precipitated and was filtered off. By addition of alcoholic hydrogen chloride to the filtrate, the

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[16] Reichert and Wegner, *Ber.*, **71**, 1254 (1938).

amine hydrochloride precipitated in crystalline form. It crystallized from alcohol–ether in white, short matted needles, m. p. 254–256°, yield 50%.

Anal. Calcd. for $C_{16}H_{16}NCl$: C, 74.55; H, 6.26. Found: C, 74.50; H, 5.97.

Formyl Derivative.—This compound was prepared like the corresponding derivative of V. It crystallized from benzene–petroleum ether in small white leaflets, m. p. 122–124° (corr.), yield 61%.

Anal. Calcd. for $C_{17}H_{15}ON$: N, 5.62. Found: N, 5.84.

9-(2-Aminoethyl)-phenanthrene (VIII).—This compound was prepared like its 3-isomer. Its hydrochloride crystallized from alcohol–ether in colorless needles, m. p. 307–309° (dec.), yield 57%.

Anal. Calcd. for $C_{16}H_{16}NCl$: C, 74.55; H, 6.26. Found: C, 74.78; H, 6.13.

Formyl Derivative.—Small, white leaflets, m. p. 111–112°, yield 70%.

Anal. Calcd. for $C_{17}H_{15}ON$: N, 5.62. Found: N, 5.56.

2-(2-Aminoethyl)-phenanthrene (VI).—This compound was obtained by electrolytic reduction, like the 3- and 9-isomers, but under somewhat different conditions. Three grams of 2-(2-nitrovinyl)-phenanthrene was suspended in a mixture of 40 cc. of alcohol, 75 cc. of glacial acetic acid, and 8 cc. of concentrated hydrochloric acid. The temperature was kept at 25–30° for the first two hours and at 30–40° for the remainder of the time (nine hours). A current of 3.1 amperes was maintained throughout the whole reaction. No clear solution was obtained, varying amounts of a brown fluffy solid always remaining in the cathode compartment. The amine hydrochloride crystallized from alcohol–ether in colorless leaflets, m. p. 317–318°; average yield 35–40%.

Anal. Calcd. for $C_{16}H_{16}NCl$: C, 74.55; H, 6.26; Cl, 13.76. Found: C, 74.67; H, 6.18; Cl, 13.79.

The picrate crystallized from alcohol in large yellow needles, m. p. 225–226°.

Anal. Calcd. for $C_{22}H_{18}O_7N_4$: N, 12.44. Found: N, 12.09.

3-(2-Amino-1-chloroethyl)-phenanthrene Hydrochloride.—Five grams of finely powdered 3-(2-amino-1-hydroxyethyl)-phenanthrene[9] was added in small amounts to a suspension of 6 g. of phosphorus pentachloride in 50 cc. of dry chloroform (vigorous mechanical stirring is necessary). The amino alcohol dissolved immediately and the hydrochloride of the chloro compound began to precipitate. The stirring was continued for another half hour and ether was added to the suspension in order to facilitate the filtration of the hydrochloride. It was recrystallized from alcohol–ether as colorless square plates, m. p. 219–220° (dec.), (the melt resolidifies at 225° and melts then gradually in the wide range of 226–295°); yield 73%.

Anal. Calcd. for $C_{16}H_{15}NCl_2$: Cl, 24.27. Found: Cl, 24.20.

Conversion to 3-(2-Aminoethyl)-phenanthrene, VII.—After varying the catalyst (palladium, palladium on charcoal or calcium carbonate, platinum oxide) and the concentration of the alcohol (100, 95, 90, 75, 50%) in the catalytic dechlorination, the phenanthrylethylamine (VII) finally was obtained in a satisfactory yield (approximately 75%) by employing 0.02 g. of platinum oxide and 25 cc. of 70% alcohol per gram of hydrochloride of the chloro compound. After the hydrogen absorption came to a standstill the resulting clear solution was filtered from the catalyst and evaporated to dryness. The crystalline residue was dissolved in water and the solution made alkaline and extracted with ether. The ether residue was distilled slowly in an oil-pump vacuum at 120°. The oily distillate was dissolved in a very small amount of ether in order to remove the by-product, which crystallized gradually from this solution. The hydrochloride of the 3-(2-aminoethyl)-phenanthrene was prepared and purified as described above and was identical in every respect with the compound prepared from 3-(2-nitrovinyl)-phenanthrene. The crystalline by-product was shown by melting point, mixture melting point with an authentic sample, and analysis to be 3-(2-amino-1-hydroxyethyl)-phenanthrene.

1,2,3,4-Tetrahydrodibenz[f,h]isoquinoline (X).—In the preparation of the tetrahydroisoquinoline derivatives we followed partly Buck's[17] directions developed for the preparation of various tetrahydroisoquinoline derivatives substituted in the benzene nucleus with O-alkyl groups.

A mixture of VIII prepared freshly from 8.5 g. of the hydrochloride, and 3.4 cc. of 40% formaldehyde solution, was heated on the steam-bath for one-half hour. The reaction mixture was evaporated in a vacuum to dryness. To the condensation product was added 12 cc. of 23% hydrochloric acid and the mixture was heated for one-half hour on the steam-bath. The hydrochloride of the tetrahydroisoquinoline compound precipitated almost at the start of heating as a white and voluminous mass. The reaction mixture was diluted with water, made alkaline, and extracted with benzene. The residue from the benzene solution was treated with alcoholic hydrogen chloride and ether. The hydrochloride was recrystallized from alcohol–ether, m. p. 304–306° (dec.), average yield 65%.

Anal. Calcd. for $C_{17}H_{16}NCl$: C, 75.69; H, 5.98. Found: C, 75.96; H, 5.96.

The free base may be obtained with loss by evaporating the benzene extract to a small volume and allowing it to stand in the cold. It consists of white needles, m. p. 223–225°.

Methiodide of 2-Methyl-1,2,3,4-tetrahydrodibenz[f,h]-isoquinoline (XIII).—To a solution of X, prepared from 0.6 g. of the hydrochloride, in 5 cc. of acetone was added 0.8 cc. of methyl iodide and 0.35 g. of potassium hydroxide. The quaternary salt began to precipitate immediately. After four hours 0.2 cc. of methyl iodide was added and the reaction mixture was allowed to stand for ten hours. The methiodide was filtered off, recrystallized first from water containing some potassium iodide, and finally from alcohol: colorless, square plates, m. p. 268–270° (dec.), yield 86%.

Anal. Calcd. for $C_{19}H_{20}NI$: I, 32.60. Found: I, 32.96.

This methiodide was also formed by merely mixing XIV (below) and methyl iodide in acetone solution.

2-Methyl-1,2,3,4-tetrahydrodibenz[f,h]isoquinoline (XIV).—One and five-tenths grams of the methiodide described above was heated in an oil-pump vacuum at 200–220°, whereby the N-methyl derivative distilled very

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[17] Buck, This Journal, 56, 1769 (1934).

slowly and practically no residue was left in the distillation bulb. The crystalline distillate was washed with water and taken up in ether. The ether residue sublimed in colorless needles, m. p. 113.5–114° (corr.), yield nearly quantitative.

Anal. Calcd. for $C_{18}H_{17}N$: N, 5.67. Found: N, 5.47.

The hydrochloride was prepared in the usual manner. It crystallizes from alcohol–ether in colorless lozenges.

Anal. Calcd. for $C_{18}H_{18}NCl$: C, 76.18; H, 6.39. Found: C, 75.80; H, 6.36.

1,2,3,4 - Tetrahydronaphth[1,2 - h]isoquinoline? (IX).—The free base VI obtained by liberation with alkali from 1.8 g. of the hydrochloride was condensed with formaldehyde and the condensation product was cyclized as described above in the "9-series." The resulting hydrochloride was converted to the base, which was extracted with benzene. The benzene solution left on evaporation a semi-solid base which was not very stable and was, therefore, transformed with alcoholic hydrogen chloride to the hydrochloride. This hydrochloride appeared to be not homogeneous and apparently contained a small amount of starting material, the phenanthrylethylamine hydrochloride. The difference in solubility of the hydrochlorides and picrates of the two bases was not marked enough for a practical separation. Therefore the crude hydrochloride was converted via the methiodide XI to the N-methyl compound which could be purified readily. The crude hydrochloride was obtained in a yield of 70% and melted at 270–290°. For analytical purposes a small sample was recrystallized repeatedly from alcohol–ether: white plates, m. p. 313–315° (dec.).

Anal. Calcd. for $C_{17}H_{16}NCl$: C, 75.69; H, 5.98. Found: C, 75.57; H, 6.28.

The mixture melting point with the hydrochloride of VI of m. p. 317–318° was indefinite, 275–314°.

Methiodide of 3-Methyl-1,2,3,4-tetrahydronaphth[1,2-h]isoquinoline (XI).—Eight-tenths gram of crude hydrochloride of m. p. 270–290° (see above) was converted to the quaternary methiodide as described in the preparation of XIII. After one crystallization from water, 0.7 g. of methiodide of m. p. 227–233° was obtained. For analysis it was recrystallized twice from alcohol as white plates, m. p. 244.5–246° (dec.).

Anal. Calcd. for $C_{19}H_{20}NI$: I, 32.60. Found: I, 32.41.

3 - Methyl - 1,2,3,4 - tetrahydronaphth[1,2 - h]isoquinoline (XII).—Five-tenths gram of an impure methiodide (m. p. 235–240°) was decomposed in an oil-pump vacuum at 200°. The oily distillate was taken up in ether and the ether residue was converted into the hydrochloride in the usual manner. This crude hydrochloride (0.25 g., m. p. 232–242°) was recrystallized first from a small volume of alcohol and then from alcohol–ether: white hexagonal crystals, m. p. 257–259° (dec.).

Anal. Calcd. for $C_{18}H_{18}NCl$: C, 76.18; H, 6.39. Found: C, 76.13; H, 6.38.

In some instances, particularly when a less pure methiodide was decomposed, it was possible to isolate from the mother liquors of the hydrochloride of XII, 2-(2-dimethylaminoethyl)-phenanthrene hydrochloride of m. p. 247–249°.

Anal. Calcd. for $C_{18}H_{20}NCl$: C, 75.62; H, 7.05. Found: C, 75.41; H, 6.91.

A compound in every respect identical with this hydrochloride (melting point and mixture melting point) was prepared by complete methylation of VI and subsequent heat decomposition of the resulting methiodide. The mixture melting point with the hydrochloride of XII was at 230–240°.

The above description of the preparation of IX and its derivatives is a typical average of twelve experiments each starting with from 1 to 3 g. of the 2-(2-aminoethyl)-phenanthrene (VI). In one instance, the tetrahydroisoquinoline derivative IX was obtained as the only reaction product in the cyclization of the formaldehyde condensation product. In another instance, when an impure phenanthrylethylamine was used, no cyclization took place and practically all of the starting material could be recovered.

Summary

The synthesis of phenanthrylethylamines $C_{14}H_9$-$CH_2CH_2NH_2$ and phenanthrylethylamino ethers $C_{14}H_9CHOCH_3CH_2NH_2$ is described.

Cyclizations to isoquinoline derivatives were attempted according to the general methods of Bischler–Napieralski and of Decker and Becker. Only the method of Decker and Becker applied to the phenanthrylamines of the 2- and 9-series gave positive results.

University, Virginia

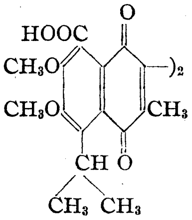
Received October 19, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

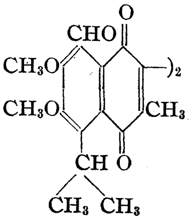
Structure of Gossypol. XVI. Reduction Products of Gossypolone Tetramethyl Ether and Gossypolonic Acid Tetramethyl Ether[1]

BY ROGER ADAMS, T. A. GEISSMAN AND R. C. MORRIS

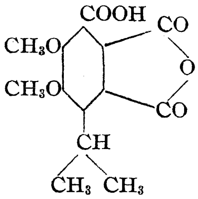
Gossypolonic acid tetramethyl ether, obtained by the oxidation of gossypol hexamethyl ether with dilute nitric acid,[2] was assigned the structure I, and gossypolone tetramethyl ether, derived from gossypol hexamethyl ether by chromic acid oxidation,[2] was assigned the structure II.[1]



I



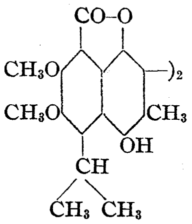
II



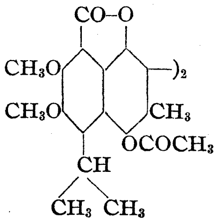
III

These structures were assumed largely on the basis of the analytical figures, coupled with the facts that I was easily soluble in sodium bicarbonate solution, II formed an anilino derivative, mild oxidation converted II into I and that both I and II yielded gossic acid (III) on oxidation with potassium permanganate. No direct evidence was presented to show that the compounds were quinones, though by a comparison of these and their degradation products with apogossypolone tetramethyl ether, desapogossypolone tetramethyl ether and their degradation products,[3] quinone structures appeared likely. The results described in this paper offer more direct evidence for the correctness of the structures I and II for these compounds.

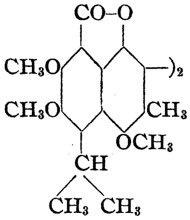
Gossypolonic acid tetramethyl ether can be reduced with zinc and acetic acid to a compound having the properties of the hydroxy lactone (IV) and reductively acetylated with zinc and acetic anhydride to the acetoxy lactone (V). It is also possible to obtain V by acetylation of IV with acetic anhydride in pyridine.



IV

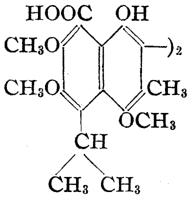


V



VI

Methylation of the hydroxy compound (IV) yielded the methoxy lactone (VI). This compound was insoluble in cold alcoholic alkali but dissolved on warming. When the alkaline solution was acidified, the hydroxy acid (VII) was obtained as a colorless crystalline compound, soluble in cold, dilute aqueous alkali. This establishes the presence of the lactone grouping in VI and by analogy in IV and V.



VII

The free hydroxy compound (IV) is readily soluble in cold, dilute alcoholic alkali to a deep wine-red solution which on warming becomes first brown, then a deep blue-green identical in appearance with that obtained by dissolving gossypolonic acid tetramethyl ether (I) in alcoholic alkali of the same strength. This points to an opening of the lactone linkage followed by air oxidation. The blue-green solution contains decomposition products of gossypolonic acid tetramethyl ether since none of this compound could

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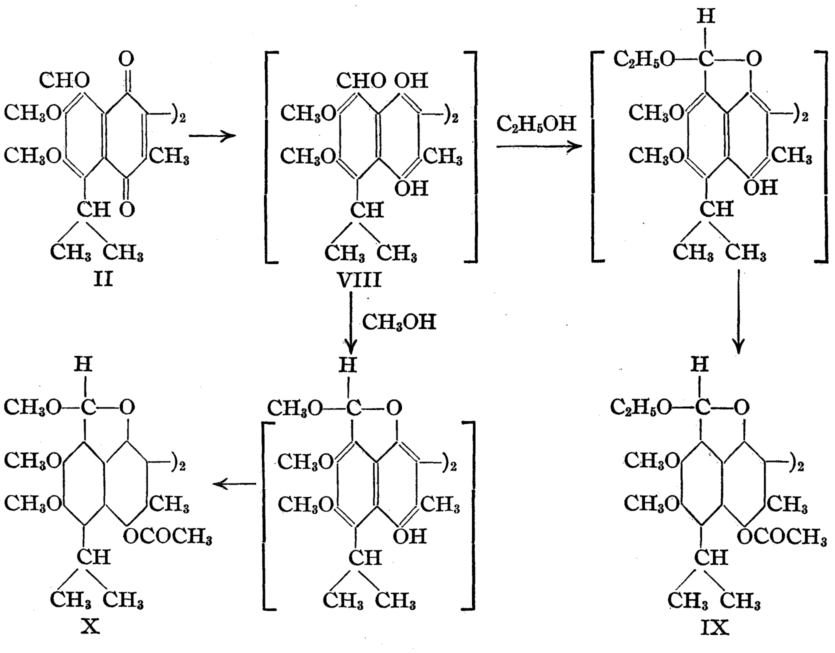
[1] For previous paper see Adams, Morris, Geissman, Butterbaugh and Kirkpatrick, THIS JOURNAL, **60**, 2193 (1938).

[2] Adams, Morris and Kirkpatrick, *ibid.*, **60**, 2170 (1938).

[3] Adams and Butterbaugh, *ibid.*, **60**, 2174 (1938).

be obtained from it on acidification. The free hydrogossypolonic acid tetramethyl ether (hydroquinone of I) could not be obtained crystalline.

The reduction of gossypolone tetramethyl ether (II) was much more difficult because of the extreme sensitivity of the compound. It was finally accomplished by adding an aqueous solution of sodium hydrosulfite to its ethanolic solution; reduction took place smoothly, the solution, deep yellow at first, becoming deep brown and then changing to a pale yellow. Rapid isolation of the unstable reduction product by means of ether extraction followed by treatment with pyridine and acetic anhydride in the cold led to the isolation of a colorless crystalline compound. This compound, however, did not give analytical figures consistent with a simple reduction and acetylation of the quinone linkage, but it was readily reconverted into the original quinone (II) by oxidation with chromic acid, indicating that no deep-seated change had taken place. By carrying out the reduction in methanol solution, following the same procedure as outlined above, a different compound was obtained, lending support to the assumption that acetal formation had occurred in the primary reduction product (VIII). The compound obtained, therefore, when the reduction was carried out in ethanol was diacetoxy gossypol tetramethyl diethyl ether (IX), and in methanol was diacetoxy gossypol hexamethyl ether (X)



Experimental

Improved Procedure for the Preparation of Gossypol Hexamethyl Ether.—Gossypol hexamethyl ether has been one of the important derivatives of gossypol used in degradation studies. An improved method of preparation has been found which deserves detailed description.

A solution of 25 g. of once recrystallized gossypol-acetic acid is prepared by gentle warming in a mixture of 80 cc. of methanol and 80 cc. of redistilled dimethyl sulfate. The solution is cooled under the tap and 110 cc. of 10% methanolic potassium hydroxide is added in 10-cc. portions with continued cooling. After all of the alkali is added the mixture is allowed to stand at room temperature, with occasional shaking, for two days. The solid which precipitates is collected on a filter and washed with methanol, then thoroughly with water. There remains undissolved 21–23 g. of yellowish, crystalline tetramethyl ether melting around 165° and giving a scarlet color with concentrated sulfuric acid.

This crude material is methylated further by dissolving it in a mixture of 100 cc. of benzene and 60 g. of dimethyl sulfate and adding to the warm solution a 20% solution of potassium hydroxide in methanol until the solution is alkaline. An additional 40 g. of dimethyl sulfate is then added, followed by 20% methanolic potassium hydroxide until the solution is again alkaline. The mixture is then evaporated to a sludge on the steam-bath (with stirring), methanol being added frequently and the evaporation continued until most of the benzene has been removed. The final sludge is cooled and filtered. The solid is washed with methanol until the filtrates are colorless and then washed thoroughly with water to remove potassium salts. The product remaining on the filter is white, crystalline hexamethyl ether. The yield in this step is nearly quantitative. The product is pure enough for most purposes. It gives a yellow-orange color with concentrated sulfuric acid and melts, depending upon the purity of the gossypolacetic acid used, at from 195–210°. It can be recrystallized most conveniently from ligroin (b. p. 90–110°), from which it is obtained in clusters of long white needles, m. p. 175°.

Hydroxygossylic Acid Lactone Tetramethyl Ether (IV).—To a solution of 0.50 g. of gossypolonic acid tetramethyl ether[1] in 10 cc. of boiling glacial acetic acid, zinc dust was added in small portions. The solution first turned a reddish-yellow color and on continued addition of zinc dust became a clear pale yellow. Yellow crystals separated from the hot solution. The zinc dust was removed by filtration and boiled several times with small portions of acetic acid to remove admixed reduction product, and the combined filtrates diluted to incipient cloudiness and cooled. The product (0.38 g.) was purified from glacial acetic acid and formed tiny canary-yellow prisms melting at 320° (bloc Maquenne).

Anal. Calcd. for $C_{34}H_{34}O_{10}$: C, 67.77; H, 5.65. Found: C, 67.60; H, 5.64.

The compound gives a deep yellow color with concentrated sulfuric acid and a deep wine-red solution in methanolic potassium hydroxide.

Acetoxygossylic Acid Lactone Tetramethyl Ether (V). (a).—To a mixture of 0.5 g. of gossypolonic acid tetramethyl ether, 0.5 g. of fused sodium acetate and 5 cc. of boiling acetic anhydride, zinc dust was added in small portions until the color of the solution had become a pale yellow. The solution was filtered onto ice and allowed to stand until the acetic anhydride had decomposed, the product collected and triturated with boiling methanol. The pale yellow prisms obtained weighed 0.40 g. After two recrystallizations from acetone–methanol the product formed tiny rosets of colorless prisms, m. p. 231–233° (corr.).

Anal. Calcd. for $C_{38}H_{38}O_{12}$: C, 66.47; H, 5.54. Found: C, 66.32; H, 5.50.

The product gives a deep yellow color in concentrated sulfuric acid. It is insoluble in cold methanolic alkali, but dissolves on heating with the formation of a deep wine-red solution.

(b).—The same compound is formed when the hydroxy lactone (IV) is acetylated with acetic anhydride in pyridine.

Methoxygossylic Acid Lactone Tetramethyl Ether (VI).—To a suspension of 0.5 g. of hydroxygossylic acid lactone tetramethyl ether in a cooled mixture of 5 cc. of dimethyl sulfate and 5 cc. of methanol was added 7 cc. of 10% methanolic potassium hydroxide. The solution, originally deep red, gradually turned yellow. The addition of further 1-cc. portions of alcoholic alkali was continued until a further addition no longer produced the red color. The mixture was concentrated under reduced pressure to a mush, filtered, the solid washed with methanol and the salt removed by washing with water. There remained on the filter 0.30 g. of yellow crystalline product. After several recrystallizations from dilute acetic acid and from acetone–methanol, the compound formed pale yellow needles, m. p. 273–274° (corr.).

Anal. Calcd. for $C_{36}H_{38}O_{10}$: C, 68.57; H, 6.03. Found: C, 68.46; H, 6.01.

The compound gives a clear yellow color with concentrated sulfuric acid and is insoluble in cold alcoholic alkali.

Methoxygossylic Acid Tetramethyl Ether (VII).—A solution of 0.20 g. of methoxygossylic acid lactone tetramethyl ether (VI) in 10 cc. of 10% methanolic potassium hydroxide was boiled with a pinch of zinc dust and a few cubic centimeters of water until the originally red-brown color had faded to yellow. The solution was filtered into dilute sulfuric acid and extracted with ether. The ether solution was dried, concentrated and diluted with petroleum ether (b. p. 30–60°). The hydroxy acid separated as tiny white needles, weighing 0.1 g. After recrystallization from ether–petroleum ether it formed tiny, soft white needles which sintered over a broad range and melted at 270–272° (corr.). When a sample was plunged into a bath preheated to 250° it melted instantly with vigorous decomposition, crystallized on cooling, then remelted at 273–274° (corr.).

Anal. Calcd. for $C_{36}H_{42}O_{12}$: C, 64.83; H, 6.36. Found: C, 64.70; H, 6.36.

The compound is readily soluble in cold, dilute sodium hydroxide solution. It gives no color with ferric chloride and a pale yellow color with concentrated sulfuric acid. The methoxy lactone (VI) is regenerated on warming the hydroxy acid in acetic anhydride.

Reduction and Acetylation of Gossypolone Tetramethyl Ether in Ethanol (Compound IX).—An aqueous solution of sodium hydrosulfite was added in portions to a hot solution of 1.0 g. of gossypolone tetramethyl ether in 25 cc. of absolute ethanol. The solution first became deep brown in color and upon continued addition of the reducing agent changed to a pale yellow color. At this point, it was poured into iced water, quickly extracted with ether, the ether solution washed with a solution of sodium hydrosulfite and dried by shaking it with anhydrous sodium sulfate. The ether was removed quickly, at first on the hot-plate, then under reduced pressure, and to the residual dark red oil was added a mixture of 15 cc. of pyridine and 7 cc. of acetic anhydride. The bright red solution was allowed to stand at room temperature for two hours, poured into water and the pink solid collected. The product was dissolved in warm methanol, from which it crystallized quickly as short white needles, weighing 0.18 g. After recrystallization from acetone–methanol the compound formed soft white needles, m. p. 264–265° (corr.).

Anal. Calcd. for $C_{42}H_{50}O_{12}$: C, 67.52; H, 6.75. Found: C, 67.18, 67.37; H, 6.91, 6.50.

Reduction by means of zinc dust and acetic acid in presence of sodium acetate, zinc dust in acetic anhydride with sodium acetate, zinc dust in pyridine and acetic anhydride and zinc dust in ethanolic calcium chloride was unsuccessful. Acid reducing agents were excluded, as gossypolone tetramethyl ether is converted to uncrystallizable tars in acid solution.

Oxidation of this compound with 10% aqueous chromic acid in acetic acid gave a yellow crystalline compound which was proved by melting point, mixed melting point, preparation of the anilino derivative and color in sulfuric acid to be identical with II.

Reduction and Acetylation of Gossypolone Tetramethyl Ether in Methanol (Compound X).—The reduction was run in exactly the same manner as given above when ethanol was used as the solvent. The crude crystalline material obtained from methanol formed tiny pink nodules and weighed 0.23 g. Recrystallized from acetone–methanol it formed tiny, soft white needles, m. p. 266–267° (corr.).

Anal. Calcd. for $C_{40}H_{46}O_{12}$: C, 66.85; H, 6.41. Found: C, 66.65; H, 6.34.

A mixture of the ethyl acetal (IX), m. p. 264–265°, and of the methyl acetal (X), m. p. 266–267°, melted at 245–253°.

The compound gives a yellow-orange color in concentrated sulfuric acid.

Oxidized with chromic acid it yielded gossypolone tetramethyl ether (II).

Summary

1. Support for the previously proposed structures of gossypolonic acid tetramethyl ether and of gossypolone tetramethyl ether as quinones has now been furnished. These products have been converted to reduction products.

2. Gossypolonic acid tetramethyl ether gives hydroxy gossylic acid lactone tetramethyl ether which may be acetylated to the corresponding acetyl derivative or methylated to the methyl ether. The latter can be transformed by the action of alkali into the corresponding gossylic acid derivative; thus the presence of the lactone linkage is demonstrated.

3. Gossypolone tetramethyl ether is a much more sensitive compound and most alkaline and acid reducing agents cause decomposition. However, a solution of sodium hydrosulfite in ethanol and methanol gives successful results. Diacetoxygossypol tetramethyl diethyl ether forms when ethanol is used as a solvent, and diacetoxygossypol hexamethyl ether when methanol is employed.

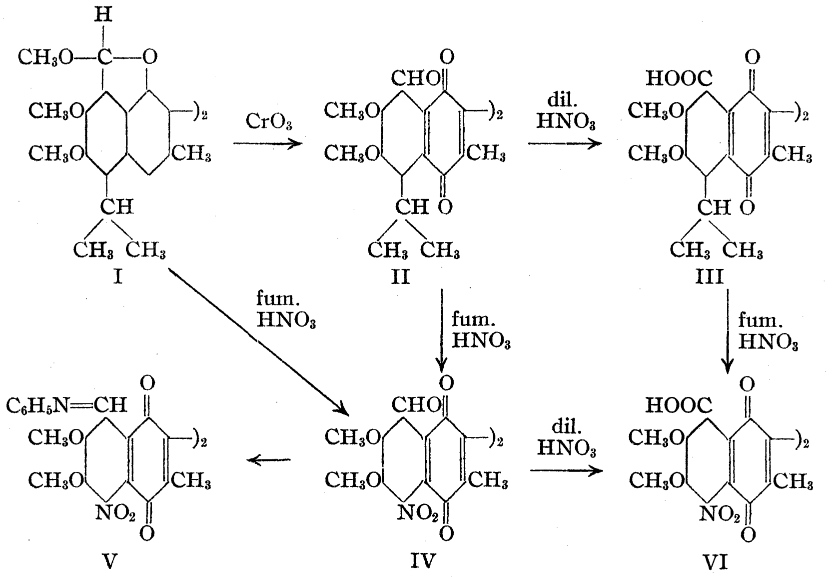
URBANA, ILLINOIS RECEIVED OCTOBER 17, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Structure of Gossypol. XVII. Nitration Products of Gossypol Hexamethyl Ether, Gossypolone Tetramethyl Ether and Gossypolonic Acid Tetramethyl Ether[1]

BY ROGER ADAMS, T. A. GEISSMAN AND R. C. MORRIS

The structural relationship between gossypol hexamethyl ether (I), gossypolone tetramethyl ether (II) and gossypolonic acid (III) has been substantiated in part by studies of oxidation[2] and other degradation reactions[3] of gossypol derivatives and by the coördination of these structures in a consistent picture of the properties and reactions of gossypol.[1,4]



Further confirmation has been found in a study of the action of fuming nitric acid on these compounds, products being obtained whose analyses and properties allow their formulation in accord with the above structures.

By the action of fuming nitric acid on gossypol hexamethyl ether (I), there is obtained a crystalline compound to which has been assigned the structure IV, since it forms an anilino derivative formulated as V. Compound IV also results from the action of fuming nitric acid on gossypolone tetramethyl ether (II). Treatment of gossypolonic acid tetramethyl ether (III) with fuming nitric acid under similar conditions results in the formation of an acidic compound (VI) which is assumed to be the carboxylic acid corresponding to the aldehyde (IV). This assumption is substantiated by the fact that oxidation of IV with dilute nitric acid results in the formation of the acid (VI). This is exactly analogous to the oxidation of gossypolone tetramethyl ether (II) to gossypolonic acid tetramethyl ether (III) by means of dilute nitric acid.

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(1) For previous paper, see Adams, Geissman and Morris, THIS JOURNAL, **60**, 2967 (1938).

(2) Adams, Morris and Kirkpatrick, *ibid.*, **60**, 2170 (1938).

(3) Adams and Geissman, *ibid.*, **60**, 2184 (1938).

(4) Adams, Morris, Geissman, Butterbaugh and Kirkpatrick, *ibid.*, **60**, 2193 (1938).

The replacement of an isopropyl group by a nitro group during nitration has been observed in other, although not strictly analogous, cases. The nitration of *p*-cymene has been found to yield nitrated toluenes along with simple nitration products,[5] while dinitrothymol yields trinitro-*m*-cresol upon further nitration.[6] A similar elimination of the isopropyl group from a gossypol derivative has been observed in the formation of desapogossypol hexamethyl ether from apogossypol hexamethyl ether by the action of concentrated sulfuric acid,[7] although the elimination by means of sulfuric acid may follow a different course from that in the replacement by a nitro group during nitration.

Experimental

Nitration of Gossypol Hexamethyl Ether; Compound IV.—To 15 cc. of fuming nitric acid (sp. gr. 1.50) cooled to −5° was added 1 g. of gossypol hexamethyl ether. The compound dissolved instantly to give a deep red-brown solution which was immediately poured onto ice. The product from five such runs was collected, dried and dissolved in a small amount of boiling methanol. A yellow crystalline material separated and after cooling was filtered; weight 0.5 g. It was purified from acetone–methanol, forming bright yellow prisms. The product has no sharp melting point but when placed in a preheated bath darkens at about 220° and decomposes at 257–262° (corr.).

Anal. Calcd. for $C_{28}H_{20}O_{14}N_2$: C, 55.26; H, 3.29; N, 4.60. Found: C, 54.91, 54.90, 55.28; H, 3.41, 3.33, 3.22; N, 4.47, 4.64, 4.86.

The compound gives a clear brownish-red color with concentrated sulfuric acid and reduces Tollens' reagent quickly in pyridine solution in the cold. It is insoluble in alcoholic alkali, although it decomposes slowly on standing in contact with the reagent.

Nitration of Gossypolone Tetramethyl Ether; Compound IV.—To 5 cc. of fuming nitric acid (sp. gr. 1.50) cooled in ice–salt was added in small portions 0.25 g. of gossypolone tetramethyl ether. As soon as solution had taken place, the red-brown reaction mixture was poured onto ice. The insoluble material was collected and dissolved in a small amount of methanol, from which 0.1 g. of yellow crystalline material separated. After recrystallization from acetone–methanol bright yellow, flat prisms were obtained.

The compound gave the same type of decomposition as the product previously described, alone or when mixed with the product made by the other procedure. It also gave the same analytical results and the same color in sulfuric acid.

Anilino Derivative of Compound IV; Compound V.—An excess of aniline was added to a suspension of compound IV in boiling benzene. A red solution formed. After a few minutes ligroin (b. p. 90–110°) was added and the mixture concentrated and cooled. The product which separated was recrystallized from benzene–ligroin. It forms tiny, brownish-orange prisms which do not melt, but darken at about 210° and become charred at about 260°.

Anal. Calcd. for $C_{40}H_{30}O_{12}N_4$: C, 63.32; H, 3.96; N, 7.39. Found: C, 63.92; H, 4.17; N, 7.63.

The compound gives a yellow-orange color in concentrated sulfuric acid.

Nitration of Gossypolonic Acid Tetramethyl Ether; Compound VI.—To 2.5 cc. of yellow fuming nitric acid (sp. gr. 1.5) at 0° was added in portions with stirring 0.1 g. of gossypolonic acid tetramethyl ether. Solution took place rapidly and, as soon as complete, the reaction mixture was poured onto ice. The precipitate was washed, dried and recrystallized from methanol. It forms light yellow crystals which become brown at about 220° and darken at 260–270°; yield 0.04 g.

Anal. Calcd. for $C_{28}H_{20}O_{16}N_2$: C, 52.50; H, 3.12; N, 4.38. Found: C, 52.18; H, 3.43; N, 4.43.

The product gives no color with cold concentrated sulfuric acid and a green-violet color upon heating.

Oxidation of Compound IV to Compound VI by Means of Dilute Nitric Acid.—Two procedures for this oxidation were used:

(a).—To a solution of 0.20 g. of compound IV in 5 cc. of acetic anhydride was added gradually 20 cc. of a mixture of equal parts of acetic acid, concentrated nitric acid and water. The acetic anhydride decomposed vigorously at the beginning and when complete the remainder of the 20 cc. was added all at once. A small amount of compound V crystallized and was filtered. The filtrate was treated with 10 cc. of concentrated nitric acid and the solution refluxed for two hours. Upon cooling, the product V separated. It was purified by dissolving in acetic anhydride, decomposing the anhydride with water and diluting. About 0.05 g. of shining buff leaflets was obtained. The compound does not melt up to 320° (bloc Maquenne).

Anal. Calcd. for $C_{28}H_{20}O_{16}N_2$: C, 52.50; H, 3.12. Found: C, 52.42; H, 3.32.

The product is soluble in sodium bicarbonate solution; it gives no color with concentrated sulfuric acid in the cold but a green color upon warming.

(b).—A solution of the compound IV in hot, concentrated nitric acid was diluted with a few drops of water. A small amount of material separated. The mixture was heated for an hour on the steam-bath. Enough concentrated nitric acid was then added to bring all the solid into solution at the boiling point, the solution boiled a short time, diluted with water and cooled. The solid was recrystallized as in (a), and was identical in solubility in sodium bicarbonate solution, color in sulfuric acid and melting point behavior with VI as prepared above.

Anal. Calcd. for $C_{28}H_{20}O_{16}N_2$: C, 52.50; H, 3.12. Found: C, 52.69; H, 3.71.

Summary

1. Gossypol hexamethyl ether by the action of fuming nitric acid is converted into a derivative of gossypolone tetramethyl ether in which the iso-

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[5] Alfthan, *Ber.*, **53**, 78 (1920).

[6] Armstrong and Rennie, *Chem. News*, **47**, 115 (1883).

[7] Adams and Butterbaugh, THIS JOURNAL, **60**, 2174 (1938).

propyl groups are replaced by nitro groups. The same compound also may be produced directly by nitration of gossypolone tetramethyl ether.

2. Gossypolonic acid tetramethyl ether by a similar procedure is converted into a derivative with the isopropyl groups replaced by nitro groups.

3. Just as gossypolone tetramethyl ether can be oxidized to the corresponding carboxylic acid by means of dilute nitric acid, so can the nitration product of gossypol hexamethyl ether or gossypolone tetramethyl ether be converted into the corresponding nitration product of gossypolonic acid tetramethyl ether.

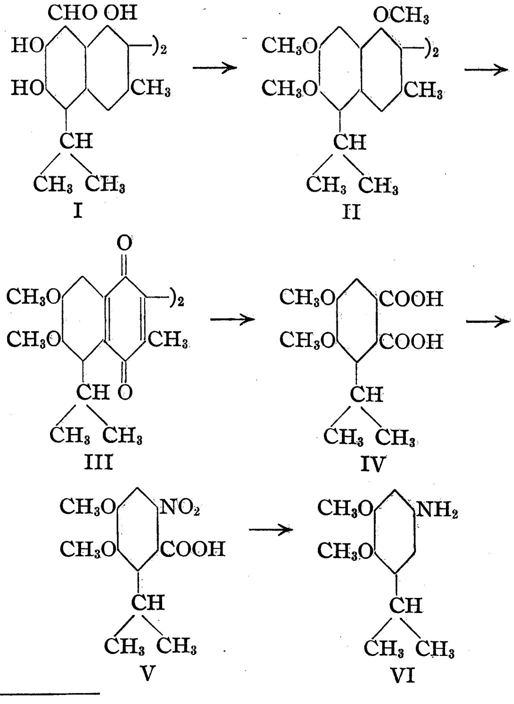
URBANA, ILLINOIS RECEIVED OCTOBER 17, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

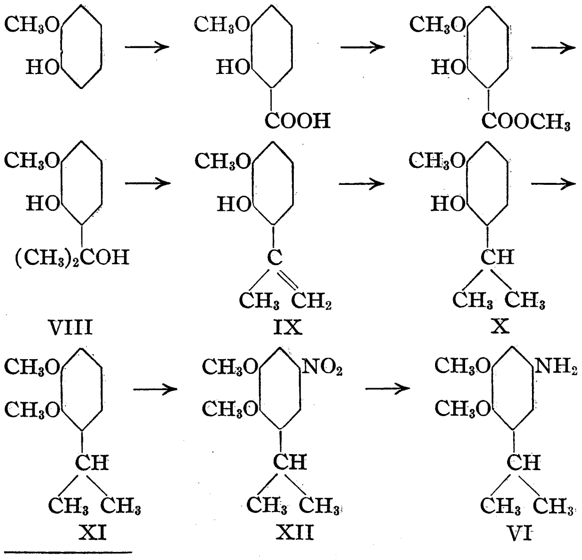
Structure of Gossypol. XVIII. Synthesis of 1,2-Dimethoxy-3-isopropyl-5-aminobenzene, a Degradation Product of Gossypol[1]

BY ROGER ADAMS, MADISON HUNT AND R. C. MORRIS

Structure I has been assigned to gossypol.[2] By the action of concentrated alkali, gossypol loses two aldehyde groups and is converted into the unstable apogossypol. The latter product is stabilized by the formation of the hexamethyl ether. Apogossypol hexamethyl ether (II) upon oxidation with chromic acid gives apogossypolone tetramethyl ether (III) which is further oxidized with potassium permanganate to apogossypolic acid (IV). Nitration of this last product results in a mononitro monocarboxylic acid (V) which upon reduction and sublimation of the product gives a decarboxylated amine (VI).[3] The amine is converted to a diacetyl derivative by the action of acetic anhydride and sodium acetate. Whether the 5-carboxyl or the 4-carboxyl in apogossypolic acid (IV) is replaced by a nitro group was not certain so that the amine which was assigned structure VI might have an isomeric formula, with the amino group in the 4-position.



The compound 1,2-dimethoxy-3-isopropyl-5-aminobenzene has now been synthesized by methods leaving little doubt as to its complete structure and no doubt as to the relative positions of the two dimethoxy and the isopropyl groups. It proved to be identical with the compound VI obtained by degradation of gossypol as shown by melting point and mixed melting points of the two amines and their acetyl derivatives. The synthesis employed is shown by the following series of reactions



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[1] For previous paper see Adams, Geissman and Morris, THIS JOURNAL, **60**, 2970 (1938).

[2] Adams, Morris, Geissman, Butterbaugh and Kirkpatrick, *ibid.*, **60**, 2193 (1938).

[3] Adams, Morris, Butterbaugh and Kirkpatrick, *ibid.*, **60**, 2191 (1938).

The structure of compound XI, 1,2-dimethoxy-3-isopropylbenzene, cannot be questioned. The 5-position for the nitro group in compound XII was assigned after consideration of the nitration of the analogous 1,2-dimethoxy-3-methylbenzene which was proven in two ways to give the 1,2-dimethoxy-3-methyl-5-nitro derivative.[4] The amino group in compound VI is, therefore, in the 5-position.

The identity of the synthetic product, 1,2-dimethoxy-3-isopropyl-5-aminobenzene, and the gossypol degradation product allows important conclusions to be drawn concerning the gossypol molecule. It confirms (1) the presence of isopropyl groups, and (2) the relative positions of two hydroxyls to the isopropyl groups in the gossypol molecule.

If these established facts are considered in conjunction with the method of preparation and relationship of gossic to apogossypolic acid, it may be deduced that the aldehyde groups in gossypol are in the same rings as the isopropyl groups and indeed *para* to these groups. The lactone formation in gossypol derivatives containing the aldehyde groups oxidized to carboxylic acid groups makes positive the presence of hydroxyl groups in the positions *peri* to the aldehyde groups. Thus, proof of the substituent groups in the 1-, 5-, 6-, 7- and 8-positions of the two naphthalene nuclei of gossypol is conclusive.

Experimental

3-Methoxysalicylic Acid.—To a mole equivalent of sodium in absolute ethanol, 124 g. of guaiacol was added. The alcohol was removed by distillation and the residue washed with dry ether. The solid product was dried *in vacuo* at room temperature. The solid sodium guaiacolate was finely ground and heated for eight hours under pressure at 115° with excess of carbon dioxide. The reaction mixture was dissolved in 400 cc. of water and the solution extracted with ether to remove unchanged guaiacol. The aqueous layer was acidified with hydrochloric acid, and the product separated. The yield was 55 g. (33%) which melted low and required a crystallization from water to bring it up to 150° (corr.). The yield depends to a large extent on the dryness of the sodium guaiacolate. Heyden reported a melting point of 148–150°.[5]

Methyl 3-Methoxysalicylate.—The esterification was carried out by refluxing for twelve hours a mixture of 25 g. of crude 3-methoxysalicylic acid, 65 cc. of methanol and 5.7 cc. of concentrated sulfuric acid. Dilution with ether and extraction of the ether solution with aqueous sodium bicarbonate, then distillation, gave essentially a quantitative yield of product, b. p. 134–136° (2 mm.). The distilled product solidified and was purified by crystallization from dilute methanol, m. p. 61° (corr.). Fritsch reported a melting point of 63°.[6]

Dimethyl-(3-methoxy-2-hydroxyphenyl)-carbinol (VIII).—A dry ether solution of 22 g. of methyl 3-methoxysalicylate was added with cooling to a cooled solution of Grignard reagent prepared from excess methyl chloride and 13.9 g. of magnesium. The reaction mixture was then refluxed for three hours. It was decomposed with dilute acetic acid and the product extracted with ether. After washing with water and aqueous 5% sodium bicarbonate, the ether solution was dried over anhydrous magnesium sulfate and the ether removed. The solid residue was purified by crystallization from benzene–petroleum ether (b. p. 60–110°) and formed white needles, m. p. 126° (corr.); yield, 10.5 g. (48%).

Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.89; H, 7.75. Found: C, 65.86; H, 7.80.

1-Methoxy-2-hydroxy-3-isopropenylbenzene (IX).—Upon heating 5 g. of the dimethyl-(3-methoxy-2-hydroxyphenyl)-carbinol for ten minutes at 195–200°, water was lost. The product distilled at 122–124° (14 mm.); n^{20}_D 1.5518; d^{20}_{20} 1.072; yield, 4.2 g. (93%).

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.13; H, 7.37. Found: C, 73.14; H, 7.50.

1-Methoxy-2-hydroxy-3-isopropylbenzene (X).—A solution of 4 g. of 1-methoxy-2-hydroxy-3-isopropenylbenzene in 25 cc. of 95% ethanol was hydrogenated at 2–3 atm. pressure with Raney nickel as a catalyst. The product distilled at 123–125° (8 mm.); n^{20}_D 1.5203; d^{20}_{20} 1.049; yield, 3.8 g. (94%).

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.25; H, 8.49. Found: C, 72.38; H, 8.50.

1,2-Dimethoxy-3-isopropylbenzene (XI).—To a solution of 2.3 g. of 1-methoxy-2-hydroxy-3-isopropylbenzene in 14 cc. of normal sodium methylate was added 1.3 cc. of dimethyl sulfate. The solution was refluxed for ten minutes and then treated with a second similar portion of sodium methylate and dimethyl sulfate and the heating repeated. After evaporating almost to dryness, the reaction mixture was treated with 15 cc. of water and extracted with ether. After extraction of the ether solution twice with 10% aqueous sodium hydroxide, the solvent and then the product was distilled; b. p. 119–121° (24 mm.); n^{20}_D 1.5068; d^{20}_{20} 1.019; yield, 2.1 g. (84%).

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.28; H, 8.95. Found: C, 73.34; H, 8.99.

1,2-Dimethoxy-3-isopropyl-5-nitrobenzene (XII).—To a cold solution of 1 g. of 1,2-dimethoxy-3-isopropylbenzene in 8 cc. of glacial acetic acid was added 0.24 cc. of nitric acid (sp. gr. 1.50). The mixture was kept at 0° for thirty minutes and then was poured into 35 cc. of ice water. The oil which separated was extracted with ether and the ether solution washed with bicarbonate solution. After drying and removing the ether, the residue was dissolved in methanol. Upon cooling in an ice–salt mixture, the product separated and was recrystallized from methanol, yellow crystals, m. p. 53° (corr.); yield, 0.85 g. (68%).

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[4] (a) Cain and Simonsen, *J. Chem. Soc.*, **105**, 156 (1914); (b) Majima and Okazaki, *Ber.*, **49**, 1482 (1916).

[5] Heyden, *ibid.*, **23**, 418 (1890).

[6] Fritsch, *Ann.*, **301**, 352 (1898).

Anal. Calcd. for $C_{11}H_{15}NO_4$: C, 58.64; H, 6.72; N, 6.22. Found: C, 58.91; H, 6.60; N, 6.36.

1,2-Dimethoxy-3-isopropyl-5-aminobenzene (VI).—The corresponding nitro compound was reduced in absolute ethanol solution at 2–3 atm. with Raney nickel as catalyst. The product was purified by sublimation, white crystals, m. p. 75° (corr.). The yield was 0.055 g. from 0.1 g. of nitro compound.

Anal. Calcd. for $C_{11}H_{17}O_2N$: C, 67.70; H, 8.72; N, 7.18. Found: C, 67.55; H, 8.77; N, 7.14.

This substance gave no depression in melting point when mixed with the compound assumed to have this structure and prepared from apogossypolic acid.[3]

1,2-Dimethoxy-3-isopropyl-5-diacetaminobenzene.—The amine was acetylated with acetic anhydride and sodium acetate in an 81% yield. The product was purified by washing the ether solution with 5% hydrochloric acid, evaporation of the solvent and sublimation. It formed white crystals, m. p. 86° (corr.).

Anal. Calcd. for $C_{15}H_{21}O_4N$: C, 64.52; H, 7.53; N, 5.02. Found: C, 64.57; H, 7.41; N, 5.01.

A mixed melting point of this product with the diacetyl derivative of the amine obtained by degradation of apogossypolic acid gave no depression.[3]

1,2-Dimethoxy-3-isopropyldinitrobenzene.—By nitrating 1,2-dimethoxy-3-isopropylbenzene as previously described except that excess nitric acid was used, a dinitro derivative was obtained. It was purified from methanol in yellow crystals, m. p. 106° (corr.).

Anal. Calcd. for $C_{11}H_{14}N_2O_6$: N, 10.31. Found: N, 10.10.

Whether the two nitro groups are both in the benzene ring or one in the ring and the other replacing the tertiary hydrogen of the isopropyl group was not determined. By analogy to the dinitro derivative of 1,2-dimethoxy-3-methylbenzene, it is probable that the two nitro groups occupy the 5-, 6-positions.[4b]

1,2-Dimethoxy-3-isopropyldiaminobenzene.—The reduction of the dinitro compound in absolute ethanol with Raney nickel as catalyst gave a diamine which was purified by sublimation to white crystals, m. p. 75° (corr.). This product was very unstable to atmospheric oxygen and turned brown rapidly.

Anal. Calcd. for $C_{11}H_{18}O_4N_2$: N, 13.13. Found, N, 13.14.

Summary

The synthesis of 1,2-dimethoxy-3-isopropyl-5-aminobenzene has been accomplished. It proved to be identical with the compound prepared from apogossypolic acid by nitration, subsequent reduction and sublimation.

This synthesis confirms the character of the functional groups in the 1-, 5-, 6-, 7- and 8-positions of the naphthalene nuclei in the previously postulated formula for gossypol.

URBANA, ILLINOIS RECEIVED OCTOBER 17, 1938

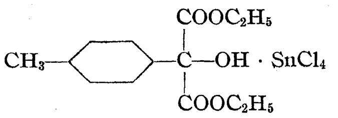
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DEPAUW UNIVERSITY]

The Preparation of Substituted Mandelic Acids and their Bacteriological Effects. II

BY J. L. RIEBSOMER, ROBERT BALDWIN, JACK BUCHANAN AND HOWARD BURKETT

It has been shown previously by work in this Laboratory[1,2] that alkyl substituted mandelic acids can be prepared readily from alkyl benzenes and ethyl oxomalonate when treated in the presence of anhydrous stannic chloride or certain other condensing agents. The intermediate condensation products are hydrolyzed and decarboxylated to form the corresponding mandelic acids. The purpose of the present work was to extend the studies reported in the first paper of this series[2] and to point out certain additional observations made on the general reaction mentioned above.

In nearly every case when anhydrous stannic chloride is added to an alkyl benzene–ethyl oxomalonate mixture a thick sticky solid separates out. With the hope that a knowledge of the composition of such a typical solid might contribute to an understanding of the mechanism of the general reaction, the solid which separated when toluene, ethyl oxomalonate and stannic chloride were mixed was purified and analyzed. This solid was very hygroscopic and immediately decomposed when added to water with the production of an oily layer. The aqueous solution gave qualitative tests for tin and chloride. The oily layers when hydrolyzed produced *p*-methylmandelic acid. A quantitative analysis for chloride indicated the compound to be an addition product as follows



This result is what would be expected from a consideration of the work of Voskresenskaya[3] who showed that the esters of several dibasic acids react with stannic chloride to form similar addition

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(1) Riebsomer, Irvine and Andrews, *Ind. Acad. Sci.*, **47**, in press (1937).

(2) Riebsomer, Irvine and Andrews, THIS JOURNAL, **60**, 1015 (1938).

(3) Voskresenskaya, *C. A.*, **32**, 2551 (1938).

TABLE I

Mandelic acid derivative	Benzene derivative or hydrocarbon used	B. p. intermediate 4–5 mm. °C.	Yield, % Intermediate	Yield, % Acid	M. p. acid, °C.	Neut. equiv. Calcd.	Neut. equiv. Found	Combustion analyses, % Calcd. C	Calcd. H	Found C	Found H
p-*n*-Propyl	*n*-Propylbenzene	170–175	40	20	126–126.5	194.1	191.7	68.08	7.22	67.77	7.20
p-*n*-Butyl	*n*-Butylbenzene	176–177	59	25	116.5–117	208.1	208.5	69.19	7.75	69.11	7.73
p-*n*-Amyl	*n*-Amylbenzene	199–204	51	8	112.5	222.1	223.6	69.92	7.92	70.11	8.14
p-Isoamyl	Isoamylbenzene			16	87–87.5	222.1	219.8	69.92	7.92	69.85	7.98
p-*t*-Amyl	*p*-*t*-Amylbenzene	178–179	95	53	73–74	222.1	220.5	69.92	7.92	69.95	8.07
p-Pentamethyl	Pentamethylbenzene			9	180–181	222.1	222.8	69.92	7.92	70.10	8.06
2,3,5,6-Tetramethyl	1,2,4,5-Tetramethylbenzene	195–210	27	1.3	163	208.1	212.0	69.19	7.75	68.68	7.60
p-Bromo	Bromobenzene			8.8	117.5	232.1	233.8				
p-Iodo	Iodobenzene		29	7.2	135–136	277.9	274.3				

products in a mole to mole ratio. Unfortunately, however, this discovery lends only little to an understanding of the mechanism of the condensation reaction. In fact it seems probable that the formation of this precipitate hinders rather than promotes the reaction because after its formation mixing is less efficient. This probably would help to account for the fact that the yields in these reactions are seldom greater than 60% of the theoretical and usually less.

When stannic chloride was mixed with ethyl oxomalonate a solid was produced which was probably another ester–stannic chloride addition product. It proved to be so unstable that an analysis was impossible. It would be difficult to explain how the formation of this product could promote the condensations.

Another condensing agent, boron trifluoride, was tried in the place of anhydrous stannic chloride. In general the yields of mandelic acids were low.

It was found that chloro-, bromo- and iodobenzene would each condense with ethyl oxomalonate by following the usual procedure. These condensation products hydrolyzed to form the corresponding *p*-halogen substituted mandelic acids. The yields in all cases were discouragingly low. But preliminary experiments indicate that benzene derivatives containing both a halogen and an alkyl substituent condense with ethyl oxomalonate to give respectable yields.

Experimental

Analysis of the Precipitate Formed when Stannic Chloride Was Added to a Mixture of Toluene and Ethyl Oxomalonate.—In a 200-cc. round-bottomed flask was placed 25 g. of toluene and 8.7 g. of ethyl oxomalonate. Ten cc. of anhydrous stannic chloride was added with stirring at a temperature of 0°. A white precipitate was formed which after two hours' stirring was filtered using a suction filter. The precipitate was washed with toluene several times and finally with petroleum ether (b. p. 30–40°). The product was transferred immediately to a vacuum desiccator and dried thoroughly under vacuum. Approximately 0.2-g. samples were weighed, water added to them and the solution titrated with standard silver nitrate. Calcd. % Cl for $CH_3C_6H_4C(OH)(CO_2C_2H_5)_2 \cdot SnCl_4$: 26.93; found, 26.83, 26.75.

Another portion of this solid was hydrolyzed with 20% aqueous potassium hydroxide, the product acidified and warmed as in the usual procedure, extracted with ether, the ether distilled off and the solid recrystallized from benzene, m. p. 145°. A mixed melting point with *p*-methylmandelic acid showed no depression.[4]

The method of preparation of these compounds was with minor alterations the same as reported in the first paper of this series.[2] Since pentamethylbenzene and tetramethylbenzene are solids, the preparation of the intermediates in these cases was carried out in chloroform solution. Chloroform had previously been shown to be satisfactory for this purpose.

Boron trifluoride instead of anhydrous stannic chloride was used to prepare the *p*-bromomandelic acid. In a typical experiment 45 g. of bromobenzene and 8.7 g. of ethyl oxomalonate were mixed in a flask and 2.5 g. of boron trifluoride was added under anhydrous conditions and at 0°. The resulting mixture was allowed to stand overnight and the product isolated in the usual way. The yield was about 9%. Similar experiments were made with chloro- and iodobenzene which resulted in even poorer yields. When stannic chloride was used in the place of boron trifluoride to produce *p*-bromomandelic acid a yield of 4% was obtained. Correspondingly low yields of *p*-chloro- and *p*-iodomandelic acids were obtained when anhydrous stannic chloride was used as the condensing agent.

Boron trifluoride was also used in the place of anhydrous stannic chloride with benzene and toluene in the general reaction, but in each case with poor results.

Table I presents a summary of the properties of the compounds. The yields were all calculated on the basis of the ethyl oxomalonate used.

In order to prove the structure of the *p*-*n*-propyl, *p*-*n*-butyl, *p*-*n*-amyl, *p*-isoamyl and *p*-*t*-amyl mandelic acids each of these compounds was treated with excess alkaline permanganate solution.[5] The acids so produced were converted into the methyl esters. In each case the ester melted at 140°, indicating dimethyl terephthalate. This established the para position for each of the alkyl groups.

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[4] The authors are indebted to Mr. John Bishop for this analysis.

[5] Mulliken, "Identification of Pure Organic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1904, p. 85.

In the cases of the tetra- and pentamethyl derivatives, the method of synthesis was regarded as sufficient proof of their structures.

p-Bromo- and *p*-iodomandelic acids are well known, hence their melting points and neutral equivalents were considered to be sufficient to identify these compounds.

A summary of the bacteriological data is presented in Table II. These tests were made *in vitro* on three different organisms (*B. coli*). The activities are compared with mandelic acid as a standard.

TABLE II

Mandelic acid derivative	Activity
Mandelic	1
p-*n*-Propyl	1 or less
p-*n*-Butyl	1 or less
p-*n*-Amyl	1 or less
p-Isoamyl	1 or less
p-*t*-Amyl	1 or less
Pentamethyl	No activity
2,3,5,6-Tetramethyl	Less than 1
p-Bromo	2–4
p-Iodo	2–4

The first seven of the compounds listed in Table II are so costly to prepare and show so little activity that further experimentation with them would appear fruitless. The two halogen derivatives possess sufficient activity to warrant animal tests to determine their efficacy as urinary tract antiseptics.

The authors are glad to acknowledge the coöperation of Dr. Robert S. Shelton of the Wm. S. Merrell Co., of Cincinnati, Ohio, who performed the bacteriological work, and wish to thank Dean William M. Blanchard of this department who was instrumental in securing financial aid from The National Research Council and from Mr. J. K. Lilly of Indianapolis, Indiana.

Summary

1. Nine substituted mandelic acids have been prepared and compared with mandelic acid with regard to bacteriological activity. Only the *p*-bromo- and *p*-iodomandelic acids show any promise as medicinals.

2. Ando's method for the synthesis of substituted mandelic acids has been extended for alkyl derivatives and has been shown to work poorly for halogen derivatives.

3. Boron trifluoride is not satisfactory to use in the place of anhydrous stannic chloride as the condensing agent.

GREENCASTLE, INDIANA RECEIVED AUGUST 8, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF TRINITY COLLEGE]

Amide Hydrolysis with High Concentrations of Mineral Acids

BY VERNON K. KRIEBLE AND KARL AUGUST HOLST

The hydrolysis of amides in dilute acid solutions has been studied repeatedly. There are, however, few studies on record for acid concentrations greater than normal, and these have nearly all been made on acetamide.

Benrath[1] had some indications that the velocity of hydrolysis of acetamide reached a maximum by increasing the acid concentration. This was definitely shown by Taylor[2] for both hydrochloric and hydrobromic acids although he did not find such a maximum for sulfuric acid. As we have been interested in the hydrolysis of nitriles it seemed worth while to extend the study to amide hydrolysis.

Materials and Procedure

Amides.—These were bought from well-known manufacturers and further purified. We did not try to remove all the water from formamide. This was allowed for in weighing out samples of this particular amide.

Formaldehyde.—Merck U. S. P. grade was used.

Calcium Hypochlorite.—The grade marked "H. T. H." and manufactured by the Mathieson Alkali Works was used. All other chemicals were of the blue label or reagent grade.

Procedure.—Exactly 200 cc. of acid, carefully standardized in terms of molality, was delivered to a glass-stoppered flask which was placed in a thermostat for one-half hour before the experiment was started. Enough amide was weighed out to make the solution contain from 0.5 to 0.8 mole of amide if the formol method of analysis was to be used and 0.05 mole if the oxidation method was to be used to follow the hydrolysis. The acid was poured on the amide which quickly dissolved. The solution after thorough mixing was poured into a series of Pyrex tubes. These were closed with rubber stoppers, wired down, and then put back in the thermostat. When a sample was to be taken, a tube was removed and a definite quantity pipetted into a titration beaker containing enough water to dilute the solution sufficiently to stop the reaction. This

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[1] Benrath, *Z. anorg. allgem. Chem.*, **151**, 53 (1926).

[2] Taylor, *J. Chem. Soc.*, 2741 (1930).

diluted solution was immediately cooled, neutralized, and analyzed for ammonia.

Method of Analysis.—When the amide is hydrolyzed the corresponding organic acid and ammonia are produced. Consequently, it is possible to follow the progress of the hydrolysis by estimating the ammonia present in the hydrolytic solution. This can be done in various ways, but in this investigation it was done by the oxidation of the ammonia with an hypohalite or else by the Sörensen formol titration. In the oxidation method the ammonia reacts with a standard hypochlorite solution releasing nitrogen.

$$4NH_3 + 3Ca(OCl_2) \longrightarrow 2N_2 + 3CaCl_2 + 6H_2O$$

The excess hypochlorite is estimated by adding potassium iodide and titrating the liberated iodine with standard sodium thiosulfate. It was found that the procedure given by Kolthoff and Stenger,[3] was to be preferred to others recorded in the literature. This method was used for most of the rates studied in connection with acetamide and with propionamide where sulfuric acid was the catalyst. It, however, could not be used in the hydrolysis of formamide, which was oxidized by the hypochlorite as well as the ammonia. So the Sörensen formol titration method following the directions given by Hawk and Bergeim[4] was tried. Here formaldehyde reacts with ammonium salts in a neutral solution forming hexamethylenetetramine and liberating an equivalent of the mineral acid which then can be titrated with a standard base.

$$6H_2CO + 4NH_4Cl \longrightarrow 4HCl + 6H_2O + N_4(CH_2)_6$$

This proved to be an excellent method. In any given experiment the velocity constants for various time intervals were much more consistent than by the oxidation method. It was used exclusively with formamide and would have been used with the other amides had we been familiar with its accuracy when the research was started. The rates for acetamide with 1.5 and 3 molal hydrochloric acid were followed by this method and are in line with those determined by the oxidation method.

Order of the Reaction.—The velocity constants were calculated by the monomolecular formula

$$K = \frac{1}{t} \ln \frac{a}{a - x}$$

the time being taken in hours. For the same acid concentration equally good constants were obtained even though the amide concentration varied from 0.05 to 0.8 mole. Benrath also found that whenever the acid concentration exceeded that of the amide the monomolecular formula held. Taylor likewise used this formula in dealing with high concentration of mineral acids on acetamide. Table I illustrates two typical hydrolyses and shows that the velocity is well maintained to more than 85% of completion.

TABLE I

H_2SO_4, 2.0 molal $HCONH_2$, 0.52 mole			HCl, 9.5 molal $HCONH_2$, 0.8 mole		
t, hrs.	% hydrolyzed	*K*	*t*, hrs.	% hydrolyzed	*K*
0.166	16.9	1.11	0.26	27.2	1.23
.416	37.0	1.11	.42	39.4	1.20
.75	55.0	1.06	.58	51.8	1.25
1.18	70.4	1.02	.75	61.3	1.26
1.50	80.9	1.10	1.00	72.5	1.29
1.75	85.4	1.10	1.25	79.5	1.26
2.00	88.4	1.07	1.50	85.5	1.28

In any experiment the velocity constant recorded represents an average of at least six time intervals taken between 18 and 85% of complete hydrolysis. It was seldom that any points averaged varied more than 5% from the mean.

Experimental Results

Hydrolysis of Formamide

Table II

Molality HCl	*K*
2	.82
4	1.59
5	1.74
6	1.84
7	1.78
8	1.62
9.5	1.27

Table III

Molality H_2SO_4	*K*
2	1.08
2.9	1.51
3.5	1.62
4.5	1.72
5.0	1.73
6	1.54
8	1.12

Hydrolysis of Acetamide

Table IV

Molality HCl	*K*
1.50	0.025
2.67	.038
2.91	.039
4.13	.035
5.00	.026

Table V

Molality H_2SO_4	*K*
0.97	0.024
2.00	.032
2.50	.033
3.00	.032
4.14	.027

Hydrolysis of Propionamide

Table VI

Molality HCl	*K*
1.5	0.034
3.0	.050

Table VII

Molality H_2SO_4	*K*
0.186	0.012
.97	.041

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[3] Kolthoff and Stenger, *Ind. Eng. Chem., Anal. Ed.*, **7**, 79 (1935).

[4] Hawk and Bergeim, "Practical Physiological Chemistry," P. Blakiston's Son Co., Philadelphia, Penna., 1931, p. 830.

Table VI		Table VII	
3.5	0.050	1.75	0.053
4.0	.048	3.07	.052
5.0	.042	4.13	.045
		5.29	.032
		6.00	.026
		7.51	.017
		11.20	.006

Discussion

The results obtained for the hydrolyses of the different amides may be discussed from several angles. In every case there is a concentration in which the rate of hydrolysis of the amide is maximum. This concentration is not the same for different amides nor is it the same for hydrochloric acid and sulfuric acid. In each case the molality of the hydrochloric acid at its highest rate is greater than the molality of sulfuric acid for its highest rate.

This is the first time that maximum rates have been observed in the hydrolysis of formamide and propionamide and also for acetamide where sulfuric acid is the catalyst. It is, therefore, probably true for all amides. Benrath and Taylor investigated the hydrolysis of acetamide in concentrations up to 7 *N* sulfuric acid and found no indication of a maximum rate while both found maximum values for hydrochloric acid at approximately 3 *N* concentration. It should be pointed out that a comparison of rates of hydrolysis where high concentrations of acid are involved on a normality basis has little meaning. In the first place, the ratio of water molecules to acid molecules, for example, in a 7 *N* sulfuric acid and a 7 *N* hydrochloric acid solution is quite different and the activity of water in the higher concentrations cannot be ignored. In the second place, polybasic acids in these concentrations function only as monobasic acids. It is much better to make the comparison on a molality basis.

Comparing the effects of the same molal concentrations of the same acids on the different amides, it is apparent that the order of decreasing activity for these amides is formamide, propionamide and acetamide. It is interesting to note that propionamide is hydrolyzed faster than acetamide just as propionitrile is hydrolyzed faster than acetonitrile. This was noted by Crocker[5] also. The reverse is the case when alkali is the catalyst, as Crocker and Lowe and Calvet have pointed out.[6]

All the rates studied show that the velocity constant is not a simple function of the molality of the acid and consequently not of the acidity function of the acid. It is to be noted, however, that before the maximum velocity is reached sulfuric acid, which has a higher acidity than hydrochloric acid, is the better catalyst. After the maximum velocity hydrochloric acid is the better catalyst. In other words, acidity is an aid to the reaction up to the maximum velocity and after that a retarding influence. The maximum velocity is reached by both acids at approximately the same acidity as Table VIII shows.

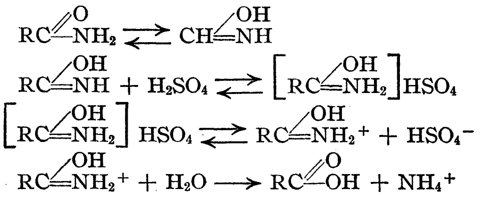
TABLE VIII

MOLALITIES AND ACIDITIES OF SOLUTIONS AT MAXIMUM VELOCITIES

Amide	Acid	Molality	H_0
Formamide	HCl	6	−1.75
Formamide	H_2SO_4	4.75	−1.70
Acetamide	HCl	3.25	−1.02
Acetamide	H_2SO_4	2.5	−0.90
Propionamide	HCl	3.20	−1.00
Propionamide	H_2SO_4	2.40	−0.88

While the velocity of amide hydrolysis, therefore, does not vary directly as the acidity, it is an important factor in the control of the velocity.

Mechanism of Reaction.—In amide hydrolysis, according to former investigators, we are possibly dealing with the following reactions



$$\mathrm{RC}\Big\langle{}^{\mathrm{O}}_{\mathrm{NH_2}} \rightleftarrows \mathrm{CH}\Big\langle{}^{\mathrm{OH}}_{\mathrm{NH}} \qquad (1)$$

$$\mathrm{RC}\Big\langle{}^{\mathrm{OH}}_{\mathrm{NH}} + \mathrm{H_2SO_4} \rightleftarrows \left[\mathrm{RC}\Big\langle{}^{\mathrm{OH}}_{\mathrm{NH_2}}\right]\mathrm{HSO_4} \qquad (2)$$

$$\left[\mathrm{RC}\Big\langle{}^{\mathrm{OH}}_{\mathrm{NH_2}}\right]\mathrm{HSO_4} \rightleftarrows \mathrm{RC}\Big\langle{}^{\mathrm{OH}}_{\mathrm{NH_2}^+} + \mathrm{HSO_4}^- \qquad (3)$$

$$\mathrm{RC}\Big\langle{}^{\mathrm{OH}}_{\mathrm{NH_2}^+} + \mathrm{H_2O} \longrightarrow \mathrm{RC}\Big\langle{}^{\mathrm{O}}_{\mathrm{OH}} + \mathrm{NH_4}^+ \qquad (4)$$

Hantzsch and Geidel[7] conclude from their absorption experiments in the ultraviolet that at equilibrium the imino form is in large excess, particularly in the aromatic amides. Pauling and Sherman[8] have calculated from the heats of formation that amides are resonating molecules and Kumler[9] that acetamide at least is largely a dimer held by hydrogen bonds. Hantzsch and Geidel also conclude that the salt formed when acid is added to the amide is the salt of the imino form because the absorption spectra agree with the salt of the imino ether. From freezing point measurements they show that the salt is highly ionized. Benrath, and Euler and Ölander,[10] and others have

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[5] Crocker, *J. Chem. Soc.*, **91**, 593 (1907).

[6] Crocker and Lowe, *ibid.*, **91**, 952 (1907); Calvet, *J. Chem. Phys.*, **30**, 1, 140, 198 (1933).

[7] Hantzsch and Geidel, *Ber.*, **64B**, 667 (1931).

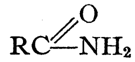
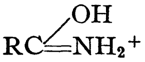
[8] Pauling and Sherman, *J. Chem. Phys.*, **1**, 606 (1933).

[9] Kumler, THIS JOURNAL, **57**, 600 (1935).

[10] Benrath, *Z. anorg. allgem. Chem.*, **151**, 53 (1926); Euler and Ölander, *Z. physik. Chem.*, **131**, 107 (1927).

come to the conclusion that it is the amide cation that hydrolyzes to the acid.

Even if all these reactions are in evidence when an amide is added to a mineral acid, it does not explain why the velocity of hydrolysis reaches a maximum and then falls off with increased acid concentration. Benrath came to the conclusion that the velocity was greatest when sufficient acid was added to convert all the amide into a cation. When the acid is increased beyond this point the cation combines with the anion to form an undissociated salt which does not react with water and hence the velocity of hydrolysis falls off. Taylor comes to a somewhat similar conclusion as he says that increased acid concentration caused the formation of an unhydrolyzable complex between the acid and the amide. If this were the true explanation, then the molality of the acid at maximum velocity should vary with the concentration of the amide, but this does not appear to be the case. Benrath used a concentration of 2.4 *N* acetamide while Taylor used 0.05 *N* and we used 0.05 to 0.8 *N*. Benrath had his maximum velocity at 3.18 molal hydrochloric acid and Taylor at 3.0 and we at 3.25.

There is another reaction of the amides which is apparently closely associated in mechanism with their hydrolysis, namely, their reaction with nitrous acid. Plimmer[11] showed that amides do not react with nitrous acid in acetic acid. We have confirmed this statement. They will not react until enough mineral acid has been added to make the solution 2 *N* according to Plimmer. Taylor[12] reports that an aqueous solution must be 4 *N* with respect to mineral acid before decomposition takes place. On the other hand, amines, amino acids and urea react with nitrous acid in acetic acid without addition of mineral acids. The alpha amino group in amino acids reacts completely in five to thirty minutes according to Van Slyke. In these compounds we have an amino group which apparently is lacking in the amides until a certain acidity is attained. It is for this reason that Plimmer concludes that the amide in solution is in the imino form, but when sufficient mineral acid is added the equilibrium is shifted in (1) to the left in favor of the true amide which then reacts with nitrous acid. If this is the true explanation for amide decomposition with nitrous acid, it also offers a plausible explanation for the maximum velocity phenomena for amide hydrolysis. From unpublished results in this Laboratory it is known that the maximum velocity for amide hydrolysis in acetic acid requires a much lower mineral acid concentration than in aqueous solutions just as it does for nitrous acid decomposition. It appears, therefore, that amide decomposition with nitrous acid and amide hydrolysis at maximum velocity are correlated with the same mineral acid concentration and perhaps with the amide imide equilibrium of reaction (1), the supposition being that increased acidity favors the  $\mathrm{RC(\!=\!O)NH_2}$ tautomer and thus lowers the cation  $\mathrm{RC(OH)\!=\!NH_2^+}$ concentration and hence the rate of hydrolysis. It is equally plausible that, so far as the nitrous acid reaction is concerned, the reason that amines and amino acids react in acetic acid while amides do not is due to the fact that the former are much more basic and therefore form salts more readily and hence react while amides do not form salts and therefore do not react.

Dr. C. D. Coryell has suggested that the abnormal amide hydrolysis might depend on the activity of water. The activity of water drops to 0.51 in an 8 molal hydrochloric acid solution and to 0.48 in the same molal concentration of sulfuric acid. According to this idea, with increase in acid concentration the ratio of the velocity to the activity of water should increase so long as the concentration of the amide cation increases faster than the proper power of the activity of water de-

TABLE IX

HYDROCHLORIC ACID ON ACETAMIDE AT 50°

Mol. HCl	$K \times 10^4$ [a]	$\frac{K \times 10^4}{\text{Act. } H_2O}$	$\frac{K \times 10^4}{(\text{Act. } H_2O)^2}$
2.5	32.4	36.2	40.0
3.19	34.1	40.0	47.5
3.87	30.0	40.7	47.0
4.56	26.5	35.0	45.5
5.27	23.0	32.5	45.0
6.75	16.9	27.5	45.0

[a] Velocity constants taken from Benrath, ref. 1.

SULFURIC ACID ON PROPIONAMIDE AT 25°

Mol. H_2SO_4	$K \times 10^3$	$\frac{K \times 10^3}{\text{Act. } H_2O}$	$\frac{K \times 10^3}{(\text{Act. } H_2O)^2}$
0.18	12	12.1	12.2
.97	41	41.6	42.6
1.75	53	57.2	61.7
3.07	52	61.7	73.7
4.13	45	58.9	77.6
5.29	33	48.7	73.9
6.00	26	41.6	67.2
7.50	17	33.1	76.3
11.20	5	19.3	71.4

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[11] Plimmer, *J. Chem. Soc.*, **127**, 2651 (1925).

[12] Taylor, *ibid.*, 2741 (1930).

creases. When, however, the amide has all been converted into a cation the velocity should decrease at the same rate as the power of activity of water or the ratio of K to the activity function of water should remain a constant. Unfortunately, the data on velocities beyond the maximum are very meager. Benrath studied the action of hydrochloric acid on acetamide up to 6 N or 6.75 molal and we studied sulfuric acid on propionamide to 11.2 molal. Table IX shows the ratio of the velocity constants to the square of the activity of water.

The constancy of the ratio of the rate constant to the square of the activity of water is striking and indicates that there may be two molecules of water involved in the hydrolysis of the amide cation. It is necessary to have more experimental data to establish definitely this point of view.

We are extending the investigation to include: (1) the action of nitrous acid on amides with varying mineral acid concentrations; (2) the hydrolysis of disubstituted amides; (3) the hydrolysis of acetamide with varying activities of water.

Summary

A study has been made of the hydrolysis of formamide, acetamide and propionamide under the influence of high concentrations of hydrochloric acid and of sulfuric acid.

Each amide has a maximum velocity of hydrolysis at one particular acid concentration. This acid concentration is not the same for both hydrochloric acid and sulfuric acid nor is it the same for different amides. The molality of hydrochloric acid is higher at maximum velocity than for sulfuric acid.

The maximum velocity is reached at about the same acidity for both acids irrespective of the amide. Formamide, however, required a higher acidity than acetamide or propionamide.

Various explanations for the maximum velocity are discussed. A new suggestion has been put forward, namely, that the decrease in the activity of water accounts for the decrease in the velocity of hydrolysis at the higher acid concentration.

HARTFORD, CONN. RECEIVED OCTOBER 17, 1938

[CONTRIBUTION FROM THE FOREST PRODUCTS LABORATORY,[4] FOREST SERVICE, U. S. DEPARTMENT OF AGRICULTURE]

The Microstructure and the Diffraction Pattern of Basswood Ash[1]

BY E. A. PARKER,[2] W. E. PATZER[3] AND GEO. J. RITTER[3]

In the burning of wood to ash it was found that an ash residue retaining the fine structure of the original wood could be obtained by carefully controlling a current of oxygen–ozone in the furnace.

Ash residues were prepared from basswood cross sections for determining the microstructure of the ash and the location of the ash-forming constituents. Ash retaining the structure of wood cubes was also made for comparison of its crystalline arrangement with that of ash from wood sawdust. Further, ash was prepared from acid-hydrolyzed wood sections to determine whether the hydrolysis affected the microstructure of the ash constituents.

Previous workers had made ash from thin wood sections in air at glowing furnace temperatures. Brown[5] believed the ash contained considerable siliceous material in the form of rodlike structures arranged parallel with the fibers. The ash structure was similar to that photographed by Ritter.[6] Uber and Goodspeed[7,8] concluded that the ash-forming constituents were distributed throughout the cell wall, but doubted their existence in the middle lamella.

Experimental

Microstructure of the Ash.—Wood specimens in the present study were burned carefully in a slow current of oxygen containing a small percentage of ozone which was generated by an ozonizer connected with the furnace (Fig. 1). The gas mixture was brought in direct contact with the specimen in the furnace, which was electrically heated to 300 to 325°. Excessive shrinkage of the thin wood sections during the burning was prevented by mounting each specimen on a glass object slide by means of a

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[1] Presented before the Division of Cellulose Chemistry, American Chemical Society, Milwaukee, Wis., September 5–9, 1938.

[2] University of Illinois, Urbana, Illinois.

[3] Forest Products Laboratory, Madison, Wis.

[4] Maintained at Madison, Wis., in coöperation with the University of Wisconsin.

[5] F. Brown, *Bull. Torrey Bot. Club*, **47**, 407 (1920).

[6] Geo. J. Ritter, *Rayon and Melliand Textile Monthly*, **16**, [9] 98–100; [10] 58–60 (1935).

[7] F. M. Uber and T. H. Goodspeed, *Proc. Nat. Acad. Sci.*, **21**, 428 (1935).

[8] F. M. Uber and T. H. Goodspeed, *ibid.*, **22**, 463 (1936).

drop of oil consisting of equal parts of ash-free linseed oil and turpentine. The oil was then hardened in a current of the oxygen–ozone at room temperature so as to hold the specimen in place.

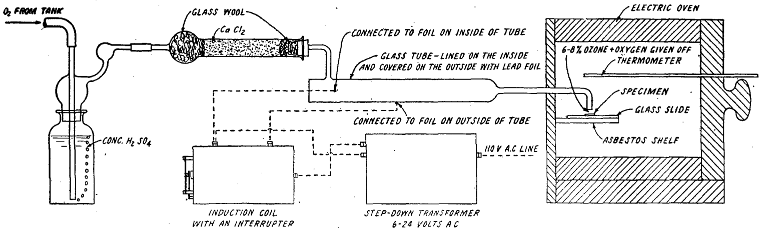
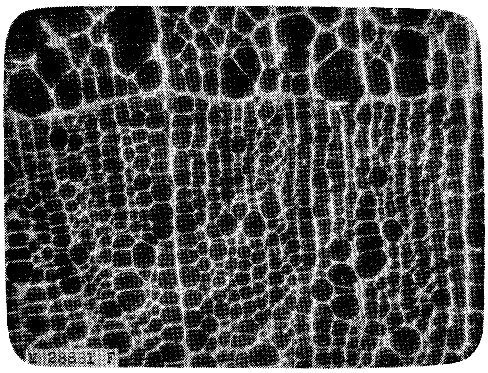


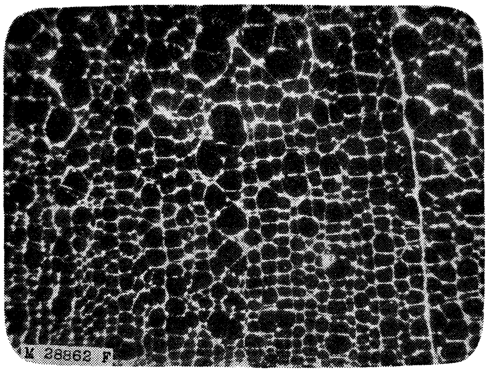
Fig. 1.—A diagram of apparatus used for ashing wood samples.

The ash from a transverse wood section 5 to 10 microns thick retained a pattern of the wood except for having thinner walls (Fig. 2a).

The ash residue from a cross section of wood treated with 35% hydrofluoric acid at 20° for seven days, then with boiling 3.0% hydrochloric acid for three hours, and finally washed with water also produced an intact pattern of the wood (Fig. 2b). Its walls were slightly thinner than those of the ash from the wood having had no acid treatment previous to burning.



(a) Ash residue from an untreated wood section (approximately 87 ×).



(b) Ash residue from wood previously treated with hydrofluoric acid, hydrochloric acid and water (approximately 87 ×).

Fig. 2.—Ash residues from transverse sections of wood.

The ash-forming constituents in wood appeared to be located throughout the cell wall. Although the walls of the final ash residue were thinner than those of the wood, microscopical examinations of cross sections in different stages of burning showed a white ash residue on the surface of the entire cell wall. As the burning proceeded to completion, the ash in the secondary wall apparently shrank toward the primary wall.

When cross esctions of wood 10 microns thick were burned, occasional checks were observed between some of the adjacent walls of the ash, whereas numerous checks were observed between the walls of the ash from wood sections 5 microns thick. The numerous checks in the thinner sections confirmed the results noted by Uber and Goodspeed,[8] whose work was confined to the thinner type of wood specimens. The many checks in the ash suggested to them that possibly no ash-forming constituents are located in the middle lamella. However, the contrast between the number of checks in the ash from the thin and the thicker wood specimens, as observed in the present study, indicates that the checks were caused by mechanical means during the sectioning of the specimens and that they became prominent during the subsequent ashing procedure.

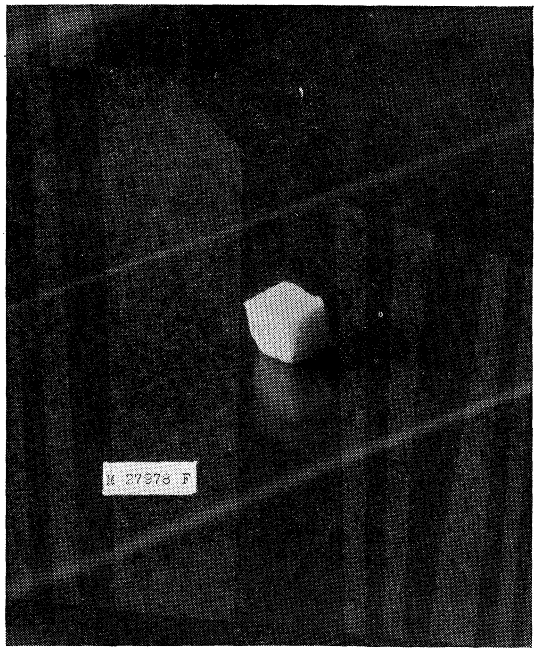


Fig. 3.—Ash residue from a wood cube.

Crystal Arrangement of the Ash.—The well-preserved structure of the ash obtained from a wood cube 3 mm. on edge (Fig. 3), suggested that the crystalline ash constituents might have a preferred orientation. Accordingly, a photographic pattern of the ash cube was made by

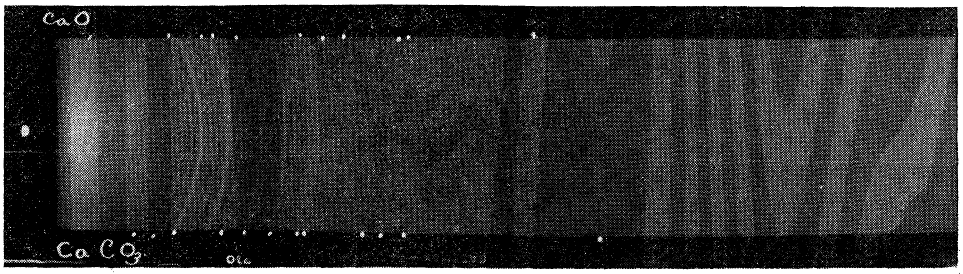


Fig. 4.—Diffraction pattern produced by ash from basswood sawdust. Lines produced by calcium oxide checked at top of pattern; lines produced by calcium carbonate checked at bottom of pattern.

passing an X-ray beam through the block perpendicular to the long axis of the fibers. The diffraction pattern, which was recorded on a flat film, indicated random arrangement of the ash crystals, the same as the arrangement of ash from sawdust of the same wood sample.

In order to facilitate the identification of the ash constituents recorded on the film, an X-ray pattern was made under the conditions employed for making reference patterns of known compounds. In this case a circular camera having a 6.4 cm. radius was used in conjunction with a fine-structure tube having a copper target, operating on 36 p. k. v. and 23 m. a. The pattern (Fig. 4) obtained under these conditions was compared with reference patterns of constituents found, in general, in wood ash. The comparison indicated that the oxide and the carbonate of calcium produced all the lines recorded. The oxide lines are checked on the top and the carbonate lines on the bottom of Fig. 4 by means of the white dots.

Why other ash constituents are not recorded on the pattern is not known. One reason advanced is that any ash constituent, other than the two of calcium, is present in too small a percentage to produce diffraction lines. Another reason is that the lattice spacing of some of the constituents might have been destroyed by a partial fusing during the preparation of the ash. We offer these reasons with no definite proof of their accuracy.

Summary

The ash residue obtained from the burning of wood forms intact skeletons of the original wood. An ash residue of a transverse wood section has walls considerably thinner than those of the original wood section. As the organic material of the cell wall burns, a lateral shrinkage of the ash cell wall occurs, the ash in the secondary layer being drawn toward the middle lamella.

It is believed that the occasional checks between two adjacent cell walls of the ash are caused by the sectioning of the wood and are no indication of the absence of ash in the middle lamella.

Ash residues from transverse wood sections indicate that the ash-forming minerals in wood are located in both the cell wall and the middle lamella.

Small blocks of the ash residue retain the shape of the original wood.

X-ray diffraction patterns of ash cubes indicate a random arrangement of the ash crystals.

By a comparison of the diffraction pattern of the ash with those of known compounds, it has been shown definitely that the carbonate and the oxide of calcium produced the only visible diffraction lines.

MADISON, WISCONSIN RECEIVED OCTOBER 17, 1938

[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY OF YALE UNIVERSITY]

The Thermodynamics of Bi-univalent Electrolytes. III. Zinc Iodide in Aqueous Solution[1]

BY ROGER G. BATES[2]

The thermodynamic behavior of zinc iodide in aqueous solution is of interest in relation to the problem of the intermediate electrolyte. Cadmium iodide has been shown[1b,3,4] to represent an extreme case of incomplete dissociation in solution. Little is known, however, regarding the degree to which this abnormality extends to zinc iodide.

Van Name and Brown found[5] that the tri-iodide equilibrium constant determined with zinc iodide–iodine solutions retained its normal value over a considerable range of electrolyte concentration. Grimm has likewise reported[6] lattice energy calculations for zinc iodide that lead one to expect a high degree of electrolytic dissociation of the salt in solution. A forty-eight-hour exposure of a concentrated zinc iodide solution failed to yield any perceptible Raman lines,[7] although a strong iodine coloration may have interfered.

The transference studies of Hittorf, on the other hand, have shown[8] that the transference number of zinc becomes negative in strong solutions of zinc iodide, while Van Rysselberghe, Grinnell and Carlson found[9] that the conductivities of zinc iodide–potassium iodide mixtures showed large deviations from the mixture rule above a total concentration of 4 *N*.

Measurements of the electromotive force of the cell

$$\text{Zn–Hg (2-phase)}/\text{ZnI}_2\ (m)/\text{AgI–Ag} \qquad (1)$$

have been made at 5° intervals from 5 to 40°, inclusive, and over a range of zinc iodide molality extending from 0.005 to 0.8. From the results, the standard potential of the cell has been evaluated, and calculations of the activity coefficients, relative partial molal heat content and relative partial molal specific heat of the salt have been made. Zinc iodide in aqueous solution has been found to behave as a normal bi-univalent electrolyte over the range of concentration studied.

Experimental Methods

An amalgam containing 5% of zinc by weight was used in most of the cells, although preparations containing as little as 4.5% zinc or as much as 5.5% were tried without noticeable difference in results. According to Puschin,[10] these amalgams are saturated over the temperature range studied. The best grade of Kahlbaum zinc and thrice-distilled mercury were employed, and the preparations were stored under hydrogen in an amalgam pipet. Previous to the preparation of each electrode, the pipet was warmed in an oven until its contents were entirely fluid; a portion of amalgam was then drawn through an ungreased stopcock of large bore into the evacuated cell vessel. The electrodes used in this work were shown to be identical with a zinc amalgam electrode prepared from a sample of spectroscopically pure zinc kindly furnished by the Research Laboratory of the New Jersey Zinc Co.

The silver–silver iodide electrodes were formed on small platinum spirals by the thermal decomposition of a paste composed of 90% silver oxide and 10% silver iodide. Ten to fifteen minutes at about 450° was found to be a satisfactory decomposition time. Silver iodide was prepared by precipitation and was digested three days under water at about 80°. It was found necessary to employ electrodes of 20–25% silver iodide for measurements in zinc iodide solutions stronger than 0.2 molal. The solubility of silver iodide in iodide solutions rises extremely rapidly as the iodide ion concentration is taken above about 0.4 gram ions per liter.

Electrodes prepared by the decomposition of oxide–iodate mixtures by the method of Owen[11] were tried and found to be less reproducible in the more concentrated zinc iodide solutions than those prepared from oxide–iodide mixtures. It has been shown recently[12] that silver iodate decomposes at about 390° but that a period of one to two hours is required for complete decomposition at 400 or 450°. Table I gives a comparison of the decomposition temperatures of the silver salts commonly used for thermal electrodes. It is evident that the high temperatures requisite for the complete and rapid decomposition of the iodate may cause considerable loss of silver iodide, whereas the same temperature is quite satis-

TABLE I

DECOMPOSITION TEMPERATURES OF SILVER SALTS

	$AgXO_3$	AgX
X = Cl	270°	1550° (boils)
X = Br	*ca.* 330	700
X = I	*ca.* 390	552

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[1] Previous papers in this series are (a) Bates and Vosburgh, THIS JOURNAL, **59**, 1583 (1937); and (b) Bates and Vosburgh, *ibid.*, **60**, 137 (1938).

[2] Sterling Fellow.

[3] McBain, Van Rysselberghe and Squance, *J. Phys. Chem.*, **35**, 999 (1931).

[4] Riley and Gallafent, *J. Chem. Soc.*, 514 (1932).

[5] Van Name and Brown, *Am. J. Sci.*, **44**, 105 (1917).

[6] Grimm, *Z. physik. Chem.*, **102**, 113, 141 (1922).

[7] Venkateswaran, *Proc. Ind. Acad. Sci.*, **1**, 850 (1935).

[8] Hittorf, *Pogg. Ann.*, **106**, 513 (1859).

[9] Van Rysselberghe, Grinnell and Carlson, THIS JOURNAL, **59**, 336 (1937).

[10] Puschin, *Z. anorg. Chem.*, **36**, 201 (1903).

[11] Owen, THIS JOURNAL, **57**, 1526 (1935).

[12] G. R. Cooper, M. A. thesis, Duke University, 1938.

TABLE II

ELECTROMOTIVE FORCES OF THE CELL

Zn–Hg (2-phase)/ZnI_2 (m)/AgI–Ag

m	E_5	E_{10}	E_{15}	E_{20}	E_{25}	E_{30}	E_{35}	E_{40}
0.001182					0.8584			
.002026					.8379			
.004140					.81190			
.004692	0.80114	0.80304	0.80475	0.80628	.80753	0.80862	0.80967	0.81057
.005683	.79510	.79689	.79855	.79983	.80103	.80212	.80296	.80365
.008455	.78235	.78403	.78531	.78645	.78739	.78829	.78888	.78944
.009650	.77791	.77934	.78064	.78174	.78271	.78347	.78408	.78453
.01277	.76871	.76995	.77114	.77223	.77302	.77365	.77417	.77422
.01801	.75742	.75858	.75952	.76028	.76088	.76131	.76165	.76170
.02675	.74515	.74607	.74680	.74739	.74782	.74802	.74814	.74810
.04294	.73023	.73085	.73135	.73165	.73189	.73185	.73159	.73122
.05619	.72103	.72156	.72187	.72212	.72222	.72204	.72173	.72121
.06068	.71853	.71905	.71939	.71955	.71957	.71944	.71915	.71872
.07441	.71239	.71267	.71281	.71286	.71286	.71261	.71216	.71163
.1224	.69573	.69572	.69563	.69540	.69502	.69439	.69360	.69270
.1771	.68283	.68268	.68241	.68198	.68138	.68070	.67985	.67889
.3289	.66015	.65960	.65896	.65820	.65725	.65618	.65504	.65375
.4176	.64983	.64911	.64827	.64735	.64629	.64515	.64386	.64251
.8008	.61789	.61671	.61551	.61425	.61292	.61158	.61011	.60864

factory for the formation of silver bromide and silver chloride.

Several zinc iodide stock solutions were used. These solutions were prepared by dissolving the salt, recrystallized from oxygen-free conductivity water, in a quantity of boiled conductivity water through which purified hydrogen had been bubbled for some time. The careful exclusion of air at all times was imperative. Zinc iodide reacts with oxygen and with carbon dioxide and is oxidized rapidly when in contact with cellulose, both in solution and in the solid condition.[13] Sintered glass filters were used in all filtrations.

Weighed samples of the stock solutions were analyzed for iodide by the Volhard method. All solutions were kept under hydrogen in flasks from which they could be expelled by hydrogen pressure as desired. Weighed amounts of water were added to weighed quantities of stock solution in making the dilutions. Vacuum corrections were made for all weighings. No precipitation of hydroxide or basic salt was observed.

The cells vessels were similar to those described by Bates and Vosburgh.[1a] To permit the use of the vessels in water thermostats, the electrode contacts were made through mercury wells. The use of Pyrex glass with tungsten contacts served to prevent the occasional breakage of vessels observed when zinc amalgam is in contact with sealed-in platinum wires.[14]

The process of making a cell was carried out entirely in the absence of air. The vessel, containing a silver iodide electrode and a portion of amalgam, was evacuated with an oil pump for ten to fifteen minutes and filled with hydrogen. Two portions of cell solution were admitted from a saturator flask to each arm of the vessel and expelled through the side tubes provided for the purpose. The cell electrolyte was then introduced.

Cells were made in triplicate at each concentration. Within the optimum range of concentration (0.01 to 0.2 m) triplicate cells deviated from the mean electromotive force by less than 0.1 mv. when equilibrium conditions had been attained, usually within two to five hours. Between 0.2 and 0.8 m, where the solubility of silver iodide in the electrolyte is large, the agreement was as satisfactory, but the time of attainment of equilibrium and the life of the cell were much shorter than was the case at the lower concentrations. Below 0.01 m the cells ordinarily required overnight to come to satisfactory equilibrium. The reproducibility was of the order of 0.2 mv. Temperature coefficient runs were completed within a period of ten hours after they were begun. It was observed that most of the cells began to decrease slowly in electromotive force after approximately thirty-six hours. A separate temperature run was made for each group of three cells. Upon change of temperature most of the cells attained constant values in twenty to thirty minutes, although marked hysteresis was noted in those with electrolytes more dilute than 0.005 molal. The temperature of initial measurement was 25°, and all cells were brought back to this temperature at the completion of the run. The original 25° values were usually satisfactorily resumed, and the results for cells showing unusual drifts during the run were rejected as unreliable.

The electromotive forces were measured by means of a Leeds and Northrup Type K potentiometer. The standard cell was frequently checked against the laboratory standards. Thermometers were standardized against a calibrated platinum resistance thermometer. The temperatures were probably accurate to ±0.03°.

Experimental Results

The electromotive forces obtained in the best runs are recorded in Table II. These values were fitted to the quadratic equation

$$E_t = E_{25} + a(t - 25) + b(t - 25)^2 \qquad (2)$$

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[13] Berridge, *B. A. Rep.*, 658 (1895).

[14] Cowperthwaite and La Mer, THIS JOURNAL, **53**, 4333 (1931).

by the method of Harned and Nims.[15,16] The electromotive forces at 25° at round molalities were read from a large scale plot of E *versus* $\log m$. These values are recorded in Table III with the smoothed a and b constants.

TABLE III

CONSTANTS OF EQUATION (2)

m	E_{25}	$a \times 10^6$	$b \times 10^6$
0.002	0.83845		
.003	.82360		
.005	.80556	241	−3.68
.007	.79392	206	−3.64
.008	.78930	193	−3.62
.01	.78150	169	−3.55
.02	.75780	96	−3.39
.03	.74395	55	−3.28
.05	.72654	3	−3.13
.07	.71502	− 31	−3.02
.1	.70256	− 67	−2.91
.2	.67683	−139	−2.64
.5	.63765	−233	−1.89
.7	.62018	−256	−1.31
.8	.61295	−263	−1.09
	E^0_{25}	$a_0 \times 10^6$	$b_0 \times 10^6$
E^0:	0.61055	−428	−3.91

The Standard Potential of the Cell

The electromotive force of cell (1) may be represented by the equation

$$E = E^0 - 2.3026(RT/2F) \log \mathbf{a}_{\mathrm{ZnI_2}} = E^0 - k \log 4m^3\, \gamma_\pm^{\,3} \qquad (3)$$

in which E^0 is the standard potential of the cell, E the observed electromotive force, $\mathbf{a}_{\mathrm{ZnI_2}}$ the activity of zinc iodide in a solution of molality m, k equals $2.3026(RT/2F)$ and $\gamma_\pm$ is the stoichiometrical activity coefficient of zinc iodide.

The evaluation of E^0 may be accomplished, as pointed out by Hitchcock,[17] by the substitution of the Debye–Hückel limiting law

$$-\log \gamma_\pm = u'\sqrt{c} + Pc = u'\sqrt{md} + Pmd \qquad (4)$$

in the right-hand term of equation (3) and extrapolating this function of the original electromotive forces to zero concentration, bearing in mind that in dilute solutions c, the molar concentration, is very nearly equal to md, where d is the density of the solution. The expression for $E^{0\prime}$, the apparent standard potential, then becomes

$$E^{0\prime} = E^0 + 3kPmd = E + k \log 4 + 3k \log m - 3k\, u'\sqrt{md} \qquad (5)$$

in which u' is the limiting slope of the Debye–Hückel theory, varying inversely as $(DT)^{3/2}$, where D is the dielectric constant of the solvent[18] and T is the absolute temperature. P is an empirical constant. Equation (4) is valid only at extremely low concentrations of zinc iodide.

Scatchard and Tefft have shown[19] that the incomplete dissociation of the intermediate ion, MX^+, of a bi-univalent salt causes a hump in the plot of $E^{0\prime} - E^0$ against $c^{1/2}$. By the matching of theoretical plots constructed for various values of K_2, the dissociation constant of the intermediate ion, with the plot of experimental data it is possible to obtain an estimate of the second dissociation constant of the salt.[20] The character of the zinc iodide results when treated in this manner indicated a high degree of dissociation, with a constant greater than 10 for the ZnI^+ ionization process. Therefore, in the further treatment of the results complete ionization was assumed.

The activity coefficient in equation (3) may be represented with somewhat more accuracy by the Hückel equation[21]

$$-\log \gamma_\pm = \frac{u\sqrt{3c}}{1 + A\sqrt{3c}} + Bc - \log(1 + 0.054m) \qquad (6')$$

or, less exactly

$$-\log \gamma_\pm = \frac{u\sqrt{\mu d}}{1 + A\sqrt{\mu d}} + B''\mu d \qquad (6)$$

where μ is the ionic strength, $\mu = \sum m_i z_i^{\,2}/2 = 3m$, u is a constant related to u' of equation (4) by the expression, $u' = u\sqrt{3}$, B and B'' are empirical constants and

$$A = Ka \qquad (7)$$

K is a quantity varying as $(DT)^{-1/2}$ and a is the mean distance of approach of the ions. This ion size parameter for a highly dissociated electrolyte is independent of temperature over the ordinary range of measurement.[14,22]

Since $3k \log (1 + 0.054m)$ amounts only to 0.09 mv. for $m = 0.05$, the highest concentration employed in obtaining E^0, the omission of the third term on the right of equation (6′) is of no appreciable influence on the course of the extrapolation. Combining equation (3) with equation (6) gives

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(15) Harned and Nims, THIS JOURNAL, **54**, 423 (1932).

(16) The average deviations of the observed electromotive forces at the eight temperatures from the quadratic equation were of the order of 0.02–0.05 mv. In no case was the average deviation greater than 0.1 mv.

(17) Hitchcock, *ibid.*, **50**, 2076 (1928).

(18) The equation of Wyman, *Phys. Rev.*, **35**, 623 (1930), was used in obtaining D at the eight temperatures.

(19) Scatchard and Tefft, THIS JOURNAL, **52**, 2272 (1930).

(20) Harned and Fitzgerald, *ibid.*, **58**, 2624 (1936).

(21) Hückel, *Physik. Z.*, **26**, 93 (1925).

(22) Harned and Ehlers, THIS JOURNAL, **55**, 2179 (1933).

$$E^{0'} = E^0 + B'\mu d = E + k \log 4 + 3k \log m - \frac{3ku\sqrt{\mu d}}{1 + A\sqrt{\mu d}} \quad (8)$$

where $B' = 3kB''$.

Values of $E^{0'}$ were calculated by equation (8) and were extrapolated to zero ionic strength to obtain E^0. Figure 1 shows the extrapolations at the eight temperatures. The values of the various parameters of Hückel's equation are listed in Table IV, together with the a values that best fitted the experimental results. Approximate densities of the zinc iodide solutions were obtained from "International Critical Tables."[23]

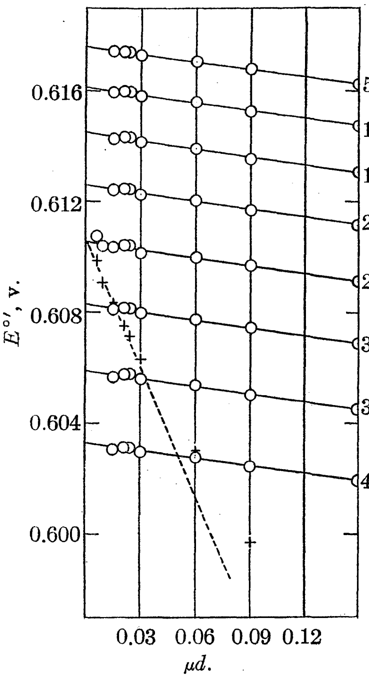

Fig. 1.—Extrapolation functions for cell (1). Circles represent plots of $E^{0'}$ according to equation (8). Crosses represent $E^{0'}$ according to equation (5). Diameter of circles, 0.4 mv.

TABLE IV

PARAMETERS OF EQUATIONS (6) AND (7)

t	u	$-B''$	$K \times 10^{-8}$	$a \times 10^8$ (cm.)
5°	0.9785	0.113	0.325	6.09
10	.9866	.111	.326	6.07
15	.9944	.109	.327	6.05
20	1.003	.107	.328	6.04
25	1.012	.105	.329	6.02
30	1.022	.103	.330	6.00
35	1.032	.102	.331	5.98
40	1.043	.100	.332	5.96

The crosses of Fig. 1 indicate $E^{0'}$ points at 25° calculated by equation (5), and the broken line has been drawn to intersect the equation (8) plot at $\mu = 0$. It is evident that the extrapolation with the use of the Debye–Hückel limiting law is rather uncertain. The E^0 obtained by the use of the extended equation, however, is thought to be quite reliable.

The standard potentials of cell (1) may be expressed by the equation

$$E_t^0 = E_{25}^0 + a_0(t - 25) + b_0(t - 25)^2 \quad (9)$$

with an average deviation of 0.03 mv. The numerical values of the constants of this equation appear at the bottom of Table III.

Standard Potentials of Zinc Electrodes

In the second and third columns of Table V are listed the standard potentials, E^0, of the zinc–silver iodide cell at 5° intervals from 5 to 40°. The potentials of the electrode, Zn–Hg (2-phase)/Zn^{++}(a = 1), are represented by $E^{0''}$ and are given in the fourth and fifth columns. These values were computed by subtracting the standard potentials of the hydrogen–silver iodide cell[11] from the standard potentials of cell (1) at corresponding temperatures. For the former cell, Owen has given the equation

$$E^0_{HI} = -0.15219 - 328 \times 10^{-6}(t - 25) - 3.6 \times 10^{-6}(t - 25)^2 \quad (10)$$

TABLE V

STANDARD POTENTIALS

Zn–Hg/ZnI_2(a = 1)/AgI–Ag, E^0

Zn–Hg/Zn^{++}(a = 1), H^+(a = 1)/E_2, $E^{0''}$

t, °C.	E^0	E^0 (Eq. 9)	$E^{0''}$	$E^{0''}$ (Eq. 11)
5	0.6176	0.61755	0.76472	0.76462
10	.6161	.61609	.76415	.76417
15	.6145	.61444	.76370	.76371
20	.6126	.61259	.76322	.76323
25	.6105	.61055	.76275	.76274
30	.6083	.60831	.76226	.76223
35	.6059	.60588	.76176	.76171
40	.6033	.60325	.76117	.76117

Subtraction of this equation from equation (9) gives

$$E^{0''} = E^0_{Zn\text{-}Hg/Zn^{++}} = 0.76274 - 0.0001(t - 25) - 0.00000031(t - 25)^2 \quad (11)$$

Since Clayton and Vosburgh[24] have shown that the electromotive force of the cell, Zn(s)/Zn^{++}/Zn–Hg (5%), is zero, it is evident that $E^{0''}$ likewise represents the standard potentials of the zinc metal electrode.

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[23] "International Critical Tables," McGraw-Hill Book Co., Inc., New York, N. Y., 1928, Vol. III, p. 65.

[24] Clayton and Vosburgh, THIS JOURNAL, **58**, 2093 (1936).

Recorded standard potentials for the zinc amalgam electrode do not agree well. Shrawder, Cowperthwaite and La Mer[25] computed the potential of this electrode from the standard potential of the zinc amalgam–lead sulfate cell[14] and an E^0 for the lead amalgam–lead sulfate electrode[26] finding a value of 0.7614 v. at 25°.

From measurements of the cell

$$\text{Zn–Hg (2-phase)/ZnCl}_2\ (m)\text{/AgCl–Ag} \qquad (12)$$

at 25° and accepted data on the Ag–AgCl electrode, Scatchard and Tefft[19] found a zinc amalgam electrode potential of 0.7610 v., while Brüll[27] calculated a value of 0.7596 v. from electromotive forces of zinc amalgam-mercurous chloride cells with zinc chloride electrolytes. The low result of Brüll can be attributed largely to the use of too high a calomel electrode potential (0.2700 v.) for the computation. Gerke[28] and Randall and Young[29] agree that the mercury–mercurous chloride electrode is 0.0455 v. more positive than the silver–silver chloride electrode, which has a value of 0.2224 v. at this temperature.[22] Subtraction of 0.2679 v. from the standard potential of Brüll's cell gives 0.7617 v. for the potential of the zinc amalgam electrode.

The E^0 of Scatchard and Tefft, and of Brüll as well, was obtained by the Hitchcock method, using an extrapolation function similar to equation (5). Since the Hückel equation gives a much more valid representation of the activity coefficient of zinc chloride than does the limiting law in solutions more concentrated than 0.005 M, it seemed worthwhile to extrapolate the results with the use of equation (8). The circles of Fig. 2 represent $E^{0\prime}$ values of Scatchard and Tefft, while the crosses indicate values of the quantity $E^{0\prime} - 0.0455$ calculated from Brüll's electromotive forces. The broken line again shows the course of the Hitchcock extrapolation. An apparent ionic diameter of 5.4 Å. made equation (8) fit the results to best advantage. Triangles represent $E^{0\prime}$ values when the parameter a is 4.0 Å., and dots were calculated for a = 6.1 Å. Inspection of $E^{0\prime}$ points computed with the three different a parameters shows that the μ = 0.13 point lies about 1 mv. too high. With this exception, the results of Scatchard and Tefft between 0.007 and 0.1 m give an unambiguous straight line extrapolation to an E^0 of 0.9850 v.; the three results of Brüll in the same range of concentration lie about 0.5 mv. higher. Below 0.007 m the $E^{0\prime}$ values of both investigations show a decrease. Scatchard and Tefft observed[19] the decreasing electromotive force of cell (12) when air was allowed to come in contact with the amalgam. Although imperfect exclusion of oxygen from the dilute solutions would explain the drop in $E^{0\prime}$, it is possible that failure of the cells to attain equilibrium conditions during the period of measurement was responsible.

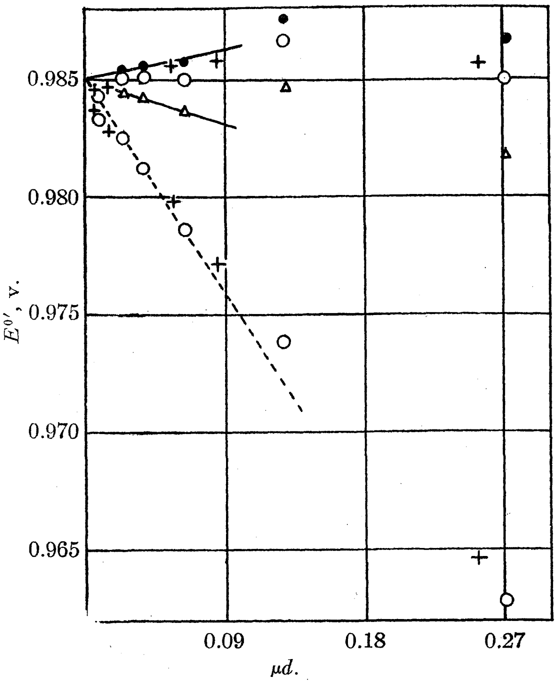

Fig. 2.—Extrapolation of electromotive forces of cell (12) to zero ionic strength at 25°. Crosses represent $E^{0\prime}$ − 0.0455 computed from measurements of Brüll.[27] Dots, circles and triangles represent $E^{0\prime}$ from data of Scatchard and Tefft.[19] Lower points were calculated by equation (5), upper points by equation (8) using a = 6.1 Å. (dots), 5.4 Å. (circles) and 4.0 Å. (triangles). Diameter of circles, 0.5 mv.

It seems likely that Scatchard and Tefft, in extrapolating to 0.9834 v., placed undue weight upon a low 0.003 m (μ = 0.009) point. On the other hand, the extrapolation to 0.9850 v. by equation (8) places considerable weight on the three next higher concentrations, μ = 0.023, 0.037 and 0.064. These points, however, represent electromotive force measurements within the optimum concentration range of zinc chloride.

Figure 2 makes it seem probable that the standard potential of cell (12) at 25° lies between

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(25) Shrawder, Cowperthwaite and La Mer, THIS JOURNAL, **56**, 2348 (1934).

(26) Shrawder and Cowperthwaite, *ibid.*, **56**, 2340 (1934).

(27) Brüll, *Gazz. chim. ital.*, **64**, 261 (1934).

(28) Gerke, THIS JOURNAL, **44**, 1684 (1922).

(29) Randall and Young, *ibid.*, **50**, 989 (1928).

TABLE VI

ACTIVITY COEFFICIENTS OF ZINC IODIDE

m	γ_5	γ_{10}	γ_{15}	γ_{20}	γ_{25}	γ_{30}	γ_{35}	γ_{40}
0.002					0.851			
.003					.833			
.005	0.808	0.803	0.802	0.800	.799	0.797	0.796	0.793
.007	.782	.776	.775	.774	.772	.770	.768	.765
.008	.772	.767	.765	.763	.761	.759	.757	.754
.01	.757	.751	.750	.748	.746	.744	.741	.738
.02	.701	.696	.694	.692	.690	.687	.684	.680
.03	.671	.666	.664	.661	.659	.655	.652	.648
.05	.634	.628	.627	.624	.621	.617	.613	.609
.07	.611	.606	.604	.601	.598	.594	.590	.585
.1	.592	.587	.585	.582	.578	.574	.570	.564
.2	.581	.575	.572	.569	.564	.559	.553	.546
.5	.650	.643	.638	.631	.624	.614	.604	.593
.7	.740	.730	.723	.713	.701	.687	.672	.656
.8	.787	.775	.766	.754	.740	.724	.706	.687

0.9845 and 0.9852 v. and, consequently, that the zinc amalgam electrode potential has a value lying between 0.7621 and 0.7628 v. This conclusion is in satisfactory accord with the value of 0.7627 v. obtained in this investigation.

Activity Coefficients

The stoichiometrical activity coefficients of zinc iodide have been calculated by equation (3) and are given in Table VI.

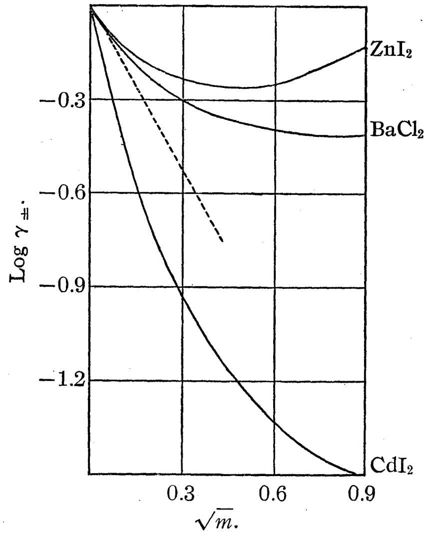

Fig. 3.—Logarithm of the stoichiometrical activity coefficients of zinc iodide, barium chloride and cadmium iodide as a function of the square root of the molality. The Debye–Hückel limiting slope is indicated by the broken line.

From an inspection of the slopes of the extrapolation plots of Fig. 1 it is clear that B' of equation (8) changes little with the temperature and has a value of -0.0093. The corresponding B'' values of equation (6) have been evaluated by dividing this quantity by $3k$ at each temperature and are given in the third column of Table IV. Equation (6), with the use of the parameters given in Table IV and a d value of unity, represents the activity coefficient of zinc iodide over the entire range of molality studied with an accuracy better than 1%.

In Fig. 3 is plotted log $\gamma_\pm$ at 25° against $m^{1/2}$. Plots of the barium chloride activity coefficients as determined by Tippetts and Newton[30] and of the cadmium iodide results of Bates and Vosburgh[1a] have been included for comparison. The broken line indicates the Debye–Hückel limiting slope. The activity of zinc iodide in solution is somewhat greater than that of barium chloride at the same molality and is considerably greater than that of the slightly dissociated cadmium iodide.

Relative Partial Molal Heat Content

The partial molal heat content (heat of transfer) relative to an infinitely dilute solution of zinc iodide was computed from the temperature coefficients of electromotive force by the use of the Gibbs–Helmholtz equation

$$\bar{L}_2 = \bar{H}_2 - \bar{H}_2^0 = \Delta H - \Delta H^0 = -nF\left[E - E^0 - T\left(\frac{\mathrm{d}E}{\mathrm{d}T}\right) + T\left(\frac{\mathrm{d}E^0}{\mathrm{d}T}\right)\right] \quad (14)$$

With the substitution of $t = T - 273.1$, the quadratic equations (2) and (9) were made to express the variation of electromotive force (or standard potential) as a function of absolute temperature:

$$E_T = A + BT + CT^2 \quad (15)$$
$$E_T^0 = A_0 + B_0T + C_0T^2 \quad (16)$$

These relationships are valid only between T =

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(30) Tippetts and Newton, THIS JOURNAL, **56**, 1675 (1934).

278.1 and 313.1°K. Equations (15) and (16) were substituted in equation (14), and the indicated differentiation was performed. Since $n = 2$ for zinc iodide, the expression becomes

$$\overline{L}_2 = -2F(A - A_0) + 2F(C - C_0)T^2 = \alpha + \beta T^2 \quad (17)$$

Equation (17) is the equation of Harned and Thomas.[31] Values of α and β for zinc iodide solutions from 0.005 to 0.8 m are given in Table VII.

TABLE VII

CONSTANTS OF EQUATIONS (17) AND (19). $\overline{L}_2$ AND $\overline{C}_p - \overline{C}_p^0$

m	$-\alpha$	$\beta \times 10^4$	$(\overline{L}_2)_{298}$ (calories)	$(\overline{C}_p - \overline{C}_p^0)_{298}$ (calories)
0.005	739	106	204	6
.007	848	125	259	7
.008	895	134	294	8
.01	1152	166	324	10
.02	1719	240	413	15
.03	2095	291	488	18
.05	2623	360	576	22
.07	3009	411	640	25
.1	3381	461	720	28
.2	4291	586	917	35
.5	6852	932	1432	56
.7	8740	1200	1922	72
.8	9405	1301	2160	78

Figure 4 is a plot of $\overline{L}_2$ against $m^{1/2}$ at 5, 15, 25 and 40°. The broken line shows the Debye–Hückel limiting slope for $\overline{L}_2$ at 25°

$$\overline{L}_2 = 3041\ c^{1/2} \quad (18)$$

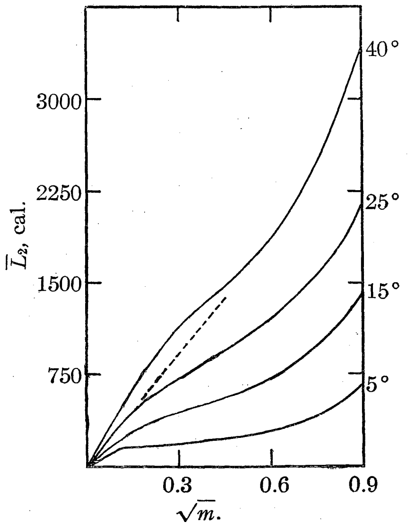

Fig. 4.—The relative partial molal heat content, $\overline{L}_2$, as a function of the square root of the molality. The broken line represents the limiting slope at 25°.

Unfortunately, no extensive calorimetric determinations of the heat contents of zinc iodide solutions have been made, and no estimate of the accuracy of the other quantities derived from the electromotive force data can be obtained from that source.

Relative Partial Molal Specific Heat

The values of the relative partial molal specific heat of zinc iodide were calculated by the equation

$$\overline{C}_p - \overline{C}_p^0 = \left(\frac{\partial \overline{L}_2}{\partial T}\right)_p = 2\beta T \quad (19)$$

The change of $\overline{C}_p - \overline{C}_p^0$ with temperature is small in the dilute solutions and amounts to but 0.5 calorie per degree at 0.8 m. The $\overline{L}_2$ and $\overline{C}_p - \overline{C}_p^0$ values for zinc iodide solutions at 25° are given in Table VII. The latter values, computed from second derivatives of the experimental results, must be considered as only approximate.

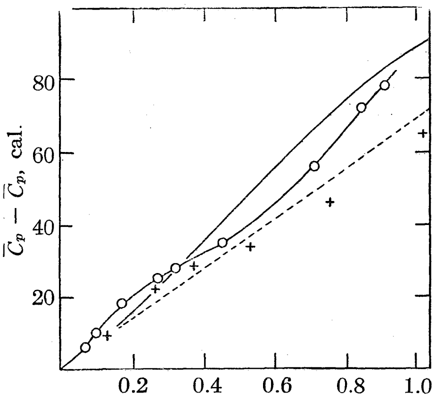

Fig. 5.—Relative partial molal specific heat at 25° as a function of the square root of the molality. Circles represent zinc iodide; crosses are for barium chloride, unbroken line for sodium sulfate. The broken line shows the limiting slope.

In Fig. 5, $\overline{C}_p - \overline{C}_p^0$ for zinc iodide is compared with the relative partial molal specific heat of sodium sulfate, computed by Randall and Rossini[32] from calorimetric data. The crosses represent values of the same quantity for barium chloride calculated by the author from the specific heats given by Richards and Dole.[33] The limiting slope of the Debye–Hückel theory is indicated by the broken line.

Grateful acknowledgment is made of the kind assistance of Professor Herbert S. Harned.

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[31] Harned and Thomas, THIS JOURNAL, **58**, 761 (1936).

[32] Randall and Rossini, *ibid.*, **51**, 323 (1929).

[33] Richards and Dole, *ibid.*, **51**, 794 (1929).

Summary

1. Electromotive force measurements of the cell

$$Zn\text{-}Hg\ (2\text{-phase})/ZnI_2\ (m)/AgI\text{-}Ag$$

have been made at 5° intervals from 5 to 40° and at molalities of zinc iodide from 0.005 to 0.8.

2. The standard potential of the cell has been evaluated, and from it the electromotive forces of the hypothetical cells

$$Zn\ (s)/Zn^{++}\ (a = 1),\ H^+\ (a = 1)/H_2,\ \text{and}$$
$$Zn\text{-}Hg\ (2\text{-phase})/Zn^{++}(a = 1),\ H^+\ (a = 1)/H_2$$

have been computed from 5 to 40°.

3. Calculations of the stoichiometrical activity coefficient, relative partial molal heat content and relative partial molal specific heat of zinc iodide in aqueous solution have been made.

4. Zinc iodide has been shown to be a normal bi-univalent electrolyte in aqueous solutions more dilute than 0.8 molal. Whereas the abnormalities of incomplete dissociation and complex ion formation indicated by transference and conductivity studies of strong zinc iodide solutions cause profound changes in the behavior of the salt in the concentrated range, they are of inappreciable influence below 0.8 *m*.

NEW HAVEN, CONN. RECEIVED AUGUST 22, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF WASHINGTON SQUARE COLLEGE, NEW YORK UNIVERSITY]

A Rapid Method for Traces of Metals by the Dropping Mercury Electrode[1]

BY RALPH H. MÜLLER AND JOHN F. PETRAS

Introduction

In developing and testing the cathode ray tube polarograph[2] the authors required some means for obtaining the conventional Heyrovsky current–potential curves. It is obvious that these can be obtained manually and indeed the earliest studies were made in this fashion. It was to relieve the tedium of this procedure that Heyrovsky developed the automatically recording polarograph. The polarograph has the further advantage of providing a permanent record. On the other hand, the "manual" curves may be obtained with relatively inexpensive and commonly available equipment. The marked symmetry of the curves at once suggests a simple and rapid increment method for determining the concentration of a given ion.[2a] The object of this paper is to demonstrate the validity of the increment method and to illustrate its applicability.

Apparatus

It is common knowledge that a potentiometer will deliver at its e. m. f. terminals the potential which is set on the dials. In our work a Leeds and Northrup student-type potentiometer was used to deliver the desired potentials. The working current of the potentiometer was balanced against a standard cell in the usual manner. The e. m. f. terminals were connected to the electrode vessel in series with a wall-type galvanometer L and N Type P, 103 megohm sensitivity, resistance 126 ohms, period 8.9 sec. The latter was used in conjunction with an Ayrton shunt carefully adjusted to provide the critical damping resistance. The suspension was turned so that readings could be taken over more than half the scale length. The entire assembly was calibrated for linearity of response and used over that range. The electrode was of the type commonly used in polarographic work,[3] and consisted of a small Erlenmeyer flask with a platinum wire inseal for making connection with the mercury anode, and a bubbler inseal for flushing the contents of the vessel with hydrogen. The capillaries for the dropping mercury cathode were hand drawn from 1-mm. capillary tubing. They were graded for suitable lumen by examination under a low power microscope fitted with a micrometer ocular. The vessel was also provided with a salt bridge communicating with a saturated calomel electrode. In this way the anode potential could be measured. A switching arrangement enabled the operator to check the anode potential with the potentiometer. The mercury dropping rate was controlled by the pressure unit previously described.[2] It was found to be far more convenient and flexible.

Solutions

The solutions used in this work were prepared from reagent quality chemicals without further purification. Eastman purified de-ashed gelatin was added to all solutions to give a final concentration of 0.2%. A wide choice of addition agents is feasible. In routine work,

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[1] Presented before the Microchemical Division of the American Chemical Society, Milwaukee, Wisconsin, Meeting, September, 1938.

[2] R. H. Müller, R. L. Garman, M. E. Droz and J. F. Petras, *Ind. Eng. Chem., Anal. Ed.*, **10**, 339 (1938).

[2a] After this paper was submitted for publication the authors learned of similar work by Petering and Daniels in which the increment technique has been applied to the micro-analysis of oxygen. Their application undoubtedly precedes this contribution, and we regard our work as a general confirmation of the validity of the increment principle. The senior author is indebted to Professor Daniels for helpful discussion and exchange of opinions at the Milwaukee meeting and subsequently at his laboratory in Madison.

[3] J. Heyrovsky, in W. Böttger, "Physikalische Methoden der chemischen Analyse," Akademische Verlagsgesellschaft m. b. H., Leipzig, 1935; Hohn, "Chemische Analysen mit dem Polarographen," Verlag von Julius Springer, Berlin, 1937.

common glue has been found satisfactory by some investigators. A fairly complete list of suitable supporting solutions is given in Hohn's monograph. The indifferent electrolyte which was used in each case is indicated in the appropriate place. Oxygen was removed from all solutions just before use by bubbling pure hydrogen through the vessel. The formation of persistent bubbles due to the gelatin content was very annoying, but it was eliminated completely by the addition of a trace of caprylic alcohol. We were agreeably surprised to note that neither the dropping rate nor values of the potentials were adversely affected.

Experimental Results

A typical current–voltage curve is shown in Fig. 1. In this case equal amounts of cadmium and zinc nitrates were used with 0.1 *M* potassium chloride as the indifferent electrolyte. At each applied potential the galvanometer deflections are pulsating due to the dropping of the mercury at the cathode. The recorded values represent the maximum "throw" or excursion of the galvanometer. These are highly reproducible and it was rarely necessary to observe more than two or three "throws." The "Halbwellen" potential, defined as that potential on the curve corresponding to one-half the distance between the horizontal plateaus, is indicated in Fig. 1, for each ion. From each potential the anode correction of 0.04 v. was subtracted, yielding Cd = −0.64 v., and Zn = −1.07 v.

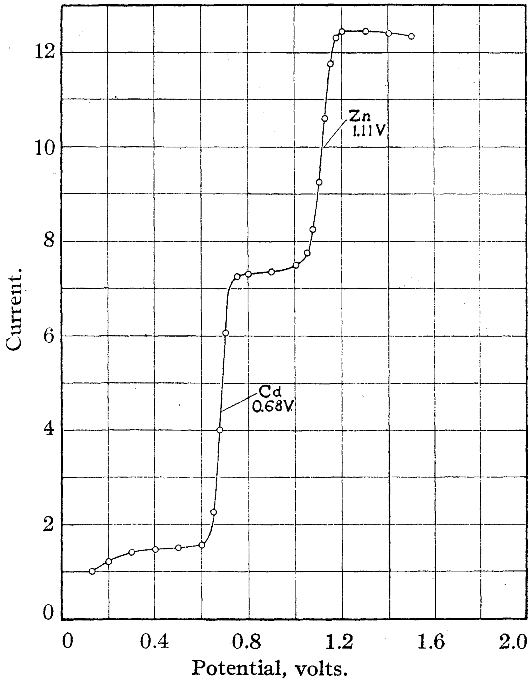

Fig. 1.—0.001 *M* $Zn(NO_3)_2$, 0.001 *M* $Cd(NO_3)_2$, 0.1 *M* KCl, 0.2% gelatin.

Figure 2 shows a family of curves obtained in this manner for cadmium at various concentrations. It is customary in polarographic work to draw the best straight line through each plateau and then estimate the difference in height (ΔI). Alternative schemes for estimating the correct wave height are discussed in the above monographs and in the paper by Borcherdt, Meloche and Adkins.[4] Due to the marked symmetry of the curves, it would seem that the current values obtained for two potentials more or less equidistant from the characteristic "Halbwellen" potential would yield a ΔI value which is equally reliable.

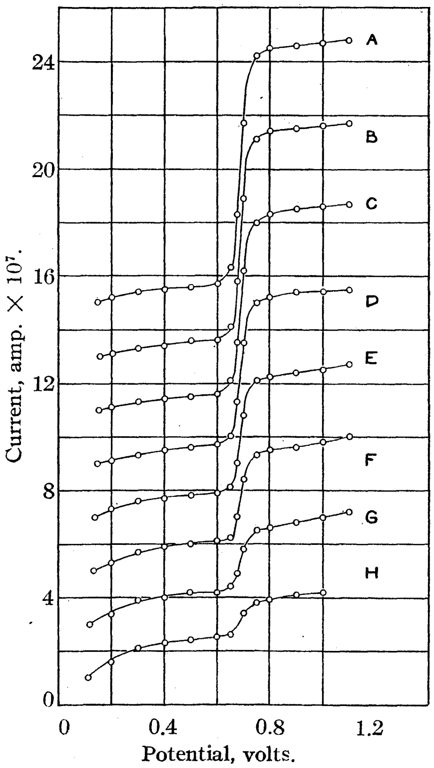

Fig. 2.—Concn. $CdCl_2$: A, 30 × 10^{-5} *M;* B, 27 × 10^{-5} *M;* C, 23 × 10^{-5} *M;* D, 19 × 10^{-5} *M;* E, 15 × 10^{-5} *M;* F, 11 × 10^{-5} *M;* G, 7.5 × 10^{-5} *M;* H, 4.0 × 10^{-5} *M.* All 0.1 *M* $BaCl_2$, 0.2% gelatin.

A cross plot of Fig. 2 is shown in Fig. 3. By inspection it was decided to select 0.6 and 0.8 v. For each concentration of cadmium the difference in current obtained at 0.8 and 0.6 v. was interpolated. These ΔI values were plotted against the

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[4] G. F. Borcherdt, V. W. Meloche and H. Adkins, THIS JOURNAL, **59** 2171 (1937).

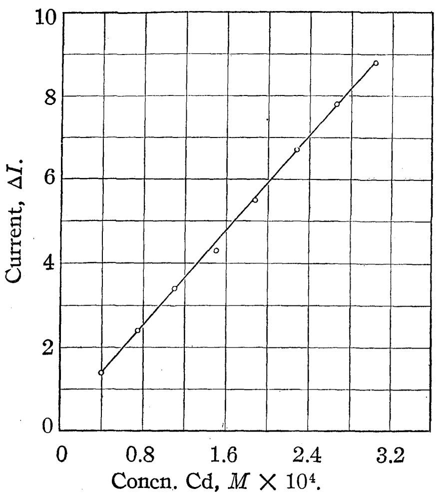

Fig. 3.—Cross plot of data in Fig. 2, illustrating linearity obtained by the increment method.

concentration of cadmium. With one exception the points lie closely on a straight line. This represents the worst condition for checking the relationship, in that considerable time elapsed in taking the whole family of curves. Succeeding runs with the simplified technique of merely measuring the respective currents for applied potentials of 0.6 and 0.8 v., amply confirmed this point.

A typical example is shown in Fig. 4. In this and all subsequent runs, a titration procedure was used to change the concentration. Specifically (Fig. 4), the electrolyte contained 0.1 M barium chloride as the indifferent electrolyte, 0.2% gelatin and to it were added from a microburet successive portions of 0.01 M cadmium chloride in 0.1 M barium chloride containing 0.2% gelatin. The final concentrations of cadmium ion were corrected for the small change in total volume.

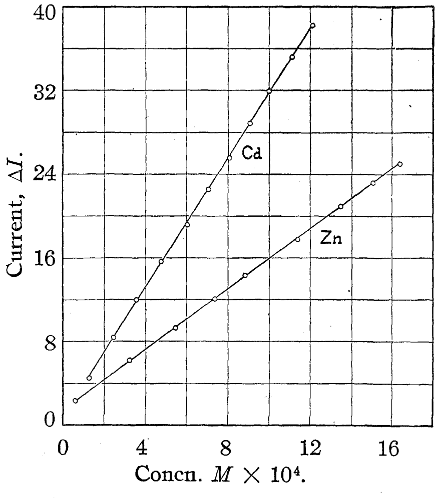

Fig. 4.—Upper curve: 0.01 M $CdCl_2$ in 0.1 M $BaCl_2$ + 0.2% gelatin titrated into 0.1 M $BaCl_2$ + 0.2% gelatin. Lower curve: 0.01 M $ZnCl_2$ in 1.0 M KOH + 0.2% gelatin titrated into 1.0 M KOH + 0.2% gelatin.

The method is quite satisfactory for traces of one ion in the presence of a large amount of other ions, provided the latter are reduced at higher potentials, and further that the interval between the respective potentials is great enough. In general the same limitations that apply to polarographic methods apply here, and certain cases can only be treated after preliminary separation or after conversion to suitable complex ions, etc.

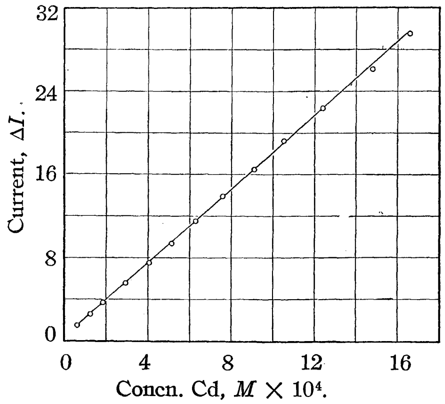

Fig. 5.—Traces of Cd in a large amount of zinc: 0.01 M $Cd(NO_3)_2$ in 0.1 M $ZnCl_2$ + 0.2% gelatin titrated into 0.1 M $ZnCl_2$ + 0.2% gelatin.

Figure 5 illustrates the results for small amounts of cadmium in the presence of a large but constant amount of zinc. It will be observed that the slopes for the ΔI–concn. curves for Cd^{++} ion in Fig. 4 and Fig. 5 are quite different. The actual slope depends upon the size of the mercury drop, the dropping rate, the concentration and nature of the indifferent electrolyte, and the galvanometer sensitivity. In a given run these factors are constant. To the extent that they might be reproduced in subsequent runs, the slopes would be correspondingly similar. For routine work this would seem to be a source of great trouble and inconvenience. This is a general limitation of all existing polarographic methods; they all assume that a preliminary calibration has been made under conditions closely approximating the intended analysis.

It is always possible, however, to include within the solution of the indifferent electrolyte a suitable "indicator" ion in known amount, preferably one which is not likely to be present in the "unknown." The indicator ion may then be used to evaluate the prevailing constants of the apparatus, thus furnishing a factor for the observed slopes.

Figure 6 shows results obtained for lead in strong alkaline solution. A complete curve for lead is shown merely to illustrate the choice of the two symmetric potentials which were selected for the analysis by the increment method. The adjoining curve shows the ΔI values as a function of lead concentration.

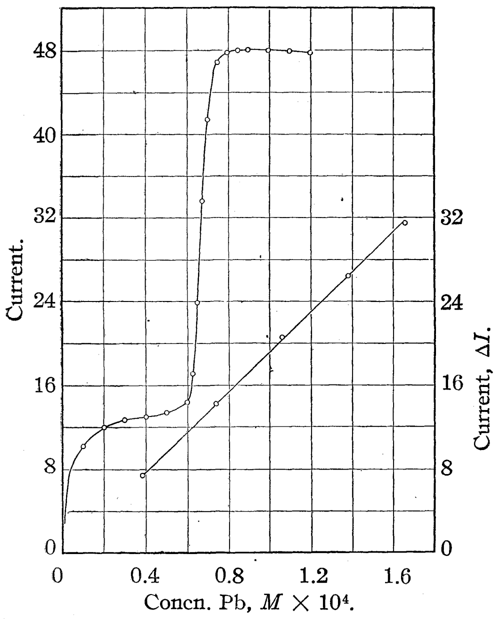

Fig. 6.—Upper curve: typical current–voltage curve for lead in alkaline solution. Lower curve: increment method, 0.01 M $Pb(NO_3)_2$ in 1.0 M KOH + 0.2% gelatin titrated into 1.0 M KOH + 0.2% gelatin.

Figure 4 is the incremental plot as a function of zinc concentration in alkaline solution and Fig. 7 shows the behavior of small amounts of lead in the presence of a large but constant amount of zinc, again in alkaline solution.

Discussion

The increment method which has been suggested for the evaluation of current–potential curves for the dropping mercury electrode has been shown to be reliable for three commonly occurring ions and mixtures of the same in neutral and alkaline solutions. In principle it is exactly similar to the practice of evaluating curves which have been recorded on a polarograph. It is extremely simple and rapid and merely assumes a reasonable degree of symmetry in the curve. Its applicability can be ascertained very quickly in any case. For cases in which the deposition potentials are too close, difficulties will be encountered to the same extent that they are in the conventional method. The use of gelatin or related substances, and the de-oxygenation by a stream of hydrogen are essential to success; the well-defined plateaus are largely dependent upon these factors.

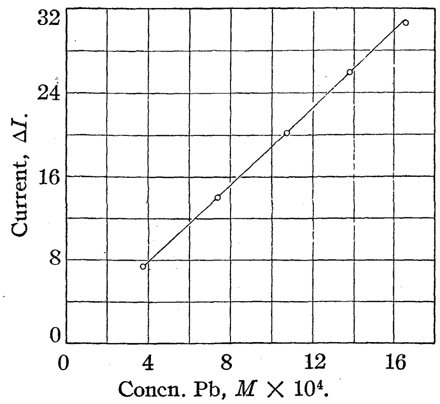

Fig. 7.—Traces of Pb in a large amount of zinc (alkaline solution): 0.01 M $Pb(NO_3)_2$ + 0.1 M $Zn(NO_3)_2$ in 1.0 M KOH + 0.2% gelatin titrated into 0.1 M $Zn(NO_3)_2$ in 1.0 M KOH + 0.2% gelatin.

For anyone slightly acquainted with electrical instruments, it will be apparent that a good potentiometer is not essential for this method. Any simple voltage divider with suitable means for adding and subtracting the required v.'s will suffice. In this general investigation we retained the more elegant arrangement because of its greater convenience and flexibility.

Summary

1. Current–potential curves may be obtained from the dropping mercury electrode with very simple equipment.

2. The marked symmetry of these curves suggests a simple increment method in which the change in current is noted for two applied potentials more or less equidistant from the characteristic "Halbwellen" potential. The current increments are a linear function of the concentration of the given ion.

3. The presence of other ions does not interfere with this relationship to any greater extent than it does with conventional polarographic methods.

4. The method has been illustrated with lead, zinc and cadmium ions, and pairs of these in neutral and alkaline solution.

NEW YORK, N. Y. RECEIVED AUGUST 19, 1938

[Contribution from the Research Laboratory of Physical Chemistry, Massachusetts Institute of Technology, No. 406]

The Heat Capacity of Potassium Sodium Tartrate Tetrahydrate from 15 to 340°K.[1]

By J. F. G. Hicks, Jr.,[2] and J. Gilbert Hooley[3]

The heat capacity of Rochelle salt ($KNaC_4H_4O_6·4H_2O$) in the regions about the Curie points (+24 and −18°) is of interest in correlating the remarkable dielectric properties of this compound.[4]

The present investigation was carried out at the suggestion of Professor Hans Mueller and was designed to cover not only the temperature region −30 to +30°, but the entire range at our disposal. Mueller,[5] by means of his phenomenological theory of Rochelle salt behavior, was able to calculate approximately the change in heat capacity at the upper Curie point. His figure,[6] $\Delta c \sim 1.5 \times 10^5$ ergs/cc./degree∼0.5 cal./mole/degree is rather too small to be positively shown by our measurements. The heat capacity of the salt at the upper Curie point where our experimental accuracy is 0.5%, is 92.5 cal./mole/degree. On the other hand, Kobeko and Nelidow[7] and Rusterholz[8] report a sharp discontinuity in the heat capacity–temperature curve at 26°. In both of these investigations the observed rise in heat capacity above the normal is about 5%.

Material.—The salt was of c. p. reagent quality and contained less than 0.01% impurities. It was allowed to stand, being mixed frequently, for two weeks at room temperature in a desiccator over 40 wt. per cent. sulfuric acid (vapor pressure 13.5 mm.) to ensure the presence of the single solid phase, $KNaC_4H_4O_6·4H_2O$.[9] Subsequently, it was found that the material at our disposal did not require this treatment.

Analysis for water by loss of weight in vacuum ($\sim 10^{-4}$ mm. and 180 to 200°) showed 25.52 and 25.49%; theoretical, 25.54. For purposes of analysis, we were unable to drive off more than 3.8 of the 4 moles of water by heating in a drying oven at 130° for one week, but found that conditions under which the tartrates themselves exhibited incipient decomposition were necessary to remove the last bit of water.

Analysis for sodium plus potassium by ignition and conversion to the chlorides showed the sample to be 99.98 and 100.06% Rochelle salt.

A solution containing 20.0 g. of Rochelle salt per 100.0 ml. of solution gave $[\alpha]^{25}_D$ +22.2° ml./gram decimeter.

All measurements were made on a single calorimeter loading of 88.760 g. *in vacuo*, or 0.31459 mole, the molecular weight of $KNaC_4H_4O_6·4H_2O$ taken as 282.14.

Method.—The apparatus, method of measurement, and calorimeter all have been described in an earlier paper of this series.[10] The temperatures were measured by means of the platinum–rhodium resistance thermometer-heater having the laboratory designation R197. It had been calibrated previously against a helium gas thermometer,[11] and the ice-point resistance showed no appreciable departure from its calibration value.

In loading the calorimeter, special precautions were taken to avoid any decomposition arising from heating the salt above 40°.[12] The two ring seals of soft solder joining the monel lid to the monel collars of the calorimeter barrel[10] were made while the calorimeter and weighed contents were immersed to within 15 mm. of the top in ice and water. The solder was then flowed on as rapidly as possible. In this manner, a tight seal could be made without the salt ever attaining the temperature of 15°. However, the contents could not be recovered without decomposition. Prior to the above operation, several centimeters of thin-walled nickel–silver tubing had been sealed to the bottom of the empty calorimeter and the end of the tube closed. After soldering the lid to the barrel, the free end of the tube was opened, cemented to the vacuum line, the calorimeter and its contents cooled to 80°K., and exhausted. After several flushings with pure helium, sufficient helium was finally admitted to exert a pressure of one atmosphere at room temperature. The calorimeter was allowed to warm, the tube clipped and soldered, and the unit suspended in the apparatus.

The e. m. f.'s were read on an Eppley microvolt potentiometer having a range of one-ninth volt to one microvolt on the dials.

The calorie used in this work is defined equal to 4.1833 int. joules. The absolute temperature of the ice-point is assumed to be 273.19°.

Heat Capacity Measurements.—The data are presented in chronological order in Table I. Series I has been omitted because of the large error in reproducibility of these points. The inaccura-

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[1] Low Temperature Studies, No. 4.

[2] Present address: Corning Glass Works, Corning, New York.

[3] Submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[4] For a review of recent work, see Staub, *Naturwissenschaften*, **23**, 728 (1935). Other substances behaving similarly are listed by Busch, *Helv. Phys. Acta*, **10**, 261 (1937).

[5] Mueller, *Phys. Rev.*, **47**, 175 (1935).

[6] Mueller, *ibid.*, **45**, 736 (1934). This value is, of course, dependent upon the Lorentz factor. If this factor be three times as great as that assumed in the calculation, the change in heat capacity should have been detected.

[7] Kobeko and Nelidow, *Phys. Z. Sowjetunion*, **1**, 382 (1932).

[8] Rusterholz, *Helv. Phys. Acta*, **8**, 39 (1935).

[9] Lowry and Morgan, This Journal, **46**, 2192 (1924).

[10] Hicks, *ibid.*, **60**, 1000 (1938).

[11] Blue and Hicks, *ibid.*, **59**, 1962 (1937).

[12] Lowry and Morgan[9] and van Leeuwen, *Z. physik. Chem.*, **23**, 33 (1897), observed that the vapor pressures of Rochelle salt at lower temperatures were not reproducible, if at any previous time the salt had been held above 40°. Lowry and Morgan do not state the composition of the other solid phase in equilibrium with Rochelle salt and water vapor when reproducible vapor pressures are obtained.

cies were traced to a poor contact in one of the potentiometer dials and the defect was remedied before observations labelled Series II.

TABLE I

T, °K.	C_p in cal. mole^{-1} degree^{-1}	T, °K.	C_p in cal. mole^{-1} degree^{-1}	T, °K.	C_p in cal. mole^{-1} degree^{-1}
Series II		246.64	80.59	26.28	6.03
59.93	24.29	248.86	81.31	29.04	7.23
63.85	26.08	250.98	82.01	31.72	8.61
69.06	28.24	253.12	81.96	34.04	9.88
73.06	30.39	255.27	82.38	36.75	11.16
77.07	31.51	252.56	81.83	40.28	13.20
81.08	33.92	254.70	82.21	43.97	15.25
85.00	35.37	256.78	83.26	47.81	17.39
88.74	36.68	259.08	83.80	52.15	19.94
92.42	38.13	265.16	85.07	56.68	22.08
96.09	39.07	270.38	85.80	61.06	24.67
99.98	41.03	275.60	87.06	65.24	26.89
103.94	41.76	280.10	88.63	69.74	28.93
107.53	43.72	286.80	89.82	74.61	31.28
111.51	44.98	293.01	91.60	Series V	
115.97	46.70	296.48	92.23	244.19	79.58
120.47	48.06	298.72	92.98	246.32	80.17
125.05	48.91	300.94	92.40	248.54	80.83
130.04	50.22			251.08	81.44
134.19	51.73	Series III		252.06	81.73
139.22	53.34	246.13	78.73	254.23	82.33
144.22	54.54	245.76	80.37	256.34	82.73
149.29	56.25	248.32	80.57	258.39	83.07
155.67	57.81	250.91	81.50	258.62	83.56
161.33	59.49	253.45	82.01	261.30	83.60
167.20	61.42	255.89	82.56	263.71	84.90
173.04	62.91	258.32	83.92		
178.84	64.73	263.60	84.56	Series VII	
184.89	66.02	267.35	84.96	244.73	80.36
187.11	66.75	287.90	89.96	300.11	93.07
192.96	68.08	292.74	91.63	303.72	94.20
201.10	69.96	295.70	91.72	307.41	95.16
210.54	72.45	298.15	92.59	311.00	95.59
217.36	73.79	299.90	93.43	314.49	96.80
223.66	75.55	302.15	91.79	317.94	98.97
229.89	77.13			321.35	100.76
226.08	76.13	Series IV		324.67	104.07
232.36	77.41	16.72	3.31	323.33	99.93
238.82	78.83	18.95	2.98	326.57	107.07
243.42	79.77	21.14	4.04	332.87	191.35
244.29	76.10	23.62	4.74	335.25	188.24

Before Series II, the calorimeter was held for two weeks at 80°K. and between Series II and III, the calorimeter was cooled directly to hydrogen temperatures and was below 80°K. for about two days during the course of Series IV measurements. It was then allowed to warm up slowly over a period of four days to 245°K. where it was held for six days. Series V data were then taken. Following these runs the calorimeter was immediately cooled to 240°K. and held just below 250°K. for one week after which Series VI observations were made. Thereafter, Series VII and the heat of transition were measured; these required three days. It is evident from the data that the variety of thermal treatments produced no effect on the heat capacity below 310°K.

The data of Table I are shown graphically in Fig. 1. The data of Series III and V are displaced, but all three curves are identical. The three dots are from Wilson's[13] work; his straight line is indistinguishable from that portion of our curve when the data are plotted on this scale. Figure 2 is a deviation plot with ordinate the observed heat capacity minus that calculated from the straight line, $C_p = 0.300T + 7.00$. The lengths of the vertical lines represent 0.5% of the total heat capacity at that temperature. The upper curve in Fig. 2 is the portion of the deviation curve from 240 to 300°K. replotted on a larger scale abscissa so that the experimental points can be distinguished.

The measurements of Series VI are listed in Table II and plotted in Fig. 3. They represent relative total heat capacities of the full calorimeter in the neighborhood of the lower Curie temperature. Each heating period was made through approximately a 0.3° interval with the shield sur-

TABLE II

T, °K.	Cal. degree^{-1}
Series VI	
249.18	55.16
249.63	55.01
250.07	54.83
250.50	55.09
250.97	54.89
251.42	55.10
251.85	54.75
252.29	55.36
252.78	54.48
253.17	55.39
253.60	55.34
254.05	55.18
254.50	55.17
254.98	55.41
255.40	54.98
256.07	55.59
256.82	55.54
257.28	55.61
257.71	55.67
258.15	55.15
258.59	55.58
259.04	55.77
259.48	55.35

TABLE III

T, °K.	C_p in cal. mole^{-1} degree^{-1}
15	1.50
20	3.40
25	5.47
30	7.71
35	10.30
40	12.96
45	15.70
50	18.56
60	24.17
70	29.08
80	33.40
90	37.17
100	40.71
120	47.36
140	53.56
160	59.47
180	64.92
200	69.77
220	74.54
240	79.10
260	83.57
280	88.30
300	93.00
310	95.86
320	99.96

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(13) A. J. C. Wilson, Doctor's Dissertation, M. I. T. Physics Department, 1938.

rounding the calorimeter maintained within ±0.2° of the calorimeter and the temperature of both rising at the same rate. The calorimeter temperature was measured by means of the attached thermocouple, the resistance thermometer not being used as such in these measurements. The data fall on a straight line within experimental error.

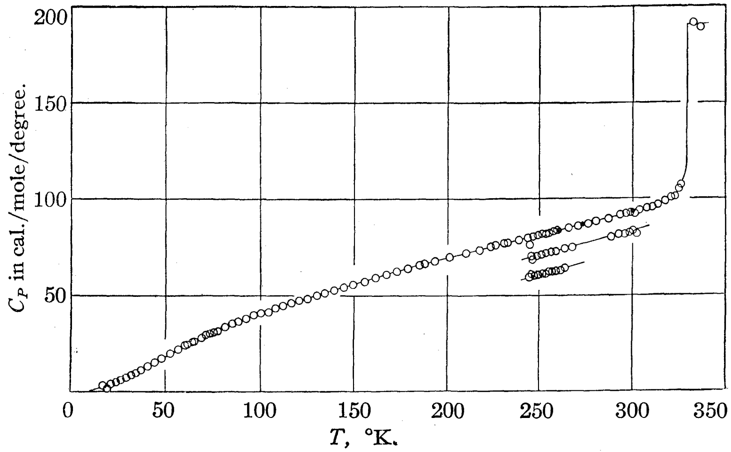

Fig. 1.—○, this research; ●, Wilson's curve.

Our data in their final form cannot be interpreted as suggesting a small anomaly at the lower Curie point as was stated previously.[14] The two low points around 245°K. and those two around 300°K. cannot be accounted for, but repeat determinations in these regions have fallen on the curve. Within experimental error, no discontinuities in the heat capacity–temperature curve are apparent at either the upper or lower Curie points. The accuracy of measurement is about that reported earlier with this apparatus,[10] *viz.*, 0.3% from 40°K. to room temperature and correspondingly lower outside this region.

Table III lists molal heat capacities at even temperatures as read from the smoothed deviation curve reproduced in Fig. 3.

Heat of Transition.—The transition (presumably decomposition into the mixed hydrated tartrates and their saturated solution) occurs sharply at 328.78°K. (55.6°C.) ±0.05°. A single measurement of the heat of transition yielded 10,218 cal. per mole absorbed. Because of the rapidly increasing slope of the curve just below 328.8°K., the method of arriving at 10,218 cal. per mole is somewhat arbitrary. However, 10,820 cal. is the measured amount of heat required to raise one mole of Rochelle salt from 328.14 to 331.62°K. In the absence of check determinations, it is difficult to assign a probable error to this figure, but it is believed to be good to ±20 cal.

Two and one-half hours were required to heat the calorimeter through the transition and during that period the maximum variation of the calorimeter thermocouple was 0.15°. At each end of the heating period, the calorimeter surface was 0.15° hotter than at the middle of this period; while during the middle two-thirds of the transition, the thermocouple did not vary by more than 0.02°.

The transition temperature has been reported by others to lie between 54 and 59°.[15]

Discussion.—The disagreement of our data with those of the European workers, and the excellent accord with Wilson's[13] work, have already been reported.[14] However, at 22°, the data of this research agree well with those of Kobeko and Nelidow[7] but are 11% lower than those of Rusterholz;[8] while our values and Wilson's[13] agree within 0.3% over the temperature interval covered by Wilson. We believe that if any discontinuities

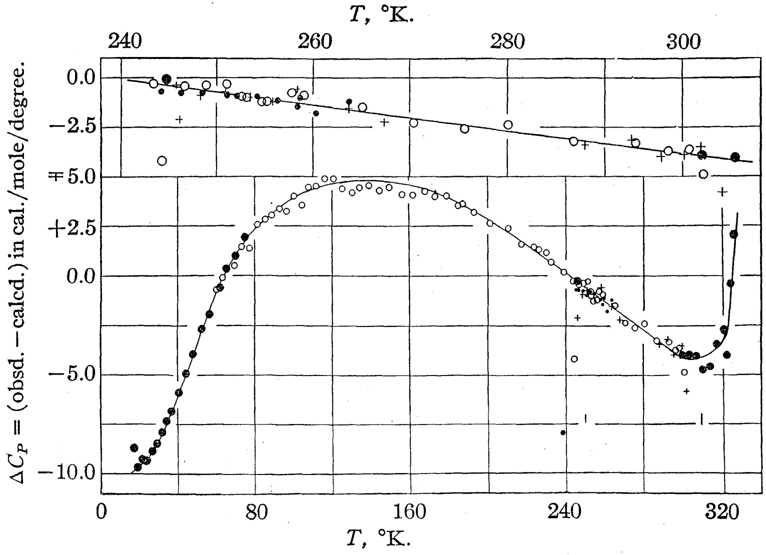

Fig. 2.—○, Series II; +, Series III; ●, Series IV and VII; ◉, Series V.

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(14) Wilson, Hicks and Hooley, *Phys. Rev.*, **54**, 87 (1938).

(15) "I. C. T.," Vol. III, p. 374.

in specific heat exist below the melting point and above 15°K., they are less than 0.5%, about ten times less than the one reported by Kobeko and Nelidow and Rusterholz[8] at the upper Curie temperature. We are unable to reconcile the previous data with our own.

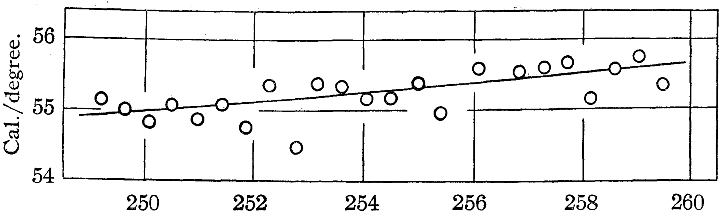

Fig. 3.—Series VI.

Additional determinations of the heat capacity between 310 and 328°K. with a wide variation in the thermal treatment of the sample would settle the question of whether or not the large slope is a characteristic of the pure salt or due to its slow decomposition. The work of Lowry and Morgan[9] and others[15] indicates decomposition, while Mueller[5] found that a Rochelle salt crystal could be annealed for several hours at 45° without impairing its "Seignette electric" properties. Because of the possibility of decomposition, the present sample was heated without repetition of measurements from 310 to 340°K. Our apparatus is not well suited to repeated loadings and maintaining the calorimeter at constant temperature in this region for periods of many hours. It is therefore not improbable that our curve between 310 and 328°K. is dependent upon the history of the sample.

A complete study of the ternary system sodium tartrate, potassium tartrate, water with special emphasis on the Rochelle salt composition would be desirable. Although it is stated in the "International Critical Tables"[15] that the transition at *ca.* 54° consists in the decomposition into sodium and potassium tartrates, both present as the dihydrates, we infer from the vapor pressure measurements undertaken by Lowry and Morgan[9] that $K_2C_4H_4O_6 \cdot {}^1/_2H_2O$ is the potassium salt to be expected.

It would be of interest to measure the heat capacities of other "Seignette electric" substances such as $NH_4H_2AsO_4$ and KH_2PO_4[14] to discover whether a marked gradual rise occurs just above the upper Curie point. In these cases no complications rising from decomposition would be encountered. It is also possible that the change in heat capacity of these salts at their Curie points would be a larger percentage of the total and therefore more susceptible to detection.

Summary

The heat capacity of Rochelle salt from 15 to 340°K. has been measured. A single measurement of the heat of transition at 328.78°K. (55.6°C.) has been made. The transition is sharp. No discontinuous changes in heat capacity were observed at the Curie points. The observations at the upper Curie point are in conflict with those reported by Kobeko and Nelidow and Rusterholz. The desirability of further investigations on Rochelle salt and other "Seignette electric" compounds has been pointed out.

CAMBRIDGE, MASS. RECEIVED SEPTEMBER 22, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY]

Measurement of Sedimentation Velocity in Simple Air-driven Tops as Ultracentrifuges

BY JAMES W. MCBAIN AND F. A. LEYDA

The ultracentrifuge is any centrifuge of low or high power in which convection does not occur, and in which it is possible to measure any redistribution of the contents. It has become one of the most important tools for investigations in colloid systems, non-aqueous systems, immunology, biochemistry, and even in simple molecular solutions. It is therefore gratifying that simple air-driven spinning tops have now been developed as ultracentrifuges, at such low cost that they may be made available in every laboratory. The very great advantage of these opaque ultracentrifuges is that they possess no optical system and require no accessories other than those everywhere to be found. They yield accurate results. Direct analysis is made by any appropriate physical, chemical or biological method.

The time would seem to be approaching when experiments with the ultracentrifuge may be included in practical courses in biochemistry, colloid and physical chemistry.

The essential feature of our ultracentrifuges is the immobilization of the liquid, usually between horizontal surfaces placed sufficiently close together that friction inhibits convection.[1] Elsewhere[1] we have reviewed the methods adopted by other investigators and also have pointed out the great possibilities of the original one-piece spinning top.

The present communication describes a simple opaque ultracentrifuge of general applicability. Two problems had to be solved: first, the design of a liquid-tight rotor, and, second, the design of suitable immobilizing inserts to place in the rotor.

The Two-Piece Rotor with Tight Seal

The rotor, shown in Fig. 1, consists of two pieces made of 4 UMA steel, a chrome manganese alloy made by the Republic Steel Corporation. The steel is oil-quenched from 1525°F. and drawn at 850°F. after making up. The top part, A, is 32.5 mm. in outside diameter and 11.5 mm. high. Its inner well into which the various inserts for immobilization are fitted is 28 mm. in diameter and 9 mm. deep.

The shell A screws into the rotor cone B to a depth of 4 mm. Thus in the centrifugal field, when the rotor is assembled, the thinner longer annular walls of the upper part bend elastically outward, engaging still more tightly into the lower part. The angle of the cone walls is 100°. The largest diameter is 38 mm. A cylindrical space 14 mm. in diameter is cut in the bottom of the cone, with screw threads to fit onto a holding jig and handle serving as a wrench for assembling the rotor, the upper shell being held by a strap wrench, or better a split ring tightened by a screw and held in a vise. In experiments of longer duration the screw threads should be kept dry, or be oiled to avoid rusting or seizing. The flutes or grooves in the conical walls of the rotor cone against which the driving air is directed are cut with one side vertical, the other sloping, and are about 8–10 mm. long. All threads on the rotor are 32 per inch (2.54 cm.).

The degree of polish on the rotor greatly affects the speed. It was found that, after a high polish had been obtained, keeping the rotor in any convenient oil, or petroleum ether, was effective in preserving the polish. If kept in oil, the rotor was washed with petroleum ether before use. The insides of both parts of the rotor are made indifferent to the materials studied by several coats of Bakelite lacquer, applied unthinned, allowed to dry in air for forty-five minutes and then baked at 135° for thirty minutes. In applying the lacquer care must be taken that none of the lacquer touches the lower edge of the upper part of the rotor that will make contact in the joint. This Bakelite coating must be replaced whenever damaged in any way.

Assembly of the Rotor.—To achieve a seal which is always leak proof, even in petroleum systems, a pliofilm or other plastic disk C, shown in Fig. 1, a loose metal disk D, 0.020 in. (0.5 mm.) thick, and a loose metal ring E, 0.0125 in. (0.3 mm.) thick, are used. The pliofilm, 250 gage P5A supplied by Goodyear Rubber Company, or even cellophane, is initially cut slightly larger than the outer diameter of the top part of the rotor. The rotor is assembled upside down. After the insert is placed in the upper shell, the plioform disk is put in place. Then while holding the cellophane by one edge, the metal disk is gently slid over the top of it, squeezing out the excess liquid. After the metal disk is carefully centered, the cellophane is trimmed to exact size with a razor blade. The metal ring is then put in place and the rotor cone screwed on. This seal has been shown to be perfectly tight, the filled rotor weighing the same within ±0.0001 g. before and after a run of many days. One or more grooves are sometimes cut the entire way around the bottom surface of the top half of the rotor, allowing the pliofilm gasket to be forced into the depressions and possibly making the seal even more ideal.

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(1) McBain and O'Sullivan, THIS JOURNAL, **57**, 780 (1935), last paragraph 4a and 4b; McBain and Stuewer, *Kolloid-Z.*, **74**, 10 (1936); McBain and Tostado, THIS JOURNAL, **59**, 2489 (1937); McBain, *Science*, **87**, 93 (1938); 15th Colloid Symposium, Cambridge, *J. Phys. Chem.*, **42**, 1063 (1938).

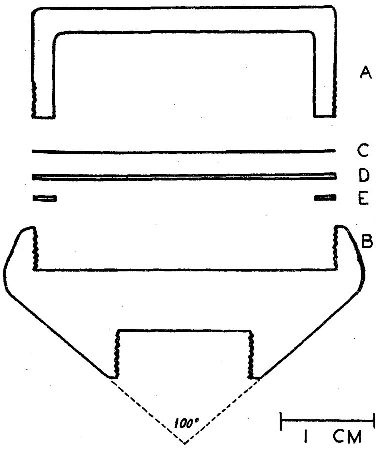

Fig. 1.—Cross section through rotor showing: A cover, B rotor cone, C film of plastic material, D loose metal disk, and E loose metal washer to facilitate slipping when assembling.

The Stator.—The stator, A, shown in Fig. 2, is made of Duralumin 17ST with a brass insert at the top edge of the inner walls for longer wear. The cone walls make an angle of 90°. The thickness of the walls may vary, being usually from about 2 to 4 mm. The air ports are so placed that they will strike at approximately the mid-point of the grooves or flutes cut in the lower part of the rotor. It is essential that the grooves do not reach the outer edge of the stator cone. The orientation of the air ports may be described by two angles, the angle with the horizontal plane through the center of the outlet of the air port and the axis of the stator being 35°, and that with the vertical plane 65°. Six to twelve of these air ports may be cut at equal distances apart around the stator.

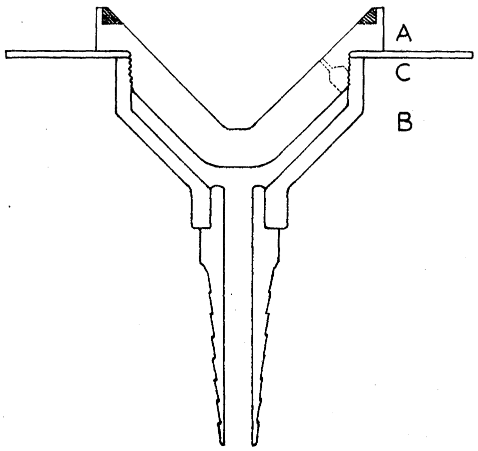

Fig. 2.—Simple form of stator showing: A the stator, B the manifold or air box, and C the steadying disk; also cross section of an air-jet and a brass inset to minimize chance wear on upper part of cone.

The stator is held in the manifold or air box B with a disk C placed in the joint. This assembly is placed in a metal guard, the disk C being steadied by sponge rubber (that used for bath mats has been found most convenient) to dampen vibration, and the central air inlet of the manifold connected to the air supply by means of heavy pressure tubing securely clamped on.

The manifold was also made of 17ST Duralumin. Its walls are about 2 mm. thick, the angle of the conical walls being 90°. The supporting disk was made of Duralumin, or Bakelite, or any convenient metal or fiber.

Whereas the stator shown in Fig. 2 is usually satisfactory, the form shown in Fig. 3 is sometimes better, especially for taller rotors, since adjustment of the air sucked in through the central tube (partly closed) with a thin rubber tube and screw clamp prevents "blooping" and sometimes increases the speed by 10% for a given pressure of driving air. The latter is fed in through the side tube.

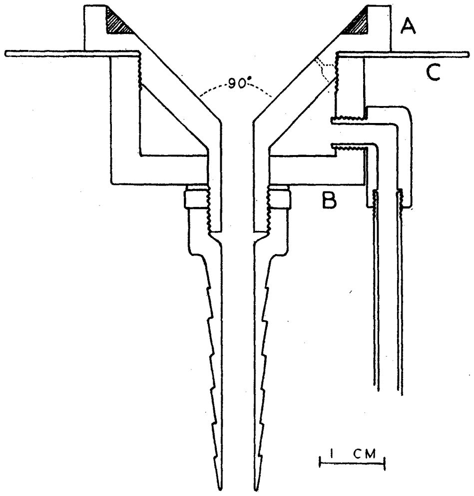

Fig. 3.—Alternative stator with adjustable central inlet for allowing air partially to relieve the vacuum below the rotor.

Temperature Control

The temperature control of these opaque ultracentrifuges is unique in that it is positive and is as accurate as a thermostat. It is that designed for the McBain–O'Sullivan transparent ultracentrifuge[2] and consists simply of passing the constant pressure driving air through a copper coil immersed in a thermostat at any desired temperature. The rotor maintains itself at the temperature of the slipstream.

The Immobilizing Inserts

While for measurement of sedimentation equilibrium it does not matter what the size or shape of the container for the liquid may be, provided that convection is suppressed and that no mixing occurs, before the samples are withdrawn for analysis, the additional conditions for sedimentation velocity are more stringent. In the first place, the radial movement of the sedimenting particles in the line of the centrifugal force must

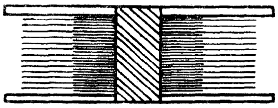

Fig. 4.—Insert consisting of piles of disks for general use in sedimentation velocity or equilibrium.

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(2) McBain and O'Sullivan, THIS JOURNAL, **57**, 2631 (1935).

be unobstructed. This is achieved by using horizontal surfaces unobstructed over the complete range of 360°, utilizing circular disks or annular washers spaced uniformly apart by others of different diameter.

In the second place, the mechanical baffles must be so far apart that there are no wall effects upon the motion of the particle. Spaces 0.08 mm. wide are 20,000 times the diameter of the smaller proteins. Experience has shown that the sedimentation velocity observed within these spaces is the same as that given by the transparent ultracentrifuges. Much wider spacings are probably satisfactory, certainly so for the more viscous petroleum systems. Narrower spacings have not yet been studied.

A further requirement for the mechanical baffles is that they must be of material, such as plastic or metal, that will not flow in the centrifugal field. For this reason pure silver, platinum, or monel metal are satisfactory for smaller diameters, but must be replaced by stainless steel or coin silver or platinum-iridium for diameters approaching three centimeters. The insert if made of metal should be all of one kind of metal to avoid electric couples.

Insert 1, Generally Useful for Velocity or Equilibrium.—The liquid to be studied may be immobilized most simply by using as insert a central pile of disks, alternately wide and narrow with a larger disk just fitting inside the rotor at top and bottom to keep them central. A vertical axial pin runs through the central solid pile of metal, holding it together. The axial pin may be replaced by a screw permitting a change of the spacing pieces to obtain a wider sedimenting column.

This insert as used for the present measurements is shown diagrammatically in Fig. 3. The disks are made of coin silver (or stainless steel), the larger ones of metal 0.004″ (0.102 mm.) thick, the smaller ones 0.003″ (0.076 mm.) thick. The larger disk at top and bottom was of metal 0.030″ (0.762 mm.) thick. The insert is made so that it just fills the space left in the top section of the rotor, as many disks being used as can be fitted in. A convenient diameter for the larger disks is 24.6 mm. and 13.6 mm. for the smaller ones. To make it possible to obtain for analysis a sample at the bottom of the sedimenting column without disassembling the rotor, a hole 1 mm. square is cut on opposite sides of the larger top disk of the insert, matching holes being cut in the bottom disk. A sample is then taken with a hypodermic pipet or syringe after the rotor is stopped.

A convenient method of filling the baffles with the solution to be studied is to place them in a small metal case filled with solution and placed in an ordinary centrifuge for a few minutes. Preliminary work on various nonaqueous solvents and stainless steel (-18-8-) baffles has given excellent results in filling by capillarity.

Insert 2, for Monodisperse Sedimentation Equilibrium Only.—This is fully described by McBain and Tostado,[1] the immobilized sedimenting liquid lying between horizontal annular washers of coin silver spaced at uniform known distances apart by using alternately narrow and wide washers. Convection is permitted in the liquid in contact and in equilibrium with the innermost part of the sedimentation column. Analysis of this liquid before and after gives the molecular weight of any monodisperse substance. For sucrose 341 was found (theory, 342). A window[1] is a convenience but by no means a necessity. It is obvious that the same method of calculation of sedimentation equilibrium is applicable to Insert 1, which is also generally more convenient.

Insert 3, for Equilibrium Only, Including Polydisperse Systems.—This is a modification of 2, permitting analysis of the liquid above and below the sedimenting column, especially for use in polydisperse systems. Here the annular washers are all alike and are merely piled loosely upon each other. They are kept centered by perforated buttresses or bosses, or by pillars, on the container. The rotor is stopped for analysis, and the liquid from the middle and the exterior withdrawn at approximately the same rate to avoid mixing.

Other Inserts.—Several other inserts have been designed and briefly referred to,[1] and they will be described in more detail when the corresponding measurements are published.

The Sedimentation Velocity of Egg Albumin

Salt-free isoelectric egg albumin was prepared by Dr. Eloise Jameson, who followed Hopkins and Pinkers' method, using acetic instead of sulfuric acid. The material was twice crystallized and furnished us in a more or less solid form mixed with ammonium sulfate. This sample was dialyzed in running distilled water during the daytime and set aside overnight in the refrigerator in distilled water saturated with toluene. The first batch dialyzed was in the process perhaps a day and a half, at the end of which it gave no test for sulfate with barium chloride. The second batch was dialyzed in a similar manner but the process lasted about two and a half days, after which it gave no test for sulfate. The first batch tested 1.36% egg albumin as first prepared and was used only on run 1. Most of it was wasted in attempts to fill the baffles by capillarity. The second batch tested 5.4%. Portions of this were diluted and used in all the remaining runs. One portion approximately 1% was used on runs 2–8 inclusive, and another similar portion was used in runs 9–15 inclusive. All 15 runs on egg albumin were completed well within a month after the samples had been prepared.

Concentrations were determined refractometrically. The refraction of proteins (at least in the concentrations and concentration range studied) follows a linear law. The relation is given by

$$(n - n_1) = ac$$

where $(n - n_1)$ is the difference in refractive index of the solution and solvent, c is the grams of protein per 100 cc. of solution, and a the constant giving the change in refractive index of solvent on the addition of 1% protein. As to the numerical value of a for egg albumin in 0 to 2% solutions, Haas[3] obtained a value of 0.00177 ± 0.00006 with a Pulfrich refractometer. Barker[4] using a Zeiss dipping refractometer obtained a value of 0.001851 ± 0.000020, and this result was used.

In assembling, care was taken to avoid entrapping air bubbles. Any liquid that was in the threads was wiped off before the rotor cone was screwed on. The assembled rotor was weighed before and after the run. This was a check not only upon the completeness of the filling, but also a proof that no evaporation occurred. The small volume of liquid above and below the insert was included in calculations in the outer non-immobilized liquid. Whether it was immobilized or not during the run was of no consequence for it ran together with the rest of the non-immobilized liquid when the rotor was taken apart for sampling.

The rotor was started at approximately 20 lb. (1.3 atm.) pressure and gradually speeded up to about 2000 r. p. s. This is easily done within a minute. In stopping the rotor, the pressure is gradually reduced to 20 lb., after which it was allowed to remain there and by placing the fingers around the rotor and exerting a slight pressure it was stopped quite smoothly. An estimated correction for the time in starting and stopping was made. An essential detail in stopping is not to allow the last few revolutions to end too abruptly. If this happens the non-immobilized liquid may have a tendency to swirl into the immobilized space and displace some of this liquid. However, only a moderate amount of care in this respect is needed.

Method of Calculation.—In the opaque ultracentrifuge all that is measured is the number or weight of molecules or particles that pass through a given radius during a given time. In complete contrast to the requirements for the transparent ultracentrifuge, it is a matter of indifference whether or not a boundary is formed or whether it is sharp or blurred by diffusion, as long as its influence does not extend to the external radius of the immobilizing disks.

Two methods of calculation were used. The first is a relation given by Tiselius, Pedersen, and Svedberg[5] requiring a knowledge of the initial concentration of the solution.

$$s_{(\text{obsd.})} = -\frac{1}{2\,\omega^2 t}\ln\left(1 - \frac{2\Delta}{q\,x\,c_0}\right)$$

where ω = angular velocity = $2\,\pi$ (r. p. s.), t is the time in seconds, Δ is the change in amount of substance above or below the level at which the separation is made, x is the distance in centimeters of this level from the center of rotation (radius of larger disks), q is the cross-sectional area of the cell at this level, and c_0 is the original concentration within the cell. ω, t, x, and q are obtained readily from the dimensions of the baffles and observations during the run. c_0 is determined by analysis. The density of the dilute solutions used was considered unity within the experimental error. Δ in grams is then given by the following relation

$$\frac{|n_f - n_i|}{0.00185} \times \frac{V_1}{100}$$

where n_f and n_i are the refractive indices of the final and initial samples of outer liquid, respectively, and V_1 is the volume of the outer convecting liquid.

After sampling the outer liquid, the rotor was thoroughly cleaned and dried. The excess solution on the outside of the baffles was wiped off. The rotor was then reassembled and allowed to spin for a minute or so to force out the liquid in the baffles to give a second sample. Then a similar formula was applied to the change in concentration of the immobilized liquid.

The second method involves calculation of the theoretical position of the idealized boundary within the immobilized liquid, as if there were no effect of diffusion. Here the boundary will be at a position x_2 between the radii a and b of the smaller and larger disks, respectively. The average concentration c_2 as measured over the whole of the immobilized liquid, V_2, between the radii a and b is determined by direct analysis of that liquid. It is likewise determinable by analysis of the outer convective liquid c_1, of total volume V_1, for

$$c_2 = \frac{(V_1 + V_2)c_0 - V_1c_1}{V_2}$$

where c_0 is the original uniform concentration.

Since the concentration decreases with time in centrifugal sedimentation, the concentration c_t at the time t beyond the sedimenting boundary x_2 is related to the original concentration c_0 by the equation

$$c_t = \frac{a^2}{x_2^2}\,c_0$$

but the total volume of the immobilized liquid

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(3) Haas, *J. Biol. Chem.*, **35**, 119 (1918).

(4) Barker, Dissertation, Stanford University, 1933.

(5) Tiselius, Pedersen, and Svedberg, *Nature*, **140**, 848 (1937).

TABLE I

SEDIMENTATION VELOCITY OF ISOELECTRIC EGG ALBUMIN IN WATER (Method of Calculation 1)

Run	Speed, r. p. s.	Time, sec.	Temp., °C.	$(n - n_{H_2O}) \times 10^5$ Initial	Final	Δ, g.	$s_{obsd.} \times 10^{13}$	Correction factor	$s_{20} \times 10^{13}$
11—outer[a]	1855	4680	20.5	174	248	0.0056	3.73	0.988	3.69
12—outer	1920	4740	23.0	173	255	.0062	3.96	.926	3.67
—inner					53	.0058	3.61		3.34
13—outer	1953	3930	20.5	178	245	.0051	3.44	.988	3.41
—inner					67	.0053	3.66		3.62
14—outer	1997	4440	22.4	175	256	.0061	3.79	.940	3.56
—inner					52	.0059	3.62		3.40
15—outer[b]	1950	4140	20.5	178	258	.0056	3.69	.988	3.65
—inner					56	.0058	3.94		3.89

Average s_{20} from outer liquid 3.60

Average s_{20} from inner liquid 3.56

Average 3.58×10^{-13}

[a] No sample from inner liquid was taken. [b] In this run a metal disk was placed in the rotor to fill up the space between the top of the baffles and the pliofilm disk. In the other runs this space was taken up by solution. Volume of liquid in outer space in this run was 1.29 cc.

below the boundary is proportional to $b^2 - x_2^2$. Therefore the total amount of material present at the time t is proportional to

$$c_0(b^2 - x_2^2)\, a^2/x_2^2 = c_2(b^2 - a^2)$$

where c_2 is again the average concentration that is measured over the whole of the immobilized liquid. From this equation the position of the boundary

$$x_2 = \sqrt{b^2H/(P + H)}$$

where H is $a^2/(b^2 - a^2)$, and $P = c_2/c_0$.

The sedimentation constant

$$s = \frac{dx}{dt}\,\frac{1}{\omega^2 x} = \frac{2.303\ (\log x_2 - \log a)}{39.48\ (\text{r.p.s.})^2\ t}$$

Results were given the usual correction of multiplying the observed value of s by

$$\frac{\eta}{\eta_{20}} \times \frac{1 - \bar{V}\rho_{20}}{1 - \bar{V}\rho}$$

where η and η_{20} are the viscosities of the solvent and of pure water at the observed temperature and at 20°, respectively, and ρ and ρ_{20} are the corresponding densities. $\bar{V}$ for egg albumin is taken as 0.749.

The following are the numerical constants of the cell used: $V_1 = 1.40$ cc., $V_2 = 0.89$ cc., $a = 0.797$ cm., $b = 1.20$ cm., $H = 0.789$, $q = 2.626$ cm.^{2}.

The Results.—The results are given in Tables I and II as calculated by methods 1 and 2, respectively, for runs 11 to 15 in which temperature control was used. It should be noted that in method 1 the concentration is explicitly derived from the refractive index, whereas in method 2 the observed increment of refractive index is used directly with no reduction to concentration.

TABLE II

SEDIMENTATION VELOCITY OF ISOELECTRIC EGG ALBUMIN IN WATER (Method of Calculation 2)

Run	P	x_2	$s_{obsd.} \times 10^{13}$	$s_{20} \times 10^{13}$
11—outer	0.329	1.008	3.70	3.66
12—outer	.252	1.047	3.92	3.63
—inner	.306	1.019	3.56	3.30
13—outer	.410	0.975	3.40	3.36
—inner	.376	0.987	3.62	3.58
14—outer	.276	1.033	3.71	3.43
—inner	.297	1.023	3.57	3.36
15—outer	.347	1.000	3.65	3.61
—inner	.315	1.014	3.88	3.83

Average s_{20} from outer liquid 3.55

Average s_{20} from inner liquid 3.52

Average 3.54×10^{-13}

Summary

1. Simple opaque ultracentrifuges capable of measuring sedimentation velocity or equilibrium in all systems with accuracy are described. They require no optical accessories, and run at constant temperature if the driving air passes through a thermostat.

2. A simple two-piece rotor with liquid-tight seal is used with any suitable immobilizing insert of which several are described.

3. The sedimentation velocity of egg albumin in water at pH 4.63 was measured as $s_{20} = 3.56 \times 10^{-13}$ in agreement with Svedberg's most recent result[6] 3.55×10^{-13}.

STANFORD UNIVERSITY, CALIF.

RECEIVED SEPTEMBER 6, 1938

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[6] Svedberg, *Ind. Eng. Chem., Anal. Ed.*, **10**, 125 (1938).

[CONTRIBUTION NO. 370 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

The Relative Stability of Aromatic and Aliphatic Monoglycerides

BY B. F. DAUBERT AND C. G. KING

Since the early investigations of Fischer[1] and associates, it has been evident that aliphatic β-monoglycerides tend to rearrange to the corresponding α-isomers, but there has been very little information available concerning the factors that accelerate the change, or concerning the relative ease of migration of the acyl group in aromatic β-mono esters.

Helferich and Sieber[2,3] prepared the β-monobenzoate of glycerol from α,α'-di-(triphenylmethyl)-β-benzoylglycerol by treatment with hydrogen bromide in glacial acetic acid, apparently with no evidence of migration. Bergmann and Carter[4] reported no shift of the β-monobenzoate, during treatment with anhydrous hydrogen chloride for drying. Hibbert and Carter,[5] however, observed a rearrangement of the β-monobenzoate, β-*p*-bromobenzoate, and β-*p*-nitrobenzoate to the α-isomers in 0.025 *N* hydrochloric acid during hydrolysis of the benzylidene compounds in 50% alcoholic solution at 80°. Jackson and King[6] observed a complete β- to α-shift of the palmityl group at temperatures as low as $-30°$ when removing (hydrogen bromide in acetic acid) the triphenylmethyl group from the α-trityl ether of 1,2-dipalmitin. In agreement with Helferich and Sieber, however, no shift was observed when the ether group was hydrolyzed from analogous aromatic esters by the use of cold hydrogen bromide–acetic acid solution. Stimmel and King[7] found that β-monopalmitin rearranged quantitatively to the α-isomer on standing for twenty-four hours at room temperature in an alcoholic solution of 0.05 *N* hydrochloric acid or 0.1 *N* ammonium hydroxide. A number of important observations concerning changes in the molecular structure of β-glycerides have been made by Verkade and associates[8] and by Fairbourne.[9]

During the course of the present investigation, in addition to studying the β- to α-changes in molecular structure, α-monopalmitin, and glycerol α-*p*-bromobenzoate were prepared with good yields, using 1,2-benzylidene glycerol as a very satisfactory intermediate for α-ester synthesis. Since the 1,2-type compound is the dominant one obtained by direct condensation, the method is a valuable one to follow in parallel with β-glyceride syntheses.

Experimental

Preparation of Esterified Acetals.—1,3-Benzylidene glycerol was prepared essentially by the method of Hibbert and Carter,[5] and purified by crystallization first from a mixture of benzene and heptane (1:1), and then from water.

2-Palmityl-1,3-benzylidene glycerol, m. p. 63.5°, was prepared by the method of Bergmann and Carter.[4] 2-*p*-Bromobenzoyl-1,3-benzylidene glycerol, m. p. 146°, was prepared by the method of Hibbert and Carter.[5]

The benzene–heptane solution remaining after the separation of 1,3-benzylidene glycerol was treated with an excess of silver hydroxide, shaken intermittently over a period of twelve hours, and suction filtered. After removing the benzene and heptane, the oily residue was fractionally distilled at 2 mm., the 1,2-benzylidene glycerol boiling at 139–141°.

To 5 g. of 1,2-benzylidene glycerol there was added 10 cc. of dry pyridine, followed by the slow addition of 7.6 g. of palmityl chloride. After allowing the mixture to stand for thirty minutes, 400 cc. of ice water was added to remove most of the pyridine. The acetal of the β-ester separated as a white solid. After washing with ice water until free from pyridine, and drying in a vacuum desiccator, the 1-palmityl-2,3-benzylidine glycerol was crystallized from absolute alcohol, m. p. 34.5°, yield 10 g. (86%).

Anal. Calcd. for $C_{26}H_{24}O_4$: C, 74.79; H, 10.12. Found: C, 74.57, 74.48; H, 10.06, 10.08.

Bergmann and Carter prepared the same compound by condensing α-monopalmitin with benzaldehyde (m. p. 35°).

1-*p*-Bromobenzoyl-2,3-benzylidene glycerol, m. p. 73°, was prepared from 1,2-benzylidene glycerol as described by Hibbert and Carter (m. p. 72°).

α-Monopalmitin and glycerol α-*p*-bromobenzoate were prepared from the above esterified acetals by the following method, given in detail for α-monopalmitin. Concentrated hydrochloric acid (25 cc.) was added, with cooling, to 8 g. of 1-palmityl-2,3-benzylidene glycerol dissolved in 20 cc. of ether. The α-monopalmitin separated as a white solid, upon the addition of 400 cc. of ice water. It was washed free of acid, dried in a vacuum desiccator, and crystallized from ether several times, m. p. 77°; yield, 7 g. (87%).

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(1) Fischer, *Ber.*, **53** 1621 (1920).

(2) Helferich and Sieber, *Z. physiol. Chem.*, **170**, 31 (1927).

(3) Helferich and Sieber, *ibid.*, **175**, 311 (1928).

(4) Bergmann and Carter, *ibid.*, **191**, 211 (1930).

(5) Hibbert and Carter, THIS JOURNAL, **51**, 1601 (1929).

(6) Jackson and King, *ibid.*, **55**, 678 (1933).

(7) Stimmel and King, *ibid.*, **56**, 1724 (1934).

(8) Verkade, Van der Lee and Meerburg, *Rec. trav. chim.*, **56**, 365, 613, 716 (1937); Verkade and Van der Lee, *Proc. Roy. Soc. Amsterdam*, **37**, 812 (1934).

(9) Fairbourne, *J. Chem. Soc.*, 369 (1930).

Preparation of β-Monoglycerides.—β-*p*-Bromobenzoate and β-monopalmitin were prepared by reduction of the corresponding esterified acetals essentially by the method of Bergmann and Carter, except that in the former case ethyl acetate was used as the solvent. It was found, as reported by Stimmel and King, that 0.5 g. of palladium black was sufficient for the reduction of approximately 10 g. of the esterified acetal.

The β-*p*-bromobenzoate (new) was crystallized twice from ethyl acetate, then from a 1:1 mixture of ether and petroleum ether, as short, colorless, prismatic crystals, m. p. 95.2°; yield, 79.2%.

Anal. Calcd. for $C_{10}H_{11}O_4Br$: Br, 29.06. Found: Br, 29.01, 29.15.

Migration of Acyl Groups.—β-Monopalmitin (0.5 g.) was dissolved in 20 cc. of alcoholic hydrochloric acid of the desired normality. After standing for twenty-four hours at room temperature (22–25°), the solution was cooled until essentially complete crystallization occurred. The crystals were suction filtered and dried in a vacuum desiccator for twenty-four hours, after which the melting points were determined. The same procedure was followed with alcoholic ammonium hydroxide. The β-*p*-bromobenzoate was recovered quantitatively from ether–petroleum ether after removal of the original alcohol under reduced pressure.

Melting Point of Recovered β-Monopalmitin (m. p. 68.5°) (m. p. of α-Monopalmitin, 77°)

Hydrochloric Acid

Normality, *N*	0.1	0.05	0.025	0.01	0.0067	0.005
M. p. of prod., °C.	77	77	66–73	51–73	50–70	68.5

Ammonium Hydroxide

Normality, *N*	0.1	0.05	0.025	0.0125	0.01
M. p. of prod., °C.	77	62–68	61–62	62–65	68.5

Melting Point of Recovered β-*p*-Bromobenzoate (m. p. 95.2°) (m. p. of α-*p*-Bromobenzoate, 74.5°)

Hydrochloric Acid

Normality, *N*	0.1	0.05	0.025	(No change with dilutions up to 0.005 *N*)
M. p. of prod., °C.	74.5	95.1	95.2	

Ammonium Hydroxide

Normality, *N*	0.1	0.05	0.025	(No change with dilutions up to 0.005 *N*)
M. p. of prod., °C.	74.5	95.2	95.2	

To check the effect of moderate heating, melting point tubes were filled partially with β-monopalmitin and β-*p*-bromobenzoate, and the tubes placed in an oven for periods of one, twelve, and twenty-four hours at approximately 7° above their melting points. After removal from the oven all of the tubes were kept at room temperature for twelve hours to permit recrystallization. Neither compound changed sufficiently to alter the melting point within one hour, but both compounds showed a marked drop in melting point after twelve hours. Neither compound changed completely to the α-isomer on prolonged heating.

Preparation of Triglycerides.—1-*p*-Bromobenzoyl-2,3-dipalmitin, m. p. 68.8°, was prepared from palmityl chloride and the above α-*p*-bromobenzoyl ester.[5]

Anal. Calcd. for $C_{42}H_{71}O_6Br$: Br, 10.63. Found: Br, 10.59, 10.51.

The symmetrical isomer, 2-*p*-bromobenzoyl-1,3-dipalmitin, m. p. 50°, was prepared both from the symmetrical dipalmitin and from the β-*p*-bromobenzoyl ester by esterification with the corresponding acyl halide. The two isomers afford another illustration of the reversal of melting point relationship between symmetrical and unsymmetrical mixed triglycerides, in comparing aromatic esters with aliphatic esters. In our experience with the latter type, the symmetrical isomers always had the higher melting point.

Anal. Calcd. for $C_{42}H_{71}O_6Br$: Br, 10.63. Found: Br, 10.54, 10.66.

Solubilities.—It is of interest to note from the data in Table I that the aromatic and aliphatic monoglycerides are reversed in their solubility ratios for α- and β-isomers. In the former case (aromatic) the β-form is less soluble, but α-monopalmitin is less soluble than β-monopalmitin. In an earlier investigation[10] it was found that the unsymmetrical mixed triglycerides of aliphatic acids were distinctly more soluble than the higher melting symmetrical isomers.

TABLE I

SOLUBILITIES OF MONOGLYCERIDES

Compound	Solvent	Temp., ±0.01° C.	Soly., g. per 100 ml.
α-*p*-Bromobenzoate	Ether	26	3.50
β-*p*-Bromobenzoate	Ether	26	3.02
α-*p*-Bromobenzoate	Alcohol	26	16.05
β-*p*-Bromobenzoate	Alcohol	26	4.41
α-Monopalmitin	Ether	25	2.75
β-Monopalmitin	Ether	25	11.15

Summary

The use of 1,2-benzylidene glycerol as an intermediate for the synthesis of α-monoglycerides was found to be satisfactory for both aliphatic and aromatic esters.

Tenth normal hydrochloric acid and ammonium hydroxide in alcoholic solution caused both aromatic and aliphatic monoglycerides to undergo a complete shift from the beta to the alpha position in a short time at room temperature. In more dilute acid or alkali, however, a marked contrast between aromatic and aliphatic β-esters was evident: *N*/150 hydrochloric acid and *N*/80 ammonium hydroxide were about as effective upon an aliphatic ester (β-monopalmitin) as *N*/20 hydrochloric acid and *N*/15 ammonium hydroxide were upon an aromatic ester (β-*p*-bromobenzoate).

Neither aromatic nor aliphatic β-esters exhibited a shift to the α-isomer when held at 7° above their melting points for one hour in the dry state.

The symmetrical and unsymmetrical *p*-bromobenzoyldipalmitins afford another example of a mixed aromatic symmetrical isomer having a

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(10) Robinson, Roche and King, THIS JOURNAL, **54**, 705 (1932).

lower melting point than the unsymmetrical isomer, a reversal of the relationship for analogous aliphatic esters.

The aromatic β-monoglyceride was less soluble and had a higher m. p. than the α-isomer, in contrast to the reverse relationship for α- and β-monopalmitins.

PITTSBURGH, PENNA. RECEIVED SEPTEMBER 26, 1938

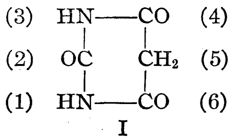
[CONTRIBUTION NO. 142 FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, THE UNIVERSITY OF TEXAS]

The Synthesis of Colored Derivatives of Nirvanol

BY JAMES J. SPURLOCK[1] WITH HENRY R. HENZE

Reports are to be found in the literature of attempts to synthesize colored compounds of pronounced physiological activity. Rising[2] and collaborators have extended this type of investigation to the field of barbituric acid derivatives and have produced, from phenobarbital, mono- and dis-azo dyes in which the chromophoric grouping is attached to a phenyl radical linked to the 5-carbon atom of the barbituric acid nucleus. Buck[3] has attacked the same problem from a different angle by producing azo dyes in which the chromophore is attached to a phenyl grouping which replaces hydrogen linked to a nitrogen atom in the 1-position of the nucleus.

The definite structural similarity of barbituric acid (I) and hydantoin (II) is well known, as is also the close analogy in the existence of compounds derived from substitution of identical groupings for the hydrogen atoms in the 1-, 3- and 5,5-positions of both heterocycles. Likewise, in at least one instance, substitution of ethyl and phenyl for the hydrogens attached at the 5,5-positions in both nuclei has produced useful sedatives, namely, phenobarbital (III) and nirvanol (IV), respectively. It seemed of interest, therefore, to attempt to convert nirvanol into azo dyes whose pharmacological properties might be studied subsequently.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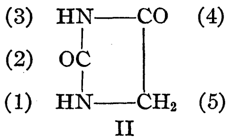
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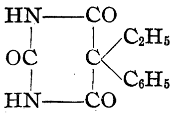
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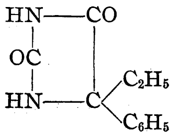
IV

Nirvanol was nitrated and yielded a material whose behavior during recrystallization indicated it to be a mixture, and a pure mononitro derivative was not obtained even after ten recrystallizations. Although this mixture could be reduced catalytically, fractional crystallization proved to be unsatisfactory as a means of separating the isomeric amines formed.

Since the structure of these products, obtained from nirvanol by nitration and subsequent reduction, was uncertain, it appeared best to approach this problem from simpler compounds of established structure. Following the nitration of propiophenone, the meta derivative[4] was separated readily from its alkali-insoluble isomers and converted into 5-*m*-nitrophenyl-5-ethylhydantoin by means of the procedure of Bucherer.[5] In turn, the nitrated hydantoin was reduced in the presence of the Adams catalyst, the anticipated *m*-amine crystallizing from water as a monohydrate.

The 5-*m*-aminophenyl-5-ethylhydantoin has been diazotized and coupled with β-naphthol, β-naphthylamine, dimethylaniline and G Salt, respectively, to form azo compounds. The dyes derived from β-naphthylamine and from dimethylaniline dye wool and silk from either acid or alkaline solution; that derived from 2-naphthol-6,8-disulfonic acid dyes only from acid solution. The azo derivative of β-naphthol possesses no dyeing properties from either alkaline solution or glacial acetic acid solution.

Experimental

Nitration of Phenylethylhydantoin.—Phenylethylhydantoin was prepared according to the method of Bucherer[5]

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(1) Presented before the Division of Medicinal Chemistry at the 95th meeting of the American Chemical Society, April 18 to 21, 1938, at Dallas, Texas.

(2) (a) Rising, Shroyer and Stieglitz, THIS JOURNAL, **55**, 2818 (1933); (b) Pierce and Rising, *ibid.*, **58**, 1361 (1936).

(3) Buck, *ibid.*, **59**, 1249 (1937).

(4) Comanducci and Pescitelli, *Gazz. chim. ital.*, **36**, II, 787 (1906).

(5) Bucherer and Lieb, *J. prakt. Chem.*, [2] **141**, 5 (1934).

and was dissolved in concd. sulfuric acid, cooled to −10° and nitrated with fuming nitric acid. After pouring into water, separating and drying the solid was twice recrystallized from alcohol; the yield represented 84% of the theoretical. After ten additional recrystallizations, the product, still not homogeneous, was reduced catalytically and yielded a mixture which could be fractionated by tedious recrystallization. The amines could be diazotized and coupled with β-naphthol forming a mass of deep red-colored crystals; analysis of the latter indicated that the hydantoin nucleus is stable toward diazotization and coupling.

Preparation of *m*-Nitrophenyl Ethyl Ketone.—One hundred twenty cc. of concd. sulfuric acid was placed in a 500-cc. three-necked flask fitted with a mechanical stirrer, dropping funnel and thermometer so placed that the bulb was immersed in the liquid in the flask. The acid was cooled to −5° and 26.8 g. (0.20 mole) of phenyl ethyl ketone was added during a period of ten minutes. There was then added, during a period of six minutes, a cooled mixture of 15 cc. of concd. sulfuric acid and 19.65 g. (0.22 mole) of 70% nitric acid. The temperature was at no time allowed to rise above 4°, and during most of the time it remained below 0°. The mixture was stirred for five minutes and poured over about 400 g. of cracked ice in a beaker. The oily mixture was allowed to come to room temperature and was then extracted three times with ether and the extracts washed with a 5% aqueous solution of sodium bicarbonate until the aqueous layer was no longer colored. This treatment removed the alkali-soluble isomers. The ether layer was washed with water, dried and the ether removed by evaporation on a steam cone. The resulting oil was dissolved in hot benzene, and petroleum ether then added until the solution began to cloud. Six and seven-tenths grams of light yellow crystals, m. p. 97–100°, was obtained, and, in addition, 7 g. of unreacted ketone was recovered. Based on the quantity of ketone which reacted, the yield of *m*-nitrophenyl ethyl ketone was 25%. Further recrystallization gave a product melting at 99–100° (corr.) as compared with 98° reported by Comanducci and Pescitelli,[4] and 100° recorded by Barry.[6]

Preparation of 5-*m*-Nitrophenyl-5-ethylhydantoin.—This compound was prepared by the method of Bucherer,[5] *i. e.*, by the interaction of ammonium carbonate, alkali cyanide and ketone. Two grams (0.011 mole) of *m*-nitrophenyl ethyl ketone (m. p. 99–100°), 1.0 g. (0.015 mole) of potassium cyanide and 4.0 g. (0.035 mole) of ammonium carbonate were placed in a 125-cc. flask together with 20 cc. of 95% ethyl alcohol and 10 cc. of water. The flask was fitted with an air condenser and the mixture heated at a temperature of 58–60° for a period of ten hours. The flask was shaken at intervals in order to facilitate solution and reaction of the ketone. At the end of this time the condenser was removed and the temperature raised to 85° in order to decompose the excess of ammonium carbonate and to evaporate much of the alcohol. After half an hour, 15 cc. of water was added, the solution cooled, acidified with dilute hydrochloric acid and filtered. After washing with water and drying, 2.7 g. of material, melting at 210–213°, was obtained. Recrystallization from dilute alcohol yielded 2.2 g. of white crystals melting at 219–220° (corr.); this amount represents a yield of 80% of the theoretical.

Anal. Calcd. for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.45; N, 16.86. Found: C, 53.10; H, 4.36; N, 16.94.

Preparation of 5-*m*-Aminophenyl-5-ethylhydantoin.—Four grams (0.016 mole) of 5-*m*-nitrophenyl-5-ethylhydantoin was suspended in 200 cc. of acetone and reduced catalytically in the presence of the Adams catalyst at room temperature and about one atmosphere pressure, the reduction being complete in two hours. The acetone was removed on a steam cone and the resulting residue crystallized from water, yielding 2.7 g. of light yellow crystals melting at 82–83° (corr.); on further heating the fused mass lost water at about 120°, solidified, and remelted at 165–166° (corr.).

Anal. Calcd. for $C_{11}H_{13}N_3O_2.H_2O$: C, 55.68; H, 6.37; N, 17.71. Found: C, 55.62; H, 6.54; N, 17.59.

Since the results of analysis of this compound indicate a monohydrate, the yield based on the amount of monohydrate theoretically obtainable is 71%. The hydrate was found to be somewhat unstable at room temperature and was dried *in vacuo* at 100° under 3 mm. pressure to obtain the anhydrous form; m. p. 165–166° (corr.).

Anal. Calcd. for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.51; H, 5.98; N, 19.13.

Preparation of 5-β-Naphthol-*m*-azophenyl-5-ethylhydantoin.—One gram (0.004 mole) of 5-*m*-aminophenyl-5-ethylhydantoin was dissolved in a mixture of 5 cc. of concd. hydrochloric acid and 50 cc. of water and cooled to −5°. Thirty-five hundredths gram (0.005 mole) of sodium nitrite was dissolved in 15 cc. of water, the solution cooled and added to that of the amine. The resulting solution of the diazonium salt was then added to 0.70 g. (0.005 mole) of β-naphthol dissolved in 100 cc. of ethyl alcohol. The mixture became light orange in color and on the addition of 10 g. of hydrated sodium acetate, dissolved in 25 cc. of water, a bulky orange-red precipitate formed. The product was allowed to stand for six hours before being filtered and recrystallized from acetic acid. The compound crystallized in bright red needles melting at 276–277° (corr.) with slight decomposition. A yield of 1.05 g., representing 67% of the theoretical, was obtained. The azo compound is very easily soluble in dilute alkali with the formation of a deep red color, is slightly soluble in glacial acetic acid, very slightly soluble in ethanol and insoluble in water.

Anal. Calcd. for $C_{21}H_{18}N_4O_3$: C, 67.37; H, 4.85; N, 14.96. Found: C, 67.31; H, 4.66; N, 15.00.

Preparation of 5-β-Naphthylamine-*m*-azophenyl-5-ethylhydantoin.—One gram (0.004 mole) of 5-*m*-amino phenyl-5-ethylhydantoin was dissolved, as before, in a solution of 5 cc. of concd. hydrochloric acid and 50 cc. of water, and cooled to −5°. There was then added the cooled solution of 0.35 g. of sodium nitrite in 20 cc. of water. After five minutes 0.3 g. of urea was added to the solution of the diazonium salt and the mixture allowed to stand for fifteen minutes, during this time some gas formation was noted. The solution was then added to one of 0.76 g. (0.005 mole) of β-naphthylamine in 100 cc. of ethyl alcohol. The solution became yellow in color, and upon the addition of 10 g. of crystalline sodium acetate, as before, an orange precipitate formed. The reaction mixture was allowed to warm slowly to room temperature and

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[6] Barry, *Ber.*, **6**, 1007 (1873).

was heated finally at 55° for five hours, cooled and filtered. Recrystallization from ethanol and ethyl acetate resulted in 1.21 g. of orange needles, a yield of 77%. On slow heating these needles sinter at 220°, then show no further change until they melt at 247–248° (corr.). When the crystals are placed in a bath at a temperature slightly below 220°, they melt at 220–221° (corr.), resolidify and melt again at 247–248° (corr.). The azo compound is soluble in concd. hydrochloric acid to form a deep red solution and in alkali to yield a bright orange solution. Also, it is slightly soluble in ethanol and in ethyl acetate, but insoluble in water.

Anal. Calcd. for $C_{21}H_{19}N_5O_2$: C, 67.55; H, 5.13; N, 18.76. Found: C, 67.48; H, 5.33; N, 18.80.

Preparation of 5-Dimethylaniline-*m*-azophenyl-5-ethylhydantoin.—One gram (0.004 mole) of 5-*m*-aminophenyl-5-ethylhydantoin was diazotized as before, with addition to the solution of diazonium salt derived from 0.56 g. (0.46 mole) of dimethylaniline dissolved in 1 cc. of concd. hydrochloric acid and 20 cc. of water. An orange precipitate formed on the addition of 10 g. of hydrated sodium acetate. The mixture was allowed to warm to room temperature, was filtered and the solid crystallized from ethanol and then from ethyl acetate. One and eleven-hundredths grams of light orange needles melting at 233–235° was obtained, or 75% of the theoretical yield. The azo dye is soluble in dilute hydrochloric acid, somewhat less soluble in dilute alkali, slightly soluble in ethanol and ethyl acetate and insoluble in water.

Anal. Calcd. for $C_{19}H_{21}N_5O_2$: C, 64.93; H, 6.02; N, 19.93. Found: C, 64.94; H, 5.92; N, 19.89.

Preparation of 5-[2-Naphthol-6,8-disulfonic acid-*m*-azophenyl]-5-ethylhydantoin.—Three grams (0.013 mole) of 5-*m*-aminophenyl-5-ethylhydantoin was diazotized using 1 g. of sodium nitrite and to the solution was added 7 g. of G Salt dissolved in 50 cc. of water. No appreciable color change was noted until the solution was made alkaline with sodium hydroxide, after which it gradually became deep red in color. The reaction mixture was allowed to stand for twenty-four hours at 0°, when an unsuccessful attempt was made to salt-out the sodium salt through addition of sodium chloride. Six grams of barium chloride dissolved in 20 cc. of water was added and the solution allowed to stand for twenty-four hours, during which time orange material separated from solution. The solid was filtered and recrystallized from water, 4.15 g. of product being obtained. Analysis of this material, dried at room temperature, indicated it to be the octahydrated barium salt; on this basis the yield represented 40% of the theoretical.

Anal. Calcd. for $C_{21}H_{16}N_4O_9S_2Ba.8H_2O$: Ba, 16.88; S, 7.88; N, 6.89. Found: Ba, 16.91; S, 8.13; N, 7.76.

The free sulfonic acid, obtained by decomposing the barium salt with the calculated amount of sulfuric acid, is very soluble in water; the aqueous solution is colored deep red by alkali and orange by acid. Because of its extremely hygroscopic nature it was not possible to prepare the disulfonic acid in a state of analytical purity.

Summary

Colored meta-azo derivatives of nirvanol have been synthesized.

AUSTIN, TEXAS RECEIVED AUGUST 5, 1938

[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

The Mutarotation of *d*-Galactose[1]

BY B. CLIFFORD HENDRICKS AND ROBERT E. RUNDLE

The mutarotation of *d*-galactose has received more attention than other sugars in recent years[2–6] due to its reaction being other than the traditional first order type.

Two groups[4,6] of investigators have developed independently what might be termed a three-sugar postulate. In the language of one group[7] "our method of analysis enables us to calculate: (1) the proportions of these sugars in the final equilibrium mixture; (2) the velocity coefficients of the four unimolecular actions by which they are converted into one another; and (3) the approximate rotatory power of the unknown intermediate sugar." The constants thus deduced by these two groups, however, do not agree. Riiber and co-workers made their deductions from dilatometer studies of *d*-galactose mutarotations while Lowry and his assistants derived theirs from polarimetric data.

One of the authors[8] has shown that the constants reported by Lowry can be used to compute the rotations of "thermal-mutarotations" and of predetermined proportions of α-*d*-galactose and β-*d*-galactose mixtures. The computed data are shown to agree with the observed values made by Isbell and Pigman[9] in a very satisfactory way while calculations made for the same conditions

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[1] Presented at the Joint Program of the Division of Organic Chemistry and the Division of Sugar Chemistry and Technology at the ninety-sixth meeting of The American Chemical Society, Milwaukee, Wisconsin, September 8, 1938.

[2] Lowry, *J. Chem. Soc.*, **85**, 1570 (1904).

[3] Hudson and Yanovsky, THIS JOURNAL, **39**, 1013 (1917).

[4] Riiber and Minsaas, *Ber.*, **59**, 2266 (1926).

[5] Worley and Andrews, *J. Phys. Chem.*, **32**, 307 (1928).

[6] Smith and Lowry, *J. Chem. Soc.*, 666 (1928).

[7] Lowry and Smith, *J. Phys. Chem.*, **33**, 7–21 (1929).

[8] Rundle, Thesis, University of Nebraska, 1938.

[9] Isbell and Pigman, *Bur. Standards J. Research*, **18**, 141 (1937).

using the Riiber constants do not at all follow the observed data. Neither of the two groups referred to presumes to state the nature of the third or "labile" sugar of the system.

A recent paper[10] proposes a pyranose–furanose interconversion as a part of the mechanism of the complex mutarotation of sugars. If such a transformation were essential in the rotations of a greater complexity than first order changes it would follow that tetramethyl hexoses would never show other than first order mutarotation. This paper reports a study of the mutarotation of tetramethyl *α-d*-galactopyranose.

The tetramethyl *α-d*-galactopyranose was prepared as indicated in another communication.[11] The constants of the sugar were: initial rotation $[\alpha]^{25}_{\mathrm{D}}$ 146.0, $[\alpha]^{0}_{\mathrm{D}}$ 150.5; equilibrium rotation $[\alpha]^{25}_{\mathrm{D}}$ 112.1°, $[\alpha]_{\mathrm{D}}$ 119.9°; and melting point 70.5–71.5°.

The polarimetric measurements were made with a Goerz instrument, which could be read to 0.01°, using a two-decimeter glass metal-jacketed tube. The light was from a General Electric sodium arc lamp. The temperature was controlled by pumping water from a bath maintained to a ±0.1° constancy at the higher temperature. The lower temperature was controlled by a water–alcohol mixture circulated through the tube jacket and a salt–ice bath with a temperature constancy of ±0.2°. The usual method of preparing the sugar solutions was used, care being exercised that volumetric flasks, water and tubes were at correct temperature during the time for dissolving the sugar. The "thermal mutarotation" procedure of Isbell and Pigman[12] was modified. The equilibrium solution was poured into a pre-cooled flask, placed in an ice-bath and shaken until the solution reached 0.0°, after which it was placed in a cold tube. This operation never took more than five minutes.

The authors consider the rotation velocity constant, $k_1 + k_2$, calculated as indicated elsewhere,[9] a means of recognizing departure from the first order type of mutarotation, hence its inclusion in the tables which follow.

Results listed in Tables I, II and III are representative samples of several runs for each type of experiment. Data from other experiments were consistent with those given above. The deviations of these values from the first order rate are smaller than for the unmethylated *α-d*-galactose and for the 25° temperature the deviations practically disappear. The suggested deviations of the rotation–time observations at 0.0° are supported by the "thermal mutarotation" measurements, though, unfortunately, in that study the change of rotation is so small that the experimental error is magnified in the calculated velocity constants. Even so it is relatively less

TABLE I

MUTAROTATION OF TETRAMETHYL *α-d*-GALACTOSE AT 25°

0.8033 g. of sugar in 25 ml. of water

Time, min. and sec.	Rotation obsd.	$(k_1 + k_2) \times 10^4$ calcd.
6′15″	11.28	
7′15″	11.23	
8′15″	11.16	138
9′10″	11.11	125
10′15″	11.06	115
12′30″	10.93	119
14′0″	10.86	117
17′20″	10.70	117
18′50″	10.64	116
22′55″	10.46	117
25′0″	10.39	121
32′15″	10.13	117
39′55″	9.91	120
49′20″	9.70	120
57′30″	9.56	119
78′30″	9.26	126
91′15″	9.20	125
97′30″	9.19	126
117′5″	9.09	126
141′0″	9.04	Av. 121
180′0″	9.01	
∞	9.00	

TABLE II

MUTAROTATION OF TETRAMETHYL *α-d*-GALACTOSE AT 0.0°

1.0007 g. of sugar in 25 ml. of water

Time, min. and sec.	Rotation obsd.	$(k_1 + k_2) \times 10^6$ calcd.
8′15″	12.03	
9′35″	12.01	
22′40″	11.93	1114
40′10″	11.84	1043
41′30″	11.80	1239
56′50″	11.73	1133
78′10″	11.64	1057
112′10″	11.56	875
162′30″	11.35	909
212′0″	11.13	972
244′0″	11.06	926
357′0″	10.82	850
521′0″	10.37	961
581′0″	10.32	917
1426′0″	9.74	867
∞	9.60	

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[10] Isbell and Pigman, *Bur. Standards J. Research*, **20**, 775 (1938).

[11] Hendricks and Rundle, THIS JOURNAL, **60**, 2563 (1938).

[12] Isbell and Pigman, *Bur. Standards J. Research*, **16**, 553 (1936).

TABLE III

THERMAL MUTAROTATION OF TETRAMETHYL α-*d*-GALACTOSE FROM 25 TO 0.0°

0.7514 g. of sugar in 20 ml. of water

Time, min. and sec.	Rotation obsd.	$(k_1 + k_2) \times 10^6$ calcd.
9'15"	8.73	
10'15"	8.74	
37'40"	8.78	2040
74'0"	8.81	1622
157'0"	8.88	1631
397'0"	8.92	866
638'0"	8.97	826
1406'0"	9.05	872
1408'0"	9.04	745
∞	9.07	

than the difference between the velocity constants of the first and second parts of the reaction and the consistent nature of this difference of the various determinations is such that the authors consider it a real difference.

The tetramethyl α-*d*-galactopyranose cannot have a furanose ring since the fourth carbon is methylated. In consequence if the differences in the mutarotation velocity constants of Tables II and III are real, then the complex mutarotation of tetramethyl α-*d*-galactose cannot require a galactofuranose as one of the sugars in the interconversion. This does not imply, however, that galactofuranose may not be involved in the complex mutarotation of unmethylated *d*-galactose.[13]

Summary

The mutarotations of solutions of tetramethyl α-*d*-galactopyranose have been studied for 25 and 0°. Velocity constants for the first part of the mutarotation at 0.0° show slightly but consistently higher values than for changes nearer the equilibrium.

"Thermal mutarotation" for tetramethyl α-*d*-galactopyranose for a 25 to 0° change has been investigated. The rotation constant, $k_1 + k_2$, is consistently larger at the first than at the last of the change by an amount which is considered in excess of the experimental error.

It is suggested that the assumed pyranose–furanose interconversion as a part of the mechanism of complex mutarotation can hardly be perfectly general.

[13] Diacetone mannose has been reported by Irvine and Skinner [*J. Chem. Soc.*, 1095 (1926)] as having a complex mutarotation. The authors repeated their work at 17° and found agreement with that report. The changes in specific rotation go from 9 to −3° back to 1°. This change hardly could be attributed to a pyranose–furanose interconversion.

LINCOLN, NEBRASKA RECEIVED SEPTEMBER 6, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

Studies of Cellulose Hydrolysis by Means of Ethyl Mercaptan. III[1]

BY M. L. WOLFROM AND JOHN C. SOWDEN[2]

Previous publications[3] from this Laboratory have described a study of the course of hydrolysis of the cellulose molecule. The method consisted of allowing a solution of high viscosity cotton linters in fuming hydrochloric acid to hydrolyze at 16° and following the course of hydrolysis by mercaptalation with ethyl mercaptan at various time intervals. Sulfur analyses on the resulting mercaptalated hydrolyzed celluloses then gave an estimate of their average molecular size. Cuprammonium viscosity measurements on the non-mercaptalated hydrolyzed products, isolated after corresponding periods of hydrolysis in the fuming hydrochloric acid, were also employed to estimate the average chain lengths by application of the formula of Kraemer and Lansing.[4] A comparison of the average molecular sizes as determined by the two methods was thus available.

The studies at 16° indicated that the sulfur analytical method gave appreciably lower values for the chain lengths than those calculated from cuprammonium viscosity data, for hydrolyzed products of above 100 glucose units in size. Thus, it is of interest to study further the earlier stages of the hydrolysis, in order to determine the nature of this difference in chain lengths as calculated by the two methods for products having degrees of polymerization greater than 100 glucose units.

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[1] Presented before the Division of Organic Chemistry at the 96th meeting of The American Chemical Society, Milwaukee, Wisconsin, September 8, 1938.

[2] Du Pont Cellulose Research Fellow.

[3] M. L. Wolfrom and Louis W. Georges, THIS JOURNAL, **59**, 282 (1937); M. L. Wolfrom, Louis W. Georges and John C. Sowden, *ibid.*, **60**, 1026 (1938).

[4] E. O. Kraemer and W. D. Lansing, *J. Phys. Chem.*, **39**, 164 (1935).

In the work herein reported, the course of hydrolysis of the same sample of cotton linters previously studied was followed during the first eight and one-half hours in fuming hydrochloric acid at 0°. The lower temperature resulted in a much slower rate of hydrolysis than that previously observed at 16°, and the products isolated had average chain lengths in the range of 100 to 300 glucose units.

A cuprammonium viscosity measurement on a sample of our stock of high viscosity cotton linters showed that no degradation had occurred during storage. In order to assure comparable conditions in the preparation of the mercaptalated and non-mercaptalated products, a stock solution of the linters in the fuming acid was prepared at 0° and divided into two equal parts. An excess of ethyl mercaptan, to provide continuous mercaptalation of the hydrolyzed celluloses, was added to one part and the hydrolysis allowed to progress at 0°. Simultaneous removal and neutralization of samples from the two hydrolysis mixtures at various time intervals then resulted in mercaptalated and non-mercaptalated products which had been subjected to comparable hydrolytic conditions in the fuming acid.

As in the previous studies at 16°,[3] ash analyses were made on the washed products to determine their sodium chloride content. Precise sulfur analyses were then made on the mercaptalated hydrolyzed products by the Parr bomb method and the viscosities of both the mercaptalated and non-mercaptalated hydrolyzed products were determined in cuprammonium solution at a concentration of 0.1%. These data are recorded in Tables II and III. Due to the opacity of the hydrolysis mixture at 0°, it was impossible to follow the course of the hydrolysis polarimetrically. Thus, the time of addition of the fuming hydrochloric acid to the linters was taken as the zero time of the hydrolysis.

The copper numbers (Hägglund–Bertrand) of the mercaptalated and non-mercaptalated hydrolyzed celluloses were determined and are recorded in Table IV. No explanation is yet at hand for the fact that the mercaptalated products, which would be expected to have a zero copper number, exhibit a low but definite reducing power. The original cotton linters were found to have a very low reducing power, as evidenced by a copper number of approximately 0.2.

In Table I are recorded the degrees of polymerization in glucose units, calculated from cuprammonium viscosity data by the formula of Kraemer and Lansing,[4] for both the mercaptalated and non-mercaptalated hydrolyzed celluloses, and also those calculated for the mercaptalated products from sulfur analytical data. The degrees of polymerization, as calculated from viscosity data, show fair agreement, the values for the mercaptalated products tending to be approximately twenty glucose units greater than those for the non-mercaptalated products.

TABLE I

DEGREE OF POLYMERIZATION (D. P.) IN GLUCOSE UNITS OF MERCAPTALATED AND NON-MERCAPTALATED HYDROLYZED CELLULOSES CALCULATED FROM SULFUR ANALYSES AND CUPRAMMONIUM VISCOSITY DATA

Time of hydrolysis, min.[a]	Mercaptalated products D. P. by S content	Mercaptalated products D. P. by viscosity	Non-mercaptalated products D. P. by viscosity
270	190	276	260
310	148[b]	255	233
350	104	228	229
390	87	226	206
430	95	218	196
470	101[b]	204	187
510	98[b]	198	174

[a] Initial time taken as time of addition of acid to the cellulose.

[b] The results of two closely agreeing sulfur analyses (see Table II) were averaged and the D. P. calculated from this average.

The average degrees of polymerization of the mercaptalated product mixtures as calculated from their sulfur content are definitely lower than those of the corresponding non-mercaptalated products as calculated from cuprammonium viscosity data. The degree of polymerization calculated from sulfur analytical data on a nonhomogeneous mixture constitutes a number average and would thus be expected to be somewhat lower than that calculated from cuprammonium viscosity based on ultracentrifuge measurements, which represents a weight average (4). This difference will not be appreciable if the degrees of polymerization of the components of the mixture do not extend over a wide range.

In the calculation of the average degree of polymerization (D. P.) from the sulfur analyses, the assumption is made that all free reducing groups have reacted completely to form thioacetals (mercaptals). Any correction of the data for incompleteness of reaction or for the reaction resulting in the formation of thioglycosides instead of thioacetals, would lead to still lower degrees of polymerization as calculated from the sulfur content. The presence of adsorbed ethyl mercaptan would lead, however, to a calculated degree of polymerization that was too low. The absence of adsorbed ethyl mercaptan in the products analyzed was accordingly demonstrated. Several of the samples were analyzed before and after extensive drying at 56.5° in high vacuum. Also, one mercaptalated product was analyzed before and after prolonged soaking in absolute ethanol. Neither of these treatments, which would be expected to remove any adsorbed ethyl mercaptan, had any appreciable effect on the observed sulfur content.

The relationship between the degrees of polymerization by the two methods with increasing time of hydrolysis is shown in Fig. 1. The difference in the values obtained by the two methods, which was observed in the range of products of 100 to 200 glucose units in size during the previous work at 16°,[3] apparently does not tend to increase in the range of degraded celluloses from 200 to 300 glucose units in size. The nature of the curves in Fig. 1 is such that extrapolations to zero time cannot be made on the basis of the data at hand.

Experimental

Cellulose Characterization.—The degree of polymerization of our stock cotton linters[5] was redetermined by measuring the viscosity of a 0.1% solution in cuprammonium solvent and applying the formula of Kraemer and Lansing:[4]

Average time of flow, solution	402.5 sec. at 25°
Average time of flow, solvent	184.9 sec. at 25°
D. P.	2023

This compares with the values 1980 and 2008 found for the same stock in the previous work.[3]

Hydrolysis and Mercaptalation of Linters.—The cotton linters (75.0 g., moisture-free basis) in a glass-stoppered bottle at 0° were treated with fuming hydrochloric acid (1500 cc.; d^{16}_4 1.205; % HCl, approx. 41) previously cooled to 0°. The mixture was maintained at 0° with occasional shaking. After three hours the resulting opaque, homogeneous mixture was equally divided and placed in two 1-liter, 3-necked flasks at 0°, equipped for rapid mechanical stirring and for rapid removal of samples through a delivery tube. One flask contained well-purified ethyl mercaptan (100 g.) at 0° to provide continuous mercaptalation of the degraded cellulose as the hydrolysis progressed. The two mixtures were stirred rapidly and maintained at 0° throughout the duration of the hydrolysis. After two hundred and seventy minutes of hydrolysis, samples of approximately 85 cc. were withdrawn simultaneously every forty minutes from each flask. The samples were withdrawn to calibrated bottles by application of suction and immediately poured, with stirring, into separate mixtures of sodium bicarbonate (96 g.) and water (300 cc.). In this way, seven samples each of mercaptalated and non-mercaptalated hydrolyzed celluloses were obtained, the time of contact with the fuming acid varying from 270 to 510 minutes. The products were collected and washed in the manner described in our previous work.[3]

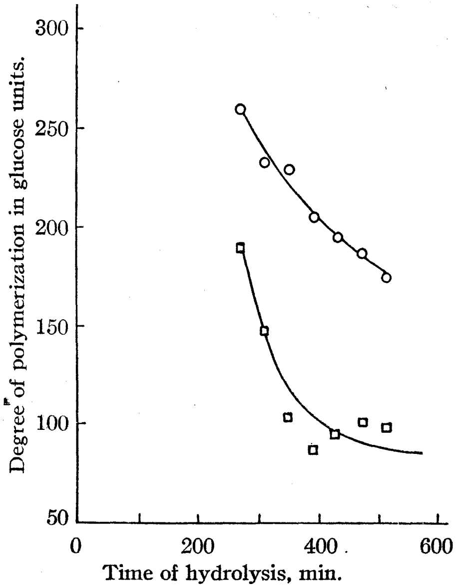

Fig. 1.—Rate of change of degree of polymerization (D. P.) of cellulose (4%) with time of hydrolysis by fuming hydrochloric acid (d^{16}_4 1.205) at 0°: ○, D. P. by cuprammonium viscosity; □, D. P. by sulfur content.

TABLE II

MERCAPTALATED PRODUCTS FROM COTTON LINTERS (c, 5 G. PER 100 CC. SOLN.) IN FUMING HYDROCHLORIC ACID (d^{16}_4 1.205) AT 0°

Time of hydrolysis, min.[a]	% ash, as NaCl	Mercaptalated product from 4.25 g. cellulose wt., g.[b]	% S		Cuprammonium viscosity, 25°, c : 0.1, time of flow in sec. Soln.	Solvent	D. P. by viscosity
270	5.29	3.62	0.210[d]		204.4	183.8	276
310	5.14	3.51	.270[d]	0.272	203.4	184.4	255
350	4.97	3.60	.384[d]		201.1	184.2	228
390	5.67	2.42[c]	.461[d]		202.0	185.2	226
430	4.24	3.55	.419[d]		201.4	185.2	218
470	4.45	3.37	.441[d]	.354	200.3	185.2	204
510	4.30	3.42	.431	.386[e]	199.5	184.9	198

[a] See footnote *a*, Table I. [b] Calculated on vacuum-dried (63°) and sodium chloride free basis. [c] Part of product lost mechanically during washing operations. [d] Sample previously dried sixteen hours at 56.5° and 0.001 to 0.0005 mm. [e] Sample previously soaked seven days in absolute ethanol.

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[5] Supplied through the courtesy of the Hercules Powder Company.

Table III

Non-mercaptalated Products from Cotton Linters (c, 5.0 G. per 100 Cc. Soln.) in Fuming Hydrochloric Acid (d^{16}_4 1.205) at 0°

Time of hydrolysis, min.[a]	% ash, as NaCl	Product from 4.25 g. cellulose, wt., g.[b]	Cuprammonium viscosity, 25°, c : 0.1, time of flow in sec. Soln.	Solvent	D. P. by viscosity
270	7.93	4.41	203.1	183.8	260
310	5.70	4.18	201.0	183.8	233
350	7.71	4.12	201.9	184.9	229
390	6.84	4.13	200.5	185.2	206
430	6.54	4.05	199.7	185.2	196
470	6.37	4.09	199.0	185.2	187
510	5.47	3.63[c]	197.7	184.9	174

[a] See footnote *a*, Table I. [b] Calculated on vacuum-dried (63°) and sodium chloride free basis. [c] Part of product lost mechanically during washing operations.

Ash and Sulfur Analyses.—The ash content of the mercaptalated and non-mercaptalated hydrolyzed celluloses was determined by ashing 0.3- to 0.4-g. samples with 2 cc. of concentrated sulfuric acid in platinum crucibles. The results were calculated in terms of sodium chloride and are recorded in Tables II and III.

The sulfur analyses were performed by the Parr bomb method in the manner described in the previous publications.[3] In the present work, somewhat larger samples were employed for the sulfur determinations, however. Two samples of approximately 0.5 g. each, on an ash free, moisture free basis, were fused separately and then dissolved in the same solution for precipitation of the barium sulfate.

From the sulfur analyses, the degree of polymerization in glucose units was calculated from the approximation

$$\text{D. P.} = \frac{100 \times 2\text{S}}{\%\text{S} \times \text{C}_6\text{H}_{10}\text{O}_5} = \frac{40}{\%\text{S}}$$

The sulfur content of the various mercaptalated products is recorded in Table II, and the degrees of polymerization calculated from these data, in Table I.

Cuprammonium Viscosities.—The viscosities of the mercaptalated and non-mercaptalated hydrolyzed celluloses were observed in cuprammonium solution[6] at 25 ± 0.03° as described previously.[3] In all instances, a concentration of 0.1% was employed. The constants of the Ostwald type viscometer used were given in the former publications.[3]

From the viscosity measurements, the degree of polymerization in glucose units was calculated by the formula of Kraemer and Lansing.[4] The results are tabulated in Tables I, II, and III.

In order to determine the effect of marked non-homogeneity on the degree of polymerization (D. P.) as determined by cuprammonium viscosity, the following experiments were performed. A mixture consisting of 49.1% of a hydrolyzed cellulose product of observed D. P. 266 and 50.9% of observed D. P. 181 gave an observed D. P. of 226 (calcd. by weight average, 223; calcd. from theoretical sulfur content, 215). A mixture consisting of 40.8% of the hydrolyzed cellulose product of observed D. P. 266 and 59.2% anhydrous glucose gave an observed D. P. of 108 (calcd. by weight average, 109).

Copper Numbers.—The copper numbers of the mercaptalated and non-mercaptalated products were determined by the Hägglund–Bertrand[7] method. Samples of 0.3 to 0.5 g., on an ash free, moisture free basis, were employed. The results are recorded in Table IV.

The copper number of the stock cotton linters, used as starting material, was also determined, in duplicate. A copper number of approximately 0.2 was observed for the original linters.

Table IV

Copper Number[a] (Hägglund–Bertrand) of Mercaptalated and Non-mercaptalated Hydrolyzed Celluloses

Time of hydrolysis, min.[b]	Mercaptalated products, copper no.[c]	Non-mercaptalated products, copper no.[c]
0		0.2[d]
270	0.90	5.26
310	1.03	5.96
350	0.49	6.75
390	1.27	7.64
430	0.58	7.89
470	.59	7.59
510	.50	8.12

[a] Copper no. is grams of copper reduced from cupric to cuprous state by 100 g. of sample. [b] See footnote *a*, Table I. [c] Calculated to a moisture free and sodium chloride free basis. [d] Original linters.

The authors are indebted to E. I. du Pont de Nemours and Company, Inc., for the fellowship grant which made this research possible.

Summary

1. High viscosity cotton linters have been hydrolyzed with fuming hydrochloric acid at 0° in the presence of an excess of ethyl mercaptan. The resulting mixtures of mercaptalated hydrolyzed celluloses were isolated at various time

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(6) Prepared according to the standards of the Cellulose Division of the American Chemical Society.

(7) E. Hägglund, *Cellulosechemie*, **11**, 1 (1930).

intervals during the first eight and one-half hours of the hydrolysis.

2. Corresponding non-mercaptalated hydrolyzed celluloses were prepared under exactly similar conditions, except that the ethyl mercaptan was omitted.

3. Sulfur analytical data indicated that the average degrees of polymerization of the mercaptalated products varied from 190 glucose units after 270 minutes to approximately 100 glucose units after 510 minutes.

4. The degrees of polymerization calculated, according to the formula of Kraemer and Lansing, from the cuprammonium viscosity data for the corresponding non-mercaptalated hydrolyzed celluloses were consistently higher than those calculated from the sulfur analytical data, and varied from 260 glucose units after 270 minutes to 174 glucose units after 510 minutes.

5. The mercaptalated hydrolyzed celluloses showed low but definite copper numbers, varying from 0.5 to 1.3. The non-mercaptalated celluloses had copper numbers increasing in value with increasing time of hydrolysis, and ranging from 5.3 to 8.1.

COLUMBUS, OHIO RECEIVED OCTOBER 8, 1938

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CALIFORNIA FRUIT GROWERS EXCHANGE]

The Bitter Constituents of Navel and Valencia Oranges

BY RALPH H. HIGBY

The production of oranges in California is largely of two varieties, the Valencia, a seeded summer orange, and the Washington Navel, a seedless winter ripening variety. The Valencia and Navel are equally good for general use but the juice from this latter variety is not used extensively for canning or for the manufacture of other juice products because of the bitter taste and astringency which develops in the juice when it is allowed to stand exposed to air, or when it is pasteurized. The degree of bitterness is largely dependent upon the maturity of the fruit, most pronounced in early season, but usually disappearing entirely with warm weather in March and April. Bitterness is found also in the juice of unripe Valencia oranges, but never in fruit of this variety which has reached commercial maturity.

Although the presence of a bitter constituent in the edible portion of the Navel orange has long been recognized, no record of its isolation or identification has appeared in the literature. Naringin, the bitter glucoside of grapefruit has long been known, it is commercially available and its properties and structure are fairly well established.

The bitter substances of citrus seeds have also been investigated rather extensively. As early as 1841, Bernay[1] isolated a strongly bitter substance from the seeds of several varieties of citrus (*C. Aurantium Risso, C. Limonum Risso,* and *C. Bigardia Loisl.*) which he named limonin and erroneously thought to be an alkaloid. Since that time, various other workers, C. Schmidt,[2] Paternò and Oglialoro,[3] and Peters and Frerich,[4] have prepared this substance and made some study of its properties. In a recent publication, Koller and Czerny[5] have reported the results of a rather comprehensive investigation of limonin, from orange seeds, and have announced the isolation of a second bitter substance, from the same source, which they have named isolimonin. Shortly thereafter Feist and Schulte[6] separated what was thought to be a third bitter substance from lemon seeds, calling it citrolimonin. Similarity in equivalent weight and specific optical rotation have led Koller and Czerny[7] to believe that limonin and citrolimonin are identical despite a considerable discrepancy in the reported melting point.

As one part of a research program directed toward the commercial utilization of Navel orange juice, a study has been made of the bitter constituents of the orange, particularly those contained in the edible portion. Bitter crystalline substances have been extracted from the pulp of the Navel orange, and from both pulp and seeds of the Valencia orange. These substances have

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(1) Bernay, *Ann.*, **40**, 317 (1841).

(2) C. Schmidt, *ibid.*, **51**, 388 (1844).

(3) Paternò and Oglialoro, *Ber.*, **12**, 685 (1879).

(4) Peters and Frerich, *Arch. Pharm.*, **240**, 661 (1902).

(5) C. Koller and H. Czerny, *Monatsh.*, **67**, 248–268 (1936).

(6) K. Feist and H. Schulte, *Ber.*, **69**, 1322 (1936).

(7) C. Koller and H. Czerny, *Monatsh.*, **70**, 26–29 (1937).

been purified and many of their properties determined.

Experimental

Isolation and Properties of the Bitter Principle of the Navel Orange.—By shaking out portions of bitter Navel orange juice with relatively immiscible solvents it was found that the bitter constituent could be extracted in benzene, toluene, butyl or amyl alcohol, butyl or isopropyl acetate or chloroform. It was not extracted by petroleum ether, gasoline or limonene. In most cases the carotenoid pigment was extracted with the bitter. Since petroleum ether readily dissolves the pigment, extraction in benzene, and treatment with petroleum ether offered a suitable means of separation.

About 22 kg. of immature Washington Navel oranges, picked November 1st, were peeled to remove the flavedo, and the peeled fruit ground in a food chopper. The mixture of albedo, pulp and juice was covered with thiophene-free benzene, stirred thoroughly and allowed to stand for sixteen hours at room temperature. The benzene and juice were separated from the pulp by pressing, and the benzene separated from the juice by decantation. The comparatively dry pulp was reëxtracted with benzene, the benzene fractions combined, washed with water to remove acid, and filtered. After concentration to a volume of about 500 ml., the bitter substance was precipitated by the addition of three volumes of petroleum ether. The amorphous precipitate was filtered off, dissolved in a mixture of equal parts of alcohol and benzene, evaporated to small volume, and allowed to crystallize. The crystals obtained were rather large colorless needles.

Several methods of purification were used.

1. Solution in acetone and precipitation by dilution with water produced shining square plates, melting at 240–242°[8] with evolution of gas.
2. Solution in dilute alcoholic alkali and precipitation by acidification with dilute hydrochloric acid produced colorless needles, m. p. 259–261° with decomposition.
3. Solution in hot alcohol and recrystallization by partial evaporation and cooling produced shining rhombic plates, m. p. 262–264° with decomposition.

The final purification of the bulk of the material was by successive application of all three methods in the order named. Variations in the melting point with method of crystallization may be due to the presence of water of crystallization, although this is not indicated by drying the material in air for sixteen hours at 105°.

The crystals resulting from this treatment were almost completely insoluble in water, slightly soluble in alcohol and benzene, moderately soluble in chloroform and easily soluble in acetone. The taste of these crystals is not bitter due to insolubility, but when dissolved in a little alcohol and diluted with water, the solution is approximately 75% as bitter as a similar solution of quinine sulfate.

Tests on the pure substance were negative for nitrogen, halogen, sulfur, and for phenol, aldehyde and ketone groups. A negative Molisch test showed that it was not a glucoside. It reduced Fehling's solution with boiling, and formed a yellow osazone, m. p. 221–225°, indicating carbonyl groups. A negative Zeisel test showed no alkoxyl groups, and failure to brominate indicated a probable absence of aliphatic double bonds. In neutral alcohol the bitter substance was non-acidic, and not titrable with a 0.1 N sodium hydroxide in the cold. Saponification with an excess of alkali in alcoholic solution gave a typical lactone titration.

The saponification values were obtained by dissolving the substance in 25 ml. of neutral alcohol, adding 10 ml. of 0.1004 N sodium hydroxide, refluxing on a hot-plate for two hours, and then titrating the excess alkali. The refluxing was then repeated with 5 ml. additional alkali to be sure the reaction was complete. A blank determination was run in parallel. Molecular weight was calculated as two equivalents. The molecular weight was also determined from depression of the melting point, using the method of Rast, as modified by Smith and Young.[9] Optical rotation of the pure compound was measured in a 200-mm. tube containing 0.2 g. of substance made up to 25 ml. with anhydrous acetone.

Anal. Calcd. for $C_{26}H_{30}O_8$: C, 66.35; H, 6.43; O, 27.22; mol. wt., 470. Found: C, 66.62; H, 6.24; O (by diff.), 27.14; equiv. wt. (by NaOH titration), 226, 227; mol. wt. (f. p. in camphor), 467, 477. *Optical rotation:* 0.2 g. in 25 ml. of acetone in 200 mm. tube, rotation −1.784°, giving specific rotation at 22° as −111.5°. Koller and Czerny report the following values for isolimonin from orange seeds—calcd. for $C_{23}H_{28}O_7$: C, 66.31; H, 6.78; mol. wt., 416. Found: C, 65.92, 66.25; H, 6.87, 6.83. The melting point was 264° in an evacuated tube.

Lacking further information, it is impossible to state definitely that our substance is identical with the isolimonin of Koller and Czerny, but the similarity of melting point makes this strongly probable. Our own data indicate that the substance is isomeric with limonin, having the same molecular weight and empirical formula. A higher carbon content is shown than that reported by them, corresponding with the formula $C_{26}H_{30}O_8$ which Feist and Schulte have suggested for citrolimonin. The compound contains two lactone groups.

Location of the Bitter Constituent in the Fruit.—From the standpoint of commercial utilization, the location of the bitter principle in the fruit is of considerable importance. To determine this, a dissection was made of moderately green Navel oranges. Three types of tissue were carefully prepared. These were: (1) the albedo, free from flavedo, and the major veins, which lie next to the section covering; (2) center fibrovascular bundle and white material of the same nature surrounding the Navel, free from section covering; (3) section covering free from albedo.

These portions were extracted with acetone, most of the acetone boiled off, and the residue diluted with water. Slight dilution brought down a copious precipitation of hesperidin, which was filtered off, before more water was added for tasting. All three extractions were extremely bitter. It appears that the bitter principle occurs in the albedo, in the center bundle and in the veins of the carpellary membrane.

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[8] All of the melting point determinations reported here were made in open tubes, using a 360° thermometer, calibrated for 70-mm. immersion, which had been checked and found correct at 285°.

[9] J. H. C. Smith and W. G. Young, *J. Biol. Chem.*, **75**, 289–298 (1927).

Since the juice from Navel oranges becomes bitter only after rupture of the cell structure, and then only after standing or heating, the existence of the bitter-forming substance in the juice itself is improbable. Tests were made in which the juice was extracted by burring, then screened immediately through a 70-mesh screen to remove broken cell tissue, and heated to 70° for fifteen minutes to develop the bitterness. Under these conditions the screened juice from immature fruit became slightly bitter, while samples containing pulp were intensely bitter. Apparently the momentary contact with the broken cell tissue was sufficient to extract some of the bitter-forming substance into the screened juice.

Since the juice was not bitter when first extracted, it is apparent that an easily water-soluble non-bitter parent substance must exist in the comparatively neutral albedo and section covering, which upon contact with the juice is extracted, and in this acid medium is then slowly converted to the intensely bitter lactone.

The acetone extraction of albedo from completely mature Navel oranges gave an extremely heavy yield of hesperidin, but no bitter substance. Hence, disappearance of the bitter substances in the fruit can be determined by acetone extraction of these portions. Until the pulp and albedo become free from bitterness, the immediate separation of pulp from the extracted juice is of primary importance in the production of non-bitter Navel juice.

Acid Hydrolysis of Navel Isolimonin.—One gram of the pure Navel isolimonin was dissolved in 50 ml. of acetone, 10 ml. of 6 *N* hydrochloric acid added and refluxed on the steam-bath for six hours. Lead carbonate was added to neutralize the acid, and the resulting precipitate filtered off. The acetone filtrate was evaporated to small volume, diluted with water and again heated. A crystalline precipitate came down, leaving an opalescent solution. The crystals were filtered off, and the filtrate allowed to stand. Overnight a white amorphous substance precipitated which was filtered off. Further evaporation of the filtrate and cooling gave nothing but a small additional quantity of the amorphous material.

This amorphous substance was purified by solution in benzene, and precipitation with petroleum ether, and several reprecipitations from hot water. From petroleum ether it separated in waxy lumps, and from ethyl ether by evaporation, it came out as a shining brittle brownish glass. This substance was readily soluble in alcohol and benzene, and moderately soluble in hot water, very slightly soluble in cold. From hot water it separated out upon cooling as cream colored, highly refractive globules, which, under the microscope, gave the water suspension the appearance of an oil in water emulsion. Water solutions were intensely bitter. It was distinctly more acidic than the other bitter substances, being partially titrable with 0.1 *N* sodium hydroxide in the cold. The substance recovered from water, after drying for two days at 45°, sintered with gas evolution at 139–140° to form a brownish wax, which melted at 175–177°. Titration gave an equivalent weight of 240. This figure and the melting point correspond exactly with those of hexahydrolimoninic acid, as reported by Koller and Czerny, who obtained this substance by the hydrogenation of limonin. The substance was found to be optically active, showing a specific rotation of −70° in acetone.

The crystalline substance was purified in the same manner as the Navel isolimonin. From hot alcohol it separated in colorless shining hexagonal leaflets, which melted at 292° with decomposition. From the appearance, crystalline structure, and high melting point, it was thought probable that this substance was limonin, as described by Koller and Czerny. Further identification is made in the following portion dealing with the bitter constituents of the Valencia orange.

Isolation of Bitter Substances from Valencia Oranges.—Approximately 11 kg. of green Valencia oranges were peeled to remove the flavedo, which was discarded. The fruit was then halved and burred to remove the juice, which was immediately screened to take out the pulp. Seeds were removed from the pulp by coarse screening, after which the pulp was mixed with the white albedo and ground in a food chopper. The seeds were similarly ground to an oily paste. Seeds, juice and pulp were then separately extracted with benzene, the extracts evaporated to small volume, and precipitated with petroleum ether. A good yield of an apparently amorphous white bitter substance was obtained from the pulp, a moderate yield from the seeds, but none from the juice, which yielded only a non-bitter brownish wax.

The bitter precipitates from the pulp, and from the seeds, were purified separately by the methods which were used for the purification of the Navel isolimonin. Both fractions crystallized from hot alcohol in thin hexagonal leaflets, m. p. 290° with decomposition. It was evident both from appearance and from the melting points that these two fractions were identical, and that they were also identical with the crystalline substance which had been obtained by the acid treatment of the Navel isolimonin. A mixed melting point of 291–292° for these three fractions establishes their identity beyond question. The solubility was similar to that of isolimonin, except for somewhat greater solubility in benzene. Water-alcohol solutions were intensely bitter.

Like isolimonin this substance formed water-soluble sodium salts with alcoholic sodium hydroxide, and was precipitated in its original form when the solution was acidified. Analysis of the three fractions separately showed equivalent weights by saponification of 229, 230, and 231. Determined molecular weights were 445, 449, and 468, respectively. Two lactone groups are indicated.

Limonin, as described by Koller and Czerny, crystallizes in thin shining rhombohedral leaflets, melting at 280° with decomposition. Titration gives an equivalent weight of 235, and two lactone groups are indicated. Feist and Schulte report that citrolimonin crystallizes in thin shining leaflets, m. p. 304°. From the combustion analysis the formula was calculated as $C_{26}H_{30}O_8$ (molecular weight 470), and by titration two lactone groups were indicated. It seems highly probable, as admitted by Koller and Czerny, that these investigators are dealing with the same substance.

The existence of the substance isolated by us as the major bitter constituent of the orange seed, is good evidence that it is actually limonin. This is confirmed by the crystalline form, by the melting point, which falls midway

TABLE I

COMPARATIVE ANALYTICAL DATA ON THE BITTER SUBSTANCES FROM VALENCIA AND NAVEL ORANGES

Properties	Isolimonin			Hexahydrolimoninic acid		Limonin				Citrolimonin
	Navel Crystallized from alcohol	Navel Crystallized from acetone and water	Reported by Koller and Czerny	From isolimonin by hydrolysis	Reported by Koller and Czerny	From isolimonin by hydrolysis	From Valencia pulp	From Valencia seeds	Reported by Koller and Czerny	Reported by Feist and Schulte
Crystalline form[a]	Rhombic plates	Square plates	Warty crystals	Light colored globular aggregates	Not described	Thin shining hexagonal leaflets	Thin shining hexagonal leaflets	Thin shining hexagonal leaflets	Thin shining leaflets	Shining plates from Me chloride
M. p. (corr.), °C.[c]	262–264 dec.	240–242 dec.	264 dec.	175–177	178 dec.	292 dec.	290 dec.	290 dec.	280 dec.	304
Specific rotation (22°) in acetone	−112°	−102°	....	−70°	....	−114°	−106°	−108°	−142.85°[b]	−135°[b]
Carbon, % (av.)	66.62	......	66.08	...	62.80	....	....	....	66.44	....
Hydrogen, % (av.)	6.24	......	6.85	...	8.03	....	....	....	6.58	....
Empirical formula (calculated)	$C_{26}H_{30}O_8$	......	$C_{23}H_{28}O_7$	...	$C_{23}H_{34}O_8$	....	....	....	$C_{23}H_{26}O_7$	$C_{26}H_{30}O_8$
Mol. wt. (calcd. from formula)	470	......	416	...	438	....	....	....	414	470
Equiv. wt. (from titration)	227	186	....	240	240	231	229	230	235	....
Mol. wt. (two equivalents)	454	372	....	480	480	462	458	460	470	....
Mol. wt. (Rast)	477	412	....	416	....	449	445	468	396	....
	467			407					447	
Taste	Very bitter	Very bitter	....	Very bitter	....	Very bitter	Very bitter	Very bitter	....	....

[a] Crystallized from 95% alcohol unless otherwise specified. [b] Determined in methylene chloride. [c] It is assumed that m. p. data taken from the literature are corrected values.

between the temperatures reported by the above workers, and by its solubility and chemical properties.

Formation of Non-bitter Salts.—By the saponification procedure which was used for the determination of equivalent weight, all the bitter substances formed easily water-soluble non-bitter sodium salts. Acidification with dilute hydrochloric acid reprecipitated the original substance. Further experimentation showed that Navel isolimonin was capable of forming similar salts with calcium, barium or magnesium hydroxide, calcium and barium chloride, and with triethanolamine. Because of scarcity of material, limonin and hexahydrolimoninic acid were tested only with sodium hydroxide.

To determine at what *p*H values the transition from the non-bitter salt to the bitter lactone took place, several series of samples were prepared containing 10% sugar, 1% citric acid, and 0.008% of the Navel isolimonin, which had been previously treated with sodium hydroxide to convert it to its tasteless form. Various amounts of sodium hydroxide were added to neutralize a portion of the acidity in each sample, producing a series of varying *p*H. These samples were heated for one hour on the steam-bath, cooled, tasted, and *p*H values determined. Bitterness developed in all samples having a *p*H value below 6.00. A similar series prepared from the bitter lactone instead of the salt showed that an excess of alkali was necessary to convert the lactone to the tasteless salt. Repetition of these tests using calcium salts instead of sodium gave similar results.

Discussion

The comparative analytical data obtained on the various bitter substances which have been prepared in this study are shown in Table I, together with the corresponding values reported by Koller and Czerny, and by Feist and Schulte for the similar bitter substances isolated by them.

A consideration of these values leaves little doubt that the Navel bitter constituent, which we have called isolimonin, is a true isomer of the citrolimonin described by the last-named workers. This is shown by apparent identity in equivalent weight, molecular weight and empirical formula. Koller and Czerny have not yet published sufficient data regarding the isolimonin obtained by them to make it entirely certain that these two substances are the same, but agreement in melting point makes it highly probable.

Navel isolimonin is precipitated in somewhat different form by dilution of an acetone solution with water. The crystals obtained in this way have a lower melting point and apparent molecular weight than those from hot alcohol, and are probably a hydrated form of the lactone. No tests have been made to determine whether this is actually the hydroxy acid or whether the differences in melting point and apparent molecular weight are merely due to the presence of water of crystallization.

From the analytical data it seems certain that the citrolimonin of Feist and Schulte is identical with the crystalline substance which we have prepared from Valencia orange seeds, from Valencia orange pulp, and by treatment of the Navel isolimonin with dilute hydrochloric acid. Since Koller and Czerny recently have acknowledged the likelihood that the limonin isolated by them is identical with citrolimonin, advancing as evidence the fact that by titration they obtained a molecular weight of 470, which corresponds with the formula $C_{26}H_{30}O_8$ as suggested by Feist and Schulte, it seems reasonable to assume that these substances are identical. The discrepancy in melting point can be attributed to difference in method, and perhaps to the degree of purity of the material used. Koller and Czerny performed all of their melting point determinations in evacuated tubes, Feist and Schulte used the micro-melting point apparatus of Kofler, while the writer used the regular open tube method. The variation in nomenclature by these investigators is unfortunate, tending to promote confusion. For this reason, it seems logical to eliminate the name "citrolimonin," referring to this compound as limonin, as originally proposed by Bernay.

From a comparison of the physical characteristics, the melting points, and equivalent weights, there can be little doubt that the apparently amorphous substance which was obtained by the acid treatment of isolimonin is identical with the hexahydrolimonic acid which Koller and Czerny prepared by the hydrogenation of limonin. Data obtained by them indicated that this substance was formed by the addition of six hydrogen atoms and one molecule of water to the limonin molecule to give an empirical formula of $C_{23}H_{34}O_8$ for the hexahydrolimoninic acid. Accepting their revised views regarding the formula for limonin ($C_{26}H_{30}O_8$) this addition would bring the empirical formula for hexahydrolimoninic acid to $C_{26}H_{38}O_9$. This is difficult to understand, since this substance also resulted from the treatment of isolimonin with hydrochloric acid.

The relationship between these three bitter substances is not clear. Although limonin has been known and subjected to investigation for almost a century, no structural formula for the substance has as yet been advanced. Recent workers agree that the substance contains two lactone groups, and Koller and Czerny point out a probable analogy of structure with columbin, and hence with the strophanthic and crotonic substances, but this has not been definitely established.

For isolimonin Koller and Czerny have suggested a formula $C_{23}H_{28}O_7$ containing two active hydroxyl groups, and differing from limonin only in degree of hydrogenation. The substance which we have designated as Navel isolimonin, with an identical melting point, corresponds more nearly with the formula for limonin, $C_{26}H_{30}O_8$, indicating that these substances differ only through some rearrangement in the molecule. Hexahydrolimoninic acid apparently results from the splitting of one of the lactone rings and the formation of a carboxyl group. The scope of our present project does not include further investigation of the structure and relationship of these bitter substances.

It has been shown that the bitter substances of the pulp and peel of the orange are either identical with or closely related to the previously isolated bitter constituents of the seeds. In the edible portion of the fruit these substances apparently occur in easily water-soluble, non-bitter form. Hydrolysis to the bitter lactone takes place slowly in the acid juice, or in water with heating.

The nature of the non-bitter parent substance has not been investigated. Hall[10] hypothesized that hesperidin occurred in the fruit as an easily hydrolyzed complex, containing in addition glucose, and a third substance. It seems possible that this substance may be isolimonin.

In the Valencia orange the bitter-forming constituent apparently exists in less soluble form than in the Navel, since the juice, even from immature fruit, is not prone to become bitter.

It is hoped that in the near future an investigation can be made regarding the nature of the non-bitter parent substance in both Navel and Valencia oranges, its probable function in the plant, and the end-products of its natural enzymic hydrolysis.

Acknowledgment.—The writer wishes to express his appreciation to his co-workers, Dr. E. F. Bryant and Mr. R. L. Logg, for their aid in the analysis and isolation of these bitter substances.

Summary

The bitter principle of the Navel orange has been isolated and identified as isolimonin, a

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[10] J. A. Hall, THIS JOURNAL, **47**, 1191 (1925).

previously reported constituent of orange seeds. This substance occurs in the albedo, the center fibrovascular bundle, and in the section covering of the fruit, in non-bitter water-soluble form. When these tissues are ruptured it is extracted into the juice, where it is slowly converted to the intensely bitter lactone form. It is shown that this substance has a higher molecular weight than that previously reported, corresponding to the formula $C_{26}H_{30}O_8$. It is apparently an isomer of limonin, and of citrolimonin. The probable identity of these last named substances is discussed.

Limonin, which has heretofore only been reported in the seeds of citrus fruit has been isolated also from the pulp of the Valencia orange.

Both limonin and isolimonin form non-bitter water-soluble salts with alkali and alkaline earth metals, from which they are precipitated unchanged upon acidification.

Treatment of isolimonin with dilute hydrochloric acid in acetone solution gave fractions of limonin, and of hexahydrolimoninic acid. This latter substance has been obtained previously only by the catalytic hydrogenation of limonin. It appears that limonin results from a molecular rearrangement in the isolimonin, and that hexahydrolimoninic acid is produced by the splitting of a lactone ring, to form a carboxyl group.

ONTARIO, CALIF. RECEIVED OCTOBER 4, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF COLUMBIA UNIVERSITY]

The Action of Chlorine Water on Some β-Amyloses

BY HARRY H. FLETCHER[1] AND T. CLINTON TAYLOR[2]

Introduction

Industrial technologists have known for over ten years that if chlorine water is mixed with a starch dispersion, the viscosity of the dispersion drops after ten to twenty minutes of treatment.[3] The appearance of this chlorine-treated starch, the optical rotation of its dispersion, and the blue color with iodine remain unchanged. Nevertheless, the viscosity drop indicates that the chlorine water probably has begun to break the starch particles into smaller ones,[4,5] although this breakdown is still in too early a stage to be detected by other means. With two exceptions, the chemical and physical nature of the action of chlorine water on starch has not been investigated. Craik[6] found that the optical rotation of a potato starch dispersion gradually increased during several days' contact with hypochlorous acid at room temperature. However, the optical rotation is not so sensitive to slight changes in the structure of the starch as is the viscosity. Recently Rassow and Lobenstein measured the viscosity decrease during the reaction between potato starch and an alkaline hypochlorite solution.[7] They noticed also that the dispersion became more acidic during the course of the reaction. This they attributed to oxidation of aldehyde groups to carboxylic acids with concurrent reduction of the hypochlorous acid to hydrochloric acid.

Rassow and Lobenstein determined the reducing power of their starch dispersions after alkaline treatment only. The work described herein extends it into acid regions. As will be shown later, the results obtained in solutions of *p*H less than 7 were, so far as we are aware, entirely new and unexpected.

Outline of Procedure

Rassow and Lobenstein used Fehling's solution to measure the reducing power of their dispersions. As this reagent is not very satisfactory for rapid analysis,[8] the recently standardized alkali-labile procedure was used in these new determinations.[9] When the hot alkaline digestion is omitted, the iodine consumption of the carbohydrate, determined and calculated in the usual manner, will be

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[2] The experimental work described herein was completed just before the death of Prof. Taylor in April, 1936. As the present author is no longer engaged in research on starch or related materials, he relinquishes this field with the hope that others will be interested in continuing this investigation.

[3] (a) Watson and Kent-Jones, U. S. Patent 1,519,014 (1924); (b) Neumann and Kalning, *Landw. Jahrb.*, **61**, 305 (1925); (c) Neumann and Kalmius, *Rass. intern. Agr.*, 444 (1926); (d) Staudt, Can. Patent 274,290 (1927); (e) Frey, U. S. Patent 1,897,251 (1933).

[4] Staudinger and Schweitzer, *Ber.*, **63B**, 2323 (1930).

[5] Hatschek, "Viscosity of Liquids," D. Van Nostrand Co., Inc., New York, 1928, pp. 196–201.

[6] Craik, *J. Soc. Chem. Ind.*, **43**, 171 (1924).

[7] Rassow and Lobenstein, *Kolloid Beihefte*, **33**, 179 (1931).

[8] Amick, *J. Phys. Chem.*, **31**, 1441 (1927).

[9] Taylor, Fletcher and Adams, *Ind. Eng. Chem., Anal. Ed.*, **7**, 321 (1935).

expressed in this paper as the "initial reducing value."

Three requirements must be met if the first stages of the reaction between β-amylose (used instead of starch because of its greater homogeneity) and any desired reagent are to be followed quantitatively. (1) The reagent must act slowly; chlorine water and alkaline hypochlorite were used at 30°. (2) A simple process for stopping the reaction quickly and completely must usually be devised; such a process will be given later in this paper. (3) Methods of magnifying and estimating slight physical or chemical changes in the carbohydrate must be employed; viscosity determinations were used for following physical changes, and the estimation of the "initial reducing value" and alkali-labile value was used for magnifying chemical changes in reducing power.

Outline of Experimental Results

By these means it was found that the reducing power and viscosity changed in two distinct ways depending on the *p*H of the halogen solution.

(1) In alkaline solutions (*p*H 10 or above) the reducing power of the β-amylose decreased gradually from that of the untreated β-amylose to substantially zero after several days' contact with the hypochlorite. The viscosity was not affected.

(2) In a neutral or acid solution the reducing power and viscosity changed in an entirely different and hitherto unsuspected way. During the first few minutes after mixing any one of four β-amylose dispersions with chlorine water almost nothing appeared to happen. The quiescent period lasted for three or four hours unless a phosphate buffer was added in order to keep the *p*H near 7. In the presence of the buffer this period was shortened to two minutes. This inactive phase of the reaction was terminated in every case by a sudden, large change in the reducing power and viscosity. The reducing power, measured both as "initial reducing value" and as alkali-labile value, rose sharply. Simultaneously, the viscosity dropped markedly. Hatschek[5] has pointed out that the viscosity of highly hydrated colloidal materials, such as starch or β-amylose,[10] varies directly with particle size. Consequently, the close inverse relationship found between reducing power and viscosity indicates strongly that the sensitivity of β-amylose to chemical attack is at least partly dependent on its particle size. This point will be developed further.

After this sudden reaction was complete, the reducing power and viscosity of the unbuffered dispersions remained relatively constant throughout thirty days' further contact with chlorine water. However, the reducing power of the buffered dispersions dropped gradually toward zero just as it did in the alkaline solutions mentioned above. The viscosity likewise was unaffected.

Theory of Reaction Mechanism

These changes in reducing power and viscosity, both in alkaline and in acid solution, can most easily be understood if we accept the micellar structure of starch proposed by Meyer and Mark[11] and elaborated by Taylor and Keresztesy.[12,13]

By using this concept of the starch micelle the action of chlorine water on β-amylose in both alkaline and acid solutions can be accounted for as the effect of one or more of three reactions—oxidation, disassociation and degradation.

In alkaline medium the major reaction is the oxidation of aldehyde groups to carboxylic groups. Hatschek's correlation[5] between viscosity and particle size, mentioned previously, leads us to the conclusion that there has been little disassociation of the micelle. Otherwise the viscosity would not have been found to remain constant throughout the reaction.

In a neutral or slightly acid medium the reaction possibly begins in the same manner as in an alkaline one: *viz.*, oxidation of aldehyde groups. However, it seems necessary to postulate that the chlorine water acts in a second, and more important, manner on the β-amylose micelle. This reagent seems to catalyze the working of the water molecules between the glucoside chains, thereby swelling the micelle and putting it under strain. As long as this strain is less than that necessary to break the coördinate linkages, the micelle will remain intact. Further swelling causes the micelle to be ruptured abruptly into its constituent chains, uncovering the shielded aldehyde groups. This disassociation should, and does, cause the re-

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[10] Kolkmeijer and Favejee, *Z. Krist.*, **88**, 226 (1934).

[11] Meyer and Mark, "Der Aufbau der hochpolymeren organischen Naturstoffe," Akademische Verlag., Leipzig, 1930.

[12] Taylor and Keresztesy, *Ind. Eng. Chem.*, **28**, 502 (1936).

[13] Throughout this paper the terms "disassociation" and "hydrolytic scission" will be used as they are by Taylor and Keresztesy. The term "degradation" will be used to refer to a shortening of the glucoside chains when we do not wish to distinguish between hydrolytic carbon–oxygen scission and carbon–carbon scission of a type similar to that proposed by Evans [*Chem. Rev.*, **6**, 28 (1929)] for the action of dilute alkali on glucose.

ducing power to rise and the viscosity to drop.

Before disassociation the micelle is probably not subject to much degradation because the most sensitive portions of the chains, the aldehyde groups and the glucoside ether linkages, are shielded from attack. However, after the sudden separation of the particle into the individual chains, degradation should proceed much more easily. The extent of degradation can be found approximately by subjecting the dispersion, after treatment with chlorine water, to the standard procedures for hydrolyzing the carbohydrate to glucose[14] and estimating it as such.[15] Although it was found that the "initial reducing value" has no simple stoichiometric relation to the β-amylose, it can be used to estimate glucose quantitatively by means of the equation

$$C_5H_{11}O_5CHO + I_2 + 3NaOH \longrightarrow C_5H_{11}O_5COONa + 2NaI + 2H_2O$$

The calculated "initial reducing value" for the glucose obtained from $(C_6H_{10}O_5)_x$ is 163.3. If we assume with Hirst[16] that the average chain contains 25 glucose residues, and that every aldehyde group is oxidized to carboxylic acid before carrying out the hydrolysis to glucose, the "initial reducing value" would drop approximately 4% to 156.8. Any experimentally obtained value much lower than this figure can be explained only by assuming either that the chain length is less than that given by Hirst or that degradation has occurred. The former assumption is considered to be untenable because Hirst's exhaustive methylation experiments prove rather conclusively that 25 is a *minimal* value which may possibly be considerably less than the true one.

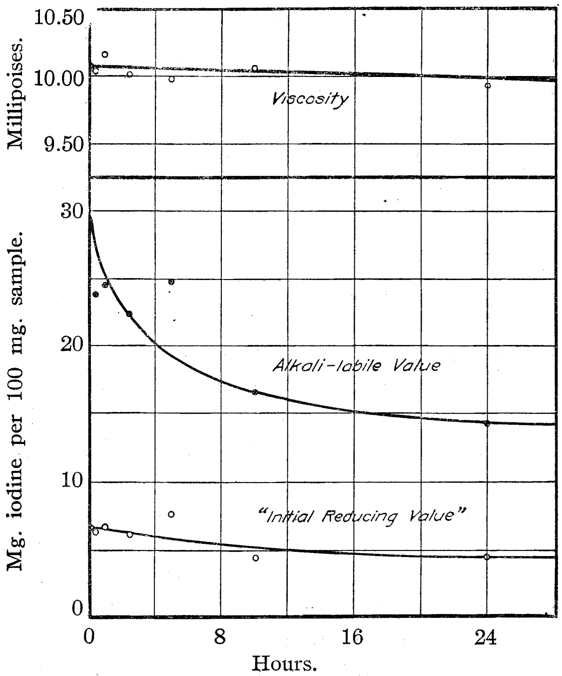

Fig. 1.—Action of alkaline hypochlorite solution on corn β-amylose ground one week.

Action of Alkaline Hypochlorite

A more detailed examination of our experimental results will now be made. In order to obtain these results it became necessary to devise a simple and rapid method of stopping all reaction at any desired time after mixing a water-dispersed β-amylose with a standardized sodium hypochlorite solution at 30°. Our method consisted in acidifying the solution with hydrochloric acid, followed by removal of most of the liberated chlorine as Cl_2 with nitrogen. The last traces of hypochlorous acid were removed from solution by reaction with ethylene, the excess of which was in its turn removed by a second addition of hydrochloric acid and nitrogen. After neutralization and dilution to standard volume the viscosity, "initial reducing value" and alkali-labile value were measured.[17]

The manner in which these three properties changed during the reaction between a sodium hypochlorite solution of *p*H greater than 13 and a dispersion of corn β-amylose ground for one week is easily seen from Fig. 1. Over thirty days' time the "initial reducing value" and the alkali-labile value dropped gradually and smoothly toward zero, while the viscosity remained constant within the limits of precision of the experiment.[18]

It should be observed that the alkali-labile value always was greater than the "initial reducing value" of the same solution. The importance of this observation will be apparent later.

On hydrolyzing[14] and estimating as glucose[15]

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[14] (a) Schulz and Steinhoff, *Z. Spiritusind.*, **56**, 63 (1933); (b) Taylor and Salzmann, THIS JOURNAL, **55**, 264 (1933).

[15] Klein and Acree, *Bur. Standards J. Research*, **5**, 1063 (1930).

[16] Hirst, Plant and Wilkinson, *J. Chem. Soc.*, 2375 (1932).

[17] So far as we are aware, the reaction between hypochlorous acid and ethylene has never before been used in quantitative analysis. The function of each reagent in this process will be given under "Experimental Details."

[18] The variations in the viscosity were caused by the differences in the amount of hydrochloric acid used to stop the hypochlorite reaction. As it seemed imperative that the freed chlorine and hypochlorous acid be removed from solution as rapidly as possible in order to eliminate the possibility of their reacting with the β-amylose, the second addition of hydrochloric acid—5 cc. concd. acid—was made by graduated cylinder with no attempt at high precision. The variations of the "initial reducing value" and alkali-labile value from the smoothed curves are of the expected order of magnitude.[9]

the material remaining after reaction for thirty days at room temperature between β-amylose and hypochlorite, the "initial reducing value" was found to be 90.2. This is only 55% of that calculated for hydrolyzed $(C_6H_{10}O_5)_x$ and only 58% of that calculated for hydrolyzed $C_6H_{11}O_6\cdot(C_6H_{10}O_5)_{23}\cdot C_5H_{10}O_4\cdot COOH$, the acid we have assumed would be formed from Hirst's glucoside chain containing 25 glucose residues.[16]

Another sodium hypochlorite solution of *p*H 10 instead of *p*H 13 was mixed with aliquots of the same corn β-amylose dispersion and tested in the same way in order to find out whether this oxidation–degradation reaction required a strongly alkaline medium. The "initial reducing value," alkali-labile value and viscosity of these aliquots changed in a manner almost identical with those shown in Fig. 1, and the hydrolytic treatment indicated that degradation took place to about the same extent.

Action of Chlorine Water on β-Amyloses

However, as indicated previously, when the reaction between hypochlorite and β-amylose was carried out in a medium more acid than *p*H 7 the viscosity and reducing power changed in a very different manner. In order to study these changes in slightly acid solutions the experimental procedure was modified by bubbling chlorine gas through the dispersions for a few minutes each day until the reaction was to be quenched. The rest of the procedure was identical with that described above.

The marked discontinuity of the viscosity, "initial reducing value" and alkali-labile value of a dispersion of corn β-amylose (ground for two weeks) is strikingly shown in Fig. 2. It will be observed that a high "initial reducing value" is always associated with a high alkali-labile value and a low viscosity, showing that there is a close correlation between reducing power and particle size. It is impossible to show in Fig. 2 the course of the reaction after the first seven hours' contact between chlorine water and carbohydrate. The viscosity and "initial reducing value" were found to remain constant within the limits of the precision of the measurement up to thirty days' reaction time, the final values being, respectively, 38.6 mg. of iodine per 100 mg. of sample and 8.97 millipoises. The alkali-labile value dropped gradually from its peak of 59.5 to a final value of 38.7.

As it might be thought that the absence of sodium ion during this reaction of β-amylose with chlorine water was responsible for the great differences between Figs. 1 and 2 this experiment in acid medium was repeated in the presence of the same amount of sodium ion, as sodium chloride, which was used in the solutions of *p*H 13. The viscosity and reducing power curves so obtained were similar to those of Fig. 2. The salt raised the viscosity of all the solutions to the same extent.

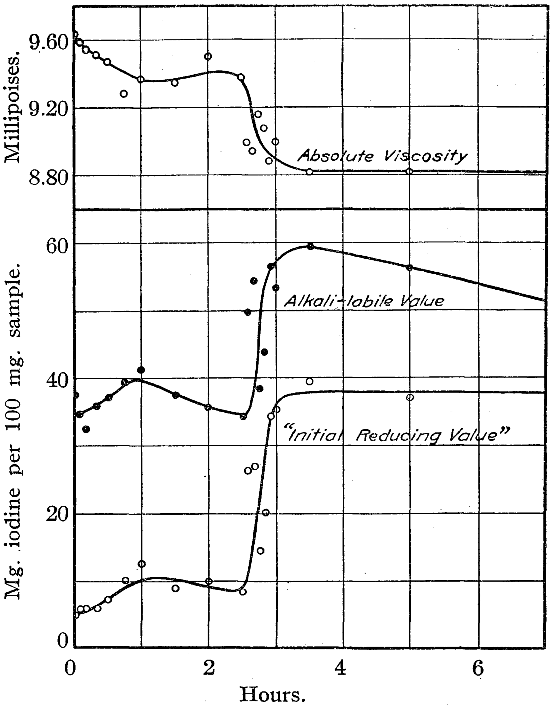

Fig. 2.—Action of chlorine water on corn β-amylose ground two weeks.

A dispersion of β-amylose from corn starch ground for one week behaved in a manner almost identical with that of the dispersion ground for two weeks except that the sudden change in magnitude of the viscosity and reducing power occurred one hour later—between two hundred and ten and two hundred and forty minutes after beginning to bubble chlorine into the dispersion. This agrees with the observation[12] that grinding of starch for a time longer than one week continues to break it down in some way not yet well understood.

Dispersions of β-amylose from tapioca and potato starches ground two weeks were also subjected to the action of chlorine water under the same conditions. The tapioca β-amylose behaved in the same manner as the corn β-amylose shown in Fig. 2. The potato β-amylose had a somewhat higher "initial reducing value" and alkali-labile value, and lower viscosity before treatment with chlorine water than the corn or tapioca. Furthermore, during the course of the reaction of chlorine water on potato β-amylose these three properties changed less abruptly and less in magnitude.

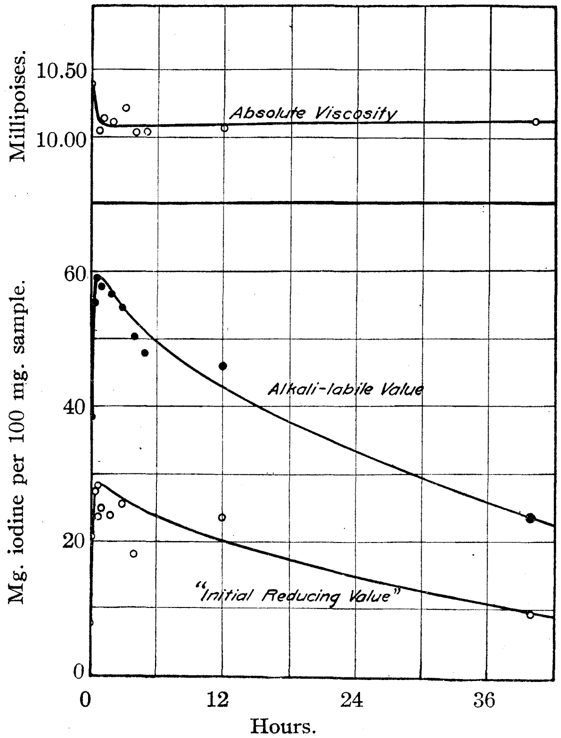

Fig. 3.—Action of chlorine water buffered by potassium phosphate on corn β-amylose ground one week.

As all four of the β-amylose dispersions mentioned above had considerable reducing power even after thirty days of contact with chlorine water—both the "initial reducing value" and alkali-labile value were between 30 and 40 in every case—it was thought probable that one or more of the products had stopped all reaction. Bunzel and Mathews[19] have shown that hydrogen ion has exactly this effect on the reaction between glucose and chlorine water. Therefore, a potassium phosphate buffer of *p*H 7 was mixed with a β-amylose dispersion from corn starch ground for one week. Table I shows to what extent the buffer held the *p*H constant. Solubility limitations forbade the use of more buffer.

TABLE I

*p*H OF β-AMYLOSE AND BUFFER SOLUTIONS AFTER MIXING WITH CHLORINE

Material	No chlorine	Chlorine for 1 hour	Chlorine for 5 hours	Chlorine for 40 hours
β-Amylose dispersion[a]	7.2	1.50	1.06	..
β-Amylose dispersion + buffer[b]	...	2.49	..	2.08

[a] From cornstarch ground for one week, 4.000% by weight. [b] Another 25.00-cc. aliquot of the same β-amylose to which had been added 4.36 g. of K_2HPO_4 and 1.22 g. of KH_2PO_4. A solution of the same quantities of these two salts in 25.00 cc. of distilled water had a *p*H of 6.92.

However, even this relatively minor change in *p*H between the buffered and unbuffered solutions of corn β-amylose was sufficient to accelerate the chlorine water reaction tremendously and to drive it practically to completion in so far as reducing power is a criterion.[20] A comparison of Figs. 3 and 2 indicates this difference in a striking manner. (The change of grinding time of the corn starch from two weeks to one is insignificant as regards the contrast between Figs. 2 and 3.) The "initial reducing value" and alkali-labile value continued to drop, although less rapidly because the hydrogen ion concentration was rising, during reaction periods longer than forty hours, the final point shown in Fig. 3. The viscosity remained almost constant. The three values after six hundred seventy-two hours of reaction time were, respectively, 3.0 and 9.7 mg. of iodine per 100 mg. sample and 9.95 millipoises. Treatment of a portion of this sample with hot hydrochloric acid did not change the reducing values, indicating that degradation had been so complete that all the chains had been broken into fragments of less than six carbons.

It is not possible to say whether this degradation is hydrolytic or not. However, we tend toward the view that it proceeds largely by scission of carbon–carbon bonds, perhaps by some mechanism related to the "enolization" breakdown of glucose in the presence of alkali as postulated by Evans.[21] We feel that the observation that all the reactions between glucose[19] or β-amylose and chlorine water are decreased in velocity by the presence of acid lends weight to this viewpoint. Further-

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(19) (a) Bunzel and Mathews, THIS JOURNAL, **31**, 464 (1909); (b) Bunzel, *J. Biol. Chem.*, **7**, 157 (1909).

(20) There is no indication that these changes in reaction rate and degree of conversion to material without reducing power are due *solely* to the action of the phosphate *as a buffer*. Phosphate *ion* greatly catalyzes the breakdown of glucose by chlorine water or hypochlorite to products containing less than six carbons at the expense of the formation of gluconic acid [Bleyer and Braun, *Biochem. Z.*, **180**, 105 (1927); **183**, 310 (1927); **199**, 186 (1928); Bernhauer and Schön, *ibid.*, **202**, 159 (1928)]. Apparently no one has heretofore considered the possibility of an analogous action of phosphate *ion* on starch or β-amylose.

(21) Evans, *Chem. Rev.*, **6**, 28 (1929).

more, Table II shows that hydrochloric acid had almost no effect on the "initial reducing value" and alkali-labile value of a dispersion of corn β-amylose ground for two weeks. This observation confirms that of Daish.[22]

TABLE II

ACTION OF HYDROCHLORIC ACID ON CORN β-AMYLOSE GROUND TWO WEEKS

(Reaction time 43 hours at room temperature)

Material	"Initial reducing value," mg. iodine/100 mg. sample	Alkali-labile value, mg. iodine/100 mg. sample
25.00 cc. 4.000% β-amylose	7.1	39.9
Same + 1.00 cc. 0.1 M HCl	6.0	37.8
Same + 1.00 cc. 1.0 M HCl	6.0	38.6
Same + 1.00 cc. 13 M HCl	5.7	37.3
Same + 5.00 cc. 13 M HCl	9.6	43.0

Action of Chlorine Water on Glucose

The conclusions already drawn concerning the mechanism of the reaction between β-amylose and chlorine water from the data presented above were deduced in part from a similar investigation of the reaction between glucose and chlorine water. It has been well established[23] that glucose is attacked in two distinct ways by chlorine or bromine water, dependent on the presence or absence of other substances. In the presence of a weakly alkaline buffer, such as barium carbonate, glucose is oxidized chiefly to gluconic acid without much carbon–carbon scission.[24] In the presence of a strong base or phosphate ion, and in the absence of any reagent other than the chlorine water itself, glucose is degraded completely into one- and two-carbon acids.[19,23]

From Fig. 4 it will be observed that glucose is converted gradually to products without reducing power, as indicated by the drop in the "initial reducing value" and alkali-labile value. The viscosity remained almost constant. Superficially these curves are similar to those of Fig. 1, but there is one fundamental difference. The "initial reducing value" of the glucose solutions is always *higher* than the corresponding alkali-labile value, whereas the "initial reducing value" of each β-amylose solution is always *lower* than the corresponding alkali-labile value. This agrees with previous work[14b] and indicates that the material present after treatment of β-amylose with alkaline hypochlorite or chlorine water cannot be glucose. Due to lack of space, Fig. 4 does not show the course of the reaction beyond the first seven hours with chlorine water. The "initial reducing value" and alkali-labile value continued to drop, although more slowly, because, as already mentioned, the rising concentration of hydrogen ion tends to stop all reaction. The viscosity showed no trend. The final values after thirty days of treatment were: "initial reducing value" 20.9 mg. iodine per 100 mg. sample, alkali-labile value 21.6, and viscosity 8.73 millipoises. The possibly fortuitous identity of the "initial reducing value" and the alkali-labile value suggests that there may be some close connection between the mechanism of the chlorine water reaction on glucose (or possibly β-amylose) and the mechanism of the alkali-labile digestion. This possibility was not investigated.

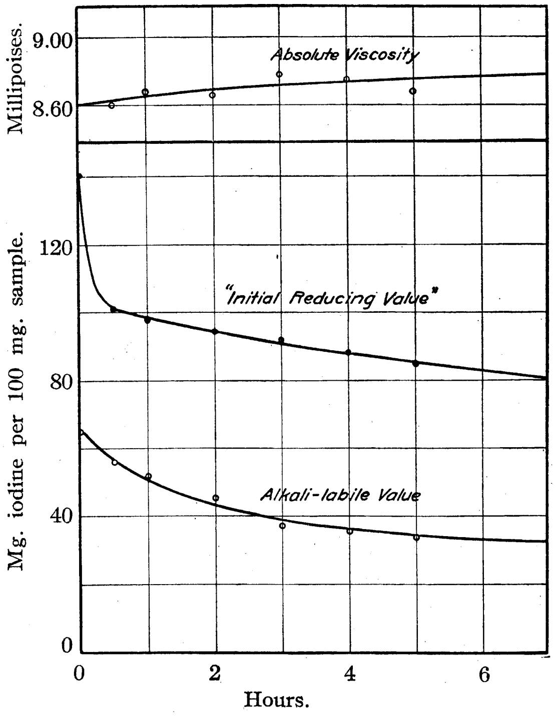

Fig. 4.—Action of chlorine water on glucose.

It was pointed out above that other workers have found that gluconic acid is not formed to any extent from glucose by chlorine water in the absence of other reagents. Table III substantiates this observation to the extent that it indicates that gluconic acid, if formed at all, is attacked in its turn. No attempt was made to follow this investigation further.

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(22) Daish, *J. Chem. Soc.*, **105**, 2053 (1914).

(23) (a) Bleyer and Braun, *Biochem. Z.*, **180**, 105 (1927); **183**, 310 (1927); **199**, 186 (1928); (b) Bernhauer and Schön, *ibid.*, **202**, 159 (1928).

(24) (a) French Patent 635,603 (1927); British Patent 289,280 (1927); British Patent 293,322 (1928); (b) Honig and Ruziczka, *Ber.* **63**, 1648 (1930); (c) Isbell and co-workers, *Bur. Standards J. Research*, **8**, 327, 614 (1932); **10**, 337 (1933).

TABLE III

ACTION OF CHLORINE WATER ON *d*-GLUCONIC ACID[a]

Treatment	"Initial reducing value" mg. iodine per 100 mg. sample	Alkali-labile value mg. iodine per 100 mg. sample
None	1.5	1.8
2.5 hours chlorine water at 30°	29.1	19.6
25.0 hours chlorine water at room temperature	25.9	20.8

[a] Prepared according to the directions of Isbell and Frush [*Bur. Standards J. Research,* **11,** 649 (1933)], seeding with crystals furnished by Dr. Isbell; m. p. 125.7°, corr. It was dissolved in distilled water in a concentration of 4.000 g. per 100 cc. of solution just before use.

Experimental Details

Commercial whole starches were ground in a ball mill[25] for the designated periods of time and then dispersed in hot distilled water. The α-amylose was removed by electrophoretic separation,[26] using platinum electrodes. Each dispersion was made up to 4.000 ± 0.005 g. per 100 cc. of solution (determined by evaporating 50-cc. samples to dryness at 80°, followed by three hours at 100° or to constant weight). Toluene was added to prevent bacterial action.

For each determination 25.00 ± 0.02 cc. of the dispersion, free from toluene droplets, was pipetted into a 250-cc. Drexel tall form gas wash bottle modified by sealing a tube containing glass beads onto the outlet in place of the regular exit tube to reduce loss by spattering to a negligible amount. All reactions lasting less than eight hours were carried out in a water-bath kept at 30.00 ± 0.03°. Reactions of longer duration were done at room temperature in the dark. Chlorine was bubbled through the dispersion for forty minutes[27] at 0.75 liter per minute (N. T. P.). More chlorine was added from time to time to be sure that an excess was always present. The reaction[27] was stopped by the following procedure:

Operation	Rate of bubbling in liters per minute (N. T. P.)	Operation time, min.
Nitrogen cylinder connected	...	0.25
Nitrogen (A. R. Co.) bubbled	2.0	2.0
Cylinders interchanged	...	0.25
Ethylene (Ohio Chem. Co. anaesthesia) bubbled	1.6	6.0
Cylinders interchanged and 5.0 cc. concd. HCl added	...	0.5
Nitrogen bubbled	2.0	30.0
Total quenching time 39.0 minutes (stop watch)		

The dispersion was then neutralized to phenolphthalein (0.05% in 50% synthetic methanol) as quickly as possible with almost saturated sodium hydroxide solution, nitrazine yellow[28] added and neutralization completed with 0.1 *M* hydrochloric acid.[29] The solution was then made up to 100.0 cc., protected against bacteria with two drops of toluene, and kept in glass-stoppered bottles for analysis.

The alkaline hypochlorite solutions were made as follows: A. Fifty grams of sodium hydroxide in 250 cc. of distilled water was treated with excess chlorine with chilling, and then 20 g. more sodium hydroxide was added. The solution was diluted to 600 cc. and kept in a "Nonsol" bottle in the ice-box until used. Available chlorine—4.33 g. Cl/100 cc. solution[30]; *p*H—above 13 (with La-Motte Purple indicator).

B. Eighteen grams of sodium hydroxide and 40 g. of anhydrous sodium carbonate in 400 cc. of distilled water were partly neutralized by 20 g. of chlorine with chilling. The solution was made up to 500 cc. and handled like "A." Available chlorine—3.20 g. Cl/100 cc. solution. *p*H—9.7 (corrected for the effect of the potassium ion on the glass electrode).

5.00 cc. of one of these two hypochlorite solutions was added to the β-amylose dispersion by pipet. To stop the reaction 2.0 cc. of concentrated hydrochloric acid was added just before beginning the nitrogen–ethylene procedure.

The viscosity was measured with an Ostwald viscometer having a time of outflow for distilled water of sixty to sixty-five seconds at 30.00 ± 0.03°. Each viscosity figure is the average of those obtained on at least two aliquots from the same sample. Each aliquot was run through the viscometer 5 or 6 times, a. d. 0.5–1.0%. The average readings of the two aliquots were within 2% of each other. The density determinations were made as directed by Findlay,[31] using a pycnometer containing about 7 cc. of solution. Weighings were made to the nearest milligram, corrected for the buoyancy of air.

The alkali-labile determinations[32] were made by the standard method[9] except for two minor changes. (1) 5.00-cc. aliquots of the carbohydrate solution (1.000 g. carbohydrate per 100 cc. solution) were pipetted into test-tubes with 5.00 cc. of standardized 0.2 *N* sodium hydroxide. (2) During the first ten minutes of the alkaline digestion in boiling water the corks were removed from the test-tubes to allow the remaining ethylene or other volatile reducing material to steam off. This procedure gave a smaller and more reproducible alkali-labile value for the blank determinations, and had no effect on the value for untreated β-amylose.

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(25) Taylor and Beckmann, THIS JOURNAL, **51,** 294 (1929).

(26) Taylor and Iddles, *Ind. Eng. Chem.,* **18,** 713 (1926).

(27) Reaction time is the period from the beginning of chlorine or hypochlorite addition to the beginning of the quenching process. In some cases it is less than forty minutes. Nitrogen alone will not remove all of the chlorine (hypochlorite), giving low reducing values. If the hydrochloric acid is not added the ethylene will not be completely removed by the nitrogen in any reasonable length of time, giving high and less reproducible reducing values.

(28) Wenker, *Ind. Eng. Chem.,* **26,** 350 (1934).

(29) If the latter indicator is added earlier it will be inactivated at the point where the concentrated alkali strikes the solution. Even without an indicator the solution can be approximately neutralized because it turns darker yellow rather suddenly when made alkaline. This color change is reversible in acid.

(30) Treadwell and Hall, "Analytical Chemistry," John Wiley and Sons, Inc., New York, Vol. II, 1924, p. 568.

(31) Findlay, "Practical Physical Chemistry," 6th ed., Longmans, Green and Co., New York, 1935, p. 72.

(32) As the ordinary determination of the alkali-labile value, in which 50-mg. samples of the starch or β-amylose are weighed into the test-tubes, does not take into account the water content of 8–10% in most starches the values for untreated β-amyloses reported in this paper are approximately 10% higher than comparable ones reported earlier.[9]

The following blank values were subtracted from the observed reducing values to correct for the non-removable reducing material introduced by the nitrogen–ethylene quenching process.

Solution	"Initial reducing value," mg. iodine/100 mg. sample	Alkali-labile value, mg. iodine/100 mg. sample
Unbuffered chlorine water	0.02 ± 0.01	0.08 ± 0.02
Chlorine water buffered by phosphate	0.04 ± 0.01	0.05 ± 0.01
Alkaline hypochlorite solution	0.02 ± 0.01	0.08 ± 0.01

The hydrolysis of β-amylose dispersions was carried out as follows: 5.00 cc. of the chlorine-treated solution containing 1.000 g. of carbohydrate per 100 cc. of solution of *p*H 7 were pipetted into a Pyrex test-tube and mixed with 5 cc. of 2 *M* hydrochloric acid. The mixture was heated in a boiling water-bath for thirty-five minutes, cooled, almost neutralized with almost saturated sodium hydroxide solution and accurately neutralized with 0.1 *N* alkali to nitrazine yellow. The "initial reducing value" was then determined as usual.

Acknowledgment.—The authors wish to thank Prof. J. M. Nelson, Dr. A. F. Knoll and Dr. C. O. Beckmann for their valuable assistance in preparing this paper. They are grateful also to Dr. H. B. Hardt for carrying out the *p*H measurements, using the glass electrode circuit of Ellis and Kiehl.[33]

Summary

1. The action of chlorine water and of alkaline hypochlorite on β-amylose has been followed quantitatively throughout its course at room temperature by measurement of the reducing power and viscosity of the β-amylose.

2. In alkaline medium the reaction is primarily an oxidation of the aldehyde groups at the ends of the glucoside chains, but is accompanied by some disintegration of the carbohydrate.

3. In acid medium the reaction proceeds differently. After a short time during which no apparent reaction occurs there is a sudden rise in reducing power and simultaneous drop in viscosity. If the acid generated during the reaction is neutralized this abrupt reaction is followed gradually by a complete breakdown of the carbohydrate to products without reducing action toward alkaline hypoiodite reagent.

4. These changes in the reducing power and viscosity can be explained easily by assuming that β-amylose exists in the form of the micelle postulated by Meyer and Mark.

5. A rapid method for the quantitative removal of hypochlorous acid from aqueous solutions has been described.

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[33] Ellis and Kiehl, *Rev. Sci. Instruments*, **4**, 131 (1933).

[CONTRIBUTION NO. 132 FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, THE UNIVERSITY OF TEXAS]

Nitrogen Compounds from Petroleum Distillates. XII. Fractional Sulfiting of Bases and Fractional Degassing of their Acid Sulfites[1,2]

BY STILES M. ROBERTS AND J. R. BAILEY

Introduction

It is well known that acid sulfites of organic nitrogen bases dissociate on heating their aqueous solutions into base, sulfur dioxide and water.

$$\text{Base } H_2SO_3 \longrightarrow \text{Base} + SO_2 + H_2O$$

In this paper, there is described how, by employing the velocity of dissociation of acid sulfites at variable temperature levels, a process of "Fractional Degassing" has been developed which can be used to advantage in resolution or organic nitrogen base mixtures into component types. This procedure is applicable especially to petroleum and coal tar base fractions.

As an experimental background for the process, a crude fraction of kero bases (kerosene bases) in the 270–280° boiling range was selected. Here have been isolated previously 2,3- and 2,4-dimethylquinoline,[3] 2,3,8-trimethylquinoline,[4] 2,4,-8-trimethylquinoline,[5] and a $C_{16}H_{25}N$ naphthenic base.[6]

The 270–280° fraction of kero bases may be arranged in three different types.

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[1] Presented before the Petroleum Division of the American Chemical Society, Dallas, Texas, April 19, 1938.

[2] "Sulfiting" implies conversion of bases to acid sulfites and "degassing" implies dissociation of the acid sulfites with the liberation of free bases and sulfur dioxide.

[3] Burnard S. Biggs and J. R. Bailey, THIS JOURNAL, **55**, 4141 (1933).

[4] W. A. King and J. R. Bailey, *ibid.*, **52**, 1245 (1930).

[5] T. S. Perrin and J. R. Bailey, *ibid.*, **55**, 4136 (1933).

[6] W. C. Thompson and J. R. Bailey, *ibid.*, **53**, 1002 (1931).

A	B	C
Aromatics Two di- and two trimethylquinolines	A $C_{16}H_{25}N$ base, probably of naphthenic structure	A complex mixture of unknown composition and representing about 70% of this fraction

The velocities of degassing at 33° of the A, B and C components are in the approximate order of 1:9:30. After degassing had practically ceased at this temperature level, it was continued by progressively raising the temperature of the sulfite brine. Around 80° evolution of sulfur dioxide stopped abruptly, although it was known that the component base acid sulfites degas readily at this temperature. The inhibition to degassing was revealed in that qualitative tests were negative for *sulfites* and positive for *sulfates*. This observation suggested that the oxidizing effect of aeration could be circumvented by carrying out degassing with the aid of inert gases such as nitrogen, carbon dioxide or natural gas. This forecast has been confirmed experimentally.

Fractional sulfiting, as shown in the Experimental Part, is comparable in efficiency to degassing and was tried on the same material as was used in the latter process. Since a combination of the two methods involves the *use* of sulfur dioxide in the first phase and its *recovery* in the second phase, an economical and practical cyclic method of resolution of base mixtures, without any consumption of chemicals, is presented.

Our results and the results of Axe and Bailey (see following paper) emphasize how cumulative extraction[5] supplements in a favorable way sulfiting and degassing in processing petroleum base fractions of straight-run distillates.

Experimental Part

Degassing Acid Sulfites of the 270–280° Kero Base Fraction.—Into a mixture of 1 liter of bases and 3 liters of water sulfur dioxide is led until complete solution results. Through this solution cooled to 20°, air is passed at approximately 0.5 liter per minute until evolution of sulfur dioxide practically ceases. The bases which layer out as a supernatant oil were withdrawn in seven fractions ranging from 20 to 147 cc., as shown in Table I. The degassing proceeded rapidly for some time and then slowed down progressively, as can be inferred from twenty-four hours being required for the separation of fraction 7 (20 cc.). Fraction 8 required three hours of degassing at 50° and fraction 9 required six hours at 80° when, due to a complete sulfite–sulfate conversion, the evolution of sulfur dioxide ceased.

TABLE I

DEGASSING OF BASES OF 270–280° BOILING RANGE

Fraction	Temp. of brine, °C.	Vol., cc.	n^{25}_{D}
1	20	59	1.5132
2	20	105	1.5183
3	20	70	1.5214
4	20	147	1.5258
5	20	40	1.5263
6	20	32	1.5276
7	20	20	1.5281
8	50	96	1.5277
9	80	18	1.5281
Residual bases from sulfates		413	1.5303
Original bases		1000	1.5267

From fraction 9 there separated 2 g. of a crystalline salt which yielded, on treatment with sodium hydroxide, 2,3,8-trimethylquinoline. The latter was identified by the usual comparison with an authentic sample.

The bases (413 cc.) recovered from the residual sulfate brine (fraction 9) were dissolved in 240 cc. of 6 *N* hydrochloric acid and seeded with 2,3,8-trimethylquinoline hydrochloride. After eighteen hours in the ice-box, 12 g. of the pure hydrochloride had separated. This characteristic salt is difficultly soluble in water as compared with the hydrochlorides of the associated kero quinolines.

The smeary residue obtained by evaporation of the filtrate was washed with five portions of hot acetone (total 75 cc.) and the bases (n^{20}_{D} 1.5142) were recovered from the solvent. The acetone insoluble hydrochlorides yielded 53 cc. of bases (n^{20}_{D} 1.5228) which were further processed through cumulative extraction.[5]

The n^{20}_{D} values, 1.5143 and 1.5501, of 22 cc. from the chloroform layer, and 30 cc. from the water layer, respectively, emphasize the efficiency of cumulative extraction in combination with sulfiting and degassing.

Table II comprises degassing data on the acid sulfite solutions of base fractions 1, 2 and 8 (Table I).

TABLE II

Source of acid sulfite	Fraction	Degassing temp. of brine, °C.	Bases liberated Vol., cc.	n^{20}_{D}
A composite of fraction 1 and 2.	1a	0	28	1.5086
	2a	0	25	1.5120
	3a	20	25	1.5152
	4a	20	19	1.5175
	5a	20	9	1.5208
	6a	..	22	1.5300
Fraction 8	1b	20	16	1.5197
	2b	20	13	1.5203
	3b	20	25	1.5218
	4b	..	42	1.5303

The residual fractions 6a and 4b underwent sulfite-sulfate conversion. However, from 6a, there separated on standing a crystalline acid sulfite from which 7 g. of 2,3,8-trimethylquinoline was obtained. Here the residue, from the evaporation of the filtrate and leaching out the smeary residue with cold acetone, yielded an additional 3 g. of the same acid sulfite.

Fractional Sulfiting of the 270–280° Kero Base Fraction.—One liter of bases was fractionally neutralized with 100-cc. portions of 8% aqueous sulfurous acid under vigor-

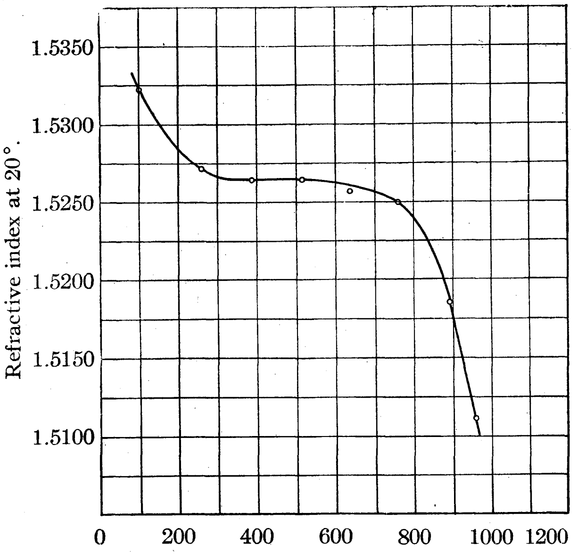

Fig. 1.—Sulfiting of crude base fraction.

ous agitation over ninety-minute periods. At the end of each extraction the aqueous layer was drawn off and the bases were liberated. The results obtained are presented in Table III.

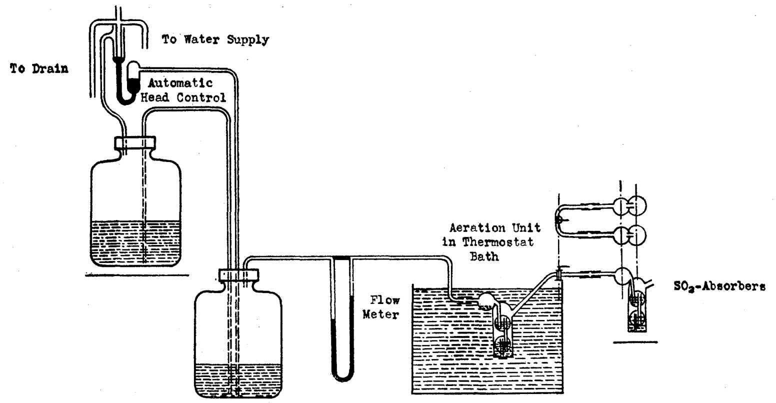

Fig. 2.—Apparatus for determination of degassing rates.

The recombinations, A, B and C, of the nine fractions corresponding to the three pronounced slopes in Fig. 1, were further processed through cumulative extraction by agitation for several hours of the base fractions, with 6 *N* hydrochloric acid and chloroform in the volume ratio of 1:1:1.2, respectively. The results are presented in Table IV.

Since a crystalline hydrochloride separated from the aqueous layer of both B and C before liberation of the bases, the 25-cc. and the 17-cc. fractions were reconverted to the hydrochlorides with the result that 7 and 3 g., respectively, of pure 2,3,8-trimethylquinoline as hydrochloride precipitated. The refractivity of the 66 cc. of non-aromatics from B approached that of the $C_{16}H_{25}N$ base ($n^{20}D$ 1.5129). In order to confirm the presence of this substance, this fraction was converted to anhydrous hydrochlorides, smeary admixtures were leached out with cold acetone, and the crystalline residue was extracted with 400 cc. of hot acetone. After filtering off the undissolved hydrochlorides, the filtrate was concentrated to a small volume, whereupon 17 g. of practically pure $C_{16}H_{25}N{\cdot}HCl$ separated.

TABLE III

FRACTIONAL ACID EXTRACTION WITH SULFUROUS ACID

Fraction	Vol. of bases from extract, cc.	$n^{20}D$	
1	95	1.5322	A
2	160	1.5272	
3	130	1.5265	B
4	130	1.5265	
5	120	1.5256	
6	125	1.5250	C
7	130	1.5186	
8	70	1.5112	

TABLE IV

CUMULATIVE EXTRACTION OF BASES FOLLOWING FRACTIONAL ACID EXTRACTION

			Bases from water layer		Bases from chloroform layer	
Combination	$n^{20}D$	Vol. used, cc.	Vol., cc.	$n^{20}D$	Vol., cc.	$n^{20}D$
A	1.5316	100	27	1.5721	73	1.5174
B	1.5258	100	25	1.5614	66	1.5120
C	1.5222	100	17	1.5624	82	1.5090

Determination of Dissociation Rates of Base Acid Sulfites.—In order to make a thorough study of the rate of dissociation of acid sulfites of nitrogen bases, a method was devised whereby solutions of the salts could be used even though there were present an undetermined excess of sulfur dioxide. This scheme was effected by consideration of the difference in the rate of evolution of sulfur dioxide during degassing from solutions containing (1) an insufficiency and (2) an excess of sulfur dioxide for salification of the base.

Through 10 cc. of an aqueous solution of a weighed quantity of base in an excess of sulfurous acid a quantity of air is passed at a constant rate (see Fig. 2). The vapor from the aeration unit is led into the sulfur di-

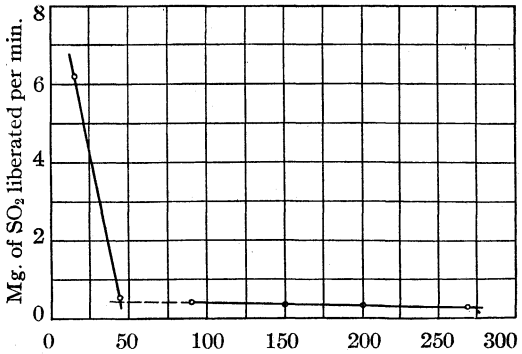

Fig. 3.—Degassing rate of the $C_{16}H_{25}N$ base acid sulfite.

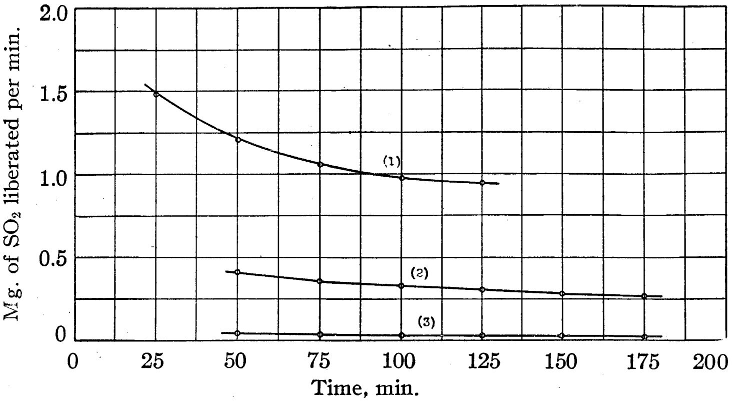

Fig. 4.—Comparison of degassing rates of: (1) non-aromatic fraction, (2) the $C_{16}H_{25}N$ naphthenic base and (3) quinoline acid sulfites.

oxide absorber containing 40% potassium hydroxide. Two absorbers, operating alternately at recorded intervals of time, are connected to the aeration unit through a two-way stopcock so that the rate of degassing can be followed without interruption. The absorbed sulfur dioxide is determined iodometrically. In a series of experiments involving three different bases, the rates of sulfur dioxide evolution from the aeration unit are deduced and plotted against time. At the inflection point of each curve, it is assumed, all of the *excess* sulfur dioxide—*and only the excess*—is removed, leaving behind only base acid sulfite. By shifting the time abscissa of the curve for each base so that the inflection points coincide, a composite set of curves follows whereby a comparison of the degassing rates is presented. Figure 3 shows the degassing rate of the $C_{16}H_{25}N$ naphthenic base. Figure 4 derived from Fig. 3, along with similar curves for quinoline and a complex non-aromatic fraction (b. p. 270–280°), denotes the comparative degassing rates of their acid sulfites.

Summary

Experience has demonstrated that, by following the old beaten track in processing coal tar bases, which are essentially of aromatic character, not much progress can be expected in isolation of the components of the far more complex straight-run petroleum base fractions.

In the present investigation, a new cyclic process of resolution is described which employs the reversible reaction

Sulfiting Degassing

$$\text{(A) Base} + SO_2 + H_2O \rightleftarrows \text{(B) Base}\cdot H_2SO_3$$

In (A), fractional acid extraction and in (B), fractional acid-sulfite dissociation are involved.

It was beyond the scope of the present investigation to effect quantitative separations of the known components of the complex mixture of the bases processed; on the contrary, the aim was to establish Fractional Sulfiting and Fractional Degassing as general procedures which can contribute to an extension of the chemistry of petroleum bases.

Austin, Texas

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[Contribution No. 133 from the Department of Chemistry and Chemical Engineering, The University of Texas]

The Nitrogen Compounds in Petroleum Distillates. XIII. Isolation of Four Quinoline Homologs and Two Aromatic Bases of Probable Trinuclear Cyclic Structure[1]

By W. Nelson Axe[2] and J. R. Bailey

Introduction

The main objective of this investigation concerned the isolation of aromatics in the 300° range of kero bases. In refining the crude material, the following steps were involved: (1) fractional acid extraction followed by a rough distillation; (2) fractional distillation of the desired cuts from (1) after appropriate recombinations in the order of boiling points and refractive indices; (3) cumulative extraction[3] of fractions from (2) preceded by the usual recombinations; (4) fractional distillation of the aromatic bases which were concentrated as hydrochlorides in the aqueous layer in step 3.

Attempts to isolate individual components in fractions from step 4 around the 295° boiling range were rewarded by the recovery of two products in poor yield of the composition $C_{13}H_{15}N$ (I) and $C_{14}H_{17}N$ (II) through fractional precipitation and recrystallization of different salts. Further work on these compounds awaits the assembling of sufficient quantities for proof of structure.

Since the results reported above were disappointing, resort was had to degassing of acid sul-

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(1) Presented before the Petroleum Division of the American Chemical Society, Dallas, Texas, April 19, 1938.

(2) From a dissertation presented by W. N. Axe to the Faculty of the Graduate School of The University of Texas in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

(3) Perrin and Bailey, This Journal, **55**, 4136 (1933).

fites. In the initial experiment on acid sulfites of aromatic fractions from cumulative extraction, the evolution of sulfur dioxide ceased abruptly when 90% of the original bases had layered out. An explanation of this observation was furnished by the discovery that, on prolonged degassing at different temperature levels, acid sulfites of aromatic bases may undergo oxidation to acid sulfates, provided aeration is employed to facilitate the removal of sulfur dioxide.[4]

From the base fractions obtained in the degassing experiment, a product of the composition $C_{14}H_{17}N$ (III) was isolated through its characteristic nitrate. The residual base fraction, obtained by sodium hydroxide precipitation of the acid sulfate solution, yielded a $C_{13}H_{15}N$ base (IV). This latter base was separated from the mixture as the characteristic acid sulfate. These bases are isomers of (II) and (I), respectively.

The structures of (III) and (IV) have been established conclusively through both degradation and synthesis. In accordance with the general observation that, in chromic acid oxidation of quinoline homologs, the stability of alkyls is in the progressive order of their positions of substitution from 1 to 8, inclusive,[5] the monocarboxylic acids from oxidation of (III) and (IV) proved to be 2,3-dimethylquinoline-8-carboxylic acid (V) and 2,3,-4-trimethylquinoline-8-carboxylic acid (VI), respectively.

Acid (V) proved identical with 2,3-dimethylquinoline-8-carboxylic acid, previously obtained in chromic acid oxidation of 2,3,8-trimethylquinoline[6] and 2,3-dimethyl-8-ethylquinoline.[7] Since this acid contains two carbons less than does base (III), it follows that the latter is a 2,3-dimethyl-8-propylquinoline. Accordingly, resort was had to synthesis to determine whether an *n*- or isopropyl was involved. The *n*-propyl isomer was prepared by a modification of Rhode's[8] synthesis of 2,3-dimethylquinoline through the action of concentrated hydrochloric acid on a mixture of *o*-amino-*n*-propylbenzene and tiglic aldehyde. The 2,3-dimethyl-8-*n*-propylquinoline, so obtained, proved identical with the kero base (III).

Decarboxylation of acid VI gave 2,3,4-trimethylquinoline, a base known to synthesis.[9] The position of the carboxyl at 8 was inferred from the fact that, among the six previously isolated quinoline homologs, none is substituted at positions 5, 6 or 7. The bases referred to include: 2,3-, 2,4-[10] and 2,8-dimethylquinoline,[11] 2,3,8-[6] and 2,4,8-trimethylquinoline,[3] 2,3-dimethyl-8-ethylquinoline.[7] The usual comparison of (IV) with a synthetic sample of 2,3,4,8-tetramethylquinoline[12] revealed the identity of the kero base.

Two transformer-oil bases of the composition $C_{15}H_{13}N$ and $C_{16}H_{15}N$ have been isolated. Obviously, they do not belong to the quinoline series, since the rather closely cut fraction of bases from which they were isolated possessed a refractive index of 1.6570 at 25°, indicating the presence of polynuclear types of a higher order. Furthermore, the empirical formulas correspond to a dimethyl and a trimethyl homolog of acridine or one of the three types of naphthoquinolines of the general formula $C_nH_{2n-17}N$, as compared with $C_nH_{2n-11}N$ for the quinoline series. Experimental evidence indicates that these provisionally assumed trinuclear types first occur in the 320° range of straight-run petroleum base fractions. Since acridine and its homologs have very high boiling points, it may be inferred that they are not represented, if at all, much below the 345° range.

Experimental

The Union Oil Company of California in processing 3000 barrels of kerosene Edeleanu extract obtained 3 barrels of bases. A supply of this crude material was partially refined in the Texas Laboratory by fractional acid extraction, followed by fractional distillation at reduced pressure.

The separate fractions, totalling 38.7 liters, which were obtained from the second distillation through recombinations in the order of boiling points and refractivities, were carried through cumulative extraction. Only the bases present as hydrochlorides in the water layer from this form of solvent extraction, and representing a relatively high concentration of aromatics, were used in this investigation. The so-called non-aromatic hydrochlorides which are segregated, in large part, in the chloroform layer have been reserved for future study. The yield of aromatic bases in this process is approximately 28% by volume. When it is considered that the average $n^{25}\text{D}$ value of the non-aromatics is not much above 1.5, while that of quinoline homologs approaches 1.6, the data in Table I emphasize the efficiency of this process.

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[4] An experimental confirmation that the temperature of dissociation of base acid-sulfites rises progressively with their ionization constants has been established. When partial sulfite–sulfate conversion takes place, as in the present case, the bases of highest ionization constants are the ones involved. Proof of these conclusions will appear in a subsequent publication.

[5] Miller, *Ber.*, **23**, 2252 (1890).

[6] King and Bailey, THIS JOURNAL, **52**, 1239 (1930).

[7] Key and Bailey, *ibid.*, **60**, 763 (1938).

[8] Rhode, *Ber.*, **20**, 1911 (1887).

[9] Von Braun, Gmelin and Petzold, *ibid.*, **57B**, 387 (1924).

[10] Biggs and Bailey, THIS JOURNAL, **55**, 4141 (1933).

[11] Lake and Bailey, *ibid.*, **55**, 4143 (1933).

[12] This compound was synthesized by C. L. Key in anticipation of its discovery among the kero bases.

TABLE I

CUMULATIVE EXTRACTION OF KERO BASES

Fraction	B. p., °C.	A n^{25}D (Mixed type)	B n^{25}D (Aromatics)	B Vol., cc. (Aromatics)
1	292	1.5449	1.5850	850
2	293	1.5483	1.5842	980
3	294	1.5488	1.5845	635
4	296	1.5494	1.5830	520
5	292	1.5510	1.5848	560
6[a]	297	1.5502	1.5850	1400
7[a]	296	1.5522		
8	303	1.5520	1.5832	900
9	301	1.5534	1.5832	850
10	307	1.5544	1.5832	760
11	300	1.5544	1.5850	650
12	304	1.5554	1.5855	780
13	303	1.5559	1.5848	1100
14	310	1.5559	1.5847	800

[a] Fractions 6 and 7 were combined prior to extraction.

Distillation data obtained on each of the fractions 1B to 7B, inclusive, showed a negligible variation in physical constants, indicating fractional distillation of the remaining fractions to be superfluous. In processing these fractions, bases (I) and (II) referred to in the introduction were isolated.

The individual fractions 8, 9, 10 and 11(B) dissolved in sulfurous acid were fractionally degassed through aeration. This procedure led to the isolation, in a favorable yield, of 2,3-dimethyl-8-*n*-propylquinoline (III) and 2,3,4,8-tetramethylquinoline (IV), neither of which was separated in applying the conventional methods hitherto employed in resolution of mixtures of bases. Table II is submitted as an example of the results obtained.

TABLE II

FRACTIONAL DEGASSING OF SULFITE SOLUTION OF FRACTION 9B (TABLE I)

Vol. 850 cc. (n^{25}D 1.5832)

Fraction	Temp., °C.	Fraction time, hrs.	Total time, hrs.	Vol., cc.	n^{25}D
1	10	6.5	6.5	135	1.5754
2	20	2.0	8.5	95	1.5754
3	20	2.0	10.5	82	1.5778
4	25	2.0	12.5	90	1.5808
5	25	18.0	30.5	160	1.5838
6	90	2.0	32.5	94	1.5889
7	90	2.0	34.5	Trace	...
8 Residue	..	..	..	164	1.5916

Fractions 1 through 7 comprise free bases which separated as a result of the dissociation of acid sulfites. The residual fraction, 8, did not degas due to oxidation of the original acid sulfites to acid sulfates.

Isolation of 2,3-Dimethyl-8-*n*-propylquinoline as the Nitrate.—To the cooled solution of each of the first seven fractions (Table II) dissolved in an equal volume of 1:1 ether–alcohol, nitric acid was added in slight excess (deduced from an assumed average base mol. wt. of 198). The precipitated nitrates after recrystallization gave the following yields: 22 g. (1), 16.5 g. (2), 8.5 g. (3) and 2.5 g. (4). Fractions 5, 6 and 7 gave negative results. This total yield of 49.5 g. came from fraction 9B (Table I). In processing fractions 8, 10 and 11(B) in a similar way, the amount of pure nitrate was increased to 112 g. This selective salt for the isolation of the dimethylpropylquinoline crystallizes from water containing a very small amount of nitric acid in slender rods melting at 169° with decomposition.

Anal. Calcd. for $C_{14}H_{17}N{\cdot}HNO_3$: C, 64.10; H, 6.91; N, 10.67. Found: C, 64.33; H, 6.93; N, 10.50.

Free Base.—The following constants were determined for the base prepared in the usual way from the pure nitrate or picrate: m. p. 14.5–15.5°; b. p. 299.5°; d^{20}_4 0.9996; n^{25}D 1.5778. It is insoluble in water and readily soluble in the common organic solvents. It is practically odorless.

Anal. Calcd. for $C_{14}H_{17}N$: C, 84.42; H, 8.54; N, 7.03. Found: C, 84.22; H, 8.58; N, 7.07.

Picrate.—This salt, which is difficultly soluble in the common solvents, crystallizes from glacial acetic acid in long lemon colored rectangular prisms which melt undecomposed at 198–199°.

Anal. Calcd. for $C_{20}H_{20}N_4O_7$: C, 56.07; H, 4.71; N, 13.08. Found: C, 55.83; H, 4.63; N, 13.14.

Acid Sulfate.—On addition of concentrated sulfuric acid to an alcohol–ether solution of the base, this salt precipitates and can be recrystallized from *t*-butyl alcohol in small rectangular prisms melting at 212–212.5°. It is readily soluble in water and ethyl alcohol.

Anal. Calcd. for $C_{14}H_{17}N{\cdot}H_2SO_4$: C, 56.56; H, 6.39; N, 4.71. Found: C, 56.20; H, 6.42; N, 4.97.

Hydrochloride.—This salt, prepared by passing hydrogen chloride into an ether solution of the base, crystallizes from acetone containing a trace of alcohol in microscopic rhombic prisms which, after drying in a vacuum desiccator, melt at 161–162°. It is readily soluble in water and alcohol.

Anal. Calcd. for $C_{14}H_{17}N{\cdot}HCl$: C, 71.31; H, 7.67; N, 5.93. Found: C, 71.32; H, 7.91; N, 6.19.

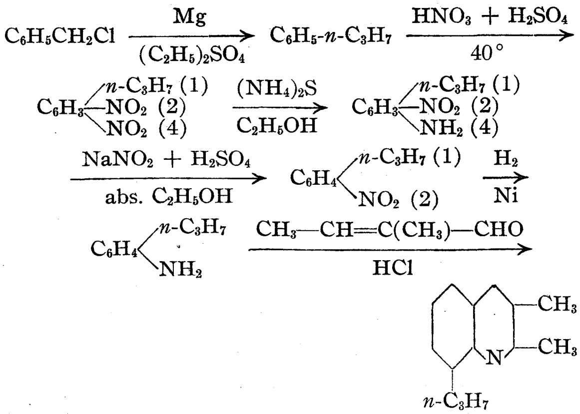
Zinc Chloride Salt.—For precipitation of this salt, an aqueous solution of zinc chloride is added to a molar amount of the base in dilute hydrochloric acid. Recrystallization from an alcohol–acetone mixture yields ill-defined microscopic crystals melting at 193–194°.

Anal. Calcd. for $C_{14}H_{17}N{\cdot}HCl{\cdot}ZnCl_2$: C, 45.19; H, 4.87; N, 3.91. Found: C, 45.09; H, 5.10; N, 3.89.

2,3-Dimethylquinoline-8-carboxylic Acid.—To a boiling solution of 5 g. of the base in 6 *N* sulfuric acid, is added, slowly, 15 g. of potassium dichromate in 23 g. of concentrated sulfuric acid diluted with 25 cc. of water. The reaction is complete in one hour. After neutralization of the sulfuric acid, the solution is extracted with chloroform. The crude product crystallizes from alcohol in needles melting at 201–202°: yield 1.75 g. or 27%. A mixture of this acid with an authentic sample of 2,3-dimethylquinoline-8-carboxylic acid showed no depression in melting point, thus confirming a propyl at position 8 of the original base. Decarboxylation of the acid through soda-lime distillation yielded the kero base 2,3-dimethylquinoline.

Anal. Calcd. for $C_{12}H_{11}O_2N$: C, 71.64; H, 5.47. Found: C, 71.43; H, 5.53.

Synthesis of 2,3-Dimethyl-8-*n*-propylquinoline.—In this synthesis the following series of reactions was involved



The *n*-propylbenzene was prepared according to the procedure of Gilman and Catlin.[13] The method described by Brady and Cunningham[14] was followed in the conversion of the hydrocarbon to *o*-nitro-*n*-propylbenzene. Reduction of the nitro compound to the corresponding amine was carried out in a high-pressure hydrogenator using a Raney nickel catalyst. Equimolecular proportions of *o*-amino-*n*-propylbenzene and tiglic aldehyde were heated with an excess of concentrated hydrochloric acid in accordance with Rhode's synthesis of 2,3-dimethylquinoline.[8]

Isolation of 2,3,4,8-Tetramethylquinoline through the Acid Sulfate.—The residual bases in Fraction 8 (Table II) were dissolved in a 1:1 alcohol–acetone solution. On the addition of concentrated sulfuric acid, a sticky mass separated which on recrystallization from water yielded a colorless crystalline product. From this salt was recovered 13 g. of pure base. The total over-all yield increased to 20.5 g. or approximately 4.5%, after fractions 8, 10 and 11 (Table I) had been processed as outlined for fraction 9 (Table II).

The acid sulfate crystallizes from alcohol in hexagonal prisms melting with decomposition at 298°.

Anal. Calcd. for $C_{13}H_{15}N \cdot H_2SO_4$: C, 55.10; H, 6.04; N, 4.94. Found: C, 54.88; H, 6.07; N, 4.87.

Free Base.—This base crystallizes from methyl alcohol in translucent, long, slender, rectangular prisms melting at 77–78°.

Anal. Calcd. for $C_{13}H_{15}N$: C, 84.32; H, 8.10; N, 7.56. Found: C, 84.41; H, 8.23; N, 7.55.

Picrate.—This salt crystallizes from glacial acetic acid in characteristic small, rectangular plates melting with decomposition at 240°. It is very difficultly soluble in other common solvents.

Anal. Calcd. for $C_{19}H_{18}N_4O_7$: C, 55.07; H, 4.35; N, 13.53. Found: C, 55.26; H, 4.48; N, 13.58.

Hydrochloride.—On addition of concentrated hydrochloric acid to an acetone solution of the base, the hydrochloride is precipitated. The salt crystallizes from an acetone–alcohol solution in ill-defined microscopic crystals melting with decomposition at 252–253°.

Anal. Calcd. for $C_{13}H_{15}N \cdot HCl$: C, 70.42; H, 7.27; N, 6.32. Found: C, 70.51; H, 7.46; N, 6.56.

Nitrate.—Concentrated nitric acid and a well-cooled alcoholic solution of the base yields a crystalline nitrate which after recrystallization from alcohol melts at 184.5° with decomposition.

Anal. Calcd. for $C_{13}H_{15}N \cdot HNO_3$: C, 62.89; H, 6.49; N, 11.29. Found: C, 63.10; H, 6.40; N, 11.30.

Zinc Chloride Salt.—The base in alcohol is treated with a molar proportion of hydrochloric acid and one-half mole of zinc chloride. The precipitated salt crystallizes from 95% alcohol in hexagonal prisms with dome-shaped end faces melting at 266–267°.

Anal. Calcd. for $(C_{13}H_{15}N \cdot HCl)_2 \cdot ZnCl_2$: C, 53.86; H, 5.56. Found: C, 53.89; H, 5.38.

Phthalone.—Molar amounts of the base and phthalic anhydride are heated for four hours at 200°, the melt is dissolved in glacial acetic acid and the phthalone is precipitated by dilution of the solution with water. Microscopic plates melting at 264° are obtained on recrystallization from alcohol.

Anal. Calcd. for $C_{21}H_{17}O_2N$: C, 79.97; H, 5.43; N, 4.43. Found: C, 79.81; H, 5.43; N, 4.40.

Chromic Acid Oxidation of the Base.—This experiment was carried out under conditions similar to those described for the oxidation of 2,3-dimethyl-8-*n*-propylquinoline. Here 5 g. of base, 8.5 g. of potassium dichromate and 12 g. of concentrated sulfuric acid diluted with 15 cc. of water were used. Four hours were required for the reaction; yield 0.8 g. of acid. After recrystallization from alcohol, the acid melted at 233.5–234°.

Anal. Calcd. for $C_{13}H_{13}O_2N$: C, 72.04; H, 6.11. Found: C, 72.35; H, 6.10.

Decarboxylation of the $C_{13}H_{13}O_2N$ Acid.—An intimate mixture of acid and soda-lime in the proportion of 1:4 was heated well above 360°. The base, extracted from the fusion residue with ether, formed a picrate melting at 220°. Comparison of this picrate with an authentic sample of 2,3,4-trimethylquinoline revealed an identity.

Synthesis of 2,3,4,8-Tetramethylquinoline.[12]—Synthesis of this base was effected by the Combes method.[15] Methylacetylacetone (0.7 mole) was condensed with *o*-toluidine (0.6 mole) in the presence of hydrochloric acid at water-bath temperature for eight hours. The base, isolated in the usual way, had the following physical constants after recrystallization from petroleum ether: m. p. 77–78°, b. p. 298–300°. The picrate melted at 240° and the acid sulfate melted with decomposition at 298°. Melting points of mixtures of the synthetic and kero base, as well as mixtures of the respective picrates, showed no depression, thus affording conclusive proof of structure.

Isolation of a $C_{15}H_{13}N$ Transformer-Oil Base.—To 54 g. of a fraction of bases (b. p. 340°, n^{25}_{D} 1.6570)[16] in an equal volume of glacial acetic acid, was added a hot acetic acid solution of 55 g. of picric acid. The reaction mixture was kept at ice-box temperature for twelve hours. The smeary picrates which separated were crystallized from

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[13] Gilman and Catlin, "Organic Syntheses," John Wiley and Sons, New York, Coll. Vol. I, 1932, p. 458.

[14] Brady and Cunningham, *J. Chem. Soc.*, 121 (1934).

[15] Combes, *Bull. soc. chim.*, [2] **49**, 91 (1888).

[16] For an investigation of the next higher boiling fraction (n^{25}_{D} 1.6605) see Axe, Henson and Schuhardt, *Ind. Eng. Chem.*, **29**, 503 (1937).

glacial acetic acid: yield 40 g., m. p. 178–183°. Two recrystallizations left 15 g. of picrates (m. p. 201–203°). Next, the crude viscous bases (n^{25}D 1.6096) liberated from the picrates were dissolved in a 1:1 alcohol–ether solution and a slight excess of concentrated sulfuric acid was added. The resulting acid sulfates after three recrystallizations from alcohol melted at 265–267° with decomposition. A base melting at 82–82.5° was liberated from the acid sulfate which after two recrystallizations from petroleum ether melted at 83.5–84°; yield of pure base, 0.7 g. The pure picrate of the base melted at 228.5–229.5°. From another fraction boiling at 340° (n^{25}D 1.6504), an additional quantity of the base was recovered, bringing the total yield up to 1.9 g.

Anal. of base. Calcd. for $C_{15}H_{13}N$: C, 86.95; H, 6.23; N, 6.76. Found: C, 86.97; H, 6.30; N, 7.00.

Anal. of picrate. Calcd. for $C_{21}H_{16}O_7N_4$: C, 57.79; H, 3.67; N, 12.84. Found: C, 58.10; H, 3.83; N, 12.97.

Isolation of a $C_{16}H_{15}N$ Transformer-Oil Base.—The bases, recovered from the residues after separation of the $C_{15}H_{13}N$ compound, were combined and processed through degassing of their sulfurous acid solution into 8 fractions of bases. To each fraction in alcohol was added a slight excess of concentrated nitric acid. Precipitates in fractions 5, 6, 7 and 8 followed immediately and appeared in very small amount in the first four fractions after seeding and prolonged stirring. The combined nitrates were recrystallized from water containing a trace of nitric acid. The base liberated from the salt melted at 86–87°. The melting point, 228–229°, of the picrate prepared from the base remained unchanged after recrystallization from glacial acetic acid.

The very slight solubility of the nitrate in water at 100°, which is approximately 1 part in 100, offers a selective method for the isolation of this base. This claim is emphasized by the isolation of only 0.6 g. of this substance, or 0.59%, calculated from the quantity of the complex mixture of bases processed.

The slight difference in melting points of this base and the $C_{15}H_{13}N$ compound, as well as the slight difference in melting points of the corresponding picrates, suggested an identity of the two bases. However, the melting point of a mixture of the two picrates showed a depression of 30°. Furthermore, the $C_{15}H_{13}N$ base possesses a pronounced sweet odor, whereas the $C_{16}H_{15}N$ base is odorless.

Anal. of base.[17] Calcd. for $C_{16}H_{15}N$: C, 86.84; H, 6.83; N, 6.32. Found: C, 87.86; H, 6.88; N, 6.60.

Anal. of picrate. Calcd. for $C_{22}H_{18}N_4O_7$: C, 58.66; H, 4.02; N, 12.44. Found: C, 58.62; H, 4.04; N, 12.46.

Summary

Fractional degassing of base acid sulfites as described in the preceding paper by Roberts and Bailey has been employed in isolation, from the 300° range of kero bases, of two quinoline homologs, 2,3-dimethyl-8-*n*-propylquinoline and 2,3,4,-8-tetramethylquinoline. The structures of these products have been established through degradation and synthesis.

Two other bases of undetermined structure of the compositions $C_{13}H_{15}N$ and $C_{14}H_{17}N$ were separated from bases boiling in the neighborhood of 295°.

Two high-boiling bases, $C_{15}H_{13}N$ and $C_{16}H_{15}N$, which are probably of the acridine or naphthoquinoline types, have been isolated from transformer-oil base fractions through employment of selective salts and fractional degassing of base acid sulfites.

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[17] The determination of carbon in the free base is obviously in error, but lack of material prevented a duplicate analysis.

AUSTIN, TEXAS RECEIVED JUNE 2, 1938

[CONTRIBUTION NO. 51 FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF UTAH]

A System Correlating Molecular Structure of Organic Compounds with their Boiling Points. I. Aliphatic Boiling Point Numbers

BY CORLISS R. KINNEY

Several systems have been devised for correlating different physical properties of organic compounds with their molecular structure and two are particularly valuable tools in organic chemistry—molecular refraction and the parachor. Unfortunately, however, these methods give no information about certain types of isomerism and the parachor often involves considerable experimental difficulties. Consequently it would be most desirable to have available another method which correlated molecular structure with an easily determined physical property which would be sensitive to types of isomerism not shown by other methods. The boiling temperature of a compound is probably more dependent upon molecular structure, and more easily determined usually, than any other physical property; and yet no attempt has been made to devise a system for correlating the molecular structure of all types of organic compounds with their boiling points. Large numbers of expressions have been devised for correlating the boiling points of members of homologous series with the molecular weight or other similar property, but no general system has been made available for correlating all types of compounds. Such a system would be especially valuable for determining the structures of unknown substances, for calculating the boiling points of substances from their structure, and for studying the effect of one group upon another in the molecule.

At the boiling point of a substance the kinetic energy of the molecules in the liquid state equals the energy associated with the attractive forces tending to hold the molecules together plus the energy required to do the necessary work against the external pressure. Since the latter energy is constant at a given pressure for all types of molecules and since the molecular attractive forces are primarily dependent upon (1) the kind, (2) the number, and (3) the arrangement of the atoms in the molecule, the boiling point of the substance may also be considered to be primarily dependent upon the kind, number, and arrangement of the atoms in the molecule. The kind and number of the atoms in the molecule, *i. e.*, the molecular formula, may be determined by qualitative and quantitative analyses together with molecular weight estimations; consequently, the effect of the structure upon the boiling point of a compound may be studied in this way. The boiling point of a compound is affected by such factors as dipole moment, hydrogen bonds, association, etc.; but, since these effects are also dependent upon the kind, number and arrangement of the atoms in the molecule they will be accounted for to a large extent. The boiling point is, of course, greatly affected by the pressure; but, by using pressures at or near the normal pressure in the following considerations, that factor has been largely eliminated.

There is no known relationship between the boiling point of a compound and atomic values such as atomic weight, atomic volume, atomic refraction, and atomic parachor; consequently, it was necessary to choose numbers for the atoms and groups in molecules which may be used with boiling point data. It was also necessary to devise an expression for equating the two. The absolute boiling temperature of members of an homologous series of organic compounds may be expressed as a function of the molecular weight raised to a fractional power using Walker's[1] formula, $T = aM^b$, where T is the absolute boiling point, M the molecular weight, "a" a constant characteristic of each homologous series and of a different value for each series, and "b" another similar constant. The value of "b" does not vary greatly from a value of one-third for most series and it becomes apparent that boiling point data may be expressed as a function of the sum of the atomic values chosen for use with boiling points raised to the one-third power. These atomic values and the expression for equating them with boiling point data were obtained in the following way.

Practically all organic compounds may be considered to be derivatives of the normal paraffin hydrocarbons or of hydrogen. Consequently, the normal paraffin hydrocarbons and hydrogen were taken to be the basis of the system. Next, various values were assigned to carbon and hydrogen and the absolute boiling points of hydrogen and the normal paraffin hydrocarbons plotted against the cube root of the sum of the different atomic numbers assigned to carbon and hydrogen. In this way it was possible to choose those values of carbon and hydrogen which cause the boiling point of molecular hydrogen to coincide most closely with the straight line of the hydrocarbon plot, thus making it possible to compare derivatives of hydrogen and of the normal paraffin hydrocarbons. The best values of carbon and hydrogen are 0.8 and 1.0 unit, respectively, and may be called the atomic boiling point numbers (b. p. n.) for these atoms. Also the equation for the hydrogen–hydrocarbon plot may be used for correlating the boiling points of derivatives of hydrogen and the normal hydrocarbons with the boiling points of those substances themselves. Two forms of this equation are given below in which B. P. is the boiling point in degrees centigrade and B. P. N. (molecular boiling point number) is the sum of the individual atomic and group boiling point numbers expressing the structure of the molecule.

$$\text{B. P.} = 230.14\sqrt[3]{\text{B. P. N.}} - 543 \quad (1)$$

$$\text{Log B. P. N.} = 3(\log(\text{B. P.} + 543) - 2.3620) \quad (2)$$

The boiling point number (B. P. N.) of derivatives of hydrogen or of the normal hydrocarbons may be considered to be composed of two parts: that due to the hydrogen atom or the hydrocarbon residue and that due to the characteristic atom or group. The latter value may be determined readily as the difference between the boiling number for the hydrogen atom or the hydrocarbon residue and the molecular boiling point number

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(1) Walker, *J. Chem. Soc.*, **65**, 193 (1894).

determined from the boiling point. For example, the branched chain hydrocarbons are considered to be alkyl derivatives of the normal hydrocarbons and the molecular boiling point number the sum of the atomic boiling point numbers for the hydrogen and carbon atoms in the normal chain plus the boiling point number which has been determined for the alkyl group. The boiling point number of the methyl group was determined from the following data, which demonstrates the method. The boiling point of 2-methylbutane is 28°, which gives an observed B. P. N. of 15.27. In the butane chain there are four carbon atoms which contribute 3.2 and nine hydrogens which contribute 9.0 units. The difference of 3.07 units is to be attributed to the side chain methyl group. As an approximation a value of 3.05 has been adopted as the b. p. n. of the side chain methyl group which gives a calculated B. P. N. of 15.25 and a boiling point of 27.75°. The b. p. n. of several of the alkyl groups together with a number of the characteristic groups present in aliphatic compounds have been determined and may be found in Table II. In Table I have been listed most of the paraffin hydrocarbons for which boiling points at atmospheric pressures have been recorded, the boiling point and the corresponding B. P. N., the calculated B. P. N., and the amount of the deviation from the calculated. Where the boiling point was recorded in the literature as a range of temperature the midpoint of the range has been taken as the boiling point. Many of the boiling points appearing in Table I were obtained at pressures considerably less than standard. This, of course, introduces quite a little error and undoubtedly accounts for, in part, the low boiling points recorded for many of the higher boiling compounds. Another source of inaccuracy is that introduced by the use of some boiling points that have been corrected and many that have not. In addition, the differences in technique in taking the boiling point must cause serious discrepancies. For example, compounds 43 and 44 in section B of Table I, 2,4,7-trimethyloctane

TABLE I

BOILING POINT NUMBERS FOR THE PARAFFIN HYDROCARBONS

	Substance	B. p., °C.	B. P. N. (obsd.)		B. P. N. (calcd.)	Deviation
			A. Normal Hydrocarbons			
0	Hydrogen	−252.8	2.005	0.0 + 2	= 2.0	+0.005
1	Methane	−161.5	4.555	.8 + 4	4.8	− .245
2	Ethane	− 88.3	7.71	1.6 + 6	7.6	+ .11
3	Propane	− 44.5	10.16	2.4 + 8	10.4	− .24
4	Butane	− 0.45	13.10	3.2 + 10	13.2	− .10
5	Pentane	+ 36.2	15.94	4.0 + 12	16.0	− .06
6	Hexane	69	18.80	4.8 + 14	18.8	± .0
7	Heptane	98.52	21.66	5.6 + 16	21.6	+ .06
8	Octane	125.8	24.54	6.4 + 18	24.4	+ .14
9	Nonane	150.72	27.38	7.2 + 20	27.2	+ .18
10	Decane	174	30.24	8.0 + 22	30.0	+ .24
11	Hendecane	195.84	33.08	8.8 + 24	32.8	+ .28
12	Dodecane	214.5	35.66	9.6 + 26	35.6	+ .06
13	Tridecane	234	38.48	10.4 + 28	38.4	+ .08
14	Tetradecane	246	40.29	11.2 + 30	41.2	− .91
15	Pentadecane	270	44.16	12.0 + 32	44.0	+ .16
16	Hexadecane	287	47.00	12.8 + 34	46.8	+ .20
17	Heptadecane	303	49.67	13.6 + 36	49.6	+ .07
18	Octadecane	317	52.18	14.4 + 38	52.4	− .22
19	Nonadecane	330	54.58	15.2 + 40	55.2	− .62
			B. Methyl Derivatives			
1	2-Methylpropane	− 10.2	12.40	2.4 + 7 + 3.05	=12.45	−0.05
2	2,2-Dimethylpropane	+ 9.5	13.84	2.4 + 6 + 6.1	14.50	− .66
3	2-Methylbutane	28	15.27	3.2 + 9 + 3.05	15.25	+ .02
4	2,2-Dimethylbutane	49	17.02	3.2 + 8 + 6.1	17.30	− .28
5	2,3-Dimethylbutane	58.1	17.82	3.2 + 8 + 6.1	17.30	+ .52
6	2,2,3-Trimethylbutane	80.9	19.92	3.2 + 7 + 9.15	19.35	+ .57
7	2,2,3,3-Trimethylbutane	106.8	22.50	3.2 + 6 + 12.2	21.40	+1.10
8	2-Methylpentane	60	17.99	4.0 + 11 + 3.05	18.05	−0.06
9	3-Methylpentane	64	18.35	4.0 + 11 + 3.05	18.05	+ .30

TABLE I (*Concluded*)

	Substance	B. p., °C.	B. P. N. (obsd.)	B. P. N. (calcd.)		Deviation
10	2,2-Dimethylpentane	80.5	19.89	4.0 + 10 + 6.1	20.10	−0.21
11	2,3-Dimethylpentane	89.7	20.77	4.0 + 10 + 6.1	20.10	+ .67
12	2,4-Dimethylpentane	83.9	20.21	4.0 + 10 + 6.1	20.10	+ .11
13	3,3-Dimethylpentane	86	20.42	4.0 + 10 + 6.1	20.10	+ .32
14	2,2,3-Trimethylpentane	110.6	22.91	4.0 + 9 + 9.15	22.15	+ .76
15	2,2,4-Trimethylpentane	98.5	21.66	4.0 + 9 + 9.15	22.15	− .49
16	2,3,3,4-Tetramethylpentane	130	25.01	4.0 + 8 + 12.2	24.20	+ .81
17	2-Methylhexane	90	20.81	4.8 + 13 + 3.05	20.85	− .04
18	3-Methylhexane	91.8	20.98	4.8 + 13 + 3.05	20.85	+ .13
19	2,2-Dimethylhexane	106.5	22.48	4.8 + 12 + 6.1	22.90	− .42
20	2,3-Dimethylhexane	113.9	23.24	4.8 + 12 + 6.1	22.90	+ .34
21	2,4-Dimethylhexane	110	22.84	4.8 + 12 + 6.1	22.90	− .06
22	2,5-Dimethylhexane	109.2	22.76	4.8 + 12 + 6.1	22.90	− .14
23	3,3-Dimethylhexane	111.5	23.00	4.8 + 12 + 6.1	22.90	+ .10
24	3,4-Dimethylhexane	116.5	23.54	4.8 + 12 + 6.1	22.90	+ .64
25	2,3,5-Trimethylhexane	129	24.90	4.8 + 11 + 9.15	24.95	− .05
26	2,2,3,4-Tetramethylhexane	156.6	28.10	4.8 + 10 + 12.2	27.0	+1.10
27	2-Methylheptane	116	23.48	5.6 + 15 + 3.05	23.65	−0.17
28	3-Methylheptane	118.8	23.77	5.6 + 15 + 3.05	23.65	+ .12
29	4-Methylheptane	118	23.69	5.6 + 15 + 3.05	23.65	+ .04
30	2,4-Dimethylheptane	130	25.01	5.6 + 14 + 6.1	25.70	− .69
31	2,5-Dimethylheptane	135	25.57	5.6 + 14 + 6.1	25.70	− .13
32	2,6-Dimethylheptane	134.5	25.52	5.6 + 14 + 6.1	25.70	− .18
33	3,3-Dimethylheptane	137.5	25.86	5.6 + 14 + 6.1	25.70	+ .16
34	2,4,6-Trimethylheptane	143	26.49	5.6 + 13 + 9.15	27.75	−1.26
35	3,3,5-Trimethylheptane	159.2	28.40	5.6 + 13 + 9.15	27.75	+0.65
36	3-Methyloctane	142.5	26.43	6.4 + 17 + 3.05	26.45	− .02
37	4-Methyloctane	141.5	26.31	6.4 + 17 + 3.05	26.45	− .14
38	2,4-Dimethyloctane	152.5	27.60	6.4 + 16 + 6.1	28.50	− .90
39	2,5-Dimethyloctane	156	28.03	6.4 + 16 + 6.1	28.50	− .47
40	2,6-Dimethyloctane	158.5	28.32	6.4 + 16 + 6.1	28.50	− .18
41	2,7-Dimethyloctane	160	28.50	6.4 + 16 + 6.1	28.50	± .0
42	3,6-Dimethyloctane	159.5	28.44	6.4 + 16 + 6.1	28.50	− .06
43	2,4,7-Trimethyloctane	167.5	29.43	6.4 + 15 + 9.15	30.55	−1.08
44	2,6,7-Trimethyloctane	158.5	28.32	6.4 + 15 + 9.15	30.55	−2.23
45	2,2,7,7-Tetramethyloctane	188	32.05	6.4 + 14 + 12.2	32.60	−0.55
46	5-Methylnonane	165	29.12	7.2 + 19 + 3.05	29.25	− .13
47	2,6-Dimethylnonane	174.5	30.31	7.2 + 18 + 6.1	31.30	− .99
48	2,6-Dimethyldecane	194.5	32.91	8.0 + 20 + 3.05	34.10	−1.19
49	2,6,9-Trimethyldecane	207	34.61	8.0 + 19 + 9.15	36.15	−1.54
	C. Ethyl Derivatives					
1	2-Ethylpentane	93.3	21.13	4.0 + 11 + 5.5	=20.50	+0.63
2	2-Methyl-3-ethylpentane	114	23.27	4.0 + 10 + 3.05 + 5.5	22.55	+ .72
3	3-Methyl-3-ethylpentane	118.8	23.78	4.0 + 10 + 3.05 + 5.5	22.55	+1.23
4	3,3-Diethylpentane	139.2	26.04	4.0 + 10 + 11.0	24.80	+1.24
5	3-Ethylhexane	118.9	23.79	4.8 + 13 + 5.5	23.30	+0.49
6	4-Ethylheptane	139	26.02	5.6 + 15 + 5.5	26.10	− .08
7	6-Methyl-7-ethyldodecane (729 mm.)	241	39.54	9.6 + 24 + 3.05 + 5.5	42.15	−2.61
	D. Propyl Derivatives					
1	2-Methyl-5-propyloctane	189	32.18	6.4 + 16 + 3.05 + 7.0	=32.45	−0.27
2	5-Propylnonane	196	33.11	7.2 + 19 + 7.0	33.20	− .09
3	4-Methyl-6-propylhendecane (729 mm.)	235.5	38.71	8.8 + 22 + 3.05 + 7.0	40.85	−2.14
4	6-Propyldodecane (729 mm.)	242	39.68	9.6 + 25 + 7.0	41.60	−1.92
	E. Butyl Derivatives					
1	5-Butylnonane	218	36.15	7.2 + 19 + 9.7	=35.90	+0.25

TABLE II

ALIPHATIC BOILING POINT NUMBERS

Derivative	B. p. n.	Derivative	B. p. n.
A. Alkyl Radical	R—	B. Chlorides	Cl—
1 Methyl	3.05	1 RCH_2Cl	7.5
2 Ethyl	5.5	2 R_2CHCl	6.5
3 Propyl	7.0	3 R_3CCl	6.0
4 Butyl	9.7		
C. Alcohols	—OH	D. Ethers	—O—
1 CH_3OH	12.8	1 CH_3OCH_3	3.8
2 RCH_2OH	10.8	2 RCH_2OCH_3, R_2CHOCH_3, R_3COCH_3	2.9
3 R_2CHOH	8.8	3 RCH_2OCH_2R, R_2CHOCH_2R, R_3COCH_2R	2.0
4 R_3COH	6.8	4 $R_2CHOCHR_2$, R_3COCHR_2	1.1
		5 R_3COCR_3	(0.2 ?)
E. Aldehydes	=O	F. Ketones	=O
1 HCHO, CH_3CHO	8.8	1 CH_3COCH_3	8.5
2 RCH_2CHO	8.2	2 RCH_2COCH_3	8.0
3 R_2CHCHO	7.6	3 $R_2CHCOCH_3$, RCH_2COCH_2R	7.5
4 R_3CCHO	7.0	4 R_3CCOCH_3, $R_2CHCOCH_2R$	7.0
		5 R_3CCOCH_2R, $R_2CHCOCHR_2$	6.5
		6 R_3CCOCH_2R	(6.0?)
		7 R_3CCOCR_3	(5.5?)
G. Acids	—COOH	H. Esters	—OO—
1 HCOOH, CH_3COOH	20.0	1 $HCOOCH_3$, CH_3COOCH_3	9.4
2 RCH_2COOH	19.3	2 RCH_2COOCH_3, CH_3COOCH_2R	8.5
3 $R_2CHCOOH$	18.6	3 $R_2CHCOOCH_3$, RCH_2COOCH_2R, $HCOOCHR_2$, $CH_3COOCHR_2$	7.6
4 R_3CCOOH	17.9	4 $R_3CCOOCH_3$, $R_2CHCOOCH_2R$, $RCH_2COOCHR_2$, $HCOOCR_3$, CH_3COOCR_3	6.7
		5 $R_3CCOOCH_2R$, $R_2CHCOOCHR_2$, RCH_2COOCR_3	5.8
		6 $R_3CCOOCHR_2$, $R_2CHCOOCR_3$	4.9
		7 $R_3CCOOCR_3$	4.0
I. Primary Amines	$—NH_2$	J. Secondary Amines	—NH—
1 CH_3NH_2	8.4	1 CH_3NHCH_3	6.0
2 RCH_2NH_2	7.3	2 RCH_2NHCH_3	5.0
3 R_2CHNH_2	6.2	3 $R_2CHNHCH_3$, RCH_2NHCH_2R	4.0
4 R_3CNH_2	5.1	4 R_3CNHCH_3, $R_2CHNHCH_2R$	3.5
		5 R_3CNHCH_2R, $R_2CHNHCHR_2$	3.0
K. Tertiary Amines	=N—		
1 $CH_3N(CH_3)_2$	2.5		
2 $RCH_2N(CH_3)_2$	2.0		
3 $R_2CHN(CH_3)_2$, $(RCH_2)_2NCH_3$	1.5		
4 $R_3CN(CH_3)_2$, $(R_2CH)_2NCH_3$, $(RCH_2)_3N$	1.25		
L. Cyanides	—CN	M. Isocyanides	—NC
1 CH_3CN	15.2	1 CH_3NC	13.3
2 RCH_2CN	14.0	2 RCH_2NC	12.2
3 R_2CHCN	12.8	3 R_2CHNC	11.1
4 R_3CCN	11.6	4 R_3CNC	10.0

and 2,6,7-trimethyloctane, have very similar structures and should have very similar boiling points; however, their recorded boiling points differ by nine degrees and, judging by their calculated boiling point numbers, both of the recorded boiling points are much too low. In spite of these difficulties in obtaining accurate boiling point data, the deviation is less than 5% in all cases except three and for two of these the boiling point was determined at 729 mm. Consequently, it appears quite likely that the general use of boiling point numbers as guide in obtaining boiling points would lead to more accurately determined and better standardized boiling points appearing in the literature. It is, of course, unfortunate that the boiling points of so few ethyl, propyl, and higher radical derivatives have been recorded at atmospheric pressure and it may be desirable later, as a consequence, to alter slightly the values assigned to these radicals when more boiling points have been recorded.

When two methyl groups are attached to the same carbon atom it would be expected, because of the steric effect, that the b. p. n. of the second methyl group would be less than the first. This is correct for the 2,2-dimethyl paraffins, such as 2,2-dimethylpropane (Table I, Sec. B, 2) and their derivatives, but does not apply to the 3,3-dimethyl derivatives such as 3,3-dimethylpentane (13), etc. The introduction of several methyl groups into the center of the carbon chain produces a marked exaltation of the boiling point. This is shown particularly by such compounds as 2,2,3,3-tetramethylbutane (7) or 2,3,3,4-tetramethylpentane (16). Young,[2] while studying the properties of 2,3-dimethylbutane (5) and 2,5-dimethylhexane (22), first noticed this behavior. The cause of this exaltation may be due to the relation of the structure of these molecules to the packing effect in the liquid state. Whether this is the cause or not, the new method of correlating boiling point data makes it possible to observe and study the various effects of structure upon the boiling point in a very striking manner. Since the maximum deviation from the calculated B. P. N. of these compounds is only about 5%, no corrective factor has been devised for the present, but for making more accurate calculations the effect of related groups upon the B. P. N. should be considered.

The introduction of other atoms or groups, in contrast with the introduction of alkyl groups, produces a very marked change in the b. p. n. depending upon the position (as well as the number) of the atoms or groups substituted into the molecule. In Table II various characteristic atoms and groups are listed giving the b. p. n. for the different positions that may be taken. For example, the values given for the b. p. n. of chlorine in the primary, secondary, and tertiary positions are 7.5, 6.5, and 6.0, respectively, and show the steric effect of the surrounding atoms in a striking manner. It is possible that the depression of the b. p. n. is due in part to a change in the dipole moment of such compounds, but insufficient data are available to make a decision. With molecular chlorine, hydrogen chloride, and methyl chloride data are available (Table III) and the change in b. p. n. corresponds to the change in dipole moment; however, the effect must be complicated by the steric effect in such a series.

TABLE III

Substance	B. p., °C.	Obsd. B. P. N.	B. p. n. of chlorine	Dipole moment $\times 10^{18}$
Chlorine	−33.7	10.48	5.24	0.0
Hydrogen chloride	−83.7	7.95	6.95	1.28
Methyl chloride	−23.7	11.49	7.69	1.86

The boiling point of a substance may be calculated from its structure in the following way provided, of course, that the b. p. n. of the various structural components are known. In Table IV the boiling points of the eight chloropentanes have been calculated and compared with the observed.

The agreement between the calculated and observed boiling points in Table IV is good with the exception of the last compound which belongs to the class of 2,2-dimethyl derivatives which, as pointed out above, show a marked depression of the boiling point. Furthermore, this compound shows the greatest depression of any examined thus far and the amount is usually less than half as much. If several tenths of a unit were subtracted to account for the behavior of the 2,2-dimethyl derivatives, the calculated boiling point would more closely approximate the observed value and this should be done in making more accurate calculations.

In calculating the structure of a substance such as an alkyl chloride from its boiling point, certain limitations are encountered. In the first place, there is no way to distinguish between those isomers in which the characteristic group is merely shifted along the carbon chain, *i. e.*, 2- or 3-chloropentane and 1- or 4-chloro-2-methylbutane which are listed in Table IV. In the second place the branched compounds have a second variable, *i. e.*, the position of the alkyl group. This requires that either the position of the alkyl group be known or that of the characteristic group. Since it is possible, usually, to determine the position of the characteristic group but not the position of the alkyl groups attached to the carbon chain, the new method becomes of especial value in determining the structure of hydrocarbon radi-

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(2) Young, *J. Chem. Soc.*, **77**, 1144 (1900); see also van Risseghem, *Bull. soc. chim. Belg.*, **30**, 8 (1921).

TABLE IV

	Substance	B. P. N. (calcd.)	B. p. (calcd.)	B. p. (obsd.)	B. P. N. (obsd.)
1	1-Chloropentane	4.0 + 11 + 7.5 = 22.5	106.7	108.35	22.67
2	2-Chloropentane	4.0 + 11 + 6.5 = 21.5	96.9	96.7	21.48
3	3-Chloropentane	4.0 + 11 + 6.5 = 21.5	96.9	97.3	21.54
4	1-Chloro-2-methylbutane	3.2 + 8 + 3.05 + 7.5 = 21.75	99.4	98.3	21.64
5	2-Chloro-2-methylbutane	3.2 + 8 + 3.05 + 6.0 = 20.25	84.3	86.0	20.41
6	3-Chloro-2-methylbutane	3.2 + 8 + 3.05 + 6.5 = 20.75	89.4	91.0	20.91
7	4-Chloro-2-methylbutane	3.2 + 8 + 3.05 + 7.5 = 21.75	99.4	99.6	21.77
8	1-Chloro-2,2-dimethylpropane	2.4 + 5 + 6.10 + 7.5 = 21.0	92.0	84.4	20.26

cals. This will be found of greatest value in the determination of the structure of hydrocarbons which have no characteristic group.

The data given in Table IV may be used in the following way to determine the nature of the hydrocarbon radical. Taking the observed boiling point of the first compound of 108.35° a B. P. N. (observed) of 22.67 is obtained. Knowing that the compound has a molecular formula of $C_5H_{11}Cl$ we may calculate the B. P. N. for the normal chloride, which always has the greatest B. P. N. by at least 0.75 unit. The calculated B. P. N. is 22.50, which tells us at once that the chloride boiling at 108.35° is *n*-pentyl chloride. The second compound boiling at 96.7° has a B. P. N. of 21.48, which is very nearly one unit less than the normal chloride, indicating that the compound is a secondary chloride with a straight chain. However, a side chain methyl group would lower the B. P. N. by 0.75 unit giving a B. P. N. of 21.75 which might be confused with the secondary chlorides when the boiling points were not carefully obtained. This difficulty is readily cleared up by determining whether compound 2 is a primary or secondary chloride. If it is shown to be a secondary chloride then it must be either 2- or 3-chloropentane and cannot have the branched chain structure. Compound 3 will, of course, yield the same results as 2. The fourth compound is a primary chloride and subtracting the value of the primary chlorine (7.5) from the observed B. P. N. of 21.64 there are 14.14 units to be attributed to the hydrocarbon radical. The normal pentyl chain has a value of 15.0, which indicates that compound 4 has a side chain methyl group which lowers the B. P. N. by 0.75 to the calculated value of 14.25. Again, there are two possible structures which satisfy these conditions, *i. e.*, 1-chloro-2-methylbutane and 4-chloro-2-methylbutane, compounds 4 and 7 in Table IV.

The fifth compound is a tertiary chloride and, subtracting 6.0 from the observed B. P. N. of 20.41, the boiling point number of the alkyl radical is found to be 14.41. This value, being approximately 0.75 unit less than the normal pentyl radical, indicates the presence of a branched chain methyl group and only 2-chloro-2-methylbutane fulfils the conditions. However, if the carbon chain were longer, it would not be possible to locate the particular carbon atom to which both the chlorine and methyl were attached. The sixth compound is a secondary chloride and the b. p. n. of the alkyl radical is again 14.41 and a derivative of isopentane. The only secondary chlorine derivative of isopentane is 3-chloro-2-methylbutane. The eighth compound is a primary chloride and the b. p. n. of the alkyl group 12.76. This value indicates that there are more than one branched chain methyl groups, in fact the depression of 2.24 units indicates the presence of three. However, that is impossible with five carbon atoms and using the rule that the 2,2-dimethyl derivatives have low boiling points, the compound may be identified as neopentyl chloride.

The b. p. n. for the various oxygen containing groups in aliphatic compounds are listed in Table II. The introduction of alkyl groups about the characteristic group lowers the b. p. n. more or less depending upon the group. The hydroxyl is affected the most, the depression being 2.0 units per alkyl group and the ketones the least where 0.5 is the observed value. The effect is probably due to the steric effect of the alkyl groups. In spite of the well-known irregularity of the alcohols, the maximum deviation from the calculated B. P. N., out of 53 alcohols examined, was 2.71 with 4-decanol while at least half of the alcohols showed a deviation of less than 1.0. The ethers behaved more regularly: the greatest variation observed being 0.72 with diisobutyl ether, while more than half deviated less than 0.2 from the calculated. Decanal, among the aldehydes, gave the greatest deviation with a value 1.31 too low. The majority of aldehydes showed a deviation of less than 0.6. Among the ketones 2-pentadecanone was too low by 1.9 while half of them deviated by 0.4 or less. The B. P. N. of decanoic acid was found to be farthest from the calculated and was 1.57 while half of the acids examined had deviations less than 0.4 unit. Among the esters methyl caprate was too low by 2.28 and half deviated by as much as 0.4 unit.

The amines, cyanides, and isocyanides have been studied among the aliphatic nitrogen compounds. The b. p. n.'s. for the various substitution products containing these characteristic groups may also be found in Table II. Using those values satisfactory results are obtained with the exception of tri-*n*-heptylamine for which a boiling point about 20° too low has been reported. This seems entirely out of line with the other tertiary amines and further investigation may show that a value nearer 350° is correct. The amine that gave the next widest variation from the calculated was di-(α-methylheptyl)-amine with 2.32. It also is high boiling and its boiling point may have been determined incorrectly. With at least half of the amines the deviation amounts to less than 0.4 unit. Among the alkyl cyanides decane nitrile gave the greatest variation of 1.42, while over half of them deviated less than 0.3. Out of ten isocyanides ethyl isocyanide deviated the most with 0.94 while half deviated 0.6 or less.

Other groups of compounds are being studied in the same way and a general survey of the field has been contemplated. The author will welcome data, suggestions, and criticism in the hope that the new method will become a particularly useful tool in organic chemistry and that many new relationships affecting the behavior of compounds will be the result. In developing the method the author is especially indebted to the late Professor E. P. Kohler and to Professors L. Pauling and H. Gilman for many valuable suggestions and encouragement.

Summary

A method has been devised for correlating the structure of organic compounds with their boiling point. Boiling point numbers for a variety of atoms, groups, and molecules have been obtained and the accuracy discussed. Methods for calculating the boiling point of a compound from its structure and the structure from the boiling point have been outlined. The combined effect of several groups in the molecule upon the boiling point has been discussed.

SALT LAKE CITY, UTAH RECEIVED JUNE 9, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSICAL CHEMISTRY AND FROM THE DEPARTMENT OF PEDIATRICS, HARVARD MEDICAL SCHOOL]

The Viscosities of Solutions of the Proteins of Horse Serum[1]

BY KATHLEEN R. FAHEY AND ARDA ALDEN GREEN

The viscosity of solutions of proteins is known to vary widely with the character of these solutes. Some, in sufficiently dilute solution, obey approximately the classical Einstein law relating viscosity and concentration. Thus Loeb,[2] in studying egg albumin, observed agreement with the Einstein equation; and Daniel and Cohn[3] noted that "the viscosity of such a protein as egg albumin is not very different from that of glycine when both solutes occupy the same volume fraction of solution. . . . Hemoglobin and serum albumin, whose molecules—according to Svedberg—are larger and not quite spherical, are, however, more viscous than demanded by the coefficient of Einstein's equation. None the less, hemoglobin like egg albumin obeys Poiseuille's law relating viscosity to pressure. A great many protein molecules are, however, highly asymmetrical in shape, and give rise both to anomalous viscosity and to double refraction of flow, in this respect resembling the long chain polymers studied by Staudinger and his collaborators."

The serum protein fractions as then separable were studied carefully by Harriette Chick[4] twenty-five years ago. She investigated their viscosities as affected by temperature and by concentrations of protein, salt and hydrogen ions. She reported, "In all cases, increase in protein concentration is accompanied by a disproportionately great in-

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(1) This study was supported in part by a grant from the Commonwealth Fund of New York.

(2) Loeb, *J. Gen. Physiol.*, **4**, 73 (1921–1922).

(3) Daniel and Cohn, THIS JOURNAL, **58**, 415 (1936).

(4) H. Chick, *Biochem. J.*, **8**, 261 (1914); H. Chick and E. Lubrzynska, *ibid.*, **8**, 59 (1914).

crease in the viscosity of the solution. The effect is greatest in case of euglobulin, solutions of which exhibit a high viscosity at a comparatively low protein content. It is least in case of serum albumin, which, for strengths of protein under about 10% behaves almost as a crystalloid. Pseudoglobulin is intermediate between the other two proteins in this respect."

Differences in viscosity of the various serum protein fractions are so great as to be determined readily, and are presumably of significance in regard to the size and shape of the molecules.

Three isoelectrically precipitable globulins, designated PI, PII and PIII, have been separated from normal horse serum.[5] Two of these, PI and PIII, have isoelectric points close to *p*H 5 and one, PII, close to *p*H 6. Since these globulin fractions differ in their method of preparation from those of Chick and other investigators, it was thought advisable to investigate their viscosities and also those of the remaining soluble serum proteins.

Experimental

The isoelectrically precipitable globulins PI, PII and PIII were prepared in the manner described in a previous communication.[5] In some instances the identical preparations were used. The essential characteristic of this method of separation of serum globulins is isoelectric precipitation in a very low concentration of salt.

The proteins precipitated from normal horse serum in solutions one-half saturated with ammonium sulfate were dialyzed against water. After dialysis dilute hydrochloric acid, approximately 0.01 *N*, was added cautiously until a precipitate formed, usually at *p*H 6.5. This precipitate was removed by centrifugation. It contained PIII as well as PII, for although the isoelectric point of PIII is close to *p*H 5, this fraction is nevertheless precipitated with PII at *p*H 6.5 because it is so very insoluble. These globulins were separated from each other by solution in acid and fractional reprecipitation with alkali. To the solution obtained after removal of PII and PIII dilute hydrochloric acid was added again until the *p*H was close to 5, and a certain amount of PI was isoelectrically precipitated. Dilution with water, further dialysis or reprecipitation with ammonium sulfate followed by dialysis brought down a further quantity of PI.

At least three or four solutions in alkali or acid and isoelectric reprecipitations were carried out on each fraction before the proteins were considered to approach homogeneity. The protein remaining in solution after all water insoluble proteins are removed by dialysis and electrodialysis from the total globulin fraction obtained by repeated precipitation with ammonium sulfate at one-half saturation was termed pseudoglobulin.

Since the euglobulins are insoluble at their isoelectric points, viscosities must be determined either in the presence of salt or at a reaction away from the isoelectric point. To obtain solutions in 0.5 *M* saline, precipitates were first dissolved in a small amount of sodium hydroxide; sodium chloride solution was then added, followed by an amount of hydrochloric acid equivalent to the amount of sodium hydroxide used to dissolve the precipitate. To prepare solutions in alkali, dialyzed suspensions of the precipitates in distilled water were treated with the minimum amounts of 0.1 *N* sodium hydroxide to bring the precipitates completely into solution. The resultant *p*H of the PIII solutions was 7.0 and 7.1, of the PII solution 8.0, and of the PI

TABLE I

VISCOSITY OF SOLUTIONS OF PROTEINS OF NORMAL HORSE SERUM

Concn. g./liter	Density ρ	Relative viscosity $\eta/\eta_0 - 1$	Concn. g./liter	Density ρ	Relative viscosity $\eta/\eta_0 - 1$
		Globulin PI			
Prepn. 1 at *p*H 6.5 in H_2O			Prepn. 2 at *p*H 5 in 0.5 *M* NaCl		
5.5	0.9983	0.053	10.2	1.0197	0.120
11.4	.9997	.126	20.3	1.0226	.280
16.8	1.0013	.204	30.5	1.0245	.465
22.1	1.0026	.290	40.6	1.0272	.673
27.6	1.0041	.387	50.8	1.0298	.999
		Globulin PII			
Prepn. 1 at *p*H 8.0 in H_2O			Prepn. 2 at *p*H 6.4 in 0.5 *M* NaCl		
10.1	0.9999	0.155	2.8	1.0182	0.036
21.0	1.0031	.384	5.7	1.0193	.083
31.0	1.0058	.758	8.5	1.0199	.110
40.8	1.0085	1.400	11.4	1.0207	.160
51.0	1.0116	2.641	14.2	1.0216	.213
		Globulin PIII			
Prepn. 1 at *p*H 7.1 in H_2O			Prepn. 2 at *p*H 7.0 in H_2O		
5.8	0.9983	0.125	5.0	0.9983	0.109
12.0	.9997	.267	10.4	.9999	.252
17.7	1.0010	.630	15.3	1.0009	.429
23.3	1.0023	1.224	20.2	1.0023	.716
29.1	1.0036	2.171	25.2	1.0039	1.023
		Pseudoglobulin			
Prepn. 1 at *p*H 6.0			Prepn. 2[6]		
20.2	1.0037	0.195	8.2	0.999	0.06
28.7	1.0055	.310	15.0	1.000	.14
35.8	1.0076	.411	28.0	1.003	.30
44.8	1.0101	.570	55.8	1.009	.82
		Serum Albumin[8]			
Prepn. 1			Prepn. 2		
29.4	1.0083	0.16	8.35	1.0023	0.046
58.8	1.0166	.37	20.96	1.0059	.116
117.6	1.0438	1.18	41.92	1.0116	.246
235.2	1.0665	9.35	104.80	1.0288	.868
			139.73	1.0394	1.568
			209.60	1.0593	5.191

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[5] A. A. Green, THIS JOURNAL, **60**, 1108 (1938).

[6] Published through the courtesy of J. D. Ferry, who made the determinations in conjunction with studies on the dielectric constants of serum proteins.[7]

[7] J. D. Ferry and J. L. Oncley, THIS JOURNAL, **60**, 1123 (1938).

[8] Earlier measurements from the Department of Physical Chemistry, Harvard Medical School,[3] hitherto unpublished in detail.

solution 6.5. The pseudoglobulin solution was electrodialyzed and its *p*H was 6.0. The amount of protein in solution was determined by heat coagulation at the isoelectric point; coagulated protein was washed on sintered glass filters till salt free and was dried at 110° to constant weight.

The viscosities were measured at 25 ± 0.1° in Ostwald viscosimeters. The densities were determined at the same temperature in a pycnometer of approximately 10 cc. volume. The relative viscosities reported are the average of at least three determinations. In calculating the relative viscosity the ratio of the time of flow of 0.5 *M* sodium chloride to water was taken as 1.015 and the density of 0.5 *M* sodium chloride and of water at 25° as 1.0173 and 0.99707, respectively. The data are recorded in Table I.

Discussion

For comparison with the existing data on the viscosities of serum proteins, the data are presented in Fig. 1, in which concentration of protein in grams per liter is plotted against the relative viscosity, η/η_0-1, where η is the viscosity of the solution and η_0 the viscosity of the solvent.

The viscosities of the serum proteins studied increase in the order albumin, pseudoglobulin, PI, PII and PIII. The pseudoglobulin and albumin values check satisfactorily with Chick's determinations,[4] and her curve for euglobulin, prepared by acidification of ten-fold diluted horse serum with acetic acid (to *p*H 5.4–6.0) lies between PI and PII.

Chick's data have been recalculated on a volume basis rather than as grams per 1000 grams. Under these circumstances curves for solutions obtained by addition of dilute sodium chloride or dilute alkali appear to be superimposable. Over the range studied our curves are also identical within the limit of error of these measurements whether the protein, PI or PII, was dissolved in 0.5 *M* sodium chloride at the isoelectric point or was in solution in dilute alkali.

Einstein,[9] in 1906, derived an equation for the viscosity of a suspension or solution of spherical particles

$$\eta/\eta_0 = (1 + 2.5\,\varphi) \qquad (1)$$

where φ is the volume fraction occupied by the particles (the solute), and η_0 the viscosity of the solvent at the same temperature. This equation is linear in φ and therefore in the concentration in grams per liter of solution if the partial specific volume of the solute is constant. It has been used by Daniel and Cohn[3] in describing the viscosities of a series of amino acids and related substances in dilute solution. They noted that

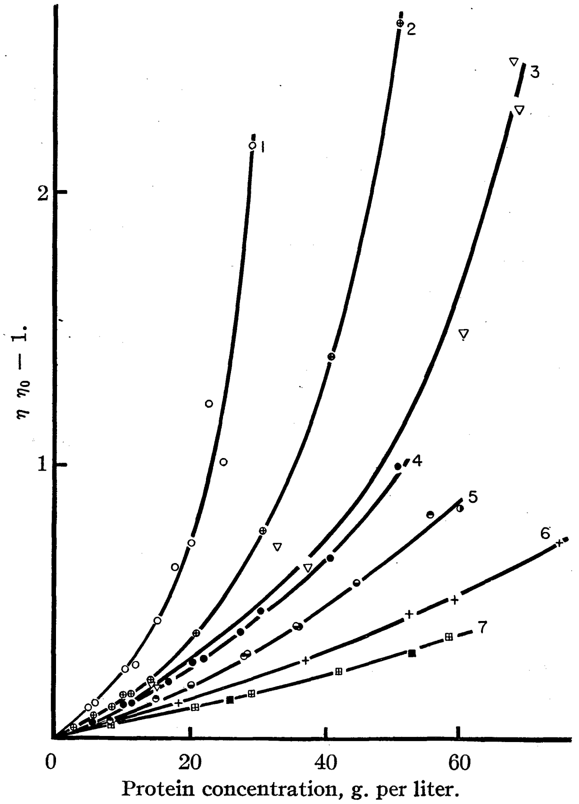

Fig. 1.—Viscosity of serum proteins: curve (1) serum globulin PIII ○; (2) PII ⊕; (3) euglobulin (Chick) ▽; (4) PI ●; (5) pseudoglobulin (this investigation ◓ ◒ and Chick ◑); (6) whole serum (Chick) +; (7) serum albumin (this investigation ⊞, Chick and Lubrzynska ■).

"measurements upon aliphatic amides, amino acids and peptides even up to viscosities more than three times that of water are given by the equation

$$(\eta/\eta_0 - 1) = 2.5\ K\varphi + (2.5\ K\varphi)^{2.8} \qquad (2)\text{''}$$

Although the viscosity curves of all proteins deviate in concentrated solutions from the linear relationship demanded by the Einstein equation, in sufficiently dilute solutions the linear relationship is approximated and the value of K may be estimated. The range over which viscosity is roughly linear with concentration is shown graphically for the serum proteins in Fig. 2. The values for K[10] are given in Table II together with

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(9) A. Einstein, *Ann. Phys.*, **19**, 289 (1906); **34**, 591 (1917).

(10) The values of K adopted were obtained from determinations of relative viscosities of solutions of low protein concentration. Even over this range, however, K, calculated by means of equation 1, shows a drift with concentration. Estimated by extrapolation to infinite dilution on the basis of a plot of C against K, the following values of K were obtained and the corresponding values of s/d are also implied:

	Serum albumin	Pseudo-globulin	Serum globulins		
			PI	PII	PIII
K	2.6	4.5	4.6	7.0	10.0
s/d	8.0	11.8	12.0	15.5	19.0

TABLE II

CONSTANTS DESCRIBING VISCOSITY DETERMINATIONS

	V	K[10]	X	Y	s/d[10]
Glycine	0.759	1.07	2.8	1	1.7
α-Alanine	.823	1.48	2.8	1	4.4
Glycylglycine	.706	1.55	2.8	1	4.7
Na ε-aminocaproic acid	.835	2.32	2.8	1	7.3
Lysylglutamic acid	.769	2.26	2.8	1	7.1
Hemoglobin[11]	.75	1.87	...	...	5.9
Egg albumin[4]	.749	2.80[12]	4.0	1.1	8.5
Serum albumin	.725	3.30	4.0	1.7	9.6
Pseudoglobulin	.715	5.70	3.6	1.4	13.7
Euglobulin[4]	.73	7.20	4.0	1.7	15.8
PI	.75	6.6	4.0	1.7	15.0
PII	.72	8.0	4.0	8.0	16.7
PIII	.78	11.5	4.0	8.0	20.5
Casein[22]	.75	18.0	...	...	26.1
Tobacco mosaic virus[18,19]	.73	35.0	...	...	36.9

values for some amino acids and related substances estimated by Daniel and Cohn. The values for the specific volume, V, have been calculated from values for concentration of protein and density in Table I and in Harriette Chick's data. The values calculated from the results of Chick are 0.725, 0.73 and 0.715 for serum albumin, euglobulin and pseudoglobulin, respectively. These are slightly smaller than the values 0.758 for serum albumin and 0.745 for serum globulin, containing both eu- and pseudoglobulin, estimated by Svedberg[13] on solutions which never exceeded 3%.

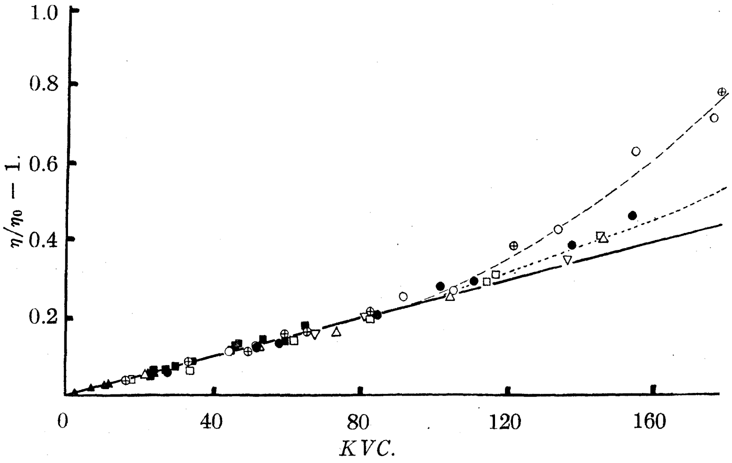

Fig. 2.—Viscosity of dilute solutions of proteins: PI ●; PII ⊕; PIII ○; pseudoglobulin □; serum albumin △; casein ▽ (Sackur[22]); hemoglobin ■ (Cohn and Prentiss[11]); and tobacco mosaic virus ▲ (Lauffer[18] Frampton and Neurath[19]).

In order to describe the deviations of viscosities from the linear relationship in the more concentrated solutions of protein, equation (2) may be modified further to give the following

$$\eta/\eta_0 - 1 = \left(\frac{2.5\ KVC}{1000}\right) + Y\left(\frac{2.5\ KVC}{1000}\right)^X \qquad (3)$$

The curves in Fig. 2 and the viscosity curves of Chick and collaborators up to $\eta/\eta_0 = 20$ given in Fig. 3 may be described in terms of the above equation using the values for K, X and Y reported in Table II.

The numerical value of K has been calculated from the linear relation in low concentration of protein. The more viscous is the protein the higher the value for K. The values for X for the serum proteins are approximately 4 and, therefore, greater than those for amino acids. The value for Y also tends to increase for the serum proteins and for the more viscous globulins, PII and PIII, is as high as 8.

The peculiarities of protein viscosity have been attributed to hydration of molecules,[4,14,15] to electrical interactions, and to shape of the molecules. W. Kuhn[16] has developed the following equation for the increase in viscosity of rod-like molecules

$$\eta/\eta_0 - 1 = 2.5\,\varphi + \frac{\varphi}{16}\left(\frac{s}{d}\right)^2 \qquad (4)$$

from which a definite relation between length, s, and width, d, of the molecule can be obtained assuming the length is much greater than the width. Guth[17] has presented a more general treatment of the problem in which the Kuhn equation is obtained as a limiting case for molecules which are ellipsoids of revolution. The relation between equation (4) and equation (1) may be expressed as follows

$$K = 1 + \frac{1}{40}\left(\frac{s}{d}\right)^2 \qquad (5)$$

The values for K adopted (Table II and footnote 10) lead to values of s/d varying from 1.7 for glycine to 26 for casein and 37 for tobacco mosaic virus.

A similar application of Kuhn's equation to the viscosity measurements on tobacco mosaic virus

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[11] Cohn and Prentiss, *J. Gen. Physiol.*, **8**, 619 (1927).

[12] Loeb[2] found that the viscosity of egg albumin follows the simple Einstein equation where K is approximately 1.0. Further determinations on the viscosity of egg albumin will be reported later.

[13] Svedberg and Sjogren, THIS JOURNAL, **50**, 3319 (1928).

[14] M. Kunitz, *J. Gen. Physiol.*, **17**, 365 (1934).

[15] S. Arrhenius, *Medd. Vetenskapakad. Nobelinst.*, **3**, No. 13 (1916); *Biochem. J.*, **11**, 112 (1917).

[16] W. Kuhn, *Z. physik. Chem.*, **A161**, 1 (1932).

[17] E. Guth, *Kolloid. Z.*, **74**, 147 (1936).

by Lauffer,[18] and Frampton and Neurath[19] results in an estimate of s/d as 35 to 36.8. Polson,[20] also, has calculated the relation of length to width of a number of proteins from viscosity measurements using the Kuhn equation in conjunction with the Arrhenius equation for estimating the viscosity increments at infinite dilution. His values of d/s for egg albumin and serum albumin are 0.142 and 0.123, respectively, which yield values of s/d of 7.05 and 8.13 of the same order of magnitude as those calculated above. On the same basis thyroglobulin and Octopus hemocyanin both have values of s/d of 10.

Staudinger[21] exhaustively studied long chained organic compounds of the paraffin series of exceptionally high viscosity and came to the conclusion that their specific viscosities depend on the length of the molecule. In the case of proteins and of acyclic amino acids and their esters with paraffin chains the situation is more complicated. The observed viscosity is higher than that calculated from chain length which he suggests is due to the numerous acid amide linkages.

Whatever the theoretical explanation of the viscosity behavior of protein solutions, it is of significance that these serum proteins vary in range of viscosity from that of the nearly spherical egg albumin molecule to that of the highly viscous casein molecule.[22] Whereas the globulin solutions of normal horse serum are largely homogeneous in the ultracentrifuge, and the titration curves differ definitely but only slightly,[5] the viscosities vary so widely as to be characteristic.

Conclusions

1. The viscosities of solutions of six protein fractions of normal horse serum have been measured and compared with those of other proteins.

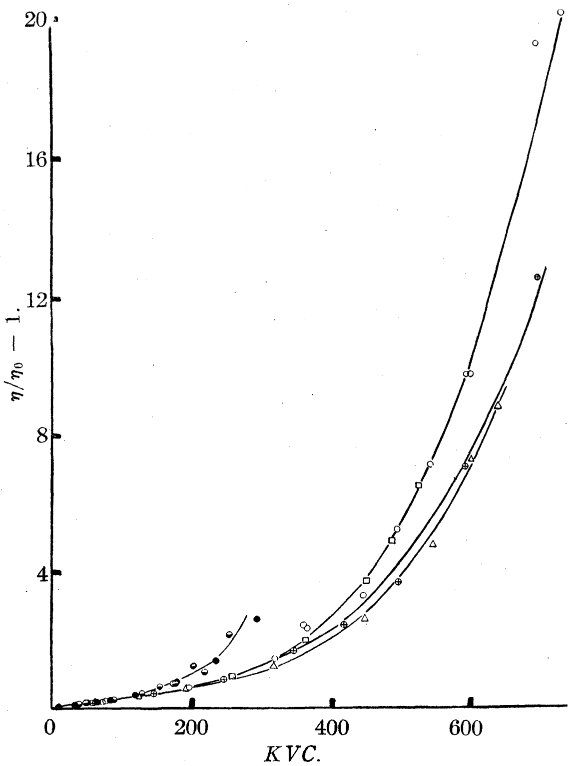

Fig. 3.—Viscosity of more concentrated protein solutions: euglobulin ○; pseudoglobulin ⊕; serum albumin □ and egg albumin △ calculated from Chick's data[4]; PII ●; and PIII ◒.

2. The viscosities of the solutions of three isoelectrically precipitable protein fractions, PI, PII and PIII increase in the order named, whereas that of pseudoglobulin is lower than any of these, and albumin is lowest of all.

3. The viscosity of concentrated protein solutions has been described by the equation

$$\eta/\eta_0 - 1 = \frac{2.5\,KVC}{1000} + Y\left(\frac{2.5\,KVC}{1000}\right)^X$$

4. The viscosities of the various serum proteins differ so greatly as to be essentially characteristic and perhaps are of significance in regard to the shape of the molecules.

BOSTON, MASS.

RECEIVED AUGUST 17, 1938

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(18) M. Lauffer, *Science*, **87**, 469 (1938).

(19) V. Frampton and H. Neurath, *ibid.*, **87**, 468 (1938).

(20) A. Polson, *Nature*, **137**, 740 (1936).

(21) H. Staudinger and H. Becher, *Ber.*, **70B**$_1$, 889 (1937).

(22) O. Sackur, *Z. physik. Chem.*, **41**, 672 (1902).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

The Photochemical Oxidation of Acetone*

BY F. O. RICE AND C. E. SCHILDKNECHT

(1) Introduction

In studying the photochemical decomposition of acetone, Damon and Daniels[1] observed that traces of oxygen produced an initial reaction much more rapid than the decomposition that occurred after all the oxygen was used up; this oxidation reaction was accompanied by a blue fluorescence and proceeded with a decrease in pressure. Damon and Daniels suggested that a chain reaction might be occurring but did not examine the products or investigate the oxidation reaction further. However, Fugassi,[1b] working in Daniels' laboratory, measured the quantum yield of the oxidation and concluded that if one molecule of oxygen reacts with one molecule of acetone, the quantum yield for the oxidation of acetone is the same as that for its decomposition. In contrast with our work, the experiments of Damon and Daniels and of Fugassi were performed with oxygen at partial pressures of less than 1% of that of the acetone.

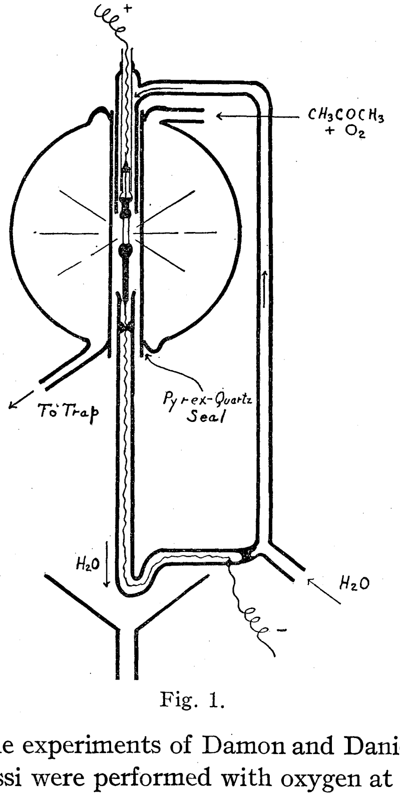

Fig. 1.

We have found that the oxidation occurs through a short chain and that the principal overall reaction may be expressed by the stoichiometric equation

$$CH_3COCH_3 + O_2 \longrightarrow CH_3COOH + HCHO$$

This is followed by a photochemical chain oxidation of the aldehyde according to the equation

$$HCHO + O_2 \longrightarrow H_2O + CO_2$$

These products are accompanied by various peroxides in smaller amount formed in secondary reactions.

The photochemical oxidations of formaldehyde and acetaldehyde have been studied by Carruthers and Norrish[2] and have been found to be short chains also. This is in marked contrast to the ordinary photodecomposition of these compounds, since the aldehyde decompositions are chains,[3] but the acetone decomposition is not a chain,[4] at least not at temperatures up to about 400°.

(2) Experimental

Various types of flowing systems were used in the work and one of them which was particularly satisfactory is shown in Fig. 1. Dry oxygen was bubbled through acetone at about 150 cc. per minute in a bubbler at 22° and gave a mixture containing about 25% of acetone. This was passed directly into the reaction vessel, a 1-liter Pyrex bulb containing a high pressure capillary quartz mercury arc of the type described by Daniels and Heidt.[5] The lamp was mounted in a quartz test-tube through which water was circulated; the temperature of the cooling water was kept at about 40° to prevent condensation of products on the walls of the tube. The lamps which we used had an output of from 0.05 to 0.2 einstein per hour between 2536 and 4350 Å. as measured by the uranyl sulfate–oxalic acid actinometer solution.[6] In the apparatus shown, a large part of the active light is absorbed and the photolysis presents a striking appearance by the condensation of droplets of products upon the walls of the jacket.

All experiments, including especially distillations, were performed behind shatter-proof glass because of the explosive nature of the peroxides formed. We had several explosions during the course of distillations but illumination of the pure acetone–oxygen mixture never resulted in an explosion. In one experiment we mixed hexane vapor with the acetone–oxygen mixture and observed that a

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(*) Present address: E. I. du Pont Plastics Department, Arlington, N. J.

[1] (a) Damon and Daniels, THIS JOURNAL, **55**, 2363 (1933); (b) Fugassi, *ibid.*, **59**, 2092 (1937).

[2] Carruthers and Norrish, *J. Chem. Soc.*, 1036 (1936).

[3] Akeroid and Norrish, *ibid.*, 890 (1936); Leermakers, THIS JOURNAL, **56**, 1537 (1934).

[4] Leermakers, *ibid.*, **56**, 1899 (1934).

[5] Daniels and Heidt, *ibid.*, **54**, 2381 (1932). In some runs we used other types of lamps, especially the mercury argon type. This of course necessitated suitable modifications of the apparatus.

[6] Leighton and Forbes, *ibid.*, **52**, 3139 (1930).

cloud formed during the course of the oxidation. After running for a few minutes, the mixture exploded, completely shattering the apparatus. The most difficult part of the work was the separation, identification and estimation of the products formed in the photoöxidation. The results of a typical run are shown in Table I.

TABLE I

PHOTOCHEMICAL OXIDATION OF ACETONE

Temp. 80–100°. Total pressure, 760 mm. Acetone, 200 mm.; O_2, 560 mm. Acetone passed, 2.73 moles; time, 16 hours. High pressure Hg arc.

Fraction	Boiling range °C.	Volume,		Composition
		Mm.	Cc.	
1	15–20	760	0.1	Dimethyl peroxide
2	20–40	760	.1	Acetone[a]
3–10	40–53	760	165	Acetone
11–14	24–45	75	3.0	Acetone[b]
15–18	45–49	75	5.0	Acetone[b]
19–20	49–50	75	3.0	Acetic acid[c]
21–22	50–54	75	3.0	Acetic acid[c]
23	30–35	13	0.5	Peroxide
24	35	13	.5	Peroxide[d]

[a] Contained some peroxide. [b] Contained some acetic acid. [c] Contained all the formaldehyde largely as paraformaldehyde. [d] Explosive white solid, m. p. ~30°.

The twenty-four fractions were obtained by distillation in a 30-cm. column with a rotating receiver and constant pressure control. Each fraction was weighed and a weighed portion of each was dissolved in water and used for quantitative estimations. The remainder was used for qualitative tests and preparation of derivatives.

Fractions (1) and (2) consisted of a gas with a sweetish, ethereal smell reminiscent of nitrous fumes but producing a stinging sensation in the nose when inhaled. The gas was soluble in water, did not give an aldehyde test and slowly liberated iodine from a potassium iodide solution acidified with acetic acid; it was very explosive. These properties and its boiling point indicate that it is dimethyl peroxide $CH_3–O–O–CH_3$.

Unreacted acetone was estimated by the iodoform method making a correction for the formaldehyde. Methanol was absent and acetaldehyde was present only in traces. Formaldehyde and its polymer were present in all the acetic acid fractions; the formaldehyde was identified as the 2,4-dinitrophenylhydrazone and was estimated volumetrically by reduction of copper.

Water was formed in the oxidation but was not estimated; free hydrogen was absent from the gases leaving the reaction vessel. There was a considerable amount of carbon dioxide formed which was estimated by absorption by Ascarite.

The last fractions, before distillation was completed, consisted of an oily residue; as this was heated to about 120° it turned reddish-brown and exploded with a bright flash of light demolishing the apparatus. Distillation at low pressure gave a white waxy solid, melting just above room temperature, which detonated violently if dropped on a hot-plate. It was sparingly soluble in water and reacted with acidified potassium iodide. This material was probably largely diacetyl peroxide which has already been reported by Carruthers and Norrish as a product of the photochemical oxidation of acetaldehyde. In Table II we summarize the analytical results for a typical run.

TABLE II

PHOTOCHEMICAL OXIDATION OF ACETONE

Conditions same as in Table I

	Moles	Moles
Acetone passed	0.582	..
Acetone recovered	.555	..
Acetone oxidized	.027	1.0
Acetic acid	.023	0.85
Carbon dioxide	.020	.74
Formaldehyde	.003	.11
Peroxide	.002	.07
Carbon monoxide	.002	.07
Water (not determined)	...	..

The quantum yield of the oxidation process had an average value of 0.3 as compared with the value 0.03 for the photochemical decomposition of acetone carried in a stream of carbon dioxide in the same flowing system. In one of these experiments a mercury–argon glow lamp was used as light source and the output of the lamp was determined in position in the reaction chamber just before and after each oxidation run by filling the jacket with actinometer solution. We assumed that the glow lamp emitted only light of wave length 2536 Å. (actually the figure is 86%) and from the extinction coefficient for acetone[7] and the dimensions of the irradiation jacket we calculated the quantum yields. In other experiments we used a capillary arc following the same method and made a graphical estimate of the distribution of energy in the spectrum of the lamp. The amount of acetone decomposed was found by titrating for acetic acid in the oxidation experiments and by estimating the carbon monoxide produced in the photodecomposition of pure acetone. The results obtained are shown in Table III.

The refractive index of the recovered acetone in the experiments in absence of oxygen was increased only very slightly (1.358 to 1.360) and no yellow color appeared on evaporation; a test for acetonylacetone was negative.

(3) Discussion of Quantum Fields

Our average value of 0.36 for the quantum yield of the oxidation process is near to Fugassi's[1b] value of 0.24, which is the number of molecules of oxygen reacting per quantum absorbed when the acetone is in very great excess. However, Damon and Daniels[1a] report a yield of 0.17 molecule per quantum for the decomposition in absence of oxy-

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(7) Porter and Iddings, THIS JOURNAL, **48**, 40 (1926).

TABLE III

QUANTUM YIELD DETERMINATIONS FOR PURE ACETONE AND FOR ACETONE + OXYGEN

Temp. 80–100°. The light source was a mercury argon lamp in Expt. (1) and a high pressure capillary arc in all the others.

Expt.	Gas present	Length of run, hrs.	Output of lamp, einsteins/hr.	Light absorbed in run, einsteins	Moles product	Quantum yield
1	O_2	4.64	0.0011	0.00088	0.00034 CH_3COOH	0.39
8	O_2	2.75	.071	.025	.009 CH_3COOH	.36
9	O_2	2.16	.071	.0152	.0061 CH_3COOH	.40
11	O_2	1.50	.050	.0104	.003 CH_3COOH	.33
12	O_2	1.90	.050	.0123	.004 CH_3COOH	.33
1P	CO_2	1.00	.070	.0091	.0003 CO	.03

gen, in contrast with our value of 0.03; they found that the quantum efficiency was diminished by increasing the light intensity and by lowering the pressure of acetone. Since we used much higher light intensities and also a lower pressure of acetone, the difference may be due to different experimental conditions. Norrish, Crone and Saltmarsh[8] also obtained results substantially in agreement with Damon and Daniels, and reported values for the quantum yield of the decomposition process in the range 0.2 to 0.4.

There is a possibility of error in our results for the quantum yield of the decomposition process because we estimated the extent of decomposition by analyzing for carbon monoxide and Barak and Style[9] have shown that acetone partly decomposes photochemically into diacetyl below 60°. Unfortunately, while we tested for acetonylacetone, and examined the refractive index of the residual acetone, we did not make a direct test for diacetyl; however, it seems highly unlikely that 80–90% of the acetone decomposed would form diacetyl under our conditions, and this amount would be necessary to bring our result up to previous values.

(4) Mechanism of the Oxidation of Acetone.—The following scheme gives a satisfactory representation of the course of the reaction from the point of view of products formed as well as from the standpoint of certain rules concerning the course of elementary reactions.[10]

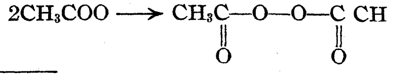
$$CH_3COCH_3 + h\nu \longrightarrow CO + 2CH_3 \qquad (1)$$

$$CH_3 + O_2 \longrightarrow CH_3{-}O{-}O \qquad (2)$$

$$CH_3O_2 \longrightarrow HCHO + OH \qquad (3)$$

$$OH + CH_3COCH_3 \longrightarrow H_2O + CH_3COCH_2 \qquad (4)$$

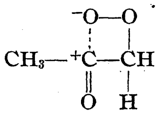
$$\left.\begin{array}{l} CH_3COCH_2 + O_2 \longrightarrow CH_3COCH_2{-}O{-}O \\ CH_3COCH_2O_2 \longrightarrow HCHO + CH_3COO \\ CH_3COO + CH_3COCH_3 \longrightarrow \\ \qquad CH_3COOH + CH_3COCH_2 \end{array}\right\}\text{Chain} \quad \begin{array}{l}(5)\\(6)\\ \\(7)\end{array}$$



$$2CH_3COO \longrightarrow \begin{array}{c}CH_3C\\ \|\\ O\end{array}{-}O{-}O{-}\begin{array}{c}C\\ \|\\ O\end{array}CH \qquad (8)$$

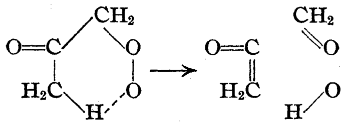
Since the oxidation occurs in the range 80–100° we have represented the primary step as a direct decomposition into carbon monoxide and methyl radicals since probably the acetyl radical is very unstable in this temperature range.[11] The reaction of methyl with oxygen (2) and the decomposition into formaldehyde and hydroxyl (3) as well as the reaction of hydroxyl with acetone (4) seem quite reasonable from the standpoint of the principle of least motion. Since the heavy fractions did not seem to contain any CH_3COOH, we have represented the radical $CH_3{-}O{-}O$ as decomposing, instead of attacking the acetone.

Presumably we can neglect any decomposition of the acetonyl radical into ketene and methyl because of the high activation energy of this process.[12] However, the decomposition of the acetonyl peroxide presents some difficulties: we may assume that there is an attraction between the positive carbon and negative oxygen as shown



$$\begin{array}{ccc} & {}^{-}O & {-}O \\ & \vdots & | \\ CH_3{-} & {}^{+}C & {-}CH \\ & \| & | \\ & O & H \end{array} \qquad (9)$$

followed by splitting off of formaldehyde, leaving an acetate radical or we may assume that the radical is chelated



(10)

and decomposes into formaldehyde, ketene and hydroxyl. The process represented by equation (6) is simpler than (10) and probably is to be preferred. Furthermore, if ketene was formed some of it probably would have escaped reaction with water formed in the chain and would have been detected by its characteristic odor. The considerable production of the solid explosive peroxide

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[8] Norrish, Crone and Saltmarsh, *J. Chem. Soc.*, 1456 (1934).

[9] Badak and Style, *Nature*, **135**, 307 (1935).

[10] Rice and Teller, *J. Chem. Phys.*, **6**, 489 (1938).

[11] Spence and Wild, *J. Chem. Soc.*, 352 (1937).

[12] Rice and Herzfeld, THIS JOURNAL, **56**, 284 (1934).

(probably diacetyl peroxide) suggests that the main chain-terminating reaction is the combination of two acetate radicals.

It is of course possible that the attack of the hydroxyl radical on acetone may be represented by the equation

$$OH + CH_3COCH_3 \longrightarrow CH_3COOH + CH_3 \quad (11)$$

instead of (4), followed by equations (2) and (3). This would also represent correctly the chemical course of the decomposition, especially if we assume that reactions (4) to (8) occur to a small extent as side reactions producing diacetyl peroxide; however, we believe that equation (4) is to be preferred to equation (11).

Summary

1. The products of the photochemical oxidation of gaseous acetone at 100° with the full radiation from a mercury vapor lamp are acetic acid and formaldehyde; the formaldehyde is largely oxidized to carbon dioxide and water; there are smaller amounts of organic peroxides formed.

2. The quantum yield of the oxidation process has been found to be about 0.3, approximately ten times the quantum yield of the photochemical decomposition in presence of carbon dioxide in the same system.

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[CONTRIBUTION FROM THE BELL TELEPHONE LABORATORIES]

The Oxide-coated Filament. The Relation between Thermionic Emission and the Content of Free Alkaline-earth Metal

BY C. H. PRESCOTT, JR., AND JAMES MORRISON

Introduction

The oxide-coated filament had its beginning in the sealing-wax era of vacuum technique. The obscure accident of its origin is not recorded, but all of our older physicists knew that an enhanced emission of electrons could be obtained by smearing sealing-wax on a platinum ribbon and burning it off in air. The first authentic study is recorded by Wehnelt,[1] who investigated the voltage-drop in a gas discharge tube with cathodes coated with various metallic oxides. Its further evolution and development to the status of a cathode in Western Electric vacuum tubes has been described by H. D. Arnold.[2] A comprehensive treatment of its history, the various modifications in current use, and divergent theories of its preparation and behavior has been given by Saul Dushman[3] in a treatise on "Thermionic Emission." A later review is given by J. H. deBoer.[4]

The present work is devoted to a quantitative determination of the relation between thermionic emission and the content of free alkaline earth metal. To this end we have employed a filament which is a platinum rhodium core coated with barium, strontium, and nickel carbonates. On heating in a reducing atmosphere this coating becomes a grossly homogeneous colloidal mixture of barium oxide, strontium oxide, and free nickel. After a thorough preliminary clean-up of the experimental tube, the requisite amounts of free alkaline-earth metal are generated by reaction with methane. The electrical measurements are summarized by the use of the Richardson equation for thermionic emission. Free alkaline earth metal has been determined by oxidation with carbon dioxide and analysis of the gaseous reaction products.

Acknowledgment is due to Mr. V. L. Ronci and his staff for their care in the assembly of the vacuum tubes used in these studies.

Experimental Procedure

The experimental tube used for these studies, as shown in Fig. 1, contains a filament whose core is a 0.0127-cm. wire of 80% platinum and 20% rhodium. The coating was applied by passing the core through a suspension of barium carbonate, barium nitrate, strontium carbonate, and basic nickelous carbonate in amyl acetate and pyroxylin. Three coats were applied after each of which the filament passed through an oven at 675° in an atmosphere of carbon dioxide. The coating vehicle largely evaporated and the fusion of barium nitrate gave the coating enough adherence to undergo the processes of assembly. The final coating is 0.0025 cm. thick to as close as we can determine.

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(1) A. Wehnelt, *Ann. Physik*, **14**, 424 (1904).

(2) H. D. Arnold, *Phys. Rev.*, **16**, 70 (1920).

(3) Saul Dushman, *Rev. Modern Phys.*, **2**, 381 (1930).

(4) J. H. deBoer, "Electron Emission and Adsorption Phenomena," Cambridge University Press, Cambridge, England, 1935.

The filament is mounted in the common axis of three cylindrical nickel plates. The central cylinder is the anode used in the measurements; the other two serve as guard rings to define a radial field about the segment of filament whose emission is measured. The filament core is scraped bare for 0.475 cm. from the welds, which just suffices to concentrate the end cooling in the bare segments. As a result the coated area runs at a uniform temperature, which is essential to ensure uniform activation and so give significance to the determination of free alkaline earth metal. Small holes (as shown in Fig. 1) are bored in the plates to permit temperature measurements of the filament which is held taut by a large molybdenum spring.

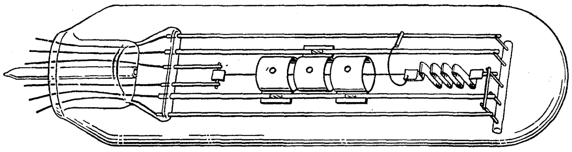

Fig. 1.—The experimental tube.

The physical dimensions of the filament and experimental tube are given in Table I.

Table I

Coated length	4.125 cm.
Plate length	0.9524 cm.
Filament core radius	.00635 cm.
Coating radius	.00889 cm.
Plate radius	.475 cm.
Coating area	.2305 sq. cm.
Emitting area	.0532 sq. cm.
Volume of bulb	245 cc.

With the exception of the filament, all metal parts, prior to assembly, were baked for four hours at 1200° in a stream of hydrogen, saturated with water at room temperature. This procedure was designed to burn out such impurities as carbon and sulfur. This treatment was found necessary in order to avoid spurious activation and large blanks in the determination of free alkaline earth metal.

We still encountered spurious activation by reaction of the oxides with carbonaceous residues from the coating bath. This necessitated a rigorous conditioning treatment. After the tube was baked out, and the plates outgassed by heating with induced high frequency current, the filament was glowed in successive samples of carbon dioxide. This treatment was continued until the carbon monoxide formed was reduced to about 0.05 cc. mm. (cubic centimeters at one millimeter pressure). The preliminary conditioning treatment is given in detail in Table II. Treatments are *in vacuo* except as specified.

Table II

1. Baked 60 min. at 400–425°
2. Glowed filament, 5 min. at 1000°
3. Glowed filament, 30 min. at 900° in 5 cc. mm. CO, 10 cc. mm. CO_2
4. Heated plates, 5 min. at 850°
5. Heated plates in 0.5 mm. H_2, 5 min. at 850°
6. Heated plates, 5 min. at 850°
7. Glowed filament in 10 cc. mm. CO_2, 30 min. at 900°
8. Baked 45 min. at 400°, measured rate of gas evolution to ensure substantial clean-up
9. Heated plates, 850°, measured rate of gas evolution
10. Glowed filament in 1–2 cc. mm. of CO_2, 30 min. at 900° and analyzed the gaseous products

The filament was activated by glowing for fifteen minutes at an uncorrected temperature of 900°, in a sample of methane. The methane was substantially decomposed, giving hydrogen and carbon monoxide, which indicate the chemical reaction

$$CH_4 + BaO = Ba + CO + 2H_2 \text{ or}$$
$$CH_4 + SrO = Sr + CO + 2H_2$$

Some of the active metal formed evaporated from the filament and reëvaporated from the plates, either during formation or in the subsequent stabilization treatment. Due to the "gettering" action of this evaporated metal, carrying down some of the gases, the reaction products were not quantitatively recovered for analysis.

Before taking electrical measurements it was necessary to denude the tube of gas and to permit diffusion to bring the filament coating into an equilibrium state. A liquid air trap was used to keep mercury vapor out of the tube during the measurements. This conditioning and stabilizing treatment is given in detail in Table III.

Table III

1. Heated plates, 3 min. at 800°
2. Baked 15 min. at 350°
3. Removed mercury vapor by use of liquid air, contd. bake for 15 min., fil. at 700° during last 5 min. of bake
4. Heated plates, 3 min. at 800°
5. Glowed filament, 15 min. at 900°
6. Glowed filament, 60 min. at 800°, 80 v. potential on plate

After the emission current at 800° and 80 v. had remained stable for a period of at least thirty minutes, the currents to the central plate were measured at a series of temperatures between 700 and 800°.

When the emission measurements were completed, the liquid air was removed, and the filament subjected to successive treatments in samples of carbon dioxide which were each collected for analysis. The total carbon monoxide found was taken as a measure of the free alkaline earth metal according to the reaction

$$CO_2 + Ba = BaO + CO$$

During this treatment a considerable proportion of the carbon dioxide was converted to barium and strontium carbonates. It should be noted, however, that the amounts were small as compared to the total amounts of barium and strontium oxides. These carbonates were subsequently decomposed and the carbon dioxide recovered, as the filament was glowed for approximately twenty minutes while the gases were pumped off for analysis.

Four tubes used in this study were each activated three times in methane and deactivated by treatments with carbon dioxide.

The Temperature Measurements

Temperatures were measured with an optical pyrometer of the disappearing filament type following in general a design by Forsythe.[5] This was calibrated from 700 to 1200° against a standard lamp obtained from the Bureau of Standards. A screen of Corning Pyrometer Red glass (effective wave length 0.66 μ) was used for temperatures above 800°. Below this temperature no screen was used, but no errors are introduced due to the predominantly red character of the light. The uncertainties in the temperature measurements are about 5°, which is within the limits of other errors in dealing with the oxide-coated filament.

Corrections were applied for a 90% transmission of the glass bulb and the emissive power of the filament which was approximately 64%. Since the sum of the emissive power and reflectivity is unity, we have been able to compute the emissive power from the diffuse reflectivity determined by a method analogous to that employed by Worthing.[6] Details of these measurements are described in another article.[7]

The experimental reflectivity (after the preliminary treatments) is approximately 36% both at room temperature and under operating conditions. There is little if any change due to activation, *i. e.*, formation of free alkaline earth metal. There is a gradual rise with time due to glowing at 900° which may be due to gradual sintering or slight loss of nickel. This introduces an uncertainty no greater than that already indicated in the temperature measurements.

The Measurements of Thermionic Emission

During emission measurements the tube was open to the vacuum pumps but protected from mercury vapor by a liquid air trap. After the filament was outgassed and stabilized, the thermionic emission was measured at a series of potentials from 0 to 100 v., and at several uncorrected temperatures ranging from 700 to 800° (corresponding to 998 to 1103°K. true temperature). Below 700° the filament could not be seen in the optical pyrometer, and above 800° the activity was unstable. At 900°, in particular, the activity rapidly dropped to a lower level, presumably characteristic of a dynamic steady state involving evaporation of active metal from the filament surface, but it recovered in a few minutes of aging at 800°. We thus were limited to a range of 100° in the region of normal operating temperatures. In this range, however, the measurements characteristic of a given state of the filament were entirely reproducible to within the limits of the temperature measurements.

Since the field within the collecting anode is strictly radial, the limiting case of temperature saturation where the current is limited by space-charge should follow the slope of the Langmuir space-charge equation.[8] This is a linear relation between the two-thirds power of the current and the applied voltage. Figures 2 and 3 show typical examples of the current–voltage relations, the two-thirds power of the current being plotted against the applied voltage. The theoretical slope is indicated by the broken line.

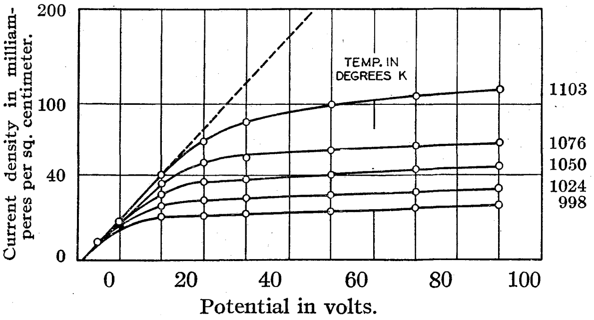

Fig. 2.—Tube A, state 4: two-thirds power of current density *vs.* applied potential.

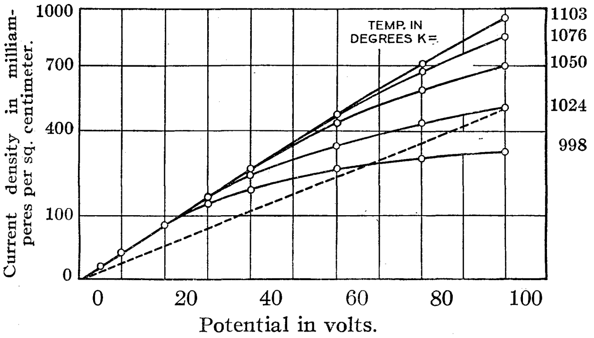

Fig. 3.—Tube C, state 3: two-thirds power of current density *vs.* applied potential.

We may note (as in Fig. 3) that, as the filaments become more active, the currents rise above the limiting values indicated by the Langmuir space-charge equation. Such an effect suggests such factors as gas ionization and spurious paths by which electrons could reach the anode. But these do not seem probable and should give curved relations and not the limiting straight lines found in all cases by experiment. We may note, however, that the theory is idealized in that it neglects the initial velocities of the electrons due to thermal agitation, and that the actual filament is rough in texture and may not conform to the theoretical conditions. It will require further work to elucidate this effect.

At higher potentials the space-charge is swept out and this region of the curves corresponds to

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(5) W. E. Forsythe, *Astrophys. J.*, **43**, 295 (1916).

(6) A. G. Worthing, *Phys. Rev.*, **10**, 377 (1917); *Z. Physik*, **22**, 9 (1924).

(7) To appear in the *Journal of the Optical Society of America.*

(8) I. Langmuir, *Phys. Rev.*, **2**, 450 (1913); Langmuir and Blodgett, *ibid.*, **22**, 347 (1923).

voltage saturation where the current is limited by the activity of the filament. In this case the emission conforms to the Richardson equation.[3]

$$i = AT^2e^{-\epsilon\phi/kT}$$

where A and $\epsilon\phi/k$ are empirical constants and ϕ (the thermionic work function) may be interpreted as the work required to remove an electron from the filament. Plotting log i − 2 log T, for the currents at 80 v., against the reciprocal temperature, as in Fig. 4, gives a family of straight lines, one corresponding to each activation state of the filaments studied. Four curves have been omitted which practically coincide with those shown in the high activity region. The deviations at higher temperatures for the more active states show the influence of space charge. With this exception the data may be summarized completely by two families of parallel straight lines, one for the active states and another for the inactive states following the preliminary clean-up. The two corresponding values of the work function are 1.37 and 1.64 v., respectively. The values of A would be given by the intercepts on the axis where $T = \infty$. These intercepts are, however, so far (on the graphs) from the region of observation that the different heights of the lines may be due in part to small changes in work function, and the absolute values of A as obtained by extrapolation would be doubtful. We have therefore taken as our measure of activity the currents corresponding to the ordinates of the lines at 1050°K. These are plotted in Fig. 6 against the content of free alkaline earth metal determined by analysis.

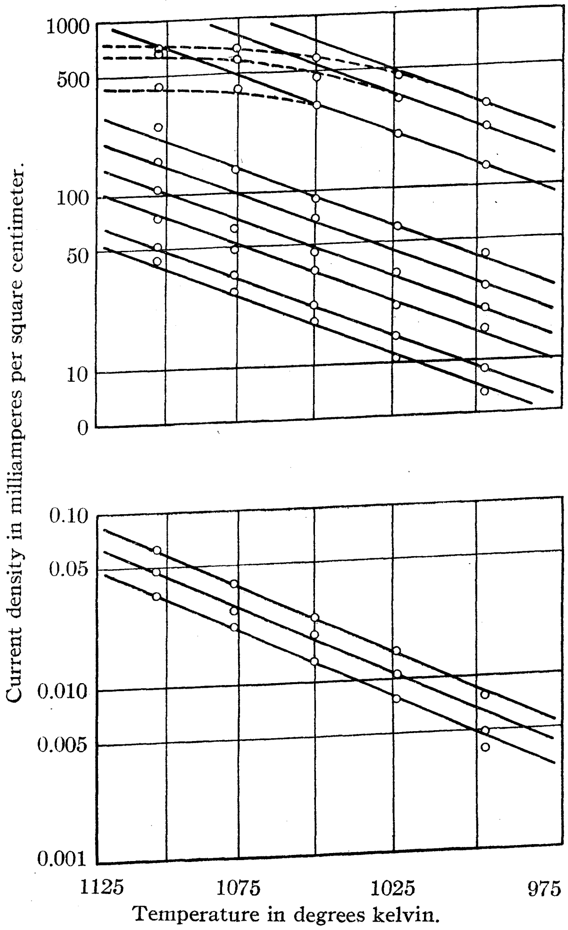

Fig. 4.—Current temperature relation for various active states. Log i/T^2 vs. $1/T$ according to the Richardson equation.

The Gas Analyses

The nucleus of the experimental methods is the equipment for gas analysis, a refinement of apparatus described by one of the authors.[9] The essential features are shown in Fig. 5. The gas for analysis is collected by a Toepler pump and measured in a capillary pipet, Fig. 5a, which operates in a fashion similar to a McLeod gage. The gas is then allowed to escape and is circulated through the absorption train. The gas is circulated by operation of the same Toepler pump and again collected for measurement. The reagents used in these analyses are copper oxide at 300°, magnesium perchlorate and soda

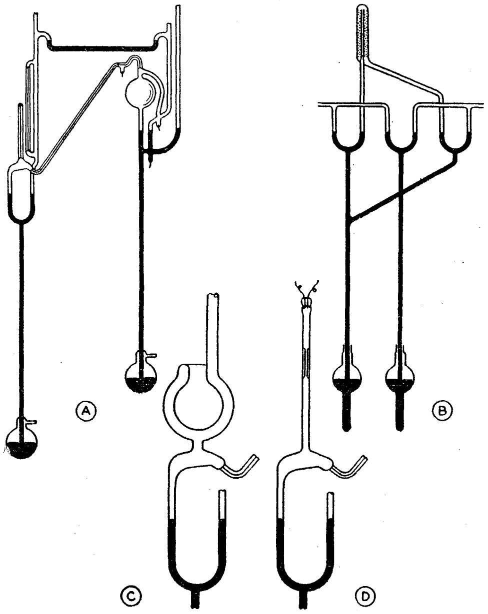

Fig. 5.—Details of the gas analysis apparatus.

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[9] C. H. Prescott, Jr., This Journal, **50**, 3237 (1928).

lime. These may be switched in and out by mercury cut-offs as shown in Fig. 5b. Auxiliary equipment includes a platinum ribbon filament in a water-cooled tube, and the explosion pipet shown in Fig. 5d with which is associated another Toepler pump. Mixtures containing H_2O, CO_2, H_2, CO, and O_2 or CH_4 can be analyzed completely. The oxygen analysis by means of the platinum filament requires an excess of hydrogen or carbon monoxide. Methane cannot be exposed to the hot filament and consequently cannot be determined when oxygen is present. When oxygen is absent, methane, which is not affected by any of the reagents, is finally mixed with oxygen and exploded. With the tubes of reagents well outgassed the sensitivity of the apparatus is about 0.02 cc. mm. (cubic centimeters at a pressure of one millimeter of mercury). This is equivalent to 0.03 microgram of carbon monoxide, approximately the amount in one square centimeter of a monomolecular layer. The accuracy, which we definitely sacrificed to sensitivity, is about 2% except on the smallest samples.

The experimental tube and the liquid air trap are mounted as shown in Fig. 5c on a structure similar to the two pipets. Methane or carbon dioxide is pumped in by a third Toepler pump. During reaction the gas is entirely confined within the experimental tube, since the mercury is raised up into the stem of the tube completely filling the space of the liquid air trap. During thermionic measurements the mercury level is drawn down to permit liquid air to be placed in the trap and connection made to the high vacuum line.

The determination of free alkaline earth metal requires, in general, four or five successive treatments of thirty minutes in carbon dioxide at 900°, following each of which the gas is recovered for analysis. For the smaller amounts of active metal this has sufficed to reduce the carbon monoxide found to about 0.02 cc. mm., which appears to be a mean blank determination for the tube and analytical apparatus, and is close to the ultimate sensitivity of the method.

This blank raises a question as to a possible reaction between carbon dioxide and nickel

$$\mathrm{Ni} + \mathrm{CO_2} = \mathrm{NiO} + \mathrm{CO} \qquad K = p_{\mathrm{CO}}/p_{\mathrm{CO_2}}$$

The equilibrium constant may be computed from data on the reduction of nickel oxide by hydrogen[10] and the water gas reaction.[11] At 1209°K., the true temperature of the carbon dioxide treatments, this is 0.012. The lowest value of the CO–CO_2 ratio in our analyses is 0.017, while several of the low terminal ratios were twice the equilibrium value. Noting that the equilibrium is independent of total pressure, this indicates that no nickel could have reacted. We thus judge this residual carbon monoxide to be a spurious evolution, possibly not even coming from the filament.

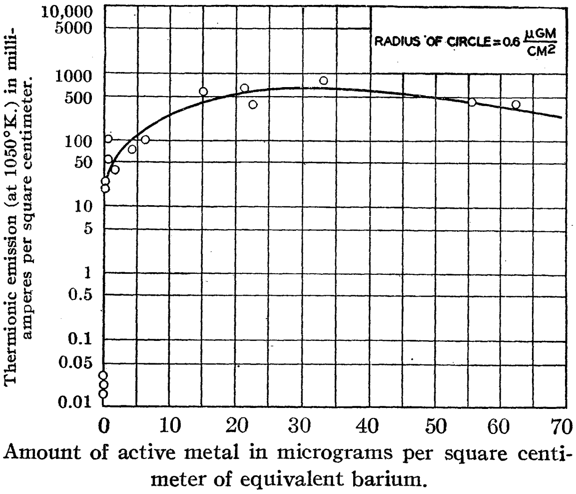

Fig. 6.—Thermionic emission *vs.* content of free alkaline earth metal.

In Table IV, following a summary of the corresponding thermionic data, we have shown the complete analytical results. Each tube is designated by a letter and each successive state of activity by a subscript. In estimating the total free alkaline earth metal for each state of activation, we have considered the results of those analyses prior to a value equal to or less than 0.02 cc. mm. subtracting 0.02 cc. mm. from each determination before summing. These are equivalent to the amounts of free alkaline earth metal shown as equivalent weights of barium.

In the fourth tube, used only for states with large amounts of active metal, the preliminary clean-up was abbreviated and the corresponding initial activity was ignored because of the uncertainty of its state. It was found that after active metal was once permitted to escape within the tube we could not reëstablish the low level of initial activity without cleaning up the whole tube again. Metal deposited on the plates redeposited on the filament when the plates were out-gassed prior to the activity measurements. Thus we have two active states B_3 and B_4 which

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[10] Pease and Cook, THIS JOURNAL, **48**, 1199 (1926).

[11] Emmett and Schultz, *ibid.*, **52**, 1782 (1930).

TABLE IV

SUMMARY OF ANALYTICAL DATA

	A_1	A_2	A_3	A_4	B_1	B_2	B_3	B_4	B_5
Current at 1050°K., ma./sq. cm.	0.0127	65.5	33.6	46.7	0.0228	21.4	94.7	16.8	564
ϕ, v.	1.64	1.37	1.37	1.37	1.64	1.37	1.37	1.37	1.37
A, amp. cm.$^{-2}$ deg.$^{-2}$	0.00082	0.221	0.114	0.157	0.00148	0.0720	0.319	0.0570	1.90
CH_4 consumed, cc. mm.	.....	0.71	0.28	1.73	.....	0.072	...	...	2.60
CO recovered, cc. mm.	.....	0.64	0.35	0.87	.....	0.059	...	...	1.68
Analyses, cc. mm. of CO		.093 .059 .026 .032 .021	.067 .018 .020	.037 .014		.022 .018 .020	.028 .028 .015 .038 .015		0.483
Blank, cc. mm. of CO		.020	.020	.020		.020	.020		
Total Ba + Sr, cc. mm. of CO		.13	.05	.02		.00	.02		(0.66)
Equivalent Ba, μ g.		.97	.35	.13		.00	.12		(4.89)
Equivalent Ba, μ g./sq. cm.		4.2	1.5	.5		.0	.5		(21.2)

	C_1	C_2	C_3	C_4	D_2	D_3	D_4
Current at 1050°K., ma./sq. cm.^{2}	0.0173	352	727	527	91.4	314	381
ϕ, v.	1.64	1.37	1.37	1.37	1.37	1.37	1.37
A, amp. cm.$^{-2}$ deg.$^{-2}$	0.00112	1.19	2.45	1.78	0.309	1.06	1.29
CH_4 consumed, cc. mm.	......	3.27	1.32	0.70	.41	2.13	3.94
CO recovered, cc. mm.	......	2.49	0.85	.41	.23	1.68	2.71
Analyses, cc. mm. of CO		1.240 0.258 .141 .117 .072	.823 .140 .074 .054 .041	.383 .077 .056 .039	.115 .072 .049 .038 .026	0.487 .131 .064 .067 .054	1.343 0.274 .192 .121 .108
Blank, cc. mm. of CO		.020	.020	.020	.020	.020	.020
Total Ba + Sr, cc. mm. of CO		1.73	1.03	.48	.20	.70	1.94
Equivalent Ba, μ g.		12.77	7.62	3.51	1.46	5.20	14.32
Equivalent Ba, μ g./sq. cm.		55.4	33.1	15.2	6.3	22.6	62.2

were obtained by reëvaporation of active metal and without use of methane. We should note, however, that this scattered free metal did not interfere with our analyses; the carbon dioxide would not react even with the active filament except at elevated temperatures. For the state B_4 we have no analysis since there was already indication that the amount of active metal was below the sensitivity of our apparatus. One further point, B_5, we have wished to include as corroborative of the other activities in its neighborhood. The tube was lost after the first analysis for this determination. But the course of successive analyses is so smooth that we have felt justified in estimating the total amount by comparison of the first analyses and interpolation between the total amounts for its neighbors.

Discussion

The results tabulated in Table IV are shown in Fig. 6 which expresses the correlation between thermionic activity (measured by the current density at 1050°K.) and the content of free alkaline earth metal. This latter is expressed as the equivalent micrograms of barium per square centimeter of superficial filament surface. The radius of the circles, 0.6 μ g./sq. cm., is equivalent to 0.02 cc. mm., the sensitivity of the gas analysis methods. The actual errors are somewhat larger, being the accumulations from several analyses each.

The lowest activity values, 20 microamperes per sq. cm., are still doubtless associated with free barium, formed by spurious activation, but an amount much less than our analytical limit of sensitivity. In the neighborhood of this limit, which corresponds to 0.6 μ g./sq. cm., the activity is 30 m. a. per sq. cm. The curve then rises to a value of 600 m. a. per sq. cm. which may be a maximum in the neighborhood of 30 μ g./sq. cm. But this maximum is not definitely established, and the most significant feature of the relation is its flatness from 15 to 60 μ g./sq. cm.

Taking a monomolecular film of barium as 0.14 μ g./sq. cm., the range 0.6-15-60 μ g./sq. cm.

is equivalent to 4-100-400 atomic layers upon the geometrical surface. Minute amounts of metal appear largely to saturate the active surfaces from which electrons are emitted. These may be the surfaces either of nickel or oxide particles. Further addition of active metal contributes little to thermionic activity, but provides a reservoir of active material.

Previous analyses of free alkaline earth metal in vacuum tubes are reported by Berdennikowa,[12] Clausing[4] (p. 348), and Fritz.[13] The water vapor method of Berdennikowa does not discriminate between active metal in the filament and elsewhere in the tube. The same criticism seems to apply to Clausing. Barium nitride formation and microanalysis, as employed by Fritz, appear selective but less sensitive. His results are equivalent to 5–15 micrograms of barium per tube.

The greater amounts found in our experiments we believe to indicate an increased retention, which may be adsorption upon or alloying with the finely divided nickel, and which may also be a factor in a very long useful life obtained with this type of coating. The contrary opinion, that barium is dissolved in barium oxide, has some support from the work of Schriel,[14] who reports a slight solubility, though no evidence for solution under vacuum conditions. From the overall composition, as shown in Table V, we conclude that the active metal is somehow dissolved, a conclusion further substantiated by the long time, upward of two hours, necessary to leach out the active metal in the carbon dioxide treatments.

TABLE V

Coating composition (referred to outside surface of coating)

SrO = 984 μ g./sq. cm.
BaO = 923 μ g./sq. cm.
Ni = 71.5 μ g./sq. cm.
Active metal = 0.6 – 65 μ g./sq. cm. as Ba

Summary

Using a filament coated with a colloidal mixture of barium oxide, strontium oxide, finely divided nickel, and free alkaline earth metal, we have investigated the quantitative relation between thermionic emission and the content of active metal. A high level of activity was found from 15 μ g./sq. cm. to 60 μ g./sq. cm. of equivalent Ba, with a slight apparent maximum at 30 μ g./sq. cm. where the thermionic current at 1050°K. is 600 m. a./sq. cm. The electron work function is 1.37 v.

The radiant emissive power at 0.66 μ is approximately 64%, independent of the content of active metal.

The free alkaline earth metal was determined by oxidation with carbon dioxide and analysis of the gaseous reaction products.

NEW YORK, N. Y. RECEIVED AUGUST 29, 1938

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[12] T. P. Berdennikowa, *Phys. Z. Sowjet.*, **2**, 77 (1932).

[13] H. Fritz, *Mikrochemie*, **17**, 191 (1935).

[14] M. Schriel, *Z. anorg. Chem.*, **231**, 313 (1937).

[CONTRIBUTION FROM THE ANALYTICAL LABORATORIES OF FORDHAM UNIVERSITY]

A Modified Method for the Preparation of Monochloropentamminocobaltic Chloride (Purpureocobaltic Chloride)

BY WALTER A. HYNES, LEO K. YANOWSKI AND MORRIS SHILLER

Monochloropentamminocobaltic chloride, or purpureocobaltic chloride, $[Co(NH_3)_5Cl]Cl_2$, is one of the earliest and best-known of the cobaltammines. During the course of work on the application of such complexes to the microscopic detection of anions,[1] it became necessary to prepare relatively large amounts of this substance in a pure state.

Purpureocobaltic chloride has been prepared and its constitution studied by numerous investigators[2] since its initial synthesis in 1851. These workers used air or pure oxygen as chief oxidants and cobaltous carbonate as the usual source of cobalt.

The chief objections to the older method of preparation are the length of time required for the preparation of the substance, the low yield of pure substance obtained and the impurity of the final product. The low yield and relative impurity of the final product obtained by the usual method are due to the presence of hexammines and other cobaltammines, only removable by repeated recrystallizations or by precipitation from cold

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[1] W. Hynes and L. Yanowski, *Mikrochemie*, **23**, 1, 143 (1937).

[2] "Gmelins Handbuch der anorganischen Chemie," 8 Aufl., 58B, Berlin, 1930, pp. 151–159.

aqueous solutions by acid, followed by separate washings with alcohol and ether.[3]

To obtain approximately 10 g. of *pure* purpureo chloride by the older method required an average of about forty hours due to time required for aeration, evaporations and extractions, whereas by our method we can obtain an average of 35 g. of pure salt in not more than five hours.

Experimental

Forty grams of coarsely ground crystalline cobaltous chloride, $CoCl_2 \cdot 6H_2O$, is added to a mixture of 50 ml. of water, 100 ml. of concentrated (28%) ammonium hydroxide and 100 g. of solid ammonium chloride in a flat porcelain dish. Twenty-five ml. of 30% hydrogen peroxide is added to this mixture with continuous stirring. The dish is then heated on the steam-bath for one hour. The paste obtained at this point is treated with 500 ml. of 3 *N* hydrochloric acid and heated, with continuous stirring, over the free flame to not more than 60°. The mass is filtered and washed with approximately 150 ml. of 2 *N* hydrochloric acid. The residue is suspended in 1500 ml. of 1.2 *N* ammonium hydroxide and heated to not more than 60° with continuous stirring, when all the purpureo chloride will be dissolved. This liquid is filtered immediately, the filtrate transferred to a 3000-ml. beaker, placed on the water-bath, and 1500 ml. of concentrated hydrochloric acid added in three 500-ml. portions at fifteen-minute intervals, stirring during each addition, and the heating continued for thirty minutes after the last addition, a total time of one hour. The liquid is filtered while still warm and the residue first washed thoroughly with 2 *N* hydrochloric acid, then with 95% alcohol until there are no further traces of hydrochloric acid in the washings and finally with four to five 25-ml. portions of ether. The residue is then dried for one hour in an oven previously raised to 60°. The yield at this point averages 34 g., equivalent to 85% of the theoretical value. The salt requires no further purification for use as a microscopic reagent or in the preparation of other compounds.

The material was analyzed for nitrogen by both micro Dumas and macro Kjeldahl, for cobalt by semi-micro determination as sulfate, and for total chlorine by the micro Pregl method,[4] and the following values were obtained.

	Nitrogen			
	Dumas	Kjeldahl	Cobalt	Chlorine
Calculated	27.96		23.53	42.47
Found	27.99	27.91	23.62	42.56
	28.04	27.89	23.62	42.59

Although several investigators have employed hydrogen peroxide as an oxidant in preparing cobaltic compounds,[5] none has specified that this substance may be used as the oxidant in preparing the purpureo chloride.

A single 1500-ml. volume of 1.2 *N* ammonium hydroxide, about one-half that used in the ordinary method, was employed as solvent to avoid numerous extractions. Heating in ammoniacal solution at 60° hastens conversion of the purpureo to the aquo salt, this temperature being quite safe, as shown by Lamb and Marden.[6] The converse transformation to the purpureo is well known, but it was deemed advisable to add the acid slowly with stirring to prevent any possible occlusion of roseo chloride by the purpureo salt.

We have noticed that the thoroughly dried purpureo chloride is non-hygroscopic, while a sample which had not been oven-dried tended to gain weight on exposure to air.

Acknowledgment is made to the Works Progress Administration for the City of New York for assistance rendered under Project No. 465-97-3-120.

Summary

1. Purpureocobaltic chloride has been prepared from $CoCl_2 \cdot 6H_2O$ using hydrogen peroxide as oxidant in the presence of ammonium chloride.

2. The product is obtained in much better yield and in a much shorter time than is required by the ordinary method.

NEW YORK, N. Y. RECEIVED MARCH 8, 1938

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[3] F. Garrick, *Nature*, **136**, 1027 (1935); *Z. anorg. Chem.*, **224**, 27 (1935).

[4] We are indebted to Mr. J. Alicino for the micro Dumas and Pregl values.

[5] A. Carnot, *Bull. soc. chim.*, [4] **21**, 212 (1917); R. Durrant, *J. Chem. Soc.*, **87**, 1781 (1905); C. Duval, *Compt. rend.*, **191**, 615 (1930); G. Morgan and J. Smith, *J. Chem. Soc.*, **121**, 1956 (1922).

[6] A. Lamb and J. Marden, THIS JOURNAL, **33**, 1873 (1911).

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF MANITOBA]

The Action of Carbon Dioxide and of Carbon Monoxide on Manganese

BY A. N. CAMPBELL AND E. A. BROWN

In the course of experimental work in this Laboratory, Mr. T. H. Martin had occasion to use carbon dioxide in scavenging apparatus containing heated metallic manganese. He found that the issuing gas was inflammable and recognized it to be carbon monoxide, the only source of which could be reduction of the carbon dioxide by the metallic manganese. Accordingly, a systematic investigation of this reaction was undertaken by the present authors.

A search of the literature revealed the following. Guntz[1] prepared metallic manganese by distilling off the mercury from a mercury amalgam, produced by electrolysis. It is important to notice that the manganese so obtained was pyrophoric, or at least had a very small particle size. He heated this manganese to 400° in a current of carbon monoxide. The manganese burned with sufficient liberation of heat to raise the mass to white heat. The carbon monoxide was absorbed so rapidly as to cause a partial vacuum in the apparatus, no carbon dioxide being formed. Guntz gives the equation

$$\mathrm{Mn} + \mathrm{CO} = \mathrm{MnO} + \mathrm{C} + 34{,}500\ \mathrm{cal.}^{2}$$

He then tried the reaction with carbon dioxide, using the same procedure, and observed the same results, in accordance with the equation

$$2\mathrm{Mn} + \mathrm{CO_2} = 2\mathrm{MnO} + \mathrm{C}$$

Nishibori[3] heated pure manganous oxide with carbon monoxide at 780°. The analysis of the gas phase gave the equilibrium proportions: $\mathrm{CO} = 93.5\%$, $\mathrm{CO_2} = 6.5\%$. Presumably the equilibrium here is

$$\mathrm{CO} + \mathrm{MnO} \rightleftarrows \mathrm{Mn} + \mathrm{CO_2}$$

Lorenz and Heusler,[4] working at low temperatures in the vicinity of 350°, made observations in agreement with those of Guntz. Insofar as their manganese was highly impure, containing 7% carbon, further detail seems inappropriate. In connection with our own observations, however, it should be mentioned that they heated the manganese in a stream of carbon dioxide, and on opening the apparatus the front end of the boat in which the manganese was heated was found to have been eaten away and a brownish manganese glass formed.

Charpy[5] has studied the reaction with carbon monoxide at 1000°, employing metallurgical products, metallic manganese and rich ferromanganese. The solid products consisted of a mixture of manganese monoxide and carbon. Heller[6] found that manganese begins to react with carbon monoxide at 330°, at 350° the reaction is fast, and at 410° very fast.

Both the reactions under consideration are heterogeneous, but they differ fundamentally from the frequently studied catalytic type, where the solid phase remains unchanged throughout. We may, however, accept the view that reaction is preceded by adsorption of the gas on the solid surface. If the adsorption is slight, the velocity measurements comply with the formula for a unimolecular reaction. When the saturation limit is approached, on the other hand, the rate of reaction is apparently independent of the concentration or pressure of the gas, until the concentration of the gas has decreased considerably. Such reactions are said to be of zero order.[7]

In the cases under consideration here, the matter is complicated by a further factor. When carbon dioxide, or carbon monoxide, reacts with metallic manganese, MnO is known to be formed. This must accumulate in an ever thickening layer around the manganese particle, and through this layer all carbon dioxide, or carbon monoxide, subsequently reacting with the manganese, must diffuse. In addition, where carbon monoxide is a product of the reaction, it must diffuse out through it. The velocity measurements give the resultant speed of three processes going on simultaneously: (1) adsorption, (2) diffusion, (3) reaction. If one process is slower than the others, its speed will be the effective speed of the three, no matter how great the velocity of the others. Diffusion may be slower, but can never be faster, than adsorption, for adsorption supplies the diffusing

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(1) A. Guntz, *Compt. rend.*, **114**, 115 (1892).

(2) For some reason not obvious, this value is about one-half that calculated from the heats of formation of reactants and products.

(3) E. Nishibori, Anniversary Volume dedicated to Masumi Chikashige, Kyoto Imp. University, 1930, pp. 295–8.

(4) Lorenz and Heusler, *Z. anorg. Chem.*, **8**, 225 (1893).

(5) G. Charpy, *Compt. rend.*, **148**, 560 (1909).

(6) W. Heller, "Beiträge zur Theorie des Eisenhochofenprozesses," (Marburg, 1905), p. 33.

(7) Hinshelwood, "Kinetics of Chemical Change in Gaseous Systems," Oxford University Press, 1929.

molecules. Similarly, reaction may be slower, but never faster than diffusion. If, in the cases under discussion, the slow process is that of diffusion, Fick's law of diffusion shows that the velocity measurements should comply with the formula of a unimolecular reaction, but we are faced with the further complication that Fick's law requires a diffusion layer of constant thickness, whereas here the layer of MnO is constantly increasing; the relative effect of increasing thickness would be greatest at first, subsequently decreasing with the thickness of the layer. Failure to comply with the unimolecular relationship will not therefore constitute evidence that diffusion is not the slow process. Furthermore, in the case of the carbon dioxide reaction, the carbon monoxide generated must diffuse out through the oxide layer, and this will have a retarding effect on the inward diffusion of carbon dioxide. It is evident from all this that any interpretation of the velocity measurements will be complicated, but certain predictions can be made. When the manganese is fresh, the oxide layer will be so thin that diffusion will produce no appreciable retardation. Accordingly, velocity measurements will give the resultant speed of adsorption and reaction together, and curves obtained by plotting composition of the gas phase against time will be similar to those for catalytic changes. When the manganese is old, and the layer of oxide thick, the increment in thickness as the reaction goes on will hardly affect the rate of diffusion. Then Fick's law will give the rate of diffusion of carbon dioxide through the layer quite accurately. This rate will be slower than the rate of reaction, which will therefore appear to be unimolecular.

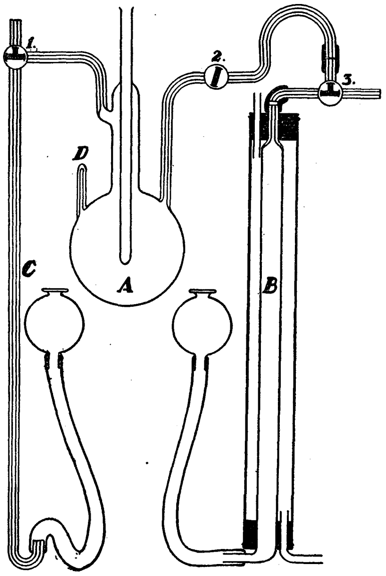

Fig. 1.

Experimental

Figure 1 is a diagram of the apparatus. The reaction chamber, A, was built from a Pyrex distilling flask of roughly 550 cc. total capacity. For temperature measurement inside this chamber an iron–constantan junction was used, the thermocouple leads running down the long tube in the neck of the flask. For measuring pressure an open manometer, C, was used, connected to the flask through the three-way cock 1; the manometer was read with a cathetometer. The free outlet of stopcock 1 led to a Hyvac pump. B is the gas buret for measuring samples taken for analysis; it was water-jacketed. The flask was filled with carbon dioxide through cock 3. After filling, the gas analysis pipets were connected to 3. An electric furnace was constructed such that flask A could be immersed completely in it, leaving only capillary tubing at uncontrolled temperature (about 0.3% of total volume). Temperatures were measured with a Leeds and Northrup potentiometer indicator, having an accuracy of 1 to 2 °F. As a check on the factory calibration, the cooling curves of pure zinc and of pure lead were taken with the instrument.

The side-arm D has the function of permitting additions of fresh manganese, without dismantling the apparatus. Carbon dioxide was prepared from limestone and hydrochloric acid and purified by passage through silver nitrate solution, calcium chloride, and phosphorus pentoxide. Carbon monoxide was prepared from sulfuric acid and sodium formate, and purified by passage through concentrated sulfuric acid, potassium hydroxide solution, calcium chloride, and phosphorus pentoxide.

The gas buret contained mercury, by lowering the level of which, samples of the gas phase could be removed and measured. The measured sample was then displaced through 3 to the gas pipets. That carbon monoxide is the sole gaseous product of the reaction was first determined by combustion with oxygen in a slow-combustion pipet. After this had been demonstrated, subsequent analyses were performed simply by determining the carbon dioxide with a potassium hydroxide pipet and obtaining carbon monoxide by difference.

Pyrophoric manganese was not used. The metal was obtained from the Johnson, Matthey Company of Toronto in the form of a powder and had the analysis: Mn, 96.84%; Fe, 1.74%; Si, 0.61%; C, 0.12%. The manganese was not in truly pulverized form but was very finely crushed and apparently had been screened to a uniform size after crushing. The mean diameter of the particles was 0.096 mm., but there were many particles much larger (> 0.16 mm.).

To determine whether or not the reaction represented by the equation

$$CO_2 + Mn = MnO + CO$$

was the sole one taking place, the flask was loaded with manganese and carbon dioxide, and its temperature gradually raised. Temperature and pressure were recorded every five minutes. Departure from Gay-Lussac law behavior began near 350° and became marked at 600°. Evidently, then, carbon dioxide is converted not only to carbon monoxide, but to a non-gaseous substance as well, for if the reaction were simply that formulated above, there would be no departure from Gay-Lussac law behavior.

That carbon monoxide is formed is beyond doubt. After one hour of heating at 600°, during which time the pressure fell over 400 mm., a sample of the gas contained only 1.0% carbon dioxide. Judging by the pressure drop, about 250 cc., at normal pressure, of gas remained. As previously mentioned, in similar preliminary experiments the carbon monoxide was determined directly by slow combustion, and it was found to correspond to 100% conversion.

After the completion of the preliminary experiments, systematic work was commenced at 600°, but owing to the frequent collapse of the flask under vacuum at this temperature, it was possible to bring only two runs to completion. The method of procedure followed throughout was to evacuate the flask, raise it to the required temperature, then fill it with the appropriate gas. The two successful runs gave the following results

Run	Duration, hr.	% CO_2 unchanged	Approximate initial press., mm.	Final press., mm.
2	1	0.0	831	646
3	0.5	0.0	869	727

The ratio of the change in pressure to the initial pressure gives the proportion of the whole going in the side reaction. This was 20.5% for run 2, and 16.3% for run 3. Since there was complete conversion to carbon monoxide in both cases, it appears to follow that the side reaction is slow compared to the main reaction, but that this deduction is not entirely justified will be seen in the sequel.

An experiment was now carried out at 500°, using 10.0021 g. manganese and 556 cc. carbon dioxide. At the end of two hours the pressure had dropped from 760 to 734 mm. and therefore the fraction of the whole being removed by the side reaction was 3.4%. The gas analysis at the end of the run showed no carbon dioxide remaining, which means that in two hours at 500°, with fresh manganese, the conversion of dioxide to monoxide is complete.

A series of runs was now undertaken in a somewhat different manner. Samples of the gas phase were withdrawn from time to time for analysis, and the whole experiment continued uninterruptedly until complete conversion was attained. Occasionally a run was carried out with carbon monoxide as starting gas, in an attempt to reach the equilibrium, if any, from the other side. Six experiments were carried out at 500°, and six at 400°, pressure readings being taken throughout, for the purpose of following the side reaction. Fresh metallic manganese was not used for each run, but a fresh charge occasionally was added to what was already present. Unimolecular "constants" were calculated for periods between consecutive analyses, and also for the period between the start and each analysis, the values being referred by calculation to a standard charge of 10 g. manganese.

The results showed that the relative speed of the side reaction is still less at 400 than at 500°. From the pressure drop, the fractions of the charge going to the side reaction are calculated as 7.3% in one and one-half hours at 500° and 4.0% in the same period at 400°. The unimolecular "constants" are by no means constant throughout any run. This can be seen from the plot of composition–time, where the curves appear to be much straighter than is required for unimolecular behavior. Figure 2 shows the composition–time curves for three runs. In each of these fresh manganese had been added recently. Runs A and B were at 500°, and run C at 400°. The curves show very well the greater speed at the higher temperature. Run B was faster than A, because the quantity of manganese was larger.

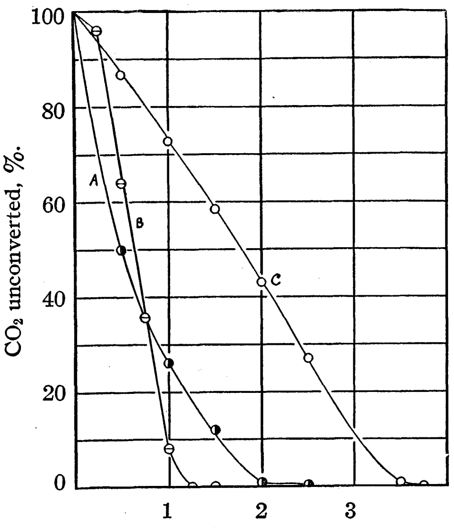

Fig. 2.—Conversion of CO_2 to CO in presence of manganese.

The form of the curves is similar to that of a zero order reaction. The long straight section shows a constant rate of conversion, indicating that adsorption of carbon dioxide is great. When conversion is nearly complete, the rate falls off because there is not enough carbon dioxide left in the gas phase to maintain the concentrated adsorption film.

When the manganese had been used for previous runs, its age began to have a retarding effect on the reaction rate. The "constants" showed this, being less numerically, with increasing use of the manganese. They did, however, show an approach to constancy with increasing use. This approach to constancy with age of the manganese was predicted in the introduction on the basis of diffusion.

In the runs that were followed right through, the final state was always one of complete conversion of carbon dioxide to the monoxide, so it was concluded that there was no appreciable equilibrium. As a check on this, two runs were carried out with carbon monoxide as the starting gas, one run for four hours at 500° and one for nineteen hours at 400°. In neither case was any carbon dioxide generated. Therefore, there is no appreciable equilibrium at 400 or 500°.

A number of runs in the neighborhood of 300° were vitiated from the following cause. A fresh supply of manganese had been obtained from Merck. This came in the form of a solid lump which was pulverized in a rock crusher. During the pulverizing, the manganese took fire for a moment. Subsequent examination showed it to contain manganese dioxide. In all attempts to use this powder it was characterized by extreme sluggishness of reaction. Apparently, then, the presence of a relatively small quantity of dioxide in the manganese insulates it more or less completely from being attacked by carbon dioxide. Fortunately there still remained some of the original manganese which was used in three experiments at 350°. These experiments showed that the reaction goes to completion at 350°.

To study the falling off in the rate of conversion with age of the manganese charge, an extended run was carried out at 500°. The reaction flask was cleaned out and 5.000 g. of fresh manganese introduced. The flask was then filled with carbon dioxide at 500° and the run continued until conversion to monoxide was just complete. The flask was then evacuated immediately and refilled with carbon dioxide. This process was repeated three times. The slowing down is illustrated by the curves of Fig. 3. Here composition is plotted against the logarithm of time, to shorten the diagram. The curves show progressively slower reaction rate with age of the manganese. When plotted against time and not log time, curve 1 has a straight portion like a zero order curve. The others curve at first and then flatten out to a line that is not far from horizontal for 3 and 4, and which approaches 0% CO_2 far out on the time axis. These curves come closer together with age of manganese, as the layer of oxide on the manganese particles becomes thicker. This increasing proximity of the curves for successive runs shows that a uniform rate of reaction is being approached, as was predicted in the introduction. Unimolecular "constants" were calculated for 3 and 4. The figures bear out what is evident from the curves, that the rate of reaction is not yet the same for successive runs. Were the manganese to be exhausted before the layer became sufficiently thick, this stage would never be reached. Comparatively coarse manganese would be more likely to give this effect.

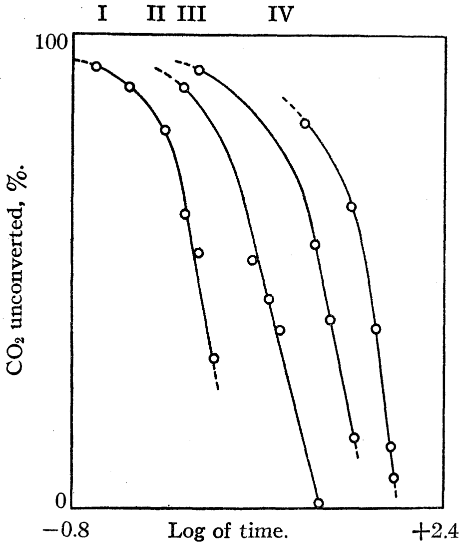

Fig. 3.—The effect of continuous use on the velocity of conversion.

Reaction between Manganese and Carbon Monoxide.—It was thought that this reaction would only attain measurable velocity above 600° and therefore a fresh apparatus was constructed. This consisted of a silica reaction flask connected to a hard glass manometer by a ground joint. The flask was embedded in a furnace capable of giving 800°. The capacity of the flask was 155 cc. and it was charged with 10 g. of manganese. The procedure was otherwise as before, except that no analysis was necessary, the course of the reaction being very simply followed by the drop in pressure.

For this work, the first consignment of manganese having been almost entirely exhausted and the second unsuitable, a third consignment was obtained from the Johnson, Matthey Co. Its analysis was much the same: Mn, 97.22%; Fe, 1.70%; Si, 0.55%; C, 0.11%, but the particle size was found to be much smaller. The average particle diameter was found to be 0.032 mm., as against 0.096 mm. for the manganese used in the earlier experiments.

Experiments were carried out at 600 and 500°. The results showed the reaction, which has been styled the "side reaction," to be unexpectedly rapid. This is undoubtedly due, at least in part, to the finer particle size. Considering consecutive experiments in which the same manganese was used, the speed of the reaction falls off rapidly with use, that is, with increasing thickness of the manganous oxide layer. The data do not comply with the requirements of a first order reaction. The reaction rate is much slower at 500 than at 600°.

An experiment was now carried out with the temperature rising from cold, to determine the temperature at which reaction became appreciable. On plotting pressure against temperature, it was seen that the reaction became rapid between 460 and 470°.

Because of the unexpected rapidity of the carbon monoxide reaction, a run was carried out at 600°, using the original coarser manganese. As was expected, the rate was much slower. Experiments were also carried out at 500°, using the coarser manganese. The velocity was less, although fresh manganese was used.

At all temperatures there is complete decomposition of the carbon monoxide by the manganese. The retarding effect of age is greater with the coarse manganese than with the fine, as would be expected.

The question now arose of whether, using the fine manganese, the same results, qualitatively at least, could be obtained, in respect of the conversion of carbon dioxide to carbon monoxide by manganese. For example, one of the early experiments gave complete conversion of carbon dioxide in two and one-half hours, using a fresh charge of 10 g. of coarse manganese at 500°. The experiment was therefore repeated at the same temperature, using the finer manganese. Pressures were read from time to time, and, after two and one-quarter hours, a sample of the gas phase was drawn off and analyzed for carbon dioxide. Conversion was practically complete and the pressure drop in two hours was 500 mm., whereas in the corresponding experiment with coarse manganese the drop in pressure was only about 40 mm. in the same time. This shows very clearly how the fineness of subdivision favors the reaction with carbon monoxide.

Presumably, if manganese is left in contact with either carbon dioxide or carbon monoxide, for a sufficient length of time, at a temperature of 500° or higher, complete decomposition of the gaseous phase to give manganous oxide and carbon, with production of zero pressure, will result. To test this point, an experiment was carried out at 600°, using carbon dioxide, and 10 g. of fresh fine manganese. Zero pressure was attained in thirty minutes.

Finally an experiment was carried out at 400°, using a carbon monoxide filling and 10 g. of the finer manganese. After two hours there was no change in pressure, indicating zero reaction velocity. It should, however, be mentioned that the manganese had been used in three previous experiments. At all events, the reaction velocity of the carbon monoxide reaction is very small at 400°. This is by no means the case with the carbon dioxide reaction.

As general conclusions to the latter part of this work, we would stress the effect of particle size. With pyrophoric manganese, at temperatures of 500° and above, it is possible that no carbon monoxide would be obtained from carbon dioxide by the action of manganese.

The Solid Phase

2.0364 grams of metallic manganese was heated in a stream of pure dry carbon dioxide in a porcelain boat contained in a wide silica tube, in an electric furnace at 600°. The charge was heated for five one-hour periods, at the end of each of which it was cooled in a stream of carbon dioxide and weighed. By the end of the fifth period the increase in weight was constant at 34.7% of original weight. The increase required for Mn–MnO is 29.2%.

The solid remaining had the characteristic dark green color of manganous oxide. An analysis of the solid product was then carried out. This gave the following figures: total Mn, 76.8%; free Mn, 4.87%; MnO_2, 1.1%; Mn as MnO_2, 0.7%; O_2 as MnO_2, 0.4%.

$$\text{Mn as MnO} = \text{Total Mn} - (\text{Mn as } MnO_2) - (\text{free Mn}) = 71.23\%$$

O_2 required for MnO	21.1%
Carbon	1.45%
	99.75%

No other oxide contains O_2 and Mn in proportions to fit the analysis. It is apparent that carbon dioxide converts metallic manganese to manganese monoxide. The reaction is therefore

$$Mn + CO_2 = CO + MnO$$

The analysis shows an increase in the amount of carbon over that of the original manganese, which contained only 0.12% carbon. This increase can be explained by the side reaction

$$CO + Mn = MnO + C$$

When the tube was removed from the furnace the section where the boat had been was found to have a frosted appearance inside as if the silica had been acted on. This is of interest as Lorenz and Heusler[4] concluded that manganese was volatile in carbon monoxide at white heat and was deposited as a dust on the interior of the tube. It seems to us more likely that a volatile and very unstable carbonyl is formed.

For study of the reaction between carbon monoxide and manganese a similar apparatus was used, except that the carbon monoxide was stagnant and a manometer was introduced to indicate absorption.

A charge of 3.0015 g. of manganese was heated for five days at 700°, then for a short period at 870°, after which there was no further indication of a drop in pressure. When the cooled furnace was opened, it was found that the interior of the silica tube was covered here and there with a greenish black deposit, while adhering to the porcelain boat was a pink deposit, which rendered weighing useless. This is further evidence supporting the contention of Lorenz and Heusler that manganese is volatile in carbon monoxide. The charge in the boat, in addition to possessing the characteristic greenish color of manganese monoxide, contained shining crystalline granules, presumably graphite. When the silica tube was removed from the furnace, it broke in two where the boat had been. This was apparently due to the silica having been attacked, for a pink layer fully 2.5 mm. thick now constituted most of the wall of the tube: only a thin shell of unchanged silica remained. The pink material was crystalline and is perhaps manganese metasilicate, $MnO{\cdot}SiO_2$. The mineral rhodonite has this composition and is pink in color. Either manganese is volatile in carbon monoxide, as claimed by Lorenz and Heusler, or it reacts with it so violently as to be almost explosively dispersed. This latter alternative does not seem likely, as no signs of excessive activity were observed in the experiments.

Total carbon in the product was determined by direct combustion, and free carbon by treatment with 50% hydrochloric acid and burning the residual carbon. Both determinations gave the same result, indicating that all the carbon is free, and not existing as carbide. The results of the analysis were:

Free carbon (= total carbon) = 14.3%
Total Mn = 66.0%
O_2 by difference = 19.7%

This corresponds to C = 14.3%; MnO = 85.7%. The reaction

$$Mn + CO = MnO + C$$

requires a percentage composition of C, 14.5%; MnO, 85.5%.

Discussion

By the use of non-pyrophoric manganese, the reaction of carbon dioxide with metallic manganese has been shown to take place in two stages, viz.,

$$CO_2 + Mn = MnO + CO \text{ (first stage)}$$
$$CO + Mn = MnO + C \text{ (second stage)}$$

The net result: $CO_2 + 2\,Mn = 2\,MnO + C$.

Lorenz and Heusler, as well as Guntz, were aware of these reactions, but did not recognize them to be stages of one reaction. Guntz used pyrophoric manganese, and the reaction was so fast that he failed to observe the first stage, and from his results formulated an equation identical with that obtained by uniting the first and second stages, as above. Lorenz and Heusler used manganese that contained so much carbon that it corresponded to the formula Mn_3C, so that it cannot be claimed that their results represented the action of metallic manganese on carbon dioxide and carbon monoxide. They did, however, observe the conversion of carbon dioxide to carbon monoxide. They also observed, as did Guntz, that manganese monoxide and carbon are formed when carbon monoxide is used.

This work has established that the only products are those indicated by the equations. It also appears that metallic manganese is volatile in carbon monoxide. This can only mean that manganese unites with carbon monoxide to form a volatile compound, presumably a carbonyl, which is almost immediately decomposed. Lorenz and Heusler stated that a carbonyl is not formed, by which they mean a carbonyl having some degree of stability. Their spectroscopic examination of the gas issuing from their apparatus showed manganese to be absent, and this proves that, if carbonyl is formed, it must be extremely unstable.

The speed of reaction depends not only on the temperature, but on the age and quantity of the manganese. With fresh manganese, reaction is fast between 500 and 600°. It is slower at 400°, and extremely slow at temperatures approaching 300°. The carbon dioxide reaction is of the zero order type, when the manganese is fresh, as shown by the curves of Fig. 2. When the layer of manganese monoxide becomes of appreciable thickness, the rate of conversion is no longer dependent on adsorption, but on the rate of diffusion through the layer. Hence, when the manganese monoxide layer becomes very thick, the reaction appears to be of the first order.

Nishibori found an equilibrium between carbon dioxide and carbon monoxide at 780°, in the presence of manganese monoxide. At the lower temperatures at which the present experiments were carried out, no such equilibrium exists. Conversion of carbon dioxide to carbon monoxide was always complete, except in experiments near 300°, where the reaction is so slow that a false equilibrium seemed to exist. It is not possible, therefore, to calculate the heat of reaction from the van't Hoff isochore. The heats of reaction can, however, be calculated from the known heats of formation, whence we obtain

$$\begin{aligned} CO_2 + Mn &= MnO + CO + 22{,}800 \text{ cal.} \\ CO + Mn &= MnO + C + 64{,}400 \text{ cal.} \\ CO_2 + 2Mn &= 2MnO + C + 87{,}200 \text{ cal.} \end{aligned}$$

These figures show that both forward reactions are exothermic and hence the back reaction is favored by raising the temperature. Nishibori obtained 6.5% carbon dioxide at 780°, while our work shows that there is no equilibrium at 600°. Somewhere between these two limits of temperature, appreciable equilibrium sets in.

Summary

It has been shown that the reaction previously formulated

$$2Mn + CO_2 = 2MnO + C$$

really consists of two consecutive stages

$$Mn + CO_2 = MnO + CO \qquad (a)$$

and

$$Mn + CO = MnO + C \qquad (b)$$

At temperatures of 400° and less reaction (a) predominates almost exclusively. At temperatures higher than 400°, the velocity of reaction (b) increases very rapidly, and, using pyrophoric manganese, this probably would result in the complete removal of the carbon monoxide formed by (a), at least above 500°.

The velocities of both reactions are principally conditioned by the rate of diffusion through the manganous oxide layer. Apparently, manganous oxide is more pervious to carbon dioxide than to carbon monoxide.

Both reactions are exothermic but no indication of a back reaction was detected up to 600°.

WINNIPEG, CANADA RECEIVED MAY 13, 1938

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Isotonic Solutions. I. The Chemical Potential of Water in Aqueous Solutions of Sodium Chloride, Potassium Chloride, Sulfuric Acid, Sucrose, Urea and Glycerol at 25°[1]

BY GEORGE SCATCHARD, W. J. HAMER[2] AND S. E. WOOD

Sinclair and Robinson[3] have developed the isotonic or isopiestic method[4] so that it is more precise than any of the direct methods of measuring the chemical potential (or activity) of the solvent in which the temperature of measurement does not vary with the concentration. We have modified their method to give a still greater precision. We believe that our error is not greater than 0.1% of ϕ, the osmotic coefficient when the total molality, νm, is greater than one molal, and not greater than 0.001 in $\phi\nu m$ for smaller concentrations.

In order to determine the chemical potential of the solvent, or any related quantity, from isotonic measurements, however, it is necessary to know it as a function of the composition for one solute. On the other hand, the method gives a way of comparing the measurements with different solutes. We have, therefore, made such measurements on aqueous solutions of sodium chloride, potassium chloride, sulfuric acid, sucrose, urea and glycerol at 25° with a triple objective: to determine to what degree of precision we can extend the method, to obtain as accurate a standard as possible, and to make a comparison between the values of the chemical potential of water determined by a variety of the most accurate methods.

To understand the reasons for our modifications it is necessary to consider the attainment of equilibrium in some detail. The isotonic method is beautifully simple. A weighed amount of a solution of known composition is placed in a tared cup; a set of such cups are allowed to come to equilibrium through the vapor phase, and each cup is weighed again. Any change in weight must be due to a gain or loss of solvent. We compare six solutions simultaneously, but the discussion of the factors which must be taken into account is clearer if we consider but two. In our apparatus each solution weighs about a gram; each cup has a volume of about 15 cc. and the volume of the whole vapor space is about 300 cc. We may suppose that the solvent is water, that the solutions are about one molal in total solutes, that the initial concentration ratio is 1.01, and that we wish to reduce it to 1.001. This will require the distillation of about 0.05 g. of water from one cup to the other. At 25° the vapor pressure of water is about 25 mm., and that of a molal solution, about 0.5 mm. less. At the start the two vapor pressures differ by 0.005 mm. or 0.02%; at the end they should differ by 0.0005 mm. or 0.002%. The 0.05 g. of water would occupy about 2000 cc. as saturated vapor. Any air would doubtless be pumped from the cup losing water, and probably much of the air in the outer volume would be concentrated in the cup gaining water. However, the hydrostatic pressure of water vapor plus air is always equal throughout the vapor space. If the partial pressure of air in the cup gaining water exceeds 0.0005 mm. near the end of the reaction, the reaction will cease until the air diffuses out. Even smaller amounts of air will slow up the reaction considerably.

The final vapor pressure difference of 0.0005 mm. corresponds to a temperature difference of about 0.00035°. If the temperature fluctuates so that the solution with the lower vapor pressure is hotter than the other by more than this amount, the distillation will tend to go in the wrong direction. Moreover, the adiabatic distillation of 0.3×10^{-6} g. of water between one gram samples is sufficient to cause this temperature difference. This is only six millionths of the water which has to be distilled. It is a simple matter to calculate the effect upon each of these quantities of changes in the initial concentrations or concentration dif-

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[1] Presented before the Division of Physical and Inorganic Chemistry of the American Chemical Society at Rochester, N. Y., September 6, 1937.

[2] Present address: National Bureau of Standards, Washington, D. C.

[3] (a) D. A. Sinclair, *J. Phys. Chem.*, **37**, 495 (1933); (b) R. A. Robinson and D. A. Sinclair, THIS JOURNAL, **56**, 1830 (1934).

[4] "Isotonic" was introduced by Hugo de Vries, who first used an isotonic method in 1882, to define solutions in equilibrium with respect to transfer of the solvent. "Isopiestic" was substituted by Bousefield in 1918 because he considered "isotonic" bound up with theories which he did not like. However, "isotonic" has the advantage of historical priority and the more important one that it stresses equilibrium, which is the important relation, while "isopiestic" overemphasizes the equality of pressure, which is no more important than the equality of several other properties.

ferences, the desired accuracy and the size of the sample.

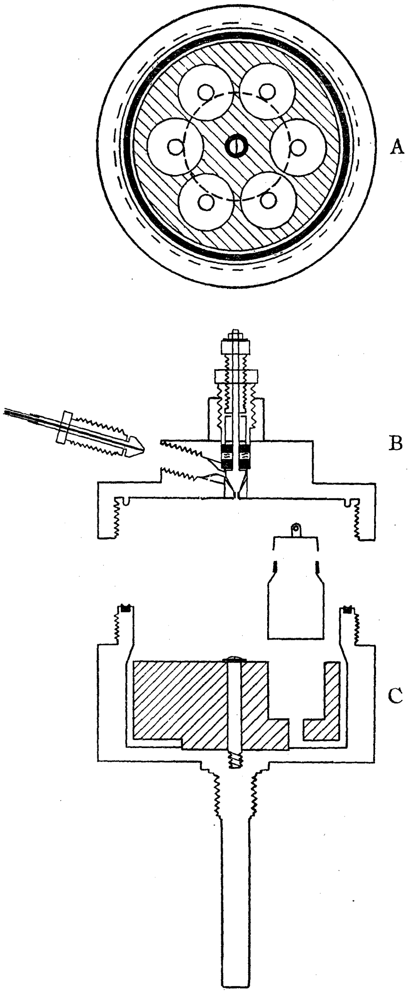

Fig. 1.—Apparatus. The left-hand side of the vertical section of the copper block is taken perpendicular to the other side.

Therefore, the essentials of the apparatus and procedure are: good heat conduction from one cup to another, a good thermal buffer to prevent fluctuations of temperature, efficient stirring to assure mixing and heat conduction without heating, evacuation adequate to remove the air, small samples to reduce the amount of distillation necessary and tight cups to permit accurate weighings. Sinclair[3a] discusses fully the heat and temperature effect, but states that thorough evacuation is unnecessary. His apparatus is as efficient as ours for the heat conduction, but we believe that our modifications give improvements in the other respects. To save space we will omit a detailed comparison and merely describe our apparatus and procedure.[5] The apparatus is illustrated in Fig. 1. The six cups are of platinum and are shaped like milk cans. Each is a cylinder 3.5 cm. high and 2.5 cm. in diameter. The top is constricted to 1.8 cm., and a nickel ring, 0.5 cm. high, is silver-soldered to the outside of the constriction. The outside of this ring is carefully ground with a 3° taper to fit a nickel lid. The bottom and lower 2 cm. of the side wall of the cup are lined with platinum gauze to increase the surface and aid the stirring and heat conduction.

The six cups fit snugly in cylindrical holes arranged symmetrically in a gold-plated copper block, 9.5 cm. in diameter and 3.5 cm. deep. This block fits into a stainless steel vessel of 12.5 cm. outside diameter and 7.5 cm. high. The cover screws on against a lead gasket and has a conical valve through which the vessel is evacuated. The male fitting for the evacuating tube is replaced by a dummy while the vessel is in the thermostat. This vessel fits on a table in the thermostat which rotates around an axis inclined at 45°. Each cup rotates about its own axis also inclined at 45°, as it revolves around the central axis.

The copper block weighs 1.6 kg. and the steel of the vessel weighs 4.6 kg. The only contact between them is over a circular area 5 cm. in diameter at the center of the bottom. They should give an effective thermal buffer. The fact that the thermostat oil must circulate around the lead counterweight and the massive steel rotating table just before it reaches the vessel increases the buffer action so that short-time temperature fluctuations must be much smaller in the vessel than in the recording thermometer. Slow changes of temperature of moderate magnitude are not troublesome.

The oil thermostat bath and thyratron regulator are similar to those described by Beattie[6] except that the plate circuit of the thyratron is connected directly to the main a. c. line instead of to the transformer, and that a mercury regulator in the bath is inserted in the galvanometer circuit to protect the galvanometer if the bath cools. This regulator maintains its temperature constant within 0.001° over an interval of a few hours and within 0.005° over a twenty-four hour period.

The composition of the most concentrated sulfuric acid solution in each series was determined

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(5) Certain of these modifications which were adopted by us in 1935 and used in this work have been previously reported by C. M. Mason, THIS JOURNAL, **60**, 1638 (1938).

(6) J. A. Beattie, *Proc. Am. Acad. Arts Sci.*, **69**, 389 (1934).

by a weight titration of sodium carbonate with methyl orange as indicator. All other solutions were made up by weight. All weights were corrected to vacuum. For solutions in which the total concentration, νm,[7] was greater than 0.4, about 1 g. of solution was weighed into each of the six cups. For more dilute solutions about 0.5 g. was used. For solutions in which νm was greater than one, six drops of water was placed at the bottom of the vessel so that their evaporation might sweep out the air from below the copper block and might reduce the evaporation from the cups. To control the evacuation and prevent splattering the vessel was not connected directly to the vacuum line but to a bulb of about the same volume as the vessel itself. The bulb could be connected to an oil pump or to the vessel. The latter connection was always made so that the passage of gas was very slow. After the pressure had reached the vapor pressure of water, the vessel was evacuated ten times more. For solutions in which νm was less than one, 20 cc. of the sodium chloride solution was put directly into the steel vessel. When the vessel tipped, this rose around the lower cups and gave better thermal contact between them and the copper block. Since it also made necessary washing and drying the cups before they were weighed, this procedure was used only for the more dilute solutions for which it was needed. The vessel was evacuated as for the more concentrated solutions and, after three hours' rotation in the thermostat, it was evacuated ten times more and then replaced in the bath.

Solutions with νm greater than one were rotated in the bath for twenty-four hours; those with νm less than 0.6 were rotated seventy-two hours, and the intermediate solutions were rotated forty-eight hours. The vessel was then removed from the bath, dry air was allowed to enter, the top was removed and the lids were placed on the cups as soon as possible, which was usually less than half a minute after the opening of the vessel. In most of the runs each cup contained a different solute. For runs 7, 9, 11, 13, 15, 17, 19 and 21, the cups were returned to the vessel after the previous run, so that each of these depended upon the same initial weighings as the previous run.

The success with which equilibrium is attained in concentrated solutions is illustrated by two preliminary experiments which are not included in our final results. The first shows how closely equilibrium is attained even when the amount of water distilled is large. The initial concentrations of urea and of sulfuric acid were adjusted so poorly that the urea lost 0.58 of its 0.92 g. of water and the sulfuric acid gained about the same amount. In spite of this huge change, the largest difference from the equilibrium value is only four-tenths of one per cent. The initial, final and equilibrium concentrations are

	Initial	Final	Equilibrium
NaCl	3.237	2.670	2.671
KCl	2.693	2.931	2.926
H_2SO_4	3.510	2.111	2.114
Sucrose	3.592	3.985	3.982
Urea	2.382	6.429	6.427
α-Met. gluc.	4.063	4.509	4.523

The other experiment illustrates the reproducibility of the equilibrium concentrations because the drops of water added before evacuating in the second of two runs with the same solutes compensated so exactly for the loss during evacuation that the average loss was only 0.05 mg., and the concentrations are almost the same for the two runs. We list the concentrations before the first run, the equilibrium concentrations after each run and the milligrams gained during the second run.

	Initial concn.	Equilibrium concn. First	Equilibrium concn. Second	Second gain, mg.
NaCl	1.5730	1.5483	1.5479	+0.25
KCl	1.6585	1.6432	1.6429	+ .17
H_2SO_4	1.3391	1.3081	1.3080	+ .03
Sucrose	2.4177	2.4186	2.4188	− .04
Urea	3.2026	3.2920	3.2925	− .15
α-Met. gluc.	2.5716	2.6083	2.6082	+ .03

The discrepancy between the two determinations of ϕ for any solute from ϕ for any other is measured in parts per thousand by the difference between the corresponding entries in the last column. The maximum discrepancy is 0.04% and the average is only 0.02%.

The isotonic method was also adapted to the simultaneous measurement of solubility and the chemical potential of water from the saturated solution. A stock solution was made up which was almost saturated. In one or two of the cups an unweighed quantity of this solution was added to about a gram of the solid. The other cups each contained a weighed quantity of the same solution or of a comparison solution. At equilibrium the concentration of the solution without excess solid must be the same as that in the solu-

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(7) ν is the number of particles from one molecule of solute, and m is the concentration in moles per kg. of water.

tion directly in equilibrium with the solid phase. So the solubility may be determined conveniently without any need of separating from the solid phase. The composition of the comparison solutions gives at the same time the potential of the solvent. This method is particularly convenient for cases of high solubility varying rapidly with the temperature, and with viscous saturated solutions. The solubility of each solid used was determined in this way. These measurements were made with cups without the nickel rings and with light platinum covers which leaked enough at this stage so that it was necessary to make two weighings and extrapolate back to the time of closing.

The equilibrium concentrations as moles per kilogram of water are given in Table I for the 32 runs which are used in the computations. About a hundred other runs were made and not used. A few were discarded because of obvious spattering, or leakage with the old platinum covers, or insufficient purification of one of the materials. However, most of these runs were made in developing the technique, particularly with dilute solutions. In some of the more concentrated solutions two cups contained the same initial solution. Both final values are given in the table, and their agreement gives another check on the accuracy of the method. The saturated solutions are indicated in the table.

TABLE I

ISOTONIC CONCENTRATIONS AT 25°

Run	NaCl	KCl	H_2SO_4	Sucrose	Urea	Glycerol
1	6.1430[a]		4.3740			
	6.1451[a]		4.3756			
2	6.1429[a]		4.3725			
	6.1461[a]		4.3742			
4	6.0781		4.3145		20.007[a]	14.572
22	5.4593		3.9289		17.078	12.583
			3.9294			12.589
23	4.6013		3.3890		13.332	10.036
			3.3895			10.036
24	4.2585		3.1668		11.957	9.0887
			3.1658			9.0889
3	4.1983	4.8029[a]			11.750	
		4.8051[a]				
5[b]				6.0526[a]	11.239	8.5959
				6.0533[a]		
25	3.7390	4.2210	2.8298	5.5266	9.9882	7.7240
26	3.3911	3.7916	2.6023	5.0110	8.7450	6.8614
27	2.5022	2.7273	1.9998	3.7462	5.8919	4.8294
29	2.4135	2.6232	1.9351	3.6210	5.6262	4.6455
28	2.0845	2.2460	1.7065	3.1646	4.6999	3.9427
30	1.6220	1.7228	1.3651	2.5172	3.4728	3.0233
31	1.1614		1.0109	1.8578	2.3669	2.1334
7	1.0010	1.0427	0.88920	1.6277	2.0088	1.8332
6	0.99954	1.0399	.88666	1.6260	2.0033	1.8318
32	.68788	0.70998	.62219		1.3375	1.2558
13	.51709	.53045	.47046	0.88639	0.99133	0.94213
12	.50593	.51923	.46089	.86829	.96818	.92265
15	.40846	.41783	.37419	.70940	.77579	.74537
14	.40034	.40838	.36619	.69549	.75828	.72942
17	.30922	.31486	.28463	.54621	.58361	.56589
16	.30303	.30896	.27916	.53546	.57270	.55533
9	.21275	.21584	.19654	.38066	.40016	.39170
19	.20603	.20893	.19006	.37043	.38766	.37918
8	.20432	.20715	.18892	.36611	.38563	.37694
18	.20120	.20444	.18577	.36229	.37746	.37002
21	.10288	.10380	.09405	.18917	.19448	.19089
10	.10014	.10059	.09079	.19297	.18866	.18587
20	.09930	.10027	.09082	.19257	.18764	.18477
11	.09918	.10098	.09095	.18303	.18845	.18766

[a] Saturated solution. [b] Compared with the standard through urea.

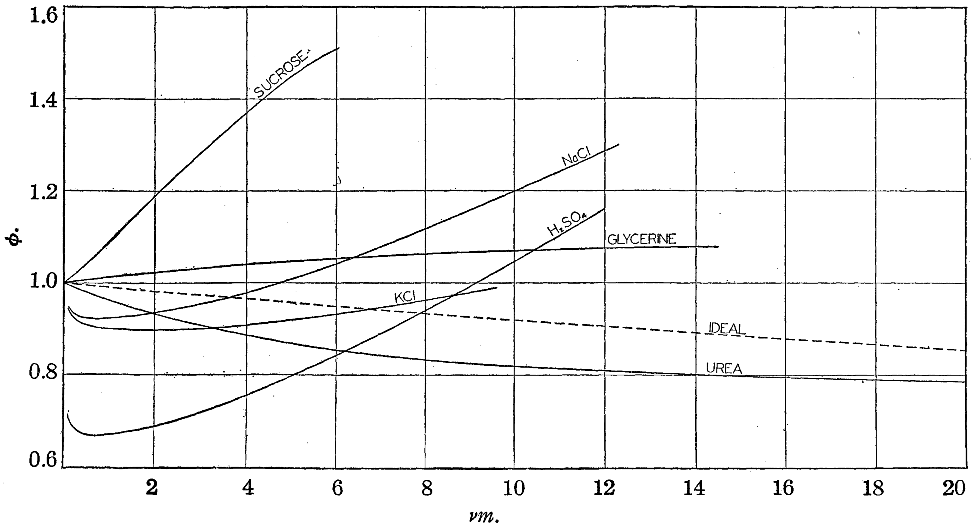

Fig. 2.—Osmotic coefficients.

A convenient way of comparing the results is in terms of the osmotic coefficient, ϕ

$$\phi = (\mu_{00} - \mu_0)/w_0RT\nu m = -(\ln a_0)/w_0\nu m \quad (1)$$

in which μ_{00} is the chemical potential of the pure solvent, μ_0 is the potential of the solvent in the solution, w_0 is one thousandth of the molecular weight of the solvent, R and T have their usual significance, ν and m have been defined above, and a_0 is the activity of the solvent. In Fig. 2 our values of ϕ are plotted against νm. The curve labeled ideal is $[\ln(1 + w_0\nu m)]/w_0\nu m$ and is the osmotic coefficient of an ideal solution, for which the activity of the solvent is equal to its mole fraction. For solutions which are isotonic, $(\mu_{00} - \mu_0)$ is the same in each solution, and therefore $\nu m\phi$ is also the same. In this diagram the isotonic lines are rectangular hyperbolas with the equations $\phi = k/\nu m$. For some purposes it is convenient to plot ϕ against $\nu m\phi$ so that the isotonic lines are all perpendicular.

In determining the best standard curve from measurements on several substances, it is convenient to assume a curve for one substance as standard and to compute each value for another solution from this curve and the concentrations of the standard and of the other solution. Then the standard curve is altered as often as necessary to give the best fit for all the measurements. We have chosen sodium chloride as the standard since it was used in almost every run; it is easily purified, and its curve is much simpler than that of sulfuric acid which is the only other substance used in all the most concentrated solutions.

The scale of Fig. 2 is much too small for comparison of our smooth curves with the experimental results. We have therefore plotted the deviation function $\Delta\phi$ which is defined for each solute under the corresponding figure. The last term for the electrolytes is the Debye–Hückel square root correction in very dilute solutions and becomes very nearly constant in more concentrated solutions.[8] The constants in the other terms are empirical. The graphs for the individual solutes all have the same scale of ordinates in which each division is 1%.

Sodium Chloride (Fig. 3).—An analytical reagent was dissolved in conductivity water and precipitated by hydrogen chloride gas. The precipitate was dried at 300° and then at room temperature by passing through the finely powdered material in a Gooch crucible a current of air which had been dried by calcium chloride. The solubility of 6.144 M may be compared with 6.145 M of the "I. C. T." (vol. IV, p. 235).

The vapor pressures of sodium chloride solutions have been measured at 25° by Frazer and S. S. Negus,[9] and by Pearce and F. Fordemwalt,[10] and at 20° by Frazer and W. R. Norris.[9] The latter were corrected to 25° through the use of the heat of dilution measurements of Gulbransen and Robinson[11] and of Lipsett, Johnson and Maass.[12] Osmotic coefficients at 25° were calculated from the freezing point measurements of Scatchard and Prentiss[13] and the first of these heat measurements. The treatment of dilute solutions will be discussed elsewhere. The os-

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[8] George Scatchard, *Chem. Rev.*, **19**, 309 (1936).

[9] J. C. W. Frazer, "The Direct Measurement of Osmotic Pressure. Contemporary Developments in Chemistry," Columbia University Press, New York, N. Y., 1927.

[10] J. N. Pearce and A. F. Nelson, THIS JOURNAL, **54**, 3544 (1932).

[11] E. A. Gulbransen and A. L. Robinson, *ibid.*, **56**, 2637 (1934).

[12] S. G. Lipsett, F. M. G. Johnson and O. Maass, *ibid.*, **49**, 1940 (1927).

[13] G. Scatchard and S. S. Prentiss, *ibid.*, **55**, 4355 (1933); **56**, 2314 (1934).

motic coefficients were also calculated from Harned's measurements of the electromotive force of cells with sodium amalgam and silver chloride electrodes[14] with the use of activity coefficients up to 0.1 *M* determined by Brown and MacInnes[15] from cells with transference and the transference numbers. Since sodium chloride was chosen as our standard, no experimental points appear in Fig. 3 for our own measurements. The freezing point values agree with the standard curve almost exactly. Below one molal the vapor pressure measurements scatter too widely to be of use. At higher concentrations those of Pearce and Fordemwalt check the curve within their fluctuations from any smooth curve. Those of Frazer and Negus agree even better except for the last two points which were measured in two steps. The measurements at 20° give values about 1% high. The electromotive force measurements agree with the standard up to 0.1 *M*; they yield osmotic coefficients lower than the standard below 1 *M* and higher above that concentration, with a maximum deviation of almost 1%.

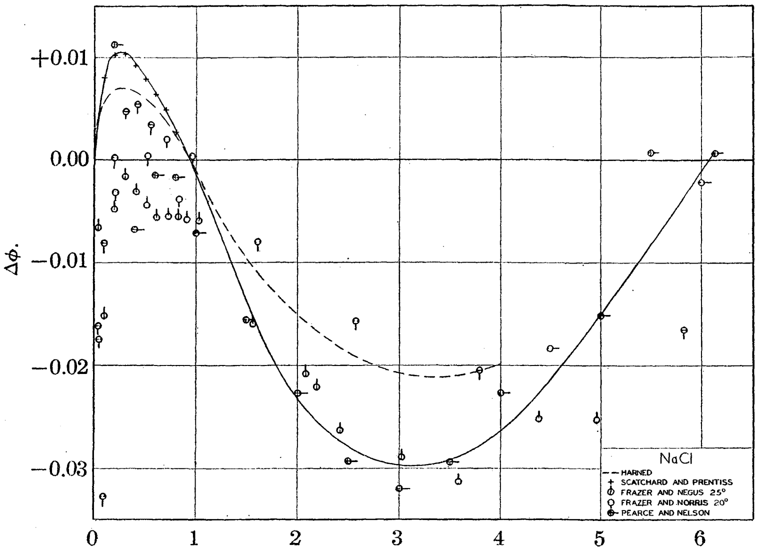

Fig. 3.—Sodium chloride deviations: $\Delta\phi = \phi - 1 - 0.07m + 1.165[1 + \sqrt{m} - 1/(1 + \sqrt{m}) - 2 \ln (1 + \sqrt{m})]/m$.

Potassium Chloride (Fig. 4).—An analytical reagent was crystallized three times from conductivity water and dried at 300° and then in a current of dry air as described for sodium chloride. The solubility of 4.804 *M* may be compared with 4.81 *M* ± 0.5% of the "I. C. T." (vol. IV, p. 239). The vapor pressure measurements of Pearce and Snow[16] are much less consistent than those from the same laboratory with sodium chloride, and the average deviation is almost one per cent. and negative. The measurements of Lovelace, Frazer and Sease[17] at 20°, computed to 25° with the use of the heat of dilution measurements of Lange and his collaborators,[18] are about 1% higher than the standard curve. The electromotive force measurements of Harned and Cook,[19,14] yield high values of the osmotic coefficient throughout the range of their measurements. The measurements of Shedlovsky and MacInnes[20] with cells with transference combined with transference numbers lead to very exact agreement up to half molal. We did not integrate their results further because the measurements are sparse and there seems to be some question of the accuracy of their measurement at 0.5 *M*. Figure 4 shows how precisely the standard curve for potassium chloride is fixed by the isotonic measurements once the curve for sodium chloride is determined.

We may also compare our measurements with Robinson and Sinclair's measurements of the isotonic ratios of sodium chloride to potassium chloride.[5b] For concentrations above one molal their ratio of sodium chloride concentration to potassium chloride concentration averages 0.1% smaller than ours. This difference is smaller than the fluctuations of their results or the accuracy they claim. Below one molal, where our fluctuations are also larger, their ratio is about 0.1% larger than ours.

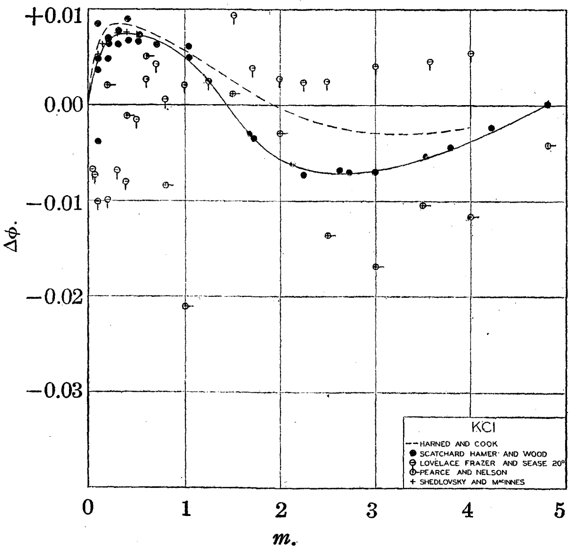

Fig. 4.—Potassium chloride deviations: $\Delta\phi = \phi - 1 - 0.026m + 1.165[1 + \sqrt{m} - 1/(1 + \sqrt{m}) - 2 \ln (1 + \sqrt{m})]/m$.

Sulfuric Acid (Fig. 5).—Chemically pure sulfuric acid was distilled very slowly in an all-glass still into conductivity water to give a solution of density 1.8. The vapor

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(14) H. S. Harned, This Journal, **51**, 416 (1929); H. S. Harned and L. F. Nims, *ibid.*, **54**, 423 (1932).

(15) A. S. Brown and D. A. MacInnes, *ibid.*, **57**, 1356 (1935).

(16) J. N. Pearce and R. D. Snow, *J. Phys. Chem.*, **31**, 231 (1927).

(17) B. F. Lovelace, J. C. W. Frazer and V. B. Sease, This Journal, **43**, 102 (1921).

(18) J. Wüst and E. Lange, *Z. physik. Chem.*, **116**, 161 (1925); E. Lange and J. Monheim, *ibid.*, **A150**, 349 (1930).

(19) H. S. Harned and M. A. Cook, This Journal, **59**, 1290 (1937).

(20) T. Shedlovsky and D. A. MacInnes, *ibid.*, **59**, 503 (1937).

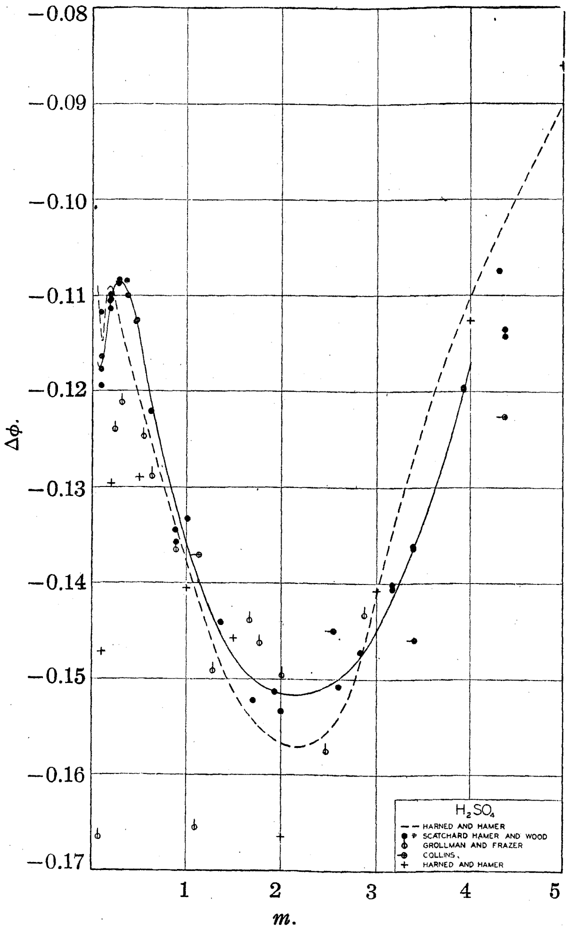

Fig. 5.—Sulfuric acid deviations: $\Delta\phi = \phi - 1 - 0.13m + 2.330[1 + \sqrt{3m} - 1/(1 + \sqrt{3m}) - 2 \ln (1 + \sqrt{3m})]/3m$.

pressure measurements of Grollman and Frazer[21] scatter about our standard curve with a small average difference. Those of Collins[22] lie slightly above it below 3 *M* and below it above 3 *M*. Harned and Hamer's measurements[23] of the cells

$$H_2,\ H_2SO_4\ (m),\ PbSO_4,\ PbO_2,\ Pt \qquad (I)$$

and

$$H_2,\ H_2SO_4\ (m),\ Hg_2SO_4,\ Hg \qquad (II)$$

may be combined to give

$$E_{I} + E_{II} - E_{I_0} - E_{II_0} = (RT/F) \ln a_0 \qquad (2)$$

However, 0.01 mv. corresponds to 1% at 1 *M* and to 0.1% at 5 *M*. The largest deviation from our standard curve corresponds to 0.03 mv. at 2 *M*. The values of ϕ determined by integration from the chemical potential of the acid measured by one of these cells singly lie below our standard curve below about 3 *M*, and above at higher concentrations, with a maximum deviation of about 0.5%. The integrated deviation curve has a minimum at about 0.1 *M*, and a maximum at about 0.2 *M* which cannot be avoided without attributing to the experiments an error much larger than appears probable. We have drawn our standard curve with a similar maximum and minimum to correspond to our measurements although these measurements are probably not precise enough to establish independently that there is such an irregularity.

Sucrose (Fig. 6).—From a nearly saturated cane sugar solution prepared by percolation the sucrose was precipitated by adding ethyl alcohol at 0°. It was dried over calcium chloride and then in a current of dried air as described for sodium chloride. To avoid errors due to hydrolysis no solution of sucrose was used which had been in contact with water more than a week. Our solubility of 6.053 *M* corresponds to 67.44% sucrose, which may be compared with the 67.89% of "I. C. T." (vol. II, p. 344). We have not found the measurements of osmotic pressure to be accurate enough for our purposes. The vapor pressures of sucrose solutions have been measured at 25° by Frazer and L. C. Beard,[9] at 20° by Frazer and H. K. Parker,[9] and at 0° and 30° by Berkeley, Hartley and Burton.[24] We have interpolated these last measurements linearly in $1/T$, which corresponds to a heat of dilution independent of the temperature, and have used the same temperature coefficient to calculate ϕ at 25° from the measurements of Frazer and Parker. Above two molal the measurements of Frazer and his collaborators are in good agreement with our standard curve. Those of Berkeley and collaborators are about 1.5% higher.

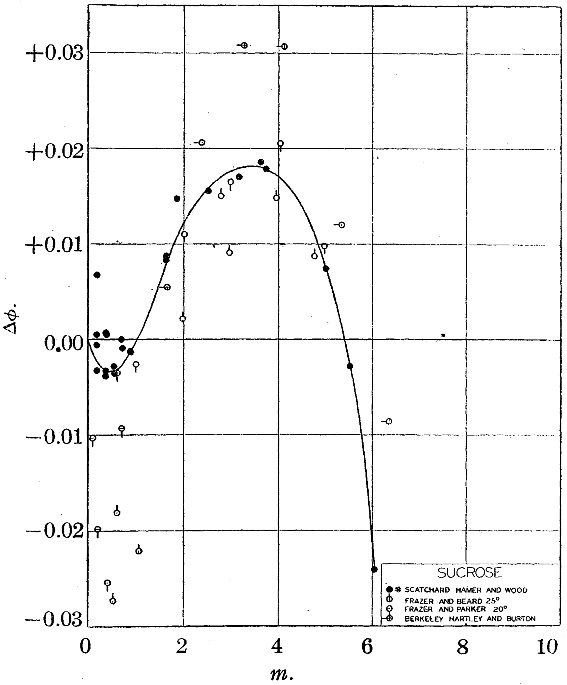

Fig. 6.—Sucrose deviations: $\Delta\phi = \phi - 1 - 0.088m$.

Urea (Fig. 7).—Synthetic urea was crystallized from conductivity water and then from ethyl alcohol, both without heating above 60°. It was dried over calcium chlo-

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[21] A. Grollman and J. C. W. Frazer, THIS JOURNAL, **47**, 712 (1925).

[22] E. M. Collins, *J. Phys. Chem.*, **37**, 1191 (1933).

[23] H. S. Harned and W. J. Hamer, THIS JOURNAL, **57**, 27 (1935).

[24] Earl of Berkeley, E. G. C. Hartley and C. V. Burton, *Phil. Trans.*, **218A**, 295 (1919); G. Scatchard, THIS JOURNAL, **43**, 2406 (1921).

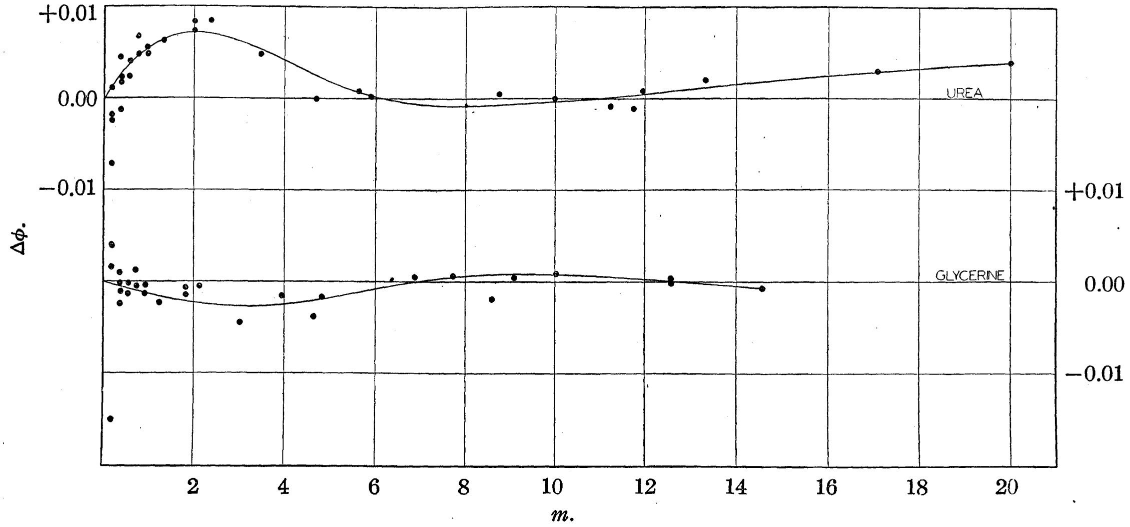

Fig. 7.—Urea and glycerol deviations: Urea, $\Delta\phi = \phi - 1 + 00.05m/(1 + 0.179m)$; Glycerol, $\Delta\phi = \phi - 1 - 0.016m/(1 + 0.1333m)$.

ride and then in a current of dry air as described for sodium chloride. To avoid errors due to hydrolysis or to rearrangement to ammonium cyanate, no urea was used which had been in contact with water more than a week. A study of 0.01, 0.1 and 1.0 *M* urea solutions showed that at room temperature it requires a month for the conductance of a urea solution to reach 0.1% of that of a sodium chloride solution of the same molality. The solubility of 20.007 *M* was confirmed by two determinations in each of which four cups contained urea solutions. These gave an average of 20.006 with an average deviation of 0.006. This checks the measurements of Pinck and Kelly[25] as closely as they can be interpolated to 25°. Values of 17, 18 and 19 *M* are also found in the literature. The vapor pressures of urea solutions have been measured at 25° by Lewis and Burrows.[26] We confirm their statement that a saturated solution is nearly ideal, but find that their measurements are otherwise not sufficiently accurate for our purposes. Urea was included in our study in the hope that the deviations from ideality would be so much smaller in dilute solutions that a simple interpolation would be justified. Figures 2 and 7 show that the difference from ideality does not decrease rapidly with decreasing concentration until the solutions are quite dilute and that the deviations from our analytical function are little, if any, simpler than for the other substances.

The measurements of Chadwell and Politi[27] yield values of ϕ at the freezing point which are very slightly higher than ours at 25° in dilute solutions but decrease more nearly linearly to 0.7646 at 8.083 *M* (the eutectic) where the value at 25° is 0.8333. This difference would correspond to a partial heat content of water 0.65 cal./mole more positive than that of pure water if this heat content difference were independent of the temperature. However, the heat capacity measurements of Gucker and Ayres[28] show that this difference is becoming more positive with decreasing temperature, and is changing more rapidly the lower the temperature. This variation together with the decrease of freezing point with increasing concentration may explain the fact that the average value of $(\mathrm{d}\phi/\mathrm{d}T)/m$ between the freezing point and 25° appears to increase rapidly with increasing concentration although ϕ/m decreases slightly. However, the value of $(\mathrm{d}\phi/\mathrm{d}T)/m$ at 8.08 molal is only about half as large as the value calculated for concentrations below one molal from Naudé's heat of dilution measurements at 18°.[29]

Glycerol (Fig. 7).—To 300 cc. of C. P. glycerol was added 25 cc. of concentrated hydrochloric acid and the mixture was heated on the water-bath for twelve hours. It was then distilled *in vacuo* and the middle portion collected and stored in small glass containers in which it was protected from the atmosphere. The vapor pressures of aqueous glycerol solutions have been measured by Drucker and Moles.[30] Their results correspond to our curve for sucrose much more closely than they do to our results for glycerol. This means a discrepancy of 40–50% in ϕ at 5 and 11 *M*. Glycerol, like urea, was chosen in the hope that the deviations from ideality would be small enough to justify a simple interpolation. The deviations of our smooth standard curve from the analytical expression are never greater than 0.3% so that our hopes appear to be realized. However, glycerol is a hygroscopic liquid and therefore it is not a convenient standard.

α-Methyl Glucoside.—Berkeley, Hartley and Burton[24] also measured the vapor pressures of aqueous solutions of α-methyl glucoside at 0 and at 30°. Therefore this substance was used in some of the preliminary runs. Eastman "Eastman Grade" product was crystallized once from synthetic methyl alcohol, and dried in a current of air as described for sodium chloride. The melting point was raised thereby from 157.5 to 164.0°. Since the small sample could not be purified further and since the vapor pressure measurements appeared to be less useful than

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[25] L. A. Pinck and M. A. Kelly, THIS JOURNAL, **47**, 2170 (1925).

[26] G. N. Lewis and G. H. Burrows, *ibid.*, **34**, 1515 (1912).

[27] H. M. Chadwell and F. W. Politi, *ibid.*, **60**, 1291 (1938).

[28] F. T. Gucker, Jr., and F. D. Ayres, *ibid.*, **59**, 2152 (1937).

[29] S. M. Naudé, *Z. physik. Chem.*, **135**, 209 (1928).

[30] K. Drucker and E. Moles, *ibid.*, **75**, 405 (1911).

those with sucrose, glycerol was substituted in the later runs. Our measurements may be represented approximately by $\Phi = 1 + 0.0785m/(1 + 0.163m)$, and a solubility of 5.55 *M*.

Table II contains the osmotic coefficients and one plus the logarithms of the activity coefficients at rounded molalities. The one is added to the logarithms of the activity coefficients to avoid negative values and to make this column, like that for ϕ, approach unity at zero concentration. We do not consider our measurements at low concentrations sufficiently accurate for the extrapolation of the activity coefficients of the electrolytes to zero concentration. We have therefore accepted the value for sodium chloride at 0.2 *M* from heat of dilution and freezing point measurements,[13,11] the value for potassium chloride at 0.1 *M* of Shedlovsky and MacInnes,[20] and the value for sulfuric acid at 0.2 *M* of Harned and Hamer.[23] The differences at other concentrations correspond, of course, to the differences in osmotic coefficients discussed above.

TABLE IIa

OSMOTIC COEFFICIENTS AND LOGARITHMS OF ACTIVITY COEFFICIENTS

	NaCl		KCl		H_2SO_4	
m	ϕ	1 + $\log\gamma$	ϕ	1 + $\log\gamma$	ϕ	1 + $\log\gamma$
0.1	0.9342	0.8928	0.9264	0.8865	0.6784	0.4239
.2	.9255	.8678	.9131	.8566	.6675	.3202
.3	.9224	.8531	.9063	.8377	.6685	.2620
.4	.9217	.8430	.9023	.8240	.6723	.2225
.5	.9224	.8358	.9000	.8134	.6773	.1931
.6	.9242	.8304	.8987	.8048	.6824	.1700
.7	.9266	.8265	.8980	.7978	.6895	.1521
.8	.9295	.8236	.8980	.7918	.6980	.1380
.9	.9329	.8214	.8982	.7867	.7075	.1269
1.0	.9363	.8199	.8985	.7822	.7176	.1181
1.2	.9434	.8135	.8996	.7751	.7396	.1061
1.4	.9509	.8179	.9008	.7685	.7634	.0997
1.6	.9589	.8188	.9024	.7635	.7888	.0977
1.8	.9681	.8209	.9048	.7596	.8154	.0992
2.0	.9786	.8243	.9081	.7568	.8431	.1034
2.5	1.0096	.8366	.9194	.7532	.9152	.1229
3.0	1.0421	.8530	.9330	.7532	.9922	.1525
3.5	1.0783	.8727	.9478	.7557	1.0740	.1902
4.0	1.1168	.8951	.9635	.7599	1.1606	.2346
4.5	1.1578	.9199	.9799	.7655		
5.0	1.2000	.9464	(.9900	.7695)[a]		
5.5	1.2423	.9742				
6.0	1.2861	1.0029				
	(1.2987	1.0114)[a]				

[a] Saturated solution. See Table I for composition.

TABLE IIb

OSMOTIC COEFFICIENTS AND LOGARITHMS OF ACTIVITY COEFFICIENTS

	Sucrose		Urea		Glycerol	
m	ϕ	1 + $\log\gamma$	ϕ	1 + $\log\gamma$	ϕ	1 + $\log\gamma$
0.1	1.0073	1.0063	0.9959	0.9964	1.0014	1.0012
.2	1.0151	1.0130	.9918	.9929	1.0028	1.0025
.3	1.0234	1.0198	.9879	.9894	1.0042	1.0037
.4	1.0319	1.0270	.9841	.9860	1.0055	1.0049
.5	1.0407	1.0343	.9804	.9827	1.0068	1.0060
.6	1.0497	1.0418	.9768	.9794	1.0081	1.0072
.7	1.0590	1.0494	.9732	.9762	1.0093	1.0083
.8	1.0684	1.0572	.9698	.9731	1.0105	1.0094
.9	1.0781	1.0652	.9664	.9700	1.0117	1.0104
1.0	1.0878	1.0732	.9631	.9669	1.0128	1.0115
1.2	1.1076	1.0895	.9567	.9610	1.0150	1.0136
1.4	1.1280	1.1062	.9506	.9552	1.0171	1.0155
1.6	1.1484	1.1231	.9447	.9496	1.0192	1.0175
1.8	1.1686	1.1400	.9390	.9442	1.0211	1.0193
2.0	1.1884	1.1567	.9346	.9389	1.0230	1.0212
2.5	1.2359	1.1978	.9206	.9262	1.0274	1.0255
3.0	1.2817	1.2382	.9087	.9143	1.0316	1.0297
3.5	1.3262	1.2778	.8976	.9031	1.0355	1.0336
4.0	1.3691	1.3166	.8877	.8925	1.0393	1.0374
4.5	1.4100	1.3542	.8783	.8824	1.0428	1.0411
5.0	1.4477	1.3902	.8700	.8730	1.0462	1.0446
5.5	1.4820	1.4244	.8612	.8641	1.0494	1.0480
6.0	1.5070	1.4540	.8555	.8559	1.0525	1.0512
6.5	(1.5090	1.4568)[a]	.8494	.8481	1.0554	1.0543
7.0			.8440	.8408	1.0580	1.0573
7.5			.8391	.8340	1.0604	1.0601
8.0			.8347	.8275	1.0626	1.0628
8.5			.8307	.8213	1.0645	1.0653
9.0			.8270	.8155	1.0663	1.0677
9.5			.8236	.8099	1.0679	1.0700
10.0			.8205	.8046	1.0694	1.0721
11.0			.8148	.7946	1.0720	1.0762
12.0			.8099	.7853	1.0741	1.0799
13.0			.8056	.7768	1.0760	1.0833
14.0			.8019	.7689	1.0777	1.0865
15.0			.7985	.7614		
16.0			.7954	.7544		
17.0			.7926	.7478		
18.0			.7901	.7415		
19.0			.7878	.7355		
20.0			.7856	.7298		
			(.7855	.7297)[a]		

[a] Saturated solutions. See Table I for compositions.

Robinson and Sinclair[3b] and Robinson in his later papers based their standard largely on the electromotive force measurements of Harned with potassium chloride[14] and it corresponds very closely to the dotted curve we have drawn from these measurements, agreeing with our standard within 0.1% up to 1 *M* and giving a maximum deviation of 0.66% at 3 *M*. Smith and Smith[31] use as standards sucrose solutions, for which they use the equation $\phi = 1 + 0.095m + 0.0013m^2$ up to 3 *M* based on the vapor pressure measurements of Berkeley, Hartley and Burton[24] and measurements of osmotic pressure. Above 0.5 *M* their values are about 0.8% higher than our standard. Our measurements permit the comparison of sixteen of the most precise series of measurements of the chemical potential of water in aqueous solutions made with four different solutes in six laboratories by six distinct methods. Although any choice of the best curve through such a mass of data must involve some subjective judgment, we believe that the uncertainty in our curve is not more than 0.2%. With the osmotic coefficient

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(31) E. R. B. Smith and P. K. Smith, *J. Biol. Chem.*, **117**, 209 (1937); **121**, 607 (1937).

in Table II any one of the five solutes may be used as standard.

Summary

A modification for precision work of the isotonic apparatus and method of Sinclair and Robinson is described.

The isotonic concentrations at 25° of aqueous solutions of sodium chloride, potassium chloride, sulfuric acid, sucrose, urea and glycerol have been determined from 0.1 M sodium chloride to the saturated solution or to a saturated solution of sodium chloride.

The solubilities in water at 25° of sodium chloride, potassium chloride, sucrose and urea have been determined in the same apparatus by a new and convenient method.

The most precise determinations of the chemical potential of water in solutions of non-volatile solutes have been compared critically by means of these isotonic measurements, and a standard curve for the osmotic coefficients of each substance has been based on all the measurements with any of these substances.

CAMBRIDGE, MASS. RECEIVED AUGUST 4, 1938

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

Transference Numbers of Lanthanum Chloride at 25° by the Moving Boundary Method

BY L. G. LONGSWORTH AND D. A. MACINNES

Introduction

In recent publications from this Laboratory Brown and MacInnes[1] and Shedlovsky and MacInnes[2] have shown that transference numbers, and electromotive forces of concentration cells, may be used in determining activity coefficients of salt solutions. The salts studied in this manner have been the chlorides of hydrogen, sodium, potassium and calcium. The results were found to be in close accord with the Debye–Hückel theory. In addition transference numbers are of utility in interpreting the results of conductance measurements according to the recent developments of the interionic attraction theory. The extension of the studies to solutions of lanthanum chloride appeared to be of interest. Since this salt is of a highly unsymmetric valence type, the data obtained should afford a severe test of the interionic attraction theory in relation to both activity coefficients and conductances. This paper describes the determination of the transference numbers of lanthanum chloride by the moving boundary method and gives data on these numbers at 25° in the concentration range 0.0075 to 0.5 normal.

Description of the Apparatus

Of the apparatus used in determining transference numbers by the moving boundary method the cell was the same as that used in recent investigations in this Laboratory and has been described fully.[3] The constant current device has, however, been much simplified, as shown in Fig. 1. In this figure a portion, B, of the storage battery, A-B, furnishing current to the moving boundary cell, C, is shunted by a potential divider, the point of contact, T, being shifted by winding resistance wire from one of the insulated cylinders, DD′, to the other. In series with this and the cell C is a decade resistance box, R, with the range 10 to 11,110 ohms, which is shunted by the galvanometer, G, and the Hulett cell, X, which is, essentially, a heavy-duty Weston unsaturated standard cell. The needle of the galvanometer carries a vane, V, of aluminum foil which serves to intercept the light to the photo-tube, PJ 23. The photoelectric current operates a thyratron, FG 57, whose plate circuit includes the electromagnet E which controls the addition of potential by the divider, DD′, by drawing the pulley P_1 against the constantly rotating disk F. On release the pulley P_2 causes an adjustment in the reverse direction. For use with continuously increasing resistance, as in the present case, P_2 may be removed.

In operation the resistance R is set at such a value that a drop of 1.0189 v., the potential of the Hulett cell, results from the passage of the current. The advantages of this arrangement over that previously described[3] are: (1) a thyratron has replaced a vacuum tube and two mechanical relays and (2) a Hulett cell and a resistance box have replaced a Weston standard cell, standard resistances, potentiometer and storage battery. The precision and convenience of the apparatus have been increased since it is no longer necessary to adjust the potentiometer current at intervals during a transference number determination. As a matter of fact, the device will operate for an indefinitely long period with an accuracy of 0.01% or better.

The frequency control of the local a. c. power supply is

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[1] Brown and MacInnes, THIS JOURNAL, **57**, 1356 (1935).

[2] Shedlovsky and MacInnes, *ibid.*, **58**, 1970 (1936); **59**, 503 (1937).

[3] MacInnes and Longsworth, *Chem. Rev.*, **11**, 171 (1932).

now of sufficient precision to warrant replacement of our original timing device by a counter driven by a synchronous motor.

Preparation of the Solutions

Lanthanum chloride from two sources was used in this investigation. Preliminary treatment of both samples included precipitation with recrystallized oxalic acid, ignition to the oxide, solution in distilled hydrochloric acid and precipitation as $LaCl_3 \cdot 7H_2O$ with hydrogen chloride gas at 0°. One sample was obtained from a German source and the second was prepared for us under the direction of Professor B. S. Hopkins of the University of Illinois. Spectroscopic examination and conductance measurements showed that the two samples were practically identical. Spectroscopic comparison with a cerium-free sample kindly given us by Professor G. Jones of Harvard and with samples to which known amounts of cerium had been added indicated that our material contained less than 0.03% of cerium and was free of other impurities. Since cerium has nearly the same mobility and equivalent weight as lanthanum the presence of this amount of cerium in our salt has no appreciable effect on either the transference or the conductance measurements. We are indebted to Dr. G. I. Lavin of these Laboratories for the spectrographic analysis of our material.

Several methods of preparing lanthanum chloride for weighing were used and the results are summarized in Table I. As much of the water of hydration as possible was removed at a low temperature in a vacuum desiccator, using "Drierite" and continuous pumping. The temperature of this desiccation is given in the first column of the table. The sample, either pure or mixed with ammonium chloride, was then placed in a Richards "bottling" apparatus and heated to a high temperature in a stream of dry hydrogen chloride gas. The treatment given the material is recorded in the second column of Table I. As is indicated in the third column, a minute trace of insoluble material, presumably the basic chloride, invariably remained when the *fused* salt was dissolved in water. Fusion with ammonium chloride, in the process of which the ammonium salt sublimes and is carried away by the stream of hydrogen chloride gas, did not prevent the formation of this basic chloride. When, however, the salt was heated to 600° the resulting solution was clear.[4] The agreement between the conductances of the various preparations as given in the last column of Table I indicates, barring improbable compensation, that the insoluble residue in the fused material and the residual water in that heated to 600° amount to less than 0.01%, which is the limit of error of the conductance measurements.

TABLE I

PREPARATION OF STOCK SOLUTIONS OF LANTHANUM CHLORIDE

Temp. of vacuum desiccation, °C.	Treatment in HCl atmosphere	Basic chloride residue	Equiv. conductance, $\Lambda_{0.1}$
140	Rapid fusion	Large	. . .
20	Slow fusion	Trace	99.02
20	Slow fusion with NH_4Cl	Trace	99.03
100 with NH_4Cl	Slow fusion with NH_4Cl	Trace	99.02
142	Slowly heated to 600°	None	99.04
100	Slowly heated to 600°	None	99.03

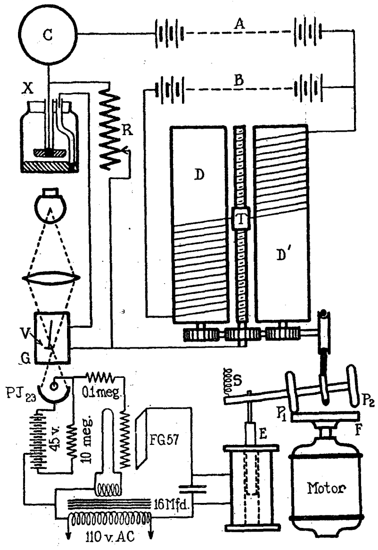

Fig. 1.

Lithium Chloride was prepared by dissolving, in hydrochloric acid, lithium carbonate that had been recrystallized from boiling water. This salt proved to be an excellent cation indicator for solutions of lanthanum chloride over the entire range of concentration studied.

Lanthanum bromate was prepared by the addition of an excess of solid silver bromate to a concentrated solution of lanthanum chloride. The trace of silver ion remaining in the solution of lanthanum bromate does not interfere with the use of this solution as anion indicator since the cation constituents migrate away from the boundary. Although the bromate ion is but slightly slower than the chloride ion it was found that satisfactory boundaries between solutions of their lanthanum salts could be obtained at 0.2 and 0.5 normal. Lanthanum bromate was used therefore to obtain confirmation of the results with lithium chloride as indicator.

Anion boundaries with lanthanum acetate were also tried but excessive heating in the indicator solution caused mixing at the boundary. Moreover, this salt appears to be appreciably hydrolyzed.

Experimental Results

The experimental results are given in Table II in which concentrations are expressed in equivalents per liter of solution at 25°. Values of the transference number obtained in individual determinations are recorded under "$T_{\pm}$ observed" and their average under "$T_{\pm}$ mean." These values are subject to two small corrections: for the conductivity of the solvent (1.5×10^{-6} mho), and for the volume changes in the closed side of the moving boundary cell, both of which are discussed in detail by MacInnes and Longsworth.[3] The

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[4] Jones and Bickford, THIS JOURNAL, **56**, 602 (1934).

TABLE II

TRANSFERENCE NUMBERS AND CONDUCTANCES OF AQUEOUS SOLUTIONS OF LANTHANUM CHLORIDE AT 25°

	T_+								T_-	
Concn. eq. per liter at 25°	0.0075	0.010	0.015	0.02	0.05	0.1	0.2	0.5	0.2	0.5
$T_\pm$ obsd.	.4636	.4620	.4600	.4575	.4486	.4387	.4261	.4020	.5742	.5986
	.4632	.4620	.4599	.4577	.4486	.4387	.4255		.5740	.5990
		.4619		.4577	.4487	.4388				
		.4620		.4576		.4387				
$T_\pm$ mean	.4634	.4620	.4599$_5$	.4576	.4486	.4387	.4258	.4020	.5741	.5988
Solvent corr.	.0008	.0006	.0004	.0003	.0002	.0001	.0000	.0000	.0000	.0000
Volume corr.	−.0001	−.0001	−.0002	−.0003	−.0006	−.0013	−.0025	−.0062	+.0025	+.0062
$T_\pm$ corr.	.4641	.4625	.4601	.4576	.4482	.4375	.4233	.3958	.5766	.6050
Λ	124.34	121.83	118.09	115.32	106.10	99.04	92.04	82.28		

volume change for both the anion and cation boundaries is

$$\Delta V = \frac{1}{3} T_+ \bar{V}_{\text{LaCl}_3} + V_{\text{Ag}} - V_{\text{AgCl}}$$

in which $\bar{V}_{\text{LaCl}_3} = 0.01615 + 0.01733 \sqrt{\text{molality}}$, $V_{\text{Ag}} = 0.0103$ and $V_{\text{AgCl}} = 0.0258$, all at 25°. These corrections are given in the fourth and fifth lines of Table II and the corrected transference numbers in the sixth line. The conductances of all solutions were measured on the bridge described by Shedlovsky[5] and are recorded in the last line of the table. A value of 0.012856[6] for the specific conductance of 0.1 demal potassium chloride was used in the determination of cell constants.

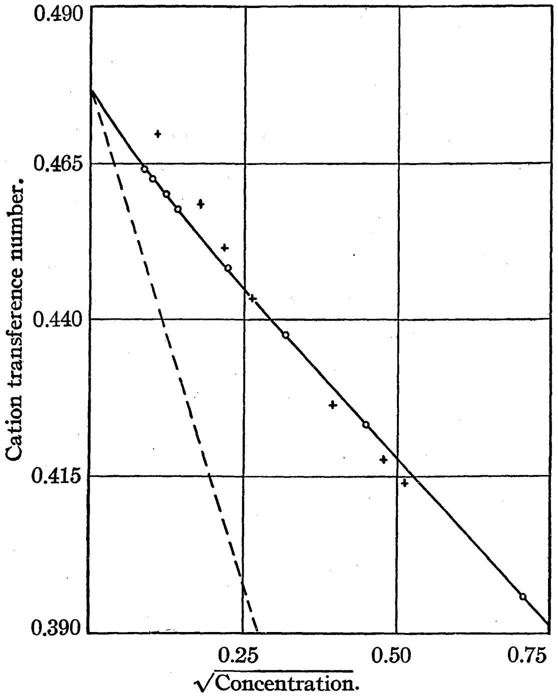

Fig. 2.

Discussion of the Results

In Fig. 2 the transference data for lanthanum chloride are plotted as ordinates against the square root of the concentration as abscissas. The values recently obtained with the Hittorf method by Jones and Prendergast[7] are indicated by the crosses while our results are plotted as circles. The differences between the results by the two methods, reaching a maximum of 0.007 for the most dilute solutions, are larger than those found in similar comparisons for lithium[8] and potassium chlorides[9] and are certainly outside the limit of error of the moving boundary measurements. That the Hittorf values for dilute solutions are not consistent with the results for other salts, and with Kohlrausch's law of independent ion mobilities, have already been pointed out by Hartley and Donaldson.[10] A test of the accuracy of our measurements is afforded by independent observation of both anion and cation boundaries with the same solution. The sum of the transference numbers thus obtained should be 1.0000. Thus from the data of Table II, $T_+ + T_- = 0.9999$ at 0.2 normal and 1.0008 at 0.5 normal. It may be noted that the conductances of Table II are in excellent agreement with the values published by Jones and Bickford.[4]

The smooth curve drawn through our data has been extrapolated to the value of 0.4768. This limiting cation transference number is based on the values of 76.34 and 145.9 for the limiting conductances of the chloride ion[11] and lanthanum chloride,[12] respectively. The dashed line in Fig. 2 is the limiting slope

$$\left(\frac{dT_+}{d\sqrt{C}}\right)_{C \to 0} = \frac{(z_+ + z_-)T_+^0 - z_+}{\Lambda_0} \beta \sqrt{z_+ + z_-} \quad (1)$$

derived by Longsworth[13] from the Onsager theory.[14] As in the case of calcium chloride the

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[5] Shedlovsky, THIS JOURNAL, **52**, 1793 (1930).

[6] Jones and Bradshaw, *ibid.*, **55**, 1780 (1933).

[7] Jones and Prendergast, *ibid.*, **58**, 1476 (1936).

[8] Longsworth, *ibid.*, **54**, 2741 (1932).

[9] MacInnes and Dole, *ibid.*, **53**, 1357 (1931).

[10] Hartley and Donaldson, *Trans. Faraday Soc.*, **33**, 457 (1937).

[11] MacInnes, Shedlovsky and Longsworth, THIS JOURNAL, **54**, 2758 (1932).

[12] Shedlovsky, unpublished results.

[13] Longsworth, THIS JOURNAL, **57**, 1185 (1935).

[14] Onsager, *Physik. Z.*, **27**, 388 (1926); **28**, 277 (1927).

experimental curve of transference numbers for lanthanum chloride apparently merges with the limiting slope only at extreme dilutions. Assuming that the salt conductances have been extrapolated correctly, we are confronted with the anomaly that these conductances appear to obey the Onsager equations to somewhat higher concentrations than do the transference numbers, although the latter are merely ratios of ionic conductances. No satisfactory explanation for this anomaly has been advanced. A similar anomaly involving the activity coefficients will be discussed in a forthcoming paper from this Laboratory.[15]

In Fig. 3 we have plotted, as ordinates, the chloride ion conductances, $\lambda_{Cl} = T_{Cl}^{MCl}\,\Lambda$, of lanthanum, calcium[13,16] and sodium chlorides[8,17] against the square root of the concentration as abscissas. The smooth curves through the experimental points are extrapolated to the limiting conductance of the chloride ion, 76.34, and the straight lines through this point are the limiting slopes given by the following Onsager equations

$$\left.\begin{aligned} \lambda_{Cl}^{NaCl} &= 76.34 - 47.2\sqrt{C} \\ \lambda_{Cl}^{CaCl_2} &= 76.34 - 74.0\sqrt{C} \\ \lambda_{Cl}^{LaCl_3} &= 76.34 - 99.1\sqrt{C} \end{aligned}\right\} \qquad (2)$$

The conductance of the chloride ion associated with a univalent cation exhibits the normal positive deviation from the limiting slope with increasing concentration. When associated with a divalent cation, however, the deviations in dilute solutions appear to be negative and still more pronounced negative deviations occur when the co-ion is trivalent as in lanthanum chloride. These negative deviations, due to the anomalous behavior of the transference numbers discussed in the preceding paragraph, do not appear to be indicative of intermediate ion formation since the salt conductances are normal.

The curves of Fig. 3 also serve to illustrate the large deviations from additivity of ion conductances when the valence of the co-ion is altered. In our study of the chloride ion conductance in solutions of uni-univalent chlorides, it was observed that this conductance was additive at concentrations below about 0.02 normal and depended only slightly upon the specific nature of the co-ion at higher concentrations. The magnitude of this dependence is indicated in Fig. 3 by the vertical line through each point for λ_{Cl}^{NaCl}. These lines were drawn to include, at each concentration, the values of λ_{Cl} for hydrogen, potassium and lithium chlorides. Marked deviations from additivity occur, however, when the valence of the co-ion is increased, as is shown by the divergence of the three curves of the figure.

Sherrill and Noyes[18] have assumed for the purpose of computation that ion conductances are additive at equal ionic strengths. This is equivalent to extending the concentration scale for a bi-univalent salt by the factor 1.5 and that for a tri-univalent salt by 2. Alteration of the concentration scales by these factors is, however, insufficient to bring the curves of Fig. 3 into coincidence. Although not strictly applicable at the concentrations for which transference data are available, the Onsager theory explains, qualitatively, this valence effect. Thus reference to equation (2) indicates that $\lambda_{Cl}^{CaCl_2}$ should equal λ_{Cl}^{NaCl} when $C_{NaCl} = (74.0/47.2)^2\, C_{CaCl_2} = 2.45C_{CaCl_2}$. The corresponding factor for C_{LaCl_3} is 4.40. Even these factors are not large enough. The ones actually required are 3.3 for calcium chloride and 10 for lanthanum chloride. Thus the open circles and crosses of the upper curve of Fig. 3 are, respectively, the observed values of $\lambda_{Cl}^{LaCl_3}$ and $\lambda_{Cl}^{CaCl_2}$ plotted on such adjusted concentration scales. The transposed points fall on the λ_{Cl}^{NaCl} curve with deviations of the same order as is observed among univalent chlorides, *i. e.*, deviations attributable to properties of the co-ion other than its valence. Although only those

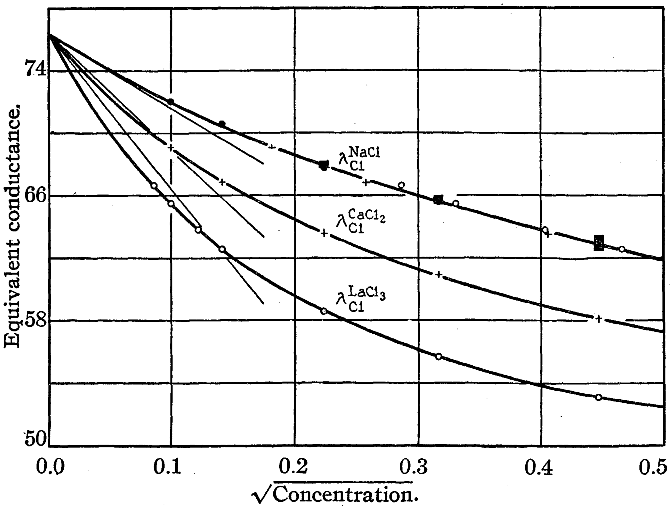

Fig. 3.

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(15) Shedlovsky and MacInnes, THIS JOURNAL, January (1939).
(16) Shedlovsky and Brown, *ibid.*, **56**, 1066 (1934).
(17) Shedlovsky, *ibid.*, **54**, 1411 (1932).
(18) Sherrill and Noyes, *ibid.*, **48**, 1861 (1926).

points on the two lower curves for which $\lambda_{Cl} > 62$ can be thus transposed, computations with the available data indicate that the curves may be thus superposed to higher concentrations.

Summary

Measurements of the transference numbers at 25° of aqueous solutions of lanthanum chloride by the method of moving boundaries have been made. The chloride ion conductances of these solutions have been compared with similar measurements of solutions of calcium chloride and sodium chloride. From this comparison an empirical rule for the effect of the valence of the co-ion on the chloride ion conductance has been obtained.

NEW YORK, N. Y. RECEIVED OCTOBER 15, 1938

[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY OF YALE UNIVERSITY]

The Electrolytic Conductivity of Zinc Sulfate and Copper Sulfate in Water at 25°[1]

BY BENTON BROOKS OWEN AND ROBERT W. GURRY[2]

Within the last decade the conductivities of a large number of electrolytes have been precisely redetermined at 25°. Most of these modern measurements have been confined to 1–1 and 2–1 valence types because they conform to the requirements of the inter-ionic attraction theory at experimentally accessible dilutions, and may therefore be readily extrapolated. The 3–1 electrolyte lanthanum chloride can possibly be satisfactorily extrapolated along the Onsager[3] slope, but no 2–2 electrolyte has yet been found amenable to this simple treatment. The extrapolation of the conductivities of zinc and copper sulfates is of particular interest because of the complications introduced by relatively large departures from the limiting slope and partial hydrolysis of the ions.

In the present research we have carefully measured the specific conductivity and *p*H of dilute solutions of these salts at 25°, and made what we believe to be adequate solvent and hydrolysis corrections. The results have been extrapolated by a number of methods fulfilling the requirements of the inter-ionic attraction theory, and which lead to essentially the same values of Λ_0. Zinc and copper sulfates are particularly well suited for this type of investigation because they can be highly purified, and their hydrolysis corrections are not too great to be estimated with sufficient accuracy. Furthermore, the supplementary thermodynamic and conductance data required in our calculations are available for these salts, and for the sulfate and hydrosulfate ions.

Materials and Technique

Merck reagent grade zinc sulfate heptahydrate was recrystallized twice from a mixture of highly purified methanol and water, and then twice from conductivity water. The last crystallization was accomplished by partial evaporation of the water at room temperatures with the necessary precautions against contamination by dust.

Merck reagent grade copper sulfate pentahydrate was recrystallized four times from conductivity water. The purified salt was crushed in an agate mortar and dried over a mixture of the penta- and trihydrates.

Stock solutions, 0.1 and 0.5 *m*, were prepared by weight and checked by gravimetric analysis. Vacuum corrections were applied throughout. Samples of the zinc sulfate solutions were evaporated at 95° and the salt dehydrated at 300° and weighed as $ZnSO_4$. The copper was determined electrolytically, with the last traces precipitated as sulfide and weighed as oxide. All duplicate analyses checked within 0.02% from the means.

The Dike[4] bridge was operated by a vacuum tube oscillator at 1000 cycles. It was calibrated against Bureau of Standard resistors with a d. c. source and a sensitive galvanometer. All measurements reported were made without shunts, and were reproducible to 0.002%.

The temperature was adjusted to 25 ± 0.005° with a platinum resistance thermometer certified by the Bureau of Standards, and thermoregulation within 0.005° was maintained during the course of the measurements.

The cells were the type B[5] generally employed in this Laboratory. The electrodes were lightly platinized. Cell constants were determined several times during the course of the measurements with 0.1 demal potassium chloride according to Jones and Bradshaw.[6] The cell constants, *l/a*, were 4.5221 for cell III and 3.7260 for cell IV. The specific conductivity of the water employed was usually less than 2×10^{-7} mho.

The *p*H values required for the solvent and hydrolysis corrections were obtained colorimetrically by the use of LaMotte indicator standards in the zinc sulfate solutions, and electrometrically with glass electrodes[7] in the copper

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[1] This communication embodies part of the experimental material contained in the thesis submitted by Robert W. Gurry to the Graduate School of Yale University in partial fulfilment of the requirements for the degree of Doctor of Philosophy (1937).

[2] Present address: Research Laboratory, United States Steel Corp., Kearny, N. J.

[3] Onsager, *Physik. Z.*, **27**, 388 (1926).

[4] Dike, *Rev. Sci. Instruments*, **2**, 379 (1931).

[5] Saxton and Meier, THIS JOURNAL, **56**, 1918 (1934).

[6] Jones and Bradshaw, *ibid.*, **55**, 1780 (1933).

[7] The authors are indebted to Professor Leslie F. Nims of the Department of Physiology for making these measurements.

sulfate solutions. The results were plotted on a large scale against $\sqrt{C}$ for interpolation at the required concentions. The pH at even values of $\sqrt{C}$ are recorded in Table III. The acidity of dilute zinc sulfate solutions has been studied recently by Kolthoff and Kameda[8] by both colorimetric and electrometric methods. Their pH values are about 0.1 unit lower than ours, but in view of the sensitivity of these unbuffered solutions to acid and basic impurities, this concordance seems satisfactory.

Experimental Results

The experimental data are recorded in Tables I and II as specific conductivities, κ, at the concentrations, C, in moles per liter of solution. The specific conductivity of the solvent, κ_0, and the cell constant, l/a, employed in each run are given at the bottom of the columns of data to which they apply.

TABLE I

SPECIFIC CONDUCTIVITY OF $ZnSO_4$ SOLUTIONS AT 25°

10^3C	$10^3\kappa$	10^3C	$10^3\kappa$	10^3C	$10^3\kappa$
0.3880	0.09163	0.4168	0.09794	0.5474	0.12578
.8532	.18766	.8614	.18933	2.2411	.43547
1.5397	.31549	1.5063	.30959	4.6463	.79904
2.3748	.45728	2.3717	.45684	8.4433	1.29735
3.6786	.65980	3.6724	.65892	16.001	2.15505
5.3712	.90040	5.0718	.85930	24.043	2.96765
6.9412	1.10832	6.8254	1.09342	32.590	3.7658
9.6428	1.44269	8.6867	1.32720	41.965	4.5894
14.3990	1.98308	11.0427	1.60707	50.634	5.3156
18.7372	2.44029	15.6522	2.11795	60.826	6.1356
		19.8362	2.55188	73.563	7.1195
				85.773	8.0279
				108.509	9.6463
				128.845	11.0273
$10^7\kappa_0$	0.955		1.534	1.471	
l/a	4.5221		3.7260	3.7260	

TABLE II

SPECIFIC CONDUCTIVITY OF $CuSO_4$ SOLUTIONS AT 25°

10^3C	$10^3\kappa$	10^3C	$10^3\kappa$	10^3C	$10^3\kappa$
0.3958	0.09375	0.3970	0.09403	0.4945	0.11496
.9365	.20341	.8572	.18813	2.0470	.39918
1.8740	.37032	1.3995	.28858	5.0349	.83767
2.6890	.50136	1.9966	.39071	8.8474	1.31259
3.6512	.64521	3.0281	.55323	13.002	1.77552
4.7890	.80429	4.1282	.71314	17.808	2.26833
6.4517	1.02163	5.5098	.90042	24.175	2.87538
8.1945	1.23519	7.1003	1.10255	31.650	3.5428
10.1478	1.46193	9.5816	1.39739	39.870	4.2369
12.6639	1.73870	11.7779	1.64307	47.151	4.8258
15.0319	1.98787			55.680	5.4912
				66.573	6.3100
				77.414	7.0973
				97.393	8.4905
				115.265	9.6845
$10^7\kappa_0$	1.861		2.073	2.780	
l/a	4.5221		3.7260	3.7260	

Although the specific conductivities are known to within 0.01%, the calculated equivalent conductivities are less accurate because of the uncertainties in the solvent and hydrolysis corrections. The maximum values of these combined corrections are about 0.2 and 0.8 conductance units in the zinc and copper solutions, respectively.

The solvent conductance was assumed to be due to hydrogen and hydroxyl ions from the ionization of the water, and a constant residual specific conductance, δ, due to unknown impurities. The latter was estimated by subtracting the specific conductance of pure water, 0.546×10^{-7}, from the measured solvent conductance, κ_0. Then. as the pH of the water was altered by hydrolysis of the salt being studied, the correction for solvent conductance becomes

$$1000\,\Delta\kappa_1 = \lambda_H C_H + \lambda_{OH} C_{OH} + 1000\delta \qquad (1)$$

For this correction we used $\lambda_H = 350$ and $\lambda_{OH} = 200$. The concentrations, C_H and C_{OH}, were determined from the pH values given in Table III. The equivalent conductance corrected for solvent is then given by

$$\Lambda_1 = \frac{1000\kappa}{2C} - \frac{1000\,\Delta\kappa_1}{2C} \qquad (2)$$

The variation of pH with total salt concentration is due to hydrolysis of the bivalent ions, and can be expressed as follows

$$Zn^{++} + H_2O \rightleftharpoons Zn(OH)^+ + H^+$$

and

$$SO_4^{=} + H_2O \rightleftharpoons HSO_4^- + OH^-$$

The formation of H_2SO_4 and $Zn(OH)_2$, or more complex ions, was assumed to be negligible in dilute solutions.

Since we are concerned with obtaining the conductance due to Zn^{++} and $SO_4^{=}$ ions only, it is necessary to correct the apparent equivalent conductivity, Λ_1, for the decrease due to replacement of a small fraction of the bivalent ions by the monovalent complex ions $Zn(OH)^+$ and HSO_4^-. The correction to be added is

$$1000\,\Delta\kappa_2 = C_{ZnOH^+}(2\lambda_{Zn^{++}} - \lambda_{ZnOH^+}) + C_{HSO_4^-}(2\lambda_{SO_4^=} - \lambda_{HSO_4^-}) \qquad (3)$$

Accordingly the desired equivalent conductance of (unhydrolyzed) zinc sulfate is given by

$$\Lambda = \Lambda_1 + \frac{1000\,\Delta\kappa_2}{2C} \qquad (4)$$

The equivalent conductances of the ions were taken as 79.8 and 50 for $SO_4^{=}$ and HSO_4^-; 53.5 and 32.1 for Zn^{++} and $ZnOH^+$; and 52.0 and 31.2 for Cu^{++} and $CuOH^+$. According to our final results $\lambda_{Cu^{++}}$ should have been nearer 54, but it would be useless to revise the corrections on this basis because λ for $ZnOH^+$ and $CuOH^+$ were merely assumed to be 0.6 of the values of the corresponding divalent ions by analogy with the

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(8) Kolthoff and Kameda, THIS JOURNAL, 53, 832 (1931).

findings of Chandler[9] and Jeffery and Vogel[10] in dealing with organic acids.

The complex univalent ion concentrations were estimated as follows. The HSO_4^- concentration was calculated from the measured *p*H and the stoichiometric $SO_4^=$ concentration, using 0.012 as the ionization constant[11] of the hydrosulfate ion, and disregarding activity coefficients. The $ZnOH^+$ (or $CuOH^+$) concentration was then found by adding the difference $C_{H^+} - C_{OH^-}$ to the HSO_4^- ion concentration, since the $ZnOH^+$ (or $CuOH^+$) and HSO_4^- concentrations would be equal at exact neutrality.

The final equivalent conductances corrected by equation (4) were interpolated graphically at even values of $\sqrt{C}$, and recorded in Table III. For this purpose we used a very large scale plot of Λ *vs.* $\sqrt{C}$ with a stiff spline, and also several plots of deviation functions of the type $[\Lambda + A\sqrt{C} - BC]$ *vs.* $\sqrt{C}$ to expose errors in curve fitting. The discordance between the values read from two curves was never greater than 0.02 conductance unit, and since this is probably the order of the uncertainty in the combined corrections used in calculating Λ, these smoothed values will be used in the extrapolations to follow.

TABLE III

INTERPOLATED VALUES OF THE *p*H AND EQUIVALENT CONDUCTIVITY

	$ZnSO_4$		$CuSO_4$	
$\sqrt{C}$	*p*H	Λ	*p*H	Λ
0.02	6.41	117.61	5.73	117.52
.025	6.37	113.33	5.57	112.89
.03	6.34	109.25	5.46	108.55
.04	6.29	101.86	5.32	100.74
.05	6.25	95.49	5.22	94.07
.06	6.21	89.99	5.15	88.35
.07	6.17	85.20	5.09	83.43
.08	6.14	81.08	5.05	79.17
.10	6.09	74.24	4.99	72.20
.12	6.04	68.86	4.95	66.72
.14	6.00	64.49	4.92	62.33
.16	5.96	60.89	4.89	58.74
.18	5.93	57.85	4.87	55.72
.20	5.90	55.26	4.84	53.16
.22	5.86	53.02	4.81	50.95
.24	5.83	51.04	4.78	49.03
.26	5.80	49.31	4.76	47.33
.28	5.78	47.71	4.74	45.83
.30	5.76	46.27	4.71	44.48
.32	5.73	45.02	4.69	43.25
.34	5.71	43.83	4.66	42.13

Extrapolations and Discussion

In the extrapolation of activity coefficient data for bi-bivalent electrolytes the initial departures from the limiting slope may be taken into account by the inclusion of higher terms[12,13] in the Debye–Hückel equation, or by the introduction of a dissociation constant to allow for the effect of relatively stable ion-pairs upon the ionic distribution.[14,15] In the absence of a numerical development of the higher terms for the Onsager equation, the modern extrapolation of bi-bivalent conductance data has always involved the concept of incomplete dissociation.

There are two techniques available for evaluating the dissociation constant, K. Onsager[16] and Davies[17] estimate K at each concentration. Fuoss and Kraus[18] determine it graphically from the slope of a suitable extrapolation function. This procedure has been greatly simplified by Fuoss,[19] and recently extended to higher concentrations by Shedlovsky.[20] All of these methods are based upon some assumption regarding the conductance, Λ_i, of the hypothetical completely ionized electrolyte. It may be assumed to obey the limiting law at the lowest experimental concentrations, or approach it asymptotically according to some arbitrary empirical function. In the extrapolation of our data we have used the limiting law and most of the empirical extensions employed for this purpose. Although all extrapolations give values of Λ_0 agreeing within 0.6 conductance unit, the apparent variation in K is over 20%, being very sensitive to the manner in which Λ_i is assumed to approach the limiting law.

In Fig. 1 we have illustrated the extrapolations which we consider most satisfactory. The open circles represent the smoothed results of Table III plotted to conform to the Fuoss[19] function

$$\Lambda/F_{(z)} = \Lambda_0 - (C\vartheta^2 y^2_{\pm})\Lambda_0/K \qquad (5)$$

and the dots are calculated according to the modification

$$\Lambda S_{(z)} = \Lambda_0 - (C\vartheta^2 y^2_{\pm})\Lambda_0/K \qquad (6)$$

proposed by Shedlovsky.[20] Equation (5) assumes the limiting law, and equation (6) allows for

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[9] Chandler, THIS JOURNAL, **30**, 694 (1908).

[10] Jeffery and Vogel, *J. Chem. Soc.*, **137**, 21 (1935).

[11] Hamer, THIS JOURNAL, **56**, 860 (1934).

[12] Gronwall, La Mer and Sandved, *Physik. Z.*, **29**, 358 (1928).

[13] Müller, *ibid.*, **28**, 324 (1927).

[14] Bjerrum, *Kgl. Danske Videnskb. Selskab, Math.-fys. Medd.*, **7**, No. 9 (1926).

[15] Fuoss and Kraus, THIS JOURNAL, **55**, 1019 (1933).

[16] Onsager, *Physik. Z.*, **27**, 277 (1927).

[17] Davies, *Trans. Faraday Soc.*, **23**, 351 (1927).

[18] Fuoss and Kraus, THIS JOURNAL, **55**, 476 (1933).

[19] Fuoss, *ibid.*, **57**, 448 (1935).

[20] Shedlovsky, *J. Franklin Inst.*, **225**, 739 (1938).

slight positive deviations from the limiting law by multiplying the slope by the factor Λ/Λ_0 which rapidly approaches unity at high dilutions. In both of these equations $Z = (\alpha\Lambda_0 + \beta)\Lambda_0^{-3/2}\sqrt{C}$, ϑ is the degree of dissociation, and $y_{\pm}$ is the mean ionic activity coefficient. The function

$$F_{(Z)} = 1 - Z(1 - Z(1 - \ldots)^{-1/2})^{-1/2})^{-1/2} \qquad (7)$$

is tabulated by Fuoss,[19] and the corresponding function of Shedlovsky[20] is given by

$$S_{(Z)} = 1 + Z + \frac{Z^2}{2} + \frac{Z^3}{8} - \ldots \qquad (8)$$

In the calculation of Z, we have used $\Lambda_0 = 132.8$ for zinc sulfate, $\Lambda_0 = 133.6$ for copper sulfate, and the theoretical values $\alpha = 1.8215$ and $\beta = 239.40$. It was not necessary to calculate the value of ϑ ($\vartheta = \Lambda/\Lambda_0 F_{(Z)} = \Lambda S_{(Z)}/\Lambda_0$) because accurate values of the stoichiometrical activity coefficient, $y_{\text{stoi.}} = \vartheta y_{\pm}$, are available[21–23] for zinc sulfate, and the values for copper sulfate are known[24] to be very similar. In the calculation of $y_{\text{stoi.}}$ at the concentrations required for our purposes, we used the extended terms[12] and an "a" value of 3.64 Å.[22]

Inspection of Fig. 1. shows that the plots according to equation (6) are more nearly linear than those based on equation (5), but they both lead to the same values of Λ_0. The limiting slopes approached by the more linear plots were used in the estimation of K. The results of the extrapolations are $\Lambda_0 = 132.8$, $K = 0.0049$ for zinc sulfate, and $\Lambda_0 = 133.6$, $K = 0.0043$ for copper sulfate. Davies[17] reported $K = 0.0045$ for both salts at 18°.

To illustrate the dependence of K upon the type of conductance function, the same values of $y_{\text{stoi.}}$ used above, and the equation

$$\Lambda_i = \Lambda_0 - (\alpha\Lambda_0 + \beta)\sqrt{C\vartheta} + BC\vartheta \qquad (9)$$

lead to $\Lambda_0 = 132.9$ and $K = 0.0047$ for zinc sulfate when B is 2350. In making this calculation, $\vartheta = \Lambda/\Lambda_i$, and Λ_0 and B are adjusted by trial to yield a constant value of K. In this particular case K showed a total variation of only 0.6% between 0.005 and 0.01 molal. A variation of four or five times this figure would seem permissible in such a determination, and it is interesting to note that within these limits we can obtain values of K as low as 0.0044, and Λ_0 as high as 133.3 for zinc sulfate by means of equation (9).

The Bjerrum equation[14] permits an independent estimate of K from activity coefficient data alone. The substitution of $a = 3.64$ Å. in this equation, with proper attention to valence, leads to $K = 0.0030$ at 25°. The discordance between this value and those derived above from conductivities is not so serious as might appear on first sight, because of the very loose physical sense in which K is defined. Even the difference between the values obtained by equations (6) and (9) shows that K for zinc sulfate is more arbitrary than that for a weak electrolyte such as acetic acid, and leads one to suspect that its present status is more of the nature of an adjustable mathematical parameter than a definite physical entity.[25]

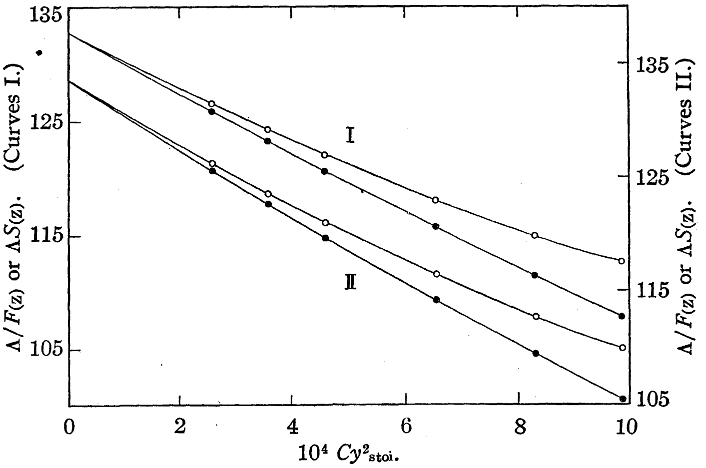

Fig. 1.—Determination of Λ_0 and K for $ZnSO_4$ (Curves I) and $CuSO_4$ (Curves II) at 25°.

In comparing the results of our extrapolations with those available in the literature we find considerable discordance. O'Connor[26] obtained $\Lambda_0 = 142$ for copper sulfate from data extending down to 0.000025 mole per liter, but reports no experimental details. We attempted to extend our measurements to 0.000087 mole per liter with the use of 30,000 ohm shunt, but have not included them in our tabulations because the shunt introduces an error of the order of ± 0.1% in κ and we feel that the pH measurements and solvent corrections are unreliable at such dilutions. It may be significant, however, that our points at $c \simeq 0.000087$ would cause the plots in Fig. 1. to curve

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(21) Bray, THIS JOURNAL, **49**, 2372 (1927).

(22) Cowperthwaite and La Mer, *ibid.*, **53**, 4333 (1931).

(23) Kielland, *ibid.*, **58**, 1855 (1936).

(24) Wetmore and Gordon, *J. Chem. Phys.*, **5**, 60 (1937).

(25) In this connection, *cf.* Cowperthwaite, *Trans. Faraday Soc.*, **29**, 593 (1933).

(26) O'Connor, *Nature*, **139**, 151 (1937).

abruptly upward and increase the intercepts by about one conductance unit.

No recent direct determination of Λ_0 at 25° for zinc sulfate has come to our attention, but Courrell, Hamilton and Butler[27] published data which, according to their observed slopes, would lead to $\Lambda_0 \simeq 125.9$ for zinc chloride or $\lambda_0 \simeq 49.6$ for the zinc ion. Using $\lambda_0 = 79.6$ for the sulfate ion, derived from Shedlovsky's value of Λ_0 for sodium sulfate quoted by Longsworth,[28] our values of λ_0 for the zinc and copper ions would be 53.1 and 53.9, respectively.

Summary

The specific conductivities and *p*H values of dilute zinc and copper sulfate solutions were measured at 25°. The results were corrected for hydrolysis, and the equivalent conductances of the hypothetical unhydrolyzed salts reported at even values of $\sqrt{C}$.

The limiting equivalent conductances and "ionization constants" of the salts were estimated by several procedures based upon the interionic attraction theory and the law of mass action. The dependence of the results upon the nature of the extrapolation function was discussed, and $\Lambda_0 = 132.8$, $K = 0.0049$ for zinc sulfate, and $\Lambda_0 = 133.6$, $K = 0.0043$ for copper sulfate were proposed as the most reliable values.

NEW HAVEN, CONN. RECEIVED OCTOBER 8, 1938

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[27] Courrell, Hamilton and Butler, *Proc. Roy. Soc.* (London), **A147**, 418 (1934).

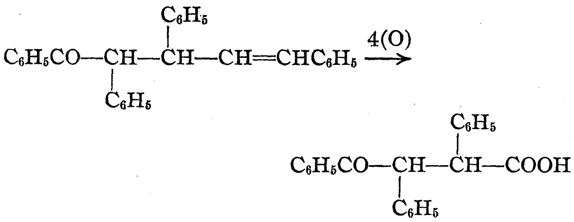
[28] Longsworth, THIS JOURNAL, **57**, 1185 (1935).

[CONTRIBUTION FROM THE SANDERS LABORATORY OF CHEMISTRY, VASSAR COLLEGE, AND THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

α,β-Diphenyl-β-benzoylpropionic Acid

BY H. MARJORIE CRAWFORD

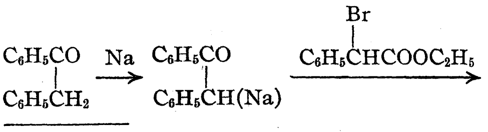
α,β-Diphenyl-β-benzoylpropionic acid has been prepared by Reimer and Reynolds[1] by the oxidation of α,β-diphenyl-γ-benzalbutyrophenone



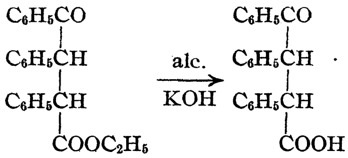
$$C_6H_5CO-\underset{C_6H_5}{CH}-\overset{C_6H_5}{CH}-CH=CHC_6H_5 \xrightarrow{4(O)} C_6H_5CO-\underset{C_6H_5}{CH}-\overset{C_6H_5}{CH}-COOH$$

They reported that the acid melted at 211–212° and crystallized from alcohol with one molecule of alcohol of crystallization. They also prepared the methyl ester which melted at 159°.

A simpler method of preparation was sought to obtain considerable quantities of the acid for use in connection with some other work. The following procedure* was adopted

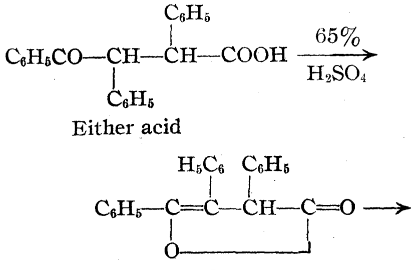


$$\begin{matrix} C_6H_5CO \\ | \\ C_6H_5CH_2 \end{matrix} \xrightarrow{Na} \begin{matrix} C_6H_5CO \\ | \\ C_6H_5CH(Na) \end{matrix} \xrightarrow{C_6H_5\overset{Br}{C}HCOOC_2H_5}$$



$$\begin{matrix} C_6H_5CO \\ | \\ C_6H_5CH \\ | \\ C_6H_5CH \\ | \\ COOC_2H_5 \end{matrix} \xrightarrow[KOH]{alc.} \begin{matrix} C_6H_5CO \\ | \\ C_6H_5CH \\ | \\ C_6H_5CH \\ | \\ COOH \end{matrix}$$

Analyses and neutralization equivalent ensured the identity of the product, but it consisted of a mixture of the two racemic modifications of the acid, one melting at 201–202° and the other melting at 211–212°. The high melting isomer yields the 159° methyl ester reported by Reimer and Reynolds. The low melting form was formed in much larger quantities. Treatment of either acid with 65% sulfuric acid gave a lactone which must have the double bond in the β,γ-position since it can be hydrolyzed to give a mixture of both acids



$$C_6H_5CO-\underset{C_6H_5}{CH}-\overset{C_6H_5}{CH}-COOH \xrightarrow[H_2SO_4]{65\%}$$

Either acid

$$C_6H_5-C=\overset{H_5C_6}{C}-\overset{C_6H_5}{CH}-C=O \longrightarrow \quad (\text{ring: } C_6H_5-C \text{ and } C=O \text{ joined through } O)$$

Lactone

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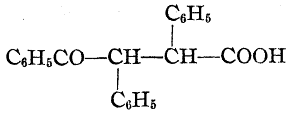
[1] Reimer and Reynolds, *Am. Chem. J.*, **40**, 435 (1908).

*** This method of preparation of the acid and other preparations and analytical results marked with an asterisk formed part of the thesis submitted by Brunhilde Reich as partial fulfilment of the requirements for the degree of Master of Arts at Vassar College.**



$$C_6H_5CO{-}\underset{C_6H_5}{CH}{-}\overset{C_6H_5}{CH}{-}COOH$$

Both acids

Rearrangement to the conjugated α,β-unsaturated lactone apparently does not occur in this case, for, if it did, hydrolysis should lead to one new racemic unsaturated hydroxy acid.

Experimental

Desoxybenzoin was prepared in 80% yields from benzoin, using the method of Ballard and Dehn.[2]

Ethyl α-bromophenylacetate was prepared in 85% yields from 136 g. (1 mole) of phenylacetic acid, 240 g. of bromine, 8 g. of red phosphorus and 100 cc. of absolute alcohol. The yield was reduced to 72% when double quantities were used.

α,β-Diphenyl-β-benzoylpropionic Acid.—After trying several methods of making the sodium derivative of desoxybenzoin, the following procedure* was adopted and gave the acid mixture in about 40% yields. Sodium powder, 2.3 g. (0.1 mole), in dry ether was treated with 19.6 g. (0.1 mole) of desoxybenzoin in a 200-cc. flask fitted with a condenser and guard tube. The mixture was warmed on the steam-bath until the sodium had practically all disappeared. This usually required about an hour and the solution became clear orange in color. Ethyl α-bromophenylacetate, 20 g. (just under 0.1 mole), was added slowly through the condenser and the heating continued for one and one-half hours. Most of the ether was then evaporated and replaced by alcohol. The mixture was then heated on the steam-bath for two hours with 85 cc. of 15% potassium hydroxide, diluted with water and filtered from unchanged desoxybenzoin and didesyl. Acidifying the filtrate with hydrochloric acid precipitated the keto acids. Several runs were made on double quantities without changing the yield. The acids from several runs were combined for recrystallization.

The low melting acid was formed in much larger quantities, and separated first from the ethyl alcohol solution of the two. Later both forms separated at the same time, but, when crystallization was carried out slowly, they were so different in appearance that the two kinds of crystals could be separated by hand. Further recrystallization of the two acids from alcohol gave pure compounds melting at 201–202° and 211–212°. The low melting acid differed from the high melting one in crystallizing from alcohol without alcohol of crystallization. Both acids are very soluble in chloroform, and acetone, soluble in alcohol, ethyl acetate, ether and benzene, and insoluble in ligroin and water. Ethyl alcohol or acetone and water were the best solvents for recrystallization. The 201° compound formed clusters of stout needles and the 211° compound separated in a mass of very fine needles.

Anal. Calcd. for $C_{22}H_{18}O_3$ (330): C, 79.98; H, 5.49. Found: C, 79.76; H, 5.67; neut. eq., 324.*

Attempts* to prepare the oxime and phenylhydrazone of the keto acids were unsuccessful.

Esters of α,β-Diphenyl-β-benzoylpropionic Acid.—Both ethyl esters could be separated from the original reaction mixture, but it was more satisfactory to prepare the esters from the pure acids by esterifying with the appropriate alcohol and a small quantity of concd. sulfuric acid. The corresponding esters of the two acids did not differ much in solubility. Both methyl esters were very soluble in acetone and chloroform, soluble in benzene and methyl alcohol and only very slightly soluble in ether, ethyl acetate and ligroin. The ethyl esters were very soluble in chloroform, benzene, acetone and ethyl acetate, soluble in ether and ethyl alcohol and insoluble in ligroin.

The methyl ester of the 211° acid melted at 158.5–159° as described by Reimer and Reynolds,[1] and was recrystallized from a mixture of methyl alcohol and acetone.

The methyl ester of the 201° acid was recrystallized from methyl alcohol and melted at 147–148°.

Anal. Calcd. for $C_{23}H_{20}O_3$: C, 80.21; H, 5.85. Found: C, 80.33; H, 6.0.

The ethyl ester of the 211° acid was recrystallized from ethyl alcohol and melted at 138–139°.

Anal. Calcd. for $C_{24}H_{22}O_3$: C, 80.40; H, 6.19. Found: C, 80.35; H, 6.32.

The ethyl ester of the 201° acid was recrystallized from ethyl alcohol and melted at 147.5–148°.

Anal. Calcd. for $C_{24}H_{22}O_3$ (358.7): C, 80.40; H, 6.19. Found: C, 80.44; H, 6.20; mol. wt.,* 352, 349.

Lactone.—When either of the acids was stirred and heated on the steam-bath with 65% sulfuric acid for several hours, the lactone, m. p. 124–125°, resulted.*. It was very soluble in chloroform and ethyl acetate, soluble in alcohol, ether and benzene and insoluble in ligroin.

Anal. Calcd. for $C_{22}H_{16}O_2$ (312.7): C, 84.59; H, 5.16. Found: C, 84.68; H, 5.26; mol. wt.,* 318, 313.

Two grams of the lactone was heated under reflux for one hour with 25 cc. of alcohol and 2 g. of potassium hydroxide. The solution was then cooled, diluted with water and acidified with hydrochloric acid. The resulting acid mixture was recrystallized from ethyl alcohol and both acids were recovered, the 201° compound in much larger quantities.

The author wishes to thank the University of Minnesota for the courtesy shown her as an Honorary Fellow of the University while on leave from Vassar College in the spring of 1938.

Summary

1. A new method of preparing α,β-diphenyl-β-benzoylpropionic acid is reported.

2. The two racemic forms of the acid and their methyl and ethyl esters are described.

3. The dehydration of either acid leads to the formation of a lactone.

POUGHKEEPSIE, NEW YORK RECEIVED OCTOBER 31, 1938

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(2) Ballard and Dehn, THIS JOURNAL, **54**, 3970 (1932).

NOTES

A Criterion for the Mechanism of the Reactions of Alkyl Halides with Hydroxylic Solvents. Reactions of Benzhydryl Chloride

By Leslie C. Bateman, Edward D. Hughes and Christopher K. Ingold

The two types of mechanism which we have postulated[1] for aliphatic substitutions, one involving bimolecular replacement in a single stage and the other preliminary ionic fission, have been discussed recently.[2] The point of interest is the ionization mechanism, which we term unimolecular and Hammett polymolecular; and although in the sequel we use our own label, we strongly agree with the purpose of Hammett's, which is to emphasize the role of the solvent. We ourselves have done this in discussions,[1c,3] pointing out, for instance, that only through solvation is the activation energy of an ionic fission reduced to accessible values.

In a number of well-established unimolecular substitutions the entrant group comes, not from the solvent, but from a reagent present in small and controllable concentration.[4] For these the observed reaction order determines the mechanism. In other substitutions, for instance, the hydrolysis and alcoholysis of alkyl halides in hydroxylic solvents, the reaction order is no longer diagnostic, and other, less direct, methods must be employed. Several have been suggested,[4] but we need here to refer only to one particular method.

This has been illustrated with respect to the simultaneous hydrolysis and alcoholysis of *t*-butyl chloride in aqueous alcohol. The total first order reaction was first investigated by Hughes,[5] who found that the rate was unaffected by hydroxonium and hydroxide ions, but was much increased with increasing water content of the solvent. He concluded that the reaction was unimolecular. Olson and Halford[2b] examined the applicability of an equation, in constructing which they assumed the reaction to be bimolecular. The formula is

$$\text{Rate} = (k_a p_a + k_w p_w) p_{\text{RCl}}$$

where the k's are rate constants, the p's partial vapor pressures, and the subscripts refer to alcohol, water and *t*-butyl chloride; and it may be used either to calculate the total rate, or, from the partial rates $k_a p_a p_{\text{RCl}}$ and $k_w p_w p_{\text{RCl}}$, to deduce the composition of the product (ROEt + ROH). Having computed k_a and k_w from observed total rates, the authors showed that their formula gave an accurate description of the variation of total rate with solvent composition, and concluded on this account that the reaction was indeed bimolecular. Then we pointed out[3] that the success with which the formula represents the total rate owes nothing to the assumed mechanism, the essential postulate, the participation of solvent in the transition state, being true for all reactions in solution, including the unimolecular process. We also noted, however, that the product compositions should be calculable with a corresponding success only if the reaction is bimolecular, for in that case the product is formed in the rate-measured reaction, so that its composition is fixed by measured rate constants, whereas in unimolecular substitution the product arises subsequently to the rate-measured stage, so that its composition cannot in principle be deduced from measured constants. An application of this criterion to the reactions of *t*-butyl chloride showed that they were not bimolecular as had been claimed, and we concluded that they were unimolecular in agreement with Hughes.

The main object of this note is to point to the analogy of a second reaction of an alkyl halide with a solvent, in which a similar criterion has been applied, with results pointing again to the unimolecular interpretation. This is the reaction of benzhydryl chloride with aqueous ethanol. Like the reaction of *t*-butyl chloride, its first order rate is unaffected by hydroxonium and hydroxide ions, but is much increased with increasing water content of the solvent. Total rates have been measured by Ward, by Norris and Morton, by Kny-Jones and Ward,[6] and by Farinacci and

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[1] (a) Hughes, Ingold and Patel, *J. Chem. Soc.*, 526 (1933); (b) Gleave, Hughes and Ingold, *ibid.*, 236 (1935); (c) Hughes and Ingold, *ibid.*, 244 (1935); (d) Hughes, Ingold and Shapiro, *ibid.*, 225 (1936).

[2] (a) Farinacci and Hammett, This Journal, **59**, 2544 (1937); (b) Olson and Halford, *ibid.*, **59**, 2644 (1937).

[3] Bateman, Hughes and Ingold, *J. Chem. Soc.*, 881 (1938).

[4] References are given in paper (3).

[5] Hughes, *J. Chem. Soc.*, 255 (1935).

[6] (a) Ward, *ibid.*, 2285 (1927); (b) Norris and Morton, This Journal, **50**, 1795 (1928); (c) Kny-Jones and Ward, *ibid.*, **57**, 2394 (1935).

Hammett,[2a] and product compositions by the last-named authors. This was before Olson and Halford's vapor pressure theory had become available, but Farinacci and Hammett noted that a bimolecular mechanism, interpreted with the aid of a concentration mass law, could not bring rates and product compositions into harmony, for when added water increased the reaction rate it did so chiefly, not by diverting the formation of benzhydryl ethyl ether into that of benzhydrol, but by accelerating the production of benzhydryl ethyl ether. Such a "catalytic" effect is, however, expected on the basis of the unimolecular mechanism.

Olson and Halford show, with respect to the example studied by them, that, whereas the vapor pressure formula exactly accounts for the variation of rate with solvent composition, a corresponding concentration formula fails completely. We have therefore considered the question of whether Farinacci and Hammett's inference is likely to be changed if this calculation is carried from the concentration basis of the assumed equation

$$\text{Rate} = (k'_{\text{a}}c_{\text{a}} + k'_{\text{w}}c_{\text{w}})c_{\text{RCl}}$$

to the vapor pressure basis of Olson and Halford's theory. We conclude that it could not be changed. The transformation cannot, as a matter of fact, be effected completely, because the partial vapor pressures of benzhydryl chloride are unknown and would be difficult to determine accurately. We can, however, convert to the new basis the treatment of the solvent components, and, assuming an approximate invariance in the Henry's law constants of benzhydryl chloride over the relevant range of solvent compositions, test for the effect of the incompleteness of our procedure by reference to the observed total rates. For this range, the representation of the total rates is in fact so good that we have the same empirical justification as Olson and Halford for proceeding to predict the separate parts of the total rate, or, what is equivalent, the product compositions; and this is the prediction that really distinguishes the bimolecular and unimolecular mechanisms. In view of the relatively low water concentrations used, we are not surprised to find that the predicted values differ relatively little from Farinacci and Hammett's, and that therefore, as the table indicates, they show correspondingly pronounced divergences from the experimental values. Bearing in mind also the more completely investigated case of *t*-butyl chloride, it cannot be doubted that Farinacci and Hammett's conclusions stand, *i. e.*, that the vapor pressure theory could not bring the hydrolysis and alcoholysis of benzhydryl chloride into harmony with the bimolecular mechanism.

REACTION OF BENZHYDRYL CHLORIDE WITH AQUEOUS ETHANOL AT 25°

H_2O Moles/l.	k (10^{-5} min.$^{-1}$) Found	k (10^{-5} min.$^{-1}$) Calcd.	Moles % ROH Found (F. and H.)	Moles % ROH Calcd.	Moles % ROH Calcd. (F. and H.)
0.000	343	..	..	0.0	0.0
.600	474	482	1.8	31.5	27.7
1.320	634	652	11.8	51.5	46.0
1.579	691	..	..	55.1	..

We take the opportunity to refer to four points raised by Hammett[2a,7] with reference to the detailed interpretation of the unimolecular mechanism, as the relevant experimental material is, and will be, considerably scattered. The first, relating to the incompleteness of racemization, is dealt with in papers[8] which were unavailable when he wrote. The second was that dissolved negative ions had not been found to participate in homogeneous solvolytic reactions. But they do participate if their concentration is adequate in relation to that of the reactive constituent of the solvent; thus chloroacetate ions form *t*-butyl chloroacetate without increasing the reaction rate in the hydrolysis of *t*-butyl chloride in moist formic acid, and chloride ions retard the hydrolysis of benzhydryl chlorides in moist acetone. The third point was that solvolytic reactions apparently require high concentrations of hydroxylic solvents, water having failed to react with α-phenylethyl chloride in moist acetone though it accelerated the total reaction in moist acetic acid. However, we regard the difference as one of degree, depending on the ionizing properties of the solvent as a whole, and can show that hydrolyses which are slow in moist acetone are rapid in equally moist sulfur dioxide, though sulfur dioxide, like acetone, is non-hydroxylic. Fourthly, the example of sulfur dioxide illustrates how poor an index to ionizing power is the dielectric constant, doubtless because of its very indirect connection with the short-range forces determining solvation. These, however, are points of detail: as to essentials we endorse Hammett's statement[7] that his views and ours are in harmony.

Summary.—Of the bimolecular and unimolecular mechanisms of aliphatic substitution,

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(7) Steigman and Hammett, *ibid.*, **59**, 2536 (1937).

(8) Hughes, Ingold and others, *J. Chem. Soc.*, 1196 *et seq.* (1937).

the former alone yields the product in a reaction stage whose rate can be measured; and therefore a comparison of rates and product compositions in competing reactions, such as those of an alkyl halide in aqueous alcohol, affords a criterion of mechanism. Such a criterion was applied by Farinacci and Hammett to the reactions of benzhydryl chloride but Olson and Halford have made proposals to change the quantitative basis of such comparisons. We consider whether Farinacci and Hammett's rejection of the bimolecular mechanism stands in the light of this work, which we have more fully examined with respect to the reactions of *t*-butyl chloride; and we conclude that it does stand. Thus the hydrolyses of *t*-butyl chloride and benzhydryl chloride are mutually confirmatory examples in which the application of the criterion mentioned favors the unimolecular mechanism, some details concerning which are discussed.

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LONDON, ENGLAND
RECEIVED MAY 17, 1938

A New Method for the Preparation of 3,5-Cholestadiene

BY KENZO HATTORI

The various methods for the preparation of the so-called cholesterilene have been discussed recently by H. E. Stavely and W. Bergmann.[1] These authors also prepared 3,5-cholestadiene (I) by the Wolf–Kishner reduction of the semicarbazone of the 7-ketocholesterilene (II). Since this procedure involves prolonged heating at 180–200°, the possibility of a rearrangement of the double bonds is not excluded. In order to eliminate such possibility, 3,5-cholestadiene was prepared by the treatment of pseudocholestene dibromide (III) with silver nitrate in pyridine solution at room temperature.[2] The diene obtained by this reaction seems to be identical with the 3,5-cholestadiene described by Stavely and Bergmann.

Nine-tenths of a gram of pseudocholestene dibromide was dissolved in 20 cc. of pyridine containing 18% of silver nitrate. The reaction mixture was kept in the dark at room temperature for one month. The solution was then diluted with water, acidified with sulfuric acid and extracted with ether. The residue obtained on evaporation of the ether extract was recrystallized from a mixture of alcohol and ether. The diene crystallizes in needles, m. p. 79–80°, $[\alpha]^{15}D$ $-68.7°$.

Anal. Calcd. for $C_{27}H_{44}$: C, 87.96; H, 12.04%. Found: C, 88.3; H, 11.7%.

The diene gave a positive reaction with Rosenheim's reagent and with antimony trichloride. Mixed with a sample of cholesterilene, prepared from cholesterol,[3] m. p. 79°, $[\alpha]^{15}D$ $-76.0°$, it gave no depression of the melting point.

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[1] W. Bergmann, *J. Org. Chem.*, **1**, 567 (1937).

[2] E. Dane, *Z. physiol. Chem.*, **245**, 80 (1937); **248**, I (1937).

[3] Mauthner, *Monatsh.*, **17**, 34 (1896).

THE PHARMACEUTICAL INSTITUTE
IMPERIAL UNIVERSITY
TOKYO, JAPAN
RECEIVED AUGUST 6, 1938

Identification of Methylisopropylcarbinol in Sharples Diethylcarbinol

BY FRANK A. KARNATZ AND FRANK C. WHITMORE

In connection with another research,[1] an attempt was made to obtain pure 3-pentanol by a series of careful fractional distillations of a sample of commercial diethylcarbinol supplied by the Sharples Solvents Corporation. It was noted that even after many fractionations the material of almost constant refractive index boiled over a range of 4°. Since the refractive index of methylisopropylcarbinol is very near that of 3-pentanol ($n^{20}D$ 1.4095 and 1.4100, respectively), the lower boiling portion of the sample was carefully refractionated by parts in an efficient column. In this way a fraction was obtained, b. p. 111.5° (732 mm.), $n^{20}D$ 1.4096, which gave the α-naphthylurethan of methylisopropylcarbinol,[2] m. p. and mixed m. p. 108–110°.

The identification of this alcohol, which had not been found in the hydrolysis products of the chloropentanes by previous investigators,[3] is of considerable theoretical interest. It demonstrates that the hydrolysis of 3-chloro-2-methylbutane to the alcohol does not involve complete rearrangement. The conversion of the alcohol to the chloride even under the mildest conditions gives the rearranged product, 2-chloro-2-methylbutane.[4] Both these conversions are being studied further to determine the relative amounts of rearranged and non-rearranged products from each.

STATE COLLEGE, PENNA.
RECEIVED SEPTEMBER 28, 1938

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[1] Whitmore and Karnatz, THIS JOURNAL, **60**, 2536 (1938).

[2] Whitmore and Johnston, *ibid.*, **55**, 5022 (1933).

[3] Ayres, *Ind. Eng. Chem.*, **21**, 899 (1929); Clark, *ibid.*, **22**, 439 (1930).

[4] Whitmore and Johnston, THIS JOURNAL, **60**, 2265 (1938).

The Stability of Dry Potassium Ferrocyanide

BY ROBERT B. LOFTFIELD[1] AND ELIJAH SWIFT, JR.

In the course of a previous investigation,[2] it was noticed that sometimes dry potassium ferrocyanide undergoes a slight decomposition. Since this salt is one of the few quadrivalent salts that is sufficiently stable to be useful in precise electrochemical investigations[3] where the effect of ionic charge on the properties of solutions is being studied, it seemed of some importance to determine the conditions under which decomposition takes place.

Mallinckrodt reagent grade potassium ferrocyanide was precipitated from saturated solution at 0° by adding an equal volume of cold 95% alcohol. The crystals were allowed to grow for several hours and then were centrifuged and washed with cold 95% alcohol. This process was repeated and the salt was dried by sucking off the excess alcohol with a water pump. After standing in a clear glass bottle exposed to the ordinary laboratory light for over a year, no change in color could be observed by comparison with freshly prepared salt, and no odor of hydrogen cyanide was perceptible in the bottle.

The salt was dehydrated as in previous investigations[3] in order to get a sample whose exact composition would be known. About 0.5 g. of the salt was placed in a platinum boat in a Richards bottling apparatus and a slow stream of nitrogen was allowed to flow over the sample while heating to 90°. The nitrogen was removed with a water pump and the tube flushed out several times with nitrogen and finally left evacuated for one to two hours while the temperature was maintained at 90–100°. The tube was then filled with nitrogen and the salt cooled in a slow stream of the gas. This method of preparing the salt was found by Jones and Jelen[3a] to give material of constant weight.

Fabris[4] has stated that there is a considerable loss of cyanide[5] when this salt is heated above 50° in air. To check this statement, samples of salt were heated to 100° for three hours in a slow stream of air, the effluent gas being passed through a solution of sodium hydroxide. The Prussian blue test applied to this solution was negative, showing that less than 0.01% of the salt was lost as cyanide in this process. Negative tests for cyanide were also obtained when samples of salt were heated in a slow current of nitrogen, using the Prussian blue test and the specific ferric thiocyanate test.[6] It seems evident that this salt may be dehydrated safely at 100°, although decomposition will take place at higher temperatures.[7]

After the dehydrated salt had come to room temperature, half of the boat was covered with platinum foil and the salts exposed to illumination. After two hours of illumination with a "Pointalite" bulb and forty hours' illumination with a 200-watt tungsten bulb 15–20 cm. above the surface, no change in the color of the salt was observed. The tube was then flushed out several times with dry oxygen and the process repeated. After about forty hours of exposure a slight change in the color of the salt was observed, and after seventy-two hours there was a decided greenish-blue color on the surface of the salt. This color was much less pronounced underneath the foil where the light could reach the salt only indirectly; while another sample kept in dry oxygen in the dark for seventy-two hours failed to show any color change whatever. Presumably the reaction involves the formation of Prussian blue, but the amount of material formed was too minute to be analyzed readily, and it was not thought worth while to investigate this reaction further. The test was repeated by placing a fresh sample in dry oxygen in direct sunlight, and the same result was observed after one or two hours' exposure. A control sample of the hydrated salt showed no reaction whatsoever under any of the above conditions.

Another sample of the anhydrous salt was placed in an atmosphere of moist oxygen and exposed to illumination. No reaction was observed, probably because the salt picked up moisture and went into the more stable hydrated form before any appreciable photochemical reaction could take place.

To determine whether the anhydrous salt is deliquescent, a sample was placed in a container saturated with water vapor at room temperature (30°). The salt quickly picked up even more than the three moles of water normally present and deliquesced to a sticky mass. Microscopic examination of the dehydrated salt showed that the crystals are practically intact after dehydration, since there is no change in the gross form and the smallest crystals appear quite as clear as before dehydration. Larger, clear crystals become translucent after dehydration, due to their breaking up into smaller units, but they also retain the same shape, and do not break up into an amorphous white powder.[8] It is probable that the dehydrated material will go back to the same photochemically stable trihydrate on exposure to moisture.

On the basis of this investigation, we believe that potassium ferrocyanide is sufficiently stable to be used in precise investigations if the following conditions are observed:

1. The salt must not be dehydrated at temperatures greater than 100°.
2. The dehydrated salt must be kept out of contact with moisture before and during weighing, but not necessarily after.
3. The dehydrated salt must be kept in the dark to prevent decomposition.

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(1) Harvard National Scholar, '41.

(2) E. Swift, Jr., THIS JOURNAL, **60**, 728 (1938).

(3) (a) Grinnell Jones and F. C. Jelen, *ibid.*, **58**, 2561 (1936); (b) Grinnell Jones and R. E. Stauffer, *ibid.*, **58**, 2558 (1936).

(4) Fabris,, *Gazz. chim. ital.*, **61**, 527 (1931).

(5) Autenrieth, "The Detection of Poisons," P. Blakiston's Son and Co., Philadelphia, Penna., 1921, p. 21, states that many other substances will react in the same way as hydrogen cyanide, and that the test used by Fabris is not conclusive evidence of the presence of this gas.

(6) According to McAlpine and Soule, "Qualitative Chemical Analysis," D. Van Nostrand Co., New York, N. Y., 1933, p. 460, the thiocyanate test is good to 1 p. p. m. or better.

(7) One sample of salt heated to 140° lost about 0.1% of cyanide.

(8) Roscoe and Schorlemmer, "Treatise on Chemistry," The Macmillan Co., New York, 1907, Vol. II, p. 1230.

We wish to thank Mr. E. B. Damon and Dr. W. A. Ray for the kind loan of apparatus used in this investigation.

HARVARD CHEMICAL LABORATORIES
CAMBRIDGE, MASSACHUSETTS
GEORGE DAVIS SCIENCE HALL
KNOX COLLEGE
GALESBURG, ILLINOIS

RECEIVED JULY 18, 1938

Changes in the Physical Properties of Regenerated Cellulose by Liquid Ammonia

BY RICHARD G. ROBERTS

During the dialysis of proteins and hormones contained in bags made from regenerated cellulose film and placed in liquid ammonia, it was observed that the bags changed in size and in flexibility. Therefore, a series of comparative tests on some of the physical properties of the film and ammonia-treated film was made. The film used in these tests was du Pont Cellophane number 600.

The film was cut into strips of convenient size and placed in a Dewar flask. Liquid ammonia, previously dried over metallic sodium, was added to immerse the film sample completely. The film was not previously dried by us. The Dewar flask was tightly stoppered, and attached to a mercury seal. The liquid ammonia boiled off in about twenty-four hours, and any excess ammonia gas was removed by a vacuum pump.

Physical properties showing an increase:	
Tear strength (Elmendorf test)	200.0%
Tensile strength	70.6%
Thickness (flat micrometer)	152.4%
Weight (per unit area)	27.3%
Physical properties showing a decrease:	
Length (with grain)	8.3%
Width (cross grain)	17.8%
Area	24.7%

Ratios: Increase of tear strength to decrease in area, approximately 8 to 1. Increase of tensile strength to decrease in area, approximately 3 to 1.

It has been shown that bags made from regenerated cellulose film may be used conveniently for dialyzing experiments in liquid ammonia, although some space must be allowed for shrinkage.

The author wishes to thank Montgomery Ward and Company, Chicago, Illinois, for the use of apparatus in their testing laboratory.

THE DEPARTMENT OF CHEMISTRY
CHICAGO MEDICAL SCHOOL
CHICAGO, ILLINOIS

RECEIVED AUGUST 29, 1938

The Specificity of the Fermentation Test for Vitamin B_1

BY ALFRED S. SCHULTZ, LAWRENCE ATKIN AND CHARLES N. FREY

The fermentation method for the determination of vitamin B_1[1–3] has been in successful operation for some time. The effect of 2-methyl-5-ethoxymethyl-6-aminopyrimidine has been described.[2] We have assayed a wide variety of substances such as non-autoclaved yeast, rice polish, vitamin pills and concentrates, solutions of crystalline vitamin, and milk, and no evidence of the interfering substance has been found. In an investigation on the metabolism of vitamin B_1,[4,5] we found reason to believe that a portion of the fermentation stimulating effect of urine is not due to vitamin B_1. While this did not appear to alter the significance of the results, it was thought very desirable to find a method for differentiating between the intact vitamin molecule and any possible breakdown product. A way of doing this has been found in the differential oxidation of the vitamin B_1 in the presence of the aminopyrimidine.

Alkaline ferricyanide in the cold will readily oxidize the vitamin to thiochrome. Preliminary experiments with a sample of thiochrome obtained from Merck and Company showed it to be inactive in the fermentation reaction. The aminopyrimidine is more resistant to oxidation and it is a simple matter to oxidize B_1 preferentially when present in addition to aminopyrimidine. A solution containing 8 gamma of the aminopyrimidine and 8 gamma of thiamin hydrochloride in a volume of 35 ml. was treated with 2.5 ml. of 1% $K_3Fe(CN)_6$ and 2.5 ml. of 50% NaOH. After standing at room temperature for five minutes the solution was neutralized with dilute sulfuric acid and made to 100 ml. A 25-ml. aliquot of this was tested in the usual manner by gas test. It gave a stimulation which corresponded exactly to 2 gamma of the aminopyrimidine (*i. e.*, the B_1 was destroyed). Parallel experiments showed that the neutralized oxidizing solution was without influence on controls with either thiamin hydrochloride or aminopyrimidine.

(1) A. S. Schultz, L. Atkin and C. N. Frey, THIS JOURNAL, **59**, 948 (1937).

(2) A. S. Schultz, L. Atkin and C. N. Frey, *ibid.*, **59**, 2457 (1937).

(3) A. S. Schultz, L. Atkin and C. N. Frey, *ibid.*, **60**, 1514 (1938).

(4) A. S. Schultz, R. F. Light and C. N. Frey, *Proc. Soc. Exptl. Biol. Med.*, **38**, 404–406 (1938).

(5) R. F. Light, A. S. Schultz, L. Atkin and L. J. Cracas, *J. Nutr.*, **16**, 333 (1938).

This technique greatly increases the specificity of the fermentation method and an investigation of the conditions necessary for its application to substances like animal tissue and excreta is under way.

THE FLEISCHMANN LABORATORIES
STANDARD BRANDS INCORPORATED
810 GRAND CONCOURSE
NEW YORK, N. Y.
RECEIVED SEPTEMBER 16, 1938

COMMUNICATIONS TO THE EDITOR

CRYSTALLINE COPPER-PROTEIN POSSESSING TYROSINASE ACTIVITY

Sir:

A crystalline material has been obtained from the aqueous extract from the wild mushroom, *Lactarius piperatus,* which may be phenol oxidase, or closely related to it. The crystals were six-sided plates and undoubtedly belonged to the hexagonal system. They were insoluble in water, dilute acids and salt solutions, but soluble in an aqueous solution of secondary sodium phosphate. Analysis showed a copper content of 0.25 and 13.6% nitrogen. Their phosphate solution was active in promoting the aerobic oxidation of *p*-cresol and catechol.

The procedure followed in obtaining the crystals can be described briefly as follows. The aqueous extract of the ground mushrooms was precipitated with 0.6 saturated ammonium sulfate, redissolved in water, the latter made 0.2 saturated with ammonium sulfate and the precipitate discarded. The filtrate obtained in the last operation was reprecipitated with 0.6 saturated ammonium sulfate, the precipitate formed redissolved in water and the solution treated with three volumes of cold acetone. The precipitate thus obtained was dissolved in water and treated with alumina. The liquid separated from the alumina contained about 50% of the active oxidase. This liquid was treated with boneblack and after filtering the filtrate was again precipitated with 0.6 saturated ammonium sulfate. The precipitate from the last operation was taken up in water and had an activity of 7000 units per cc. when determined according to the Graubard and Nelson method as modified by Adams and Nelson [THIS JOURNAL, **60,** 2472 (1938)]. When this liquid was gradually acidified by acetic acid, changing the *p*H from 6.5 to 5, and allowed to stand in the ice box, crystals separated.

DEPARTMENT OF CHEMISTRY
COLUMBIA UNIVERSITY
NEW YORK CITY

HAROLD R. DALTON
J. M. NELSON

RECEIVED NOVEMBER 25, 1938

TETRAMETHYLPLATINUM AND HEXAMETHYLDIPLATINUM

Sir:

Tetramethylplatinum has been prepared in 46% yield from trimethylplatinum iodide and methylsodium. It is the most soluble organoplatinum compound so far prepared, being readily soluble in the cold in benzene, acetone, ether and petroleum ether (b. p. 60–68°). The compound crystallizes from petroleum ether as large hexagonal crystals which decompose but do not melt at elevated temperatures. *Anal.* Pt, 76.84; C, 18.32; H, 4.31. We have found that the compound is one of several by-products of the Pope and Peachey [*J. Chem. Soc.,* **95,** 571 (1909)] reaction for the preparation of trimethylplatinum iodide from platinic chloride and methylmagnesium iodide. Hydrogen chloride converts tetramethylplatinum to trimethylplatinum chloride. *Anal.* Pt, 70.20; Cl, 13.10.

Hexamethyldiplatinum has been synthesized in 60% yield by heating trimethylplatinum iodide with powdered potassium in dry benzene. *Anal.* Pt, 81.13; C, 14.55; H, 3.92. The compound is very soluble in benzene, acetone and ether, but only slightly soluble in cold petroleum ether. It is best crystallized from a benzene–petroleum ether solution. Molecular weight determinations show that hexamethyldiplatinum is not dissociated at the freezing point of benzene [mol. wt.: calcd., 480.4; found, 482]. Iodine in ether converts the compound to the known trimethylplatinum iodide.

These two organoplatinum compounds are interesting because they demonstrate for the first time that true organoplatinum compounds not having acid radicals can be prepared. A detailed account of these and other organoplatinum compounds will be published shortly.

THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE
AMES, IOWA
HENRY GILMAN
M. LICHTENWALTER

RECEIVED OCTOBER 31, 1938

THE IDENTIFICATION OF METHYLCHAVICOL IN AMERICAN GUM SPIRITS OF TURPENTINE

Sir:

Recent investigations have shown that gum spirits of turpentine of slash and longleaf pine contain about 95% of pinenes [Dupont, *Ann. chim.*, [10] **1**, 184 (1924); Aschan, "Naftenföreningar, Terpener och Kamferarter," Helsingfors, 289 (1926); Palkin, Technical Bulletin 596, U. S. Department of Agriculture (1932)]. We have been able to obtain physical and chemical evidence, including the fact that homoanisic acid is obtained on oxidation, that the fractions boiling above those of the pinenes contain considerable amounts of methylchavicol (4-methoxyallylbenzene).

This was shown by the isolation of methylchavicol from turpentine by the method described by Balbiano [*Ber.*, **42**, 1504 (1909)], for the separation of methylchavicol from anethole. Seventy-five grams of a fraction, b. p. 88–95° at 10 mm., obtained by fractionation of steam-distilled residues of spirits of turpentine was dissolved in 400 cc. of ether and shaken for one hour with a solution of 81 g. of mercuric acetate dissolved in 350 cc. of water. After separating the ether, the aqueous solution was heated for ten hours at 70–80° with 70 g. of sodium hydroxide and 80 g. of granulated zinc. The mixture was then distilled with steam, the distillate extracted with ether and the ether solution dried and distilled, leaving 8 g. of methylchavicol, the main fraction of which boiled at 213–215°; $d^{25}{}_{25}$ 0.9600; $n^{22}{}_{D}$ 1.51372. Physical constants recorded in the literature are: b. p. 214–215° [Klages, *Ber.*, **32**, 1439 (1899); d^{21} 0.9645; n_D 1.5236; (Beilstein, "Handbuch der organischen Chemie," fourth edition, **6**, 571 (1923)]. Ten grams of this product was oxidized at room temperature with 630 cc. of 4% potassium permanganate solution. After removal of manganese dioxide, the filtrate was evaporated to about one-third of its original volume and acidified with hydrochloric acid. The precipitated anisic acid was recrystallized from water and melted at 184–185° (corr.); yield, 2.5 g. Calcd. for $C_8H_8O_3$: C, 63.18; H, 5.30. Found: C, 63.32; H, 5.46. The acid did not lower the melting point in the mixed melting point test with an authentic sample of this material.

The aqueous filtrate from which the anisic acid had been removed was evaporated to a small volume, extracted with ether and dried. The ether was distilled and about 0.3 g. of a substance, apparently homoanisic acid, was obtained. It was recrystallized from water and melted at 85.5–86.5°. Homoanisic acid melts at 85–86° [Pschorr, Wolfes and Buckow, *Ber.*, **33**, 172 (1900)]. Calcd. for $C_9H_{10}O_3$: C, 65.04; H, 6.07. Found: C, 65.30; H, 6.54.

We assume that the difference in odor between highly purified turpentine and American gum spirits of turpentine can be partly attributed to the presence of phenol ethers.

G. & A. LABORATORIES, INC.
SAVANNAH, GEORGIA
TORSTEN HASSELSTROM
BURT L. HAMPTON

RECEIVED OCTOBER 28, 1938

PANTOTHENIC ACID AS A GROWTH FACTOR FOR THE DIPHTHERIA BACILLUS

Sir:

It has been shown in experiments already presented elsewhere that β-alanine and nicotinic acid are essential for the growth of certain strains of the diphtheria bacillus [Mueller, *Proc. Am. Exptl. Biol. Med.*, **36**, 706 (1937)]. β-Alanine has long been known to be a constituent of meat extract both in the free form and also combined with histidine in the compound carnosine, in which form it has also been shown to be available to the diphtheria bacillus [Mueller, *J. Biol. Chem.*, **123**, 421 (1938)]. In a personal communication, we have recently learned from Dr. R. J. Williams that pantothenic acid [Williams, *et. al.*, THIS JOURNAL, **55**, 2912 (1933); **60**, 2719 (1938)] also yields β-alanine upon hydrolysis. Dr. Williams suggests, further, that β-alanine may be effective in producing growth with *C. Diphtheriae* only insofar as it serves as a building stone for the production of pantothenic acid, which may be the material actually required by the organism, and he has supplied us with specimens of pantothenic acid and calcium pantothenate in varying degrees of purity. With this material we have been able to test out this theory and to show that it well may be correct.

Using a control medium containing the products of complete acid hydrolysis of casein, lactic, pimelic and nicotinic acids and inorganic salts, but completely deficient in β-alanine, a series of media has been prepared in which increasing quantities of β-alanine were added to one set, pantothenic acid or calcium pantothenate to a second and the latter substance hydrolyzed by autoclaving with normal hydrochloric acid for thirty minutes at 15 lb. (1 atm.) to a third. The various media were autoclaved (*p*H 7.6) for ten minutes at 10 lb. (0.67 atm.) pressure. After inoculation with the strain of the diphtheria bacillus (Allen), and incubation for three days at 35°, the resulting bacterial growth was centrifuged down, washed and the bacterial nitrogen determined by a method already described, as a measure of bacterial growth [Mueller, *J. Bact.*, **29**, 383 (1935)]. The table shows the results obtained: A = β-alanine; B = Ca pantothenate (about 50%) stated to yield 16% β-alanine on hydrolysis; C = solution B after acid hydrolysis.

	γ added/10 cc. medium			Mg bacterial N/10 cc. medium		
	A	B	C	A	B	C
1 Control +	..	0.0	..	..	0.13	..
2 Control +	..	.31	..	..	.41	..
3 Control +	..	.62	..	..	.60	..
4 Control +	..	1.5	1.5	..	1.47	0.32
5 Control +	..	3.1	3.1	..	2.78	.16
6 Control +	1	6.2	6.2	0.39	3.67	.29
7 Control +	2.5	15.5	15.5	.24	4.70	2.05
8 Control +	5	31	31	6.12	5.35	5.76
9 Control +	10	62	62	6.78	6.60	lost[a]
10 Control +	20	125	..	7.30	7.06	..

[a] Heavy growth.

This and other similar experiments uniformly show a smooth, gradual increase in growth with the addition of pantothenic acid, whereas with β-alanine there is no definite increase over controls until a concentration of from about 2.5 γ per 10 cc. is used. At this point, initiation of growth is slow and irregular, possibly dependent on the size of the inoculum, (platinum loop of pellicle). At levels of 5, 10 and 20 γ concentration of β-alanine or its equivalent of panthothenic acid, growth is heavy and the amounts produced by the two materials are very nearly the same. Hydrolysis of pantothenic acid yields a solution with the properties of β-alanine, *i. e.*, no effect until the concentration of the latter in the hydrolytic products reaches 2.5 γ/10 cc. medium, whereas doubling this concentration regularly leads to heavy growth.

These facts tend to support the view that β-alanine must first be built up into some more complex material before it may be directly utilized by *C. Diphtheriae*, whereas with pantothenic acid no such preliminary synthesis is required.

It is interesting and significant that Snell, Brown and Peterson [THIS JOURNAL, **60**, 2825 (1938)] have shown recently that both pantothenic acid and nicotinic acid are apparently essential factors for growth of certain strains of the lactic acid bacteria. These organisms, unlike the diphtheria bacillus, seem to be unable to effect the synthesis of pantothenic acid from β-alanine, requiring the presence of the more complex material for satisfactory growth.

DEPARTMENT OF BACTERIOLOGY AND
IMMUNOLOGY J. HOWARD MUELLER
HARVARD UNIVERSITY MEDICAL SCHOOL A. W. KLOTZ
BOSTON, MASSACHUSETTS

RECEIVED NOVEMBER 23, 1938

PRESSURE–AREA RELATIONS FOR MONOMOLECULAR FILMS OF TRI-*p*-CRESYL PHOSPHATE AND RELATED COMPOUNDS

Sir:

Interesting differences in surface activity have been observed in a study of phosphorus-organic compounds closely related in structure. Monomolecular film properties of the three isomers of tricresyl phosphate (ortho, meta and para) are practically identical but quite unlike those of either tri-*p*-cresyl phosphite or tri-*p*-cresyl thiophosphate.

Pressure–area relations have been studied on a modified Cenco film-balance apparatus, using general techniques similar to those described by N. K. Adam[1] and Harkins, Ries and Carman.[2,3] The volatile solvent used for the Eastman compounds was twice-distilled benzene. Films were spread on distilled water.

Tri-*p*-cresyl phosphate forms well-behaved, compressible films, whereas the corresponding phosphite and thiophosphate show extremely poor film-forming properties. Films of the phosphite and thiophosphate require compression far beyond the minimum film area for monomolecular

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(1) N. K. Adam, "The Physics and Chemistry of Surfaces," Clarendon Press, Oxford, 1938.

(2) Harkins, Ries and Carman, THIS JOURNAL, **57**, 2224 (1935).

(3) Harkins, Carman and Ries, *J. Chem. Phys.*, **3**, 692 (1935).

thickness before an appreciable rise in pressure is observed. For example, at a pressure of only 1 dyne per cm., the tri-*p*-cresyl thiophosphate film thickness (62.9 Å.) is over five times as great as the maximum monomolecular thickness (11.6 Å.) of tri-*p*-cresyl phosphate.

An interesting correlation between polar group structure and film properties is apparent when we consider the schematic diagrams in Fig. 1.

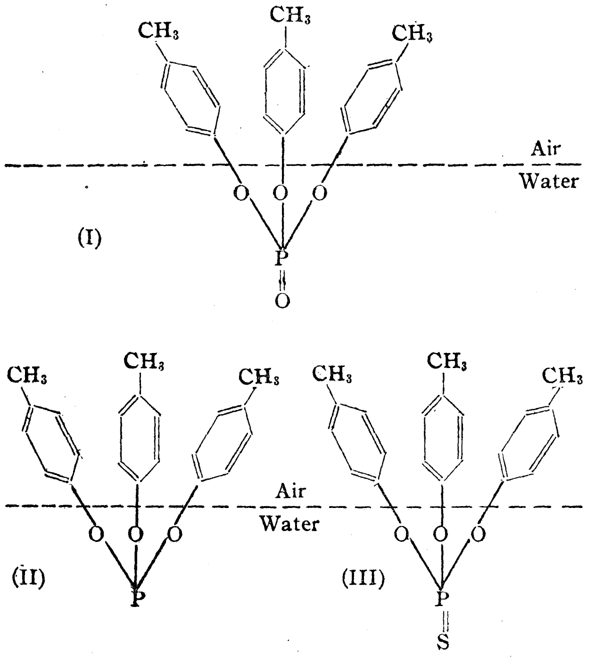

Fig. 1.—Schematic diagrams of molecular orientation at an air–water interface: (I) tri-*p*-cresyl phosphate; (II) tri-*p*-cresyl phosphite; (III) tri-*p*-cresyl thiophosphate. At expanded areas the rings are probably drawn close to the water.

The two poor film-forming compounds (II and III) differ from the tri-*p*-cresyl phosphate (I) in that they lack the P=O group. We must, therefore tentatively conclude that the important contribution to the polarity of the molecule is made by the P=O group as indicated by the superior film properties of tri-*p*-cresyl phosphate.

The most important pressure–area characteristics of a typical tri-*p*-cresyl phosphate film (27.9°) may be briefly summarized. The molecular area values at film pressures of zero (extrapolated), 5 and 8.76 dynes per cm. (the maximum) are, respectively, 99.4, 69.3 and 46.5 sq. Å. Using a density of 1.1284 g. per cc. the film thickness values at the same pressures are, respectively, 5.42, 7.78 and 11.6 Å. Partial overlapping of the molecules may perhaps account for the small areas in the final stages of the compression. The compressibility at $f = 0$, $[(a_0 - a_1)/a_0]/(f_1 - f_0)$ is 0.0607.

The above-mentioned compounds with each of the three rings attached directly to the polar group are much more compressible than the polycyclic compounds in which only one ring is attached to the principal polar group.[4] The molecular configurations of the latter type permit an approach toward vertical orientation and allow closer packing. It has been shown that films of horizontally oriented long chain molecules (polymers of ω-hydroxydecanoic acid) are much more compressible than those of vertically oriented molecules.[3] This present work indicates that perhaps the same general relationship applies to ring systems. The film compressibilities of a number of multiple ring compounds which are capable of vertical orientation range from one-sixth to about one-eighteenth that of tri-*p*-cresyl phosphate. In both types of orientation the films formed by ring compounds are, in general, more compressible than those composed of straight chain molecules. An increase in maximum film pressure with increasing vertical length of the ring system is also noted.

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[4] Pressure–area relations for such a series of three-ring and five-ring compounds have been investigated and the data tabulated.[2,5]

[5] Harkins, Carman and Ries, THIS JOURNAL, **58**, 1377 (1936).

THE RESEARCH AND DEVELOPMENT DEPARTMENT
SINCLAIR REFINING COMPANY
EAST CHICAGO, INDIANA HERMAN E. RIES, JR.

RECEIVED NOVEMBER 17, 1938

THE STRUCTURE OF LUMISTEROL

Sir:

In a memoir entitled "Photochemical Interaction between Ketones and Alcohols," Weizmann, Bergmann and Hirshberg[1] in a discussion of the mechanism of ergosterol irradiation state that "at variance with the assumption of Spring[2] that this important reaction involves primarily epimerization at C_3, Windaus and Dimroth[3] were able to demonstrate that the secondary hydroxyl group at C_3 is actually not influenced by irradiation. . . ."

In the interest of accuracy it is necessary to note that in the paper cited I state that "the reactions of lumisterol, the primary photoisomeride of ergosterol, establish that it is a stereoisomer of the latter," no suggestion being made that it is the

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[1] Weizmann, Bergmann and Hirshberg, THIS JOURNAL, **60**, 1530 (1938).

[2] Spring, *Chemistry and Industry*, **55**, 837 (1936).

[3] Windaus and Dimroth, *Ber.*, **70**, 376 (1937); *cf.* Dimroth, *ibid.*, **69**, 1123 (1936).

C_3 epimer of ergosterol. In the paper (Heilbron, Moffet and Spring[4]) of which the note cited is an abstract, the conclusion reached is that ergosterol and lumisterol differ in configuration around C_{10} and that "no information is available concerning the relative orientation of the hydroxyl groups and the C_9-hydrogen atoms of the two sterols."

Again, contrary to the statement of Weizmann, Bergmann and Hirshberg, Windaus and Dimroth did not *demonstrate* that the secondary hydroxyl group is not influenced by irradiation but include in their paper the following statement: "Einen Anhaltspunkt dafür dass sterische Änderungen an der Hydroxyl-gruppe an C_3 vor sich gehen, haben wir nicht gefunden; wir halten diese Annahme für unwahrscheinlich."[5]

NOTE BY THE EDITOR.—Dr. Bergmann has written to the Editor that he regrets that the statement of Dr. Spring relative to the photo-isomerization of ergosterol was misunderstood and therefore inaccurately quoted in the article referred to.

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[4] Heilbron, Moffet and Spring, *J. Chem. Soc.*, 411 (1937).

[5] "We have found no experimental evidence that rearrangement of the hydroxyl group on C_3 occurs spontaneously, and we believe that such a change is unlikely."

THE UNIVERSITY OF MANCHESTER F. S. SPRING
MANCHESTER, ENGLAND

RECEIVED AUGUST 9, 1938

THE REDUCTION OF α-HALOGENATED KETONES: THE SYNTHESIS OF *dl*-PSEUDOEPHEDRINE

Sir:

The great advantage of aluminum isopropylate in the reduction of aldehydes and ketones lies in its specificity for the carbonyl group, side reactions such as condensation and the like being either absent or negligible. Lund [*Ber.*, **70,** 1520 (1937)] has shown this with certain ketones with primary bromine in the α-position. This reduction without removal of the α-halogen has now been tested with α-bromo ketones which have β-hydrogen available for a loss of halogen acid. The results with open chain ketones containing secondary α-bromine show that removal of bromine, and reduction to the bromohydrin, occur in about equal amounts. Thus α-bromopropiophenone with aluminum isopropylate forms the bromohydrin in about 35% yield (b. p. 73–75° (0.1 mm.)), which in turn with methylamine yields a mixture of isomeric hydroxyamines, one of which is *dl*-pseudoephedrine, m. p. 116.5–117.0°; the hydrochloride, m. p. 162–163° (over-all yield from the bromo ketone, 10%). This was identified by comparison with an authentic sample, m. p. 116.5–117.2°, mixed m. p. 116.5–117.0°, prepared from *dl*-ephedrine kindly supplied by Dr. E. H. Volwiler, Abbott Laboratories, Chicago, Illinois, and by Dr. R. H. Manske, the Canadian National Research Council, Ottawa. Contrary to expectations, no *dl*-ephedrine was found.

Cyclic secondary α-bromo ketones, and open chain tertiary α-bromo ketones, such as 2 bromocholestanone, and α-bromoisobutyrophenone, respectively, yield products almost entirely free of bromine. This work is being continued with other types of halogenated ketones.

DEPARTMENT OF CHEMISTRY PHILIP G. STEVENS
MCGILL UNIVERSITY
MONTREAL, CANADA

RECEIVED NOVEMBER 21, 1938

NEW BOOKS

Tabellen und Vorschriften zur quantitativen Analyse. Gravimetrie, Elektroanalyse, Probierkunde der Edelmetalle und Gasanalyse. (Tables and Directions for Quantitative Analysis, Gravimetric, Electroanalysis, Assay of the Noble Metals, and Gas Analysis.) By W. D. TREADWELL, Professor in the United Technical Institute in Zurich. Verlagsbuchhandlung Franz Deuticke, Helferstorferstrasse 4, Wien, Germany, 1938. xii + 284 pp. 126 figs. 17.5 × 25 cm. Price, RM. 9.

The author states in the preface that his object is to present in the shortest possible form a selection of proved methods of analysis in order to make it possible for the analyst already acquainted with the fundamentals to do his work more easily. The reviewer cannot imagine any publication in which could be found more information concerning analytical chemistry contained in less than 300 pages. Here is evidence showing extreme energy on the part of the author in collecting valuable data concerning, and proved directions for determining, more than the usual list of cations and anions. It also shows his skill in collating such material in a very logical manner. About 275 references to original literature are given.

In the interest of economy of space the author has collected in one chapter the description of the common operations of quantitative technique, and such descriptions are almost completely omitted in the individual processes discussed throughout the book.

This book might be divided into eight parts. The first forty-one pages deal with general methods of quantitative analysis and include directions for carrying out all the common operations of analysis. This discussion is more complete, however, than is usually found in textbooks of quantitative analysis. In addition to the usual directions included here, such as those for weighing, calibration of weights, precipitations, filtration, drying, etc., are to be found desirable directions for such procedures as the determination of specific weight, ashing of organic substances, separation by extraction and distillation, and the preparation and testing of reagents.

From page 47 to page 96 are to be found directions for the determination of a very wide selection of cations. Besides all the common metals for which methods are given, one finds directions for the determination of many of the less familiar ones, such as scandium, cerium, yttrium, gallium, indium and the platinum metals. In this section, it is worthwhile to note that the author has seen fit to give methods of quantitative separation of cations which commonly occur together. It is interesting to see that considerable reference is made to the use of organic reagents as precipitants for many cations.

From page 97 to page 130 is a section on electroanalysis including theory, directions for the determination of eighteen separate metals by electrolysis, and methods of separating eleven of these from other ions likely to be present.

There follows from page 131 to page 142 a section on the assay of the noble metals. Here the principle of cupellation is discussed and methods are given for the estimation of all the noble metals usually determined by this method.

From page 142 to page 170 are to be found excellent directions for the separation and determination of all the common and some of the less common anions. The reviewer feels that this section alone would be sufficient to make it advisable to include this book in his library.

Pages 170 to 194 are devoted to distillation methods of separation and analysis. Here again are found worthwhile discussions not usually included in reference books of quantitative analysis.

The next section, pages 194 to 202, is devoted to elementary analysis which includes the determination of carbon, hydrogen, nitrogen, the halogens and sulfur. Both macro and micro methods are given.

The final section of the book, page 203 to page 259, is devoted to gas analysis. Not only the more common gases, but many of the less common, such as ethylene oxide, iron pentacarbonyl, nickel tetracarbonyl and butadiene, are included in the methods given. A page devoted to the determination of dust in gases shows the diversity of the subject matter covered.

The book is concluded with tables of gravimetric factors and logarithms.

The reviewer was well pleased with the editing and printing of the book. The binding of the reviewer's copy was poor.

Those who have a good fundamental training in analytical chemistry will welcome this book as being a good place to go to get information concerning methods. It is primarily a book for analytical chemists rather than for chemical analysts. It is one that should find its place in every reference library and on the desk of every analytical chemist.

CHESTER M. ALTER

Annual Review of Biochemistry. Vol. VII. By JAMES MURRAY LUCK, Editor, and CARL R. NOLLER, Associate Editor, Stanford University. Annual Reviews, Inc., Stanford University P. O., California, 1938. ix + 571 pp. 16 × 23 cm. Price, $5.00.

A new group of authors compiled volume seven of this series, including English, German, Swiss, Danish and Australian, as well as American contributors. Subjects covered in one or more of the preceding volumes, and the authors of each include: Biological Oxidations and Reductions, by L. Michaelis and C. V. Smythe; The Chemistry of the Carbohydrates and the Glycosides, by E. F. Armstrong; The Chemistry of the Acyclic Constituents of Natural Fats and Oils, by G. S. Jamieson; The Chemistry of Amino Acids and Proteins, by M. Bergmann and C. Niemann; The Chemistry and Metabolism of the Compounds of Phosphorus, by K. Lohmann; Carbohydrate Metabolism, by H. E. Himwich; Fat Metabolism, by F. Verzár; Metabolism of Amino Acids and Proteins, by H. A. Krebs; The Metabolism of Creatine and Creatinine, by K. Thomas; The Hormones, by O. Wintersteiner and P. E. Smith; Nutrition, by H. H. Mitchell; The Biochemistry of Muscle, by E. Lundsgaard; Liver and Bile, by A. C. Ivy and L. A. Crandall, Jr.; Animal Pigments, by R. Lemberg; The Terpenes, Saponins, and Closely Related Compounds, by W. A. Jacobs and R. C. Elderfield; The Chemistry of Bacteria, by W. H. Peterson and M. J. Johnson; Growth Regulators in the Higher Plants, by P. Boysen Jensen.

The vitamin chapter of the earlier volumes was divided in volume seven into three sections as follows: The Vitamin B group, by R. A. Peters and J. R. O'Brien; Vitamin C (Ascorbic acid, Cevitamic acid), by R. A. Peters and H. W. Davenport; the Fat-soluble Vitamins, by J. C. Drummond. The discussion of enzymes was narrowed down this year to The Chemistry of the Crystalline Enzymes, prepared by J. H. Northrop and R. M. Herriott. Pepsin, trypsin and chymotrypsin, carboxypeptidase, papain and a number of redox enzymes are covered in this review. Two wholly new topics, *viz.*, Acid–Base Metabolism, by J. Sendroy, Jr., and Organic Insecticides, by F. B. LaForge and L. N. Markwood are also reviewed in the current volume.

As heretofore, this review is a veritable mine of useful information respecting contemporary biochemical progress. One senses that each contributor has made a real effort to select carefully the useful material in his field, and present it in an adequate manner. The editors have made a careful selection of contributors, and have arranged and indexed the volume in a form which facilitates its use.

C. H. BAILEY

The Standardization of Volumetric Solutions. By R. B. BRADSTREET, B.S., formerly Analytical Chemist, U. S. Rubber Products Co. Chemical Publishing Company of New York, Inc., 148 Lafayette St., New York, N. Y., 1938. v + 126 pp. 14 × 21 cm. Price, $3.00.

The Solution of Problems in Quantitative Analysis. By SAUL B. ARENSON, Professor of Inorganic Chemistry, University of Cincinnati. Edwards Brothers, Inc., Ann Arbor, Mich., 1938. iv + 41 pp. 21.5 × 27.5 cm. Price, $0.35.

Bradstreet's book on Volumetric Solutions begins with a brief survey of definitions, standard substances, possible sources of error, calibration of apparatus, and choice of indicators, and then offers a collection of standardization methods for many of the more common quantitative analytical reagents: hydrochloric and sulfuric acids, sodium, potassium, barium and ammonium hydroxides, thiocyanate, silver nitrate, potassium ferrocyanide, iodine, sodium thiosulfate, permanganate, dichromate, ferrous salts, arsenious oxide, potassium iodate, ceric sulfate, Wijs and Hanus solutions, Chloramine T, hypochlorites, titanous salts and various indicators (with appendix tables). For each reagent there is given a brief discussion of its advantages and shortcomings, procedure for preparing the solution, and the various accepted standardization methods. The critical discussion is brief, well documented and in most cases reasonably complete and modern. Mechanically the little book is well made but is a good example of the evils of low-cost production (without the usual argument of low purchase price), being plate-printed from not too well arranged typewritten copy, which is liberally punctuated with errors (Faulk for Foulk, Yound for Young, Hammet for Hammett, as well as plain spelling and typing errors), and inconsistent and unorthodox abbreviations.

In the second title, Professor Arenson attacks a very real problem, and in chapters entitled: Computations, Gravimetric Analysis, Normal Solutions of Acids and Bases, Normal Solutions in Oxidation and Reduction, Precipitation Titrations, he gives, in conversational conference style, discussions of methods, illustrative examples and numerous problems in each of the five groups listed. Although the scope of the work and the treatment of topics are, in general, less complete as compared with Wilkinson's text [THIS JOURNAL, **60**, 1516 (1938)], this neatly lithoprinted book will be of considerable help to students wrestling with Quantitative Analysis calculations.

ALLEN D. BLISS

About Petroleum. By J. G. CROWTHER. Oxford University Press, 114 Fifth Avenue, New York, N. Y., 1938. xiv + 181 pp. Illustrated. 14 × 22.5 cm. Price, $2.25.

This is a very carefully written little book. It is something of a relief to find that, as Mr. Crowther has demonstrated, it is possible to write about petroleum without borrowing the showmanship of the promoter, the hyperbole of the high pressure salesman, or the moronic sensationalism of the tabloids.

It may seem deadly serious to some readers, but at any rate it is packed with information, which to the reviewer appears to be authentic and well selected. In such a small book restricted to technical and scientific information it is not surprising that there are many terse statements which merely whet the reader's appetite for more. In view of the political occurrences in Europe in September, 1938, it is of interest to note the following statements by Mr. Crowther:

"Large countries such as the United States are being integrated into units by the swift communications of air transport. The attitude of Englishmen toward other nations, and their conception of the role of England among the nations, are changing swiftly since London came within half an hour's journey of other lands."—And, "the importance of oil to industries and military forces, has given petroleum great political significance. The desire for oil is now one of the more important of the motives which guide the diplomatic and military policies of modern nations."

"About Petroleum" is well worth reading by teachers of chemistry and engineering as well as business men as showing the extent to which science of the most diverse branches has permeated and become vital to the modern petroleum industry. The research man in so-called pure science will note with satisfaction the following:

"The solution of the wider problems of the petroleum industry does not depend merely on the advance of the science of petroleum, but on the advance of pure science itself. The industry will have to inspire, for its own ultimate benefit, the creation of new branches of pure science."

B. T. BROOKS

Library Guide for the Chemist. By BYRON A. SOULE, Sc.D., Assistant Professor of Analytical Chemistry, University of Michigan. McGraw-Hill Book Company, Inc., 330 West 42d Street, New York, N. Y., 1938. xiii + 302 pp. 14.5 × 21.5 cm. Price, $2.75.

Here is a book for students written by a teacher who realizes the special value of including among things learned in college a knowledge of where and how to look for further information as needed. A good deal of information is given about "where" but the emphasis is on "how," on which emphasis is needed. The text is primarily a "guide to the use of keys and summaries."

The early chapters reveal the general trend in the development of chemical literature. After chapters on the arrangement of a library and on card catalogs, the investigators themselves are considered (biography), then their original reports (journals), next the initial summaries of their articles (abstracts), then the periodic digests (annual reviews), followed by surveys of smaller divisions within a field (monographs) and finally by synopses as assembled in large compendiums (encyclopedias). Then specialized reference books and tables of constants, "the last step in condensation," are classified as inorganic, organic, analytical and physical and considered in this order. Finally the patent literature, government publications and the writing of reports are discussed.

The book is filled with interesting tables compiled in a manner which should be effective for students. These are often not complete but the book does not pretend to be a complete catalog of source material. The tables on yearbooks and on monograph series are good examples.

The inclusion of an early chapter on biography was a happy thought, for chemical literature is largely a record of the achievements of earnest investigators, many of them great men, and such a beginning should help to inspire student interest. There is great value in becoming acquainted with the masters.

Another pleasing feature of this book is the author's practice of including at the beginnings of chapters pertinent "sayings" of others. These lend an authoritative kind of emphasis and seem appropriate in a book on literature even though it be scientific literature.

The author has a knack of writing short, simple definitions, such as "An abstract is essentially an annotated reference." Any lack of precision is remedied by surrounding discussion.

"Experiments have settings." The author's discussion of this fact reveals a good comprehension of the limitations of words and combinations of words in records as well as of the limitations of those who use words in making the records. This understanding adds much value to Doctor Soule's discussion of indexes and their use. This portion of the book could well be expanded, however, for an understanding of the characteristics of indexes and of their use is of primary importance in literature searching. The book would gain in value if its own index provided a better example. It is a pretty good index as indexes go but it has too many of the characteristics of word indexing as opposed to subject indexing. For example, there is a group of alphabetically arranged entries under the heading "Patent" and then a little farther on a similar group under the heading "Patents," the only difference apparently being that the singular word was used part of the time in the text and the plural part of the time. There is some scattering, as an entry "Government publications" in the G's and a separate entry "Publications, foreign government" in the P's, entries under "Periodicals" and a separate entry "Journal appraisal," etc. The inclusion of word-for-word book titles in the index has largely been responsible for such a scattering as that indicated by the following index entries:

Analytical chemistry, conductometric
Conductometric analysis
Electrometric analysis
Quantitative analysis, electrolytic methods
Electrolytic analysis
Potentiometric analysis
Potentiometric titration

Perhaps the use of italic letters for book-title entries, if they are not to be grouped under headings designating subjects, would improve the situation. The use of more cross references would be helpful.

Patents are discussed at length, both as to their legal aspects and as to their role as scientific literature. Directions for making patent searches are also given. These are particularly thorough chapters.

Your reviewer finds himself wondering a little whether he has a touch of Jehovah complex when it comes to things American or the author has a modicum of complex of the bovine variety so that the grass looks a little greener to him on the other side of the fence—or ocean. Perhaps neither is true.

Your reviewer yields to no man when it comes to the making of curious mistakes (other kinds, too) and so hesitates to refer to one in a book which seems to be quite free from mistakes but cannot resist mentioning that the journal he edits is referred to by Doctor Soule as a "*bi*-monthly appearing on the tenth and twentieth."

The first sentence in this book's preface is: "The literature of chemistry is probably more adequately classified, more thoroughly indexed, and more consistent in terminology than that of any other science." Even so the searching of chemical literature is a complex and difficult matter. None can afford to neglect to learn where and how to look and Doctor Soule's book should prove to be very useful indeed in helping students to learn this art. Doctor Soule has done a good job.

E. J. CRANE

(I) **Le Rapport entre la Spectroscopie et les Réactions initiées par la Lumière.** (Spectroscopy and Photochemical Reactions.) By W. ALBERT NOYES, JR. (II) **The Determination of the Mechanism of Photochemical Reactions.** By PHILIP A. LEIGHTON. (III) **The Photochemistry of the Halogens.** By GERHARD K. ROLLEFSON. Hermann et Cie., Éditeurs, 6 Rue de la Sorbonne, Paris, France, 1937–1938. 45 pp. 72 pp. 53 pp. 16.5 × 25.5 cm.

These three booklets, published under the direction of the first-named author, outline the present status of the subject. The first discusses typical primary photochemical processes from the standpoint of the spectral characteristics of photolytes. With a minimum of mathematics it achieves an exposition of modern theory which is at once sound and clear. The next deals with secondary reactions evoked by atoms, free radicals and excited molecules resulting from primary acts. Ammonia and hydrazine, halogens reacting upon the ethylenic linkage, oxygen and ozone, are critically discussed to illustrate the possibilities of kinetic reasoning as well as the pitfalls involved. The third supplies a coherent interpretation of the chief photochemical reactions of the halogens, including the author's extensive work upon them.

Pending the expected appearance of two, more comprehensive, books on the subject, these contributions are of very real value to French and American readers alike.

GEORGE S. FORBES

The Metabolism of Living Tissues. By ERIC HOLMES, M.A., M.D., Fellow and Tutor of Downing College and University Lecturer in Biochemistry. Cambridge University Press: The Macmillan Company, 60 Fifth Avenue, New York, N. Y., 1937. xi + 235 pp. 13 × 19 cm. Price, $2.25.

Sir Frederick Hopkins in a foreword to this book points out that its "primary aim...is to provide an adequate survey of all that is most significant in our present knowledge of the dynamic side of biochemistry. Its author has had a wide experience as a teacher of the subject, and writes with a full understanding of the needs of the student. In my opinion he here supplies a need which is real."

"The Metabolism of Living Tissues" cuts across the boundary sometimes set up between physiology and biochemistry. The tools of modern biochemical research are described in general terms. Three early chapters are devoted to enzymes, oxidations and oxidation–reduction potential, while two of the concluding chapters are concerned with hormones and vitamins. Other chapters deal with metabolic processes in the liver, in the kidney, in voluntary and cardiac muscles and in the nervous system.

The lucid explanation of the dependence of intermediary carbohydrate metabolism on coördinated functions of liver, muscles, adrenals, pancreas and pituitary should prove useful to students of physiology. Placing the emphasis on living tissues rather than on dead materials should stimulate the interest of students of biochemistry. It is among the books recommended for undergraduates in biochemical sciences at Harvard.

It is devised for the young student rather than for the research worker. There is a detailed subject index but no references to literature are given; hardly half a dozen biochemists are named, and two of these names, Hagedorn and Jensen, are spelled incorrectly. Otherwise there are almost no typographical errors.

DAVID B. DILL

Experiments in Organic Chemistry. By LUCIUS JUNIUS DESHA, Professor of Chemistry, and LARKIN HUNDLEY FARINHOLT, Associate Professor of Chemistry, Washington and Lee University. McGraw-Hill Book Company, Inc., 330 West 42d Street, New York, N. Y., 1938. xi + 233 pp. 24 figs. 14.5 × 21 cm. Price, $1.75.

As the authors state in their preface, "The purpose of this manual is to provide a program of laboratory work closely correlated with Desha's textbook *Organic Chemistry*. It is justified by the distinctive order of presentation adopted in that text. . . ." This consists of a parallel study of aliphatic and aromatic compounds, which is especially advantageous for a laboratory course. The manual contains almost no descriptive material, but specific references to the textbook head each experiment. The result is a concise set of directions for most of the syntheses commonly included in a beginning laboratory course and for an unusually large number of small scale tests. Among these the experiments entitled "General Methods of Forming Double Bonds," "Rearrangements" and "Tautomerism" seem new and especially interesting. There is no introductory chapter on manipulation, but each operation is described in the first experiment in which it is used.

Throughout the book emphasis is placed on the identification of organic compounds; a final chapter (23 pages) describes the standard procedure and refers the student to the small scale tests of the earlier parts. These include the preparation of most of the derivatives commonly used. It has recently been recognized that such material can be profitably included in a beginning laboratory course. However, in this manual so much emphasis is placed upon identification that the synthetic side of the subject is somewhat overshadowed. This is apparent not in omission of synthetic material, but in the absence of all descriptive matter and study questions which would serve to orient a particular compound, emphasize the side reactions in its preparation and present the limitations of the general reaction being studied. References to a textbook written primarily from a theoretical viewpoint do not throw much light on this practical aspect of the problem. This constitutes the principal shortcoming of an otherwise well planned and well written book.

THOMAS L. JACOBS

Gmelins Handbuch der anorganischen Chemie. (Gmelin's Handbook of Inorganic Chemistry.) Edited by R. J. MEYER. Eighth edition. System-Number 63, **Ruthenium.** Issued by the Deutsche Chemische Gesellschaft. Verlag Chemie, G. m. b. H., Corneliusstrasse 3, Berlin W 35, Germany, 1938. 124 pp. 17 × 25 cm. Price, RM. 16.50.

The publishers of the Gmelin Handbook state that this volume on Ruthenium constitutes the first installment of the complete Monograph on the platinum group metals, and that subsequent installments will follow in rapid succession. This is certainly welcome news to the inorganic chemist, as several decades have passed since the appearance of the corresponding volume in the last edition of the Gmelin Handbook. The "system number" of ruthenium (63) is not exceeded by those of any other elements except the members of the platinum group, so that practically all the compounds of ruthenium, with their chemical elements, are included in this volume.

ARTHUR B. LAMB

A Manual of Radioactivity. By GEORGE HEVESY, Copenhagen, and F. A. PANETH, London. Second edition, completely revised and enlarged. Translated by Robert W. Lawson, Sheffield. Oxford University Press, 114 Fifth Avenue, New York, N. Y., 1938. xvi + 306 pp. 54 figs. 16 × 24 cm. Price, $5.50.

Much has happened in the field of nuclear chemistry since the appearance of the first English edition of this book in 1926 (THIS JOURNAL, **49,** 305 (1927)). This is reflected in the excellent revision and expansion of the present second edition.

It is not only the subject matter in this field which has been enriched by the discovery of artificial radioactivity and of two new fundamental particles, but the entire philosophy of elements has undergone a remarkable revolution. A theory of nuclear stability and disintegration has been perfected. The new artificially radioactive elements are already more numerous than all of those previously known in the three natural families. Several new types of disintegration have been found among the new elements.

All of this, however, fits into the framework of the periodic system and the displacement law as it existed since 1913 and to which one of the authors made substantial contributions.

Four entire new chapters have been added and enough other new material to increase the total length from two hundred and fifty to four hundred pages. Nevertheless, the book has retained its character of a very readable and useful manual of radioactivity.

Some literature references have been added at the end of chapters, which is a very acceptable innovation, but still falls short of the value derived from complete literature references. The historical survey at the end has been retained and brought up to date. The more recent progress in all of the important fields is recorded. The tables of isotopes—radioactive and stable—and of the artificial radioactive elements and their properties are excellent.

S. C. LIND

Lehrbuch der Pharmakologie, Toxikologie und Arzneiverordnung. (Textbook of Pharmacology, Toxicology and Prescription Writing.) By Dr. med. EMIL STARKENSTEIN, Professor in the Dutch University in Prague. Verlag Franz Deuticke, Helferstorferstrasse 4, Wien I, Germany, 1938. xi + 758 pp. Illustrated. 17.5 × 25.5 cm. Price, RM. 20; bound, RM. 23.

This textbook is intended for medical students studying pharmacology. After a brief introduction in which the topics of general pharmacology, general toxicology and the place of pharmacology in practical therapeutics are discussed, the so-called special pharmacology is taken up and treated on the basis of physiological systems more or less in accordance with the scheme first used by Gottlieb and Meyer in their well-known textbook. The treatment of the various topics appears to be quite satisfactory and to take in account recent advances; a more complete account is given of the chemistry of the digitalis glucosides than is found in current textbooks and the sections on the hormones and vitamins are particularly good. No references are given, which detracts in many ways from the value of the book. The book will not appeal to American students, and will serve only as a textbook for a limited group.

E. K. MARSHALL, JR.

Inorganic Colloid Chemistry. Volume III. The Colloidal Salts. By HARRY BOYER WEISER, Professor of Chemistry at The Rice Institute. John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y., 1938. viii + 473 pp. 74 figs. 15.5 × 24 cm. Price, $6.00.

Weiser's three volumes constitute the readiest and most modern and complete reference works to the information extant with regard to the various inorganic colloids. They are so clearly and pleasantly written, and so well and thoroughly documented, that any of them serve as a text, although necessarily incomplete, from which to gather the theories and applications of colloid science arising from the materials studied. Many important theories are discussed for their own sake. Interesting accounts are also given of many technical materials, such as plaster of Paris, inorganic pigments, halides in photography, soil colloids, base exchanging silicate gels, and cements. "The first portion of each section is concerned with a critical survey of the conditions of formation and the general characteristics of the individual salts in the colloidal state; and the second portion, with the principles underlying their applications." It is to be hoped that as the subject advances we may look forward to further revisions of the three volumes.

Throughout the text divergences of opinion are quoted. In many cases the reader must ask why no investigator has established the facts in question which would be decisive. Presumably the answer lies in the enormous extent of the field compared with the number of available workers in any part of it. Students will note the many opportunities thus afforded for further useful research.

Professor Weiser has rendered an important service in compiling and discussing the information so far obtained with regard to all inorganic substances, elements (Vol. I), oxides and hydroxides (Vol. II), and now in the present Vol. III all remaining inorganic compounds in the colloid condition.

J. W. MCBAIN

Les Classiques de la Découverte Scientifique. Gauthier-Villars, Éditeur, 55 Quai des Grands-Augustins, Paris VI^e, France, 1938. 13.5 × 19 cm. Les Métaux Légers: Aluminium, Glucinium, Magnésium, Métaux Alcalins Mémoires de Henri Sainte-Claire Deville, Heroult, Bussy, Gay-Lussac, Thénard. Préface par LÉON GUILLET. xix + 166 pp. La Dissolution. Mémoires de Lavoisier, Gay-Lussac, Loewel, Gernez, Lescoeur, Raoult. Préface par HENRY LE CHATELIER. xvii + 148 pp. Détermination des Poids Moléculaires. Mémoires de Avogadro, Ampère, Raoult, van't Hoff, D. Berthelot. Avant-propos par R. LESPIEAU. xvii + 165 pp. Halogènes et Composés Oxygénés du Chlore. Mémoires de Scheele, Berthollet, Gay-Lussac et Thénard, Davy, Balard, Courtois, Moissan, Millon. Avant-propos par A. DAMIENS. xiv + 147 pp. Price, each, 21 francs.

The great majority of chemists read only the current or recent literature; unlike their literary brethren they know the classics of their field only by repute or in the abstracts found in textbooks. This series of Famous Scientific Papers makes accessible quite a few historically important papers collected into handy sized volumes each dealing with a broad topic. The Académie des Sciences has done the chemical world a real service by supporting this collection, which is planned to include 15 volumes. Some of these have already been reviewed in the JOURNAL.

Unlike the Alembic Club Reprints or the Ostwald's Klassiker no translations were specially prepared for these volumes, only such material was used as was already available in French. Consequently few non-Gallic writers are included and the impression is gained that this project is, in part, an attempt to glorify the achievements of the French chemists. Some of the volumes give a rather complete coverage, others contain obvious gaps. Nonetheless these collected essays are extremely interesting and valuable; many little known facts can be gleaned from their pages. Students and teachers will profit from reading these records of fundamental discoveries related by master chemists.

Each volume has a good preface by a competent authority; full page likenesses of most of the writers are given along with brief biographical sketches. The printing is nicely done on fairly good stock, the covers are paper. These economies are reflected in the extremely modest price. It would be a boon if an American or English publisher could put out comparable volumes at this price level.

RALPH E. OESPER

Molecular Beams. By R. G. J. FRASER, Ph.D., Imperial Chemical Industries, Limited. Chemical Publishing Company of New York, Inc., 148 Lafayette Street, New York, N. Y., 1938. ix + 70 pp. 22 figs. 10.5 × 17.5 cm. Price, $1.25.

In this monograph the author reviews briefly the most significant work published in this field since the appearance in 1931 of his longer monograph on Molecular Rays for the Cambridge Series of Physical Chemistry. The present booklet is, however, not merely a report of new work; it is a highly condensed outline of the entire field with a description "in something like adequate detail of its more fruitful areas only."

The chapter headings are "Molecular Beams," "Gas Kinetics," "Magnetic Moments," and "Electric Moments." The most important extension beyond the 1931 treatment occurs in the third chapter, in which the notable contributions of I. I. Rabi and co-workers, and those of O. Stern and collaborators, are reviewed under the sub-title "Nuclear Spins and Magnetic Moments." The author's own recent contribution to the molecular ray study of free radicals receives brief notice in the first chapter, and his contribution to the study of molecular scattering by the method of crossed beams is set forth in the second chapter. There are approximately sixty references to the literature of date more recent than 1931.

As to the presentation, the author's aim would seem to be at preciseness of statement together with utmost economy of words; and his style approaches to the happy state referred to in the dedicatory note: namely, that of being (like the molecular ray itself) "unidirectional and collision-free."

T. E. PHIPPS

Dipole Moments. Their Measurement and Application in Chemistry. By R. J. W. LE FEVRE, D.Sc., Ph.D., F.I.C., Lecturer in Chemistry, University College, London. Chemical Publishing Company of New York, Inc., 148 Lafayette Street, New York, N. Y., 1938. v + 110 pp. 28 figs. 10.5 × 17.5 cm. Price, $1.50.

Two books on dipole moments now appear after a period of several years during which only reviews in journals or chapters in larger works have been devoted to the subject in English. Actually, the present small volume has no greater content than might be expected of a chapter in a treatise, but, without attempting completeness, it deals with the major methods and problems of the subject. It presents the fundamentals of the theory of dielectrics and the methods by which the dipole moment is calculated. A general outline of the experimental methods for obtaining the data necessary for the calculation of the moment includes a detailed account of the method of dielectric constant measurement used by the author. An excellent summary of the various attempts to treat the solvent effect in dipole moment measurements is followed by the longest chapter of the book, which describes classical examples of the solution of structural problems through dipole moments and discusses the relation of moment values to various recent questions of molecular structure. The book closes with brief chapters on "Intramolecular Rotation and Flexibility of Molecules" and "Some Anomalous Dipole Moments" and a table of moment values selected for the most part from the appendix to the "Transactions of the Faraday Society," Volume 30, 1934.

The presentation of the material is smooth, clear and authoritative and should prove admirable for a senior, a graduate student, or an older chemist wishing to find out something about dipole moments. The investigator directly concerned with the determination or interpretation of moments will probably find, by the slight exertion of reading an easily readable book, useful comments or references to recent literature which may have escaped his attention, but cannot expect an exhaustive treatment of any particular topic, as reference is made to only a fraction of the dipole moment papers in the literature. Frequently, only the work done in England on a particular problem is mentioned when it is sufficient to show the argument and, not unnaturally, the problems investigated in England are emphasized. It is rather surprising to an American reader to note the seemingly scrupulous care with which use of the word "resonance" and mention of Pauling's work in this field are avoided. Although there is mention of "canonical structures," "mesomerism" appears to replace the phenomenon of "resonance." One should not, however, attempt a detailed criticism of so brief a book, for within the limitations imposed by its small size, it may be regarded as extremely successful.

CHARLES P. SMYTH

Crystal Chemistry. By CHARLES W. STILLWELL, Ph.D., Research Chemist, Dennison Manufacturing Company. McGraw-Hill Book Company, Inc., 330 West 42nd Street, New York, N. Y., 1938. x + 431 pp. 72 figs. 14.5 × 21 cm. Price, $4.50.

The study of crystalline substances has today reached such large proportions that it is coming to be treated in several independent parts: for example, first the concepts and language of crystal geometry; second, the several techniques for its study and their practical applications; third, the compilation of the geometrical constants of known crystals; fourth, analysis of these results, their bearing on the general subject of the atomic structure of matter, and their correlation with physical and chemical properties. In the absence of single volumes or treatises which cover all of these divisions, books like the present one, which belongs in the fourth category mentioned, are to be welcomed.

This book, like Hassel's book of the same name (reviewed in THIS JOURNAL, **57**, 964 (1935)), interprets the results of crystal structure studies for chemistry students. It is intended as a text or as a point of departure for a more thorough study of the field, and may be expected to prove useful in modernizing courses in inorganic chemistry.

The volume begins with a discussion of the sizes of atoms and ions, and how they vary with environment in crystals. There follow two valuable chapters, one on the structures and properties of the elements, with a treatment of the metallic state, the other on the nature of alloys. In the next three chapters on the structures and properties of binary and ternary compounds, the subject of ionic and covalent bonds is taken up. The principles thus outlined are applied in the following chapters on silicates, including a discussion of inorganic glasses; on Werner compounds; on isomorphism, mixed crystals and polymorphism; and on organic crystals. The two concluding chapters on natural and synthetic fibers are of technical as well as general interest.

As illustrating what is in the book, on p. 330 there is an interesting rationalization of the composition of dental enamel; on p. 390 the mechanism of the permanent wave is explained. Throughout the book is much of the fertile work of V. M. Goldschmidt, which is otherwise quite inaccessible.

As illustrating what is not in the book, on p. 178 it is not indicated that CsCl has the NaCl structure at high temperatures, nor that the potassium halides have the CsCl structure at high pressures. From the lack of mention of silicate glass fibers in the last chapters one might conclude, contrary to common sense, that they are not fibers at all because they lack the internal structure of the fibers included in the discussion. There is much on the thermodynamic and mechanical properties of crystals, but nothing on their optical properties.

The style is generally stimulating, sometimes obscure. The index is rather brief. The format is the excellent one of the International Chemical Series.

C. D. WEST

BOOKS RECEIVED

October 15, 1938–November 15, 1938

R. B. BRADSTREET. "The Standardization of Volumetric Solutions." Chemical Publishing Company of New York, Inc., 148 Lafayette St., New York, N. Y. 126 pp. $3.00.

OSCAR L. BRAUER. "Chemistry and its Wonders." American Book Co., 88 Lexington Ave., New York, N. Y. 760 pp. $2.00.

OSCAR L. BRAUER. "Exploring the Wonders of Chemistry." American Book Co., 88 Lexington Ave., New York, N. Y. 246 pp. $0.48.

ÉMILE MONNIN CHAMOT and CLYDE WALTER MASON. "Handbook of Chemical Microscopy." Vol. I. Second edition. John Wiley and Sons, Inc., 440 Fourth Ave., New York, N. Y. 478 pp. $4.50.

ARNOLD EUCKEN. "Lehrbuch der chemischen Physik. I Band. Die korpuskularen Bausteine der Materie." Second edition. Akademische Verlagsgesellschaft m. b. H., Sternwartenstrasse 8, Leipzig C 1, Germany. 717 pp. RM. 38; bound, RM. 40.

JOHN T. FOTOS and JOHN L. BRAY. "German Grammar for Chemists and Other Science Students." John Wiley and Sons, Inc., 440 Fourth Ave., New York, N. Y. 323 pp. $2.25.

C. C. HEDGES and H. R. BRAYTON. "The Application of Chemistry to Agriculture." D. Appleton-Century Co., 35 West 32d St., New York, N. Y. 238 pp. $2.00.

KARL JELLINEK. "Kurzes Lehrbuch der physikalischen Chemie." Vol. I. Æ. E. Kluver, Deventer, Holland. 314 pp. Dutch fl. 8.50.

WOLFGANG LANGENBECK. "Lehrbuch der organischen Chemie." Verlag von Theodor Steinkopff, Residenzstrasse 32, Dresden-Blasewitz, Germany. 537 pp. RM. 15.

PHILIP A. LEIGHTON. "The Determination of the Mechanism of Photochemical Reactions." Hermann et Cie., Éditeurs, 6 Rue de la Sorbonne, Paris, France. 72 pp.

HANS MEYER. "Analyse und Konstitutionsermittlung organischer Verbindungen." Verlag von Julius Springer, Linkstrasse 22–24, Berlin W 9, Germany. 886 pp. RM. 57; bound, RM. 59.70.

GERHARD K. ROLLEFSON. "The Photochemistry of the Halogens." Hermann et Cie., Éditeurs, 6 Rue de la Sorbonne, Paris, France. 53 pp.

VLADIMIR ROJANSKY. "Introductory Quantum Mechanics." Prentice-Hall, Inc., 70 Fifth Ave., New York, N. Y. 544 pp. $5.50.

ERICH VINCKE. "Vitamine und Hormone und ihre technische Darstellung. III. Darstellung von Hormonpräparaten (ausser Sexualhormonpräparaten)." Verlag von S. Hirzel, Königstrasse 2, Leipzig C 1, Germany. 162 pp. RM. 7.50.

ROBERT P. WALTON. "Marihuana, America's New Drug Problem." J. B. Lippincott Co., 226 South Sixth St., Philadelphia, Pa. 223 pp. $3.00.

CONRAD WEYGAND. "Organisch-chemische Experimentierkunst." Johann Ambrosius Barth, Salomonstrasse 18B, Leipzig C 1, Germany. 772 pp. RM. 43; bound, RM. 45.

ADDITIONS AND CORRECTIONS

Notice to Readers.—For the convenience of those who wish to cut out the corrections and attach them to the margins of the articles corrected, they have been printed upon one side of the page only.

1933, Vol. 55

M. S. Kharasch and F. R. Mayo. The Peroxide Effect in the Addition of Reagents to Unsaturated Compounds. I. The Addition of Hydrogen Bromide to Allyl Bromide.

Page 2485. In Fig. 2, percentage by volume (rather than mole fraction) of allyl bromide should have been plotted against the index of refraction of mixtures. Had this been done, deviations of the curves from straight lines would have been insignificant.

Page 2487. In experiment 217 of Table XV, aqueous potassium dichromate was used as color filter.

Page 2488. In line 3, insert "this" between "and" and "dibromide."

Page 2492. In line 7 from the bottom of the page, XVIIIC should be XVIII-C.—M. S. Kharasch.

1935, Vol. 57

Leo A. Flexser, Louis P. Hammett and Andrew Dingwall. Determination of Ionization by Ultraviolet Spectrophotometry.

Page 2106. In Table I the seventh item in the second column should read "1250" instead of "1350," and the corresponding item in the last column "4.09" instead of "3.92." The average pK should be "4.18 ± 0.09" instead of "4.16 ± 0.11."—Louis P. Hammett.

1937, Vol. 59

William G. Young, Zene Jasaitis and Leo Levanas. Investigations on the Stereoisomerism of Unsaturated Compounds. III. The Preparation of the *cis* and *trans* 4-Octenes.

Page 406. In column 2, lines 3 and 7, for "20–20.5°," read "120–120.5°." Also in line 7 for "62.9 mm." read "62.9°."—William G. Young.

Russell Bliss Akin and Marston Taylor Bogert. The Synthesis of 1,4-Dimethyl-6,7-methylenedioxyphenanthrene and of Certain Substituted 9,10-Dimethyl-1,2,-5,6-dibenzanthracenes.

Page 1567. In column 1, line 10, for "(2.94 g.)" read "(29.4 g.)."—Marston T. Bogert.

Arthur A. Vernon. The Vapor Pressure and Dissociation of Tungsten Hexachloride in the Gas Phase.

Pages 1832–1833. The author writes: "Dr. J. A. M. van Liempt of the N. V. Phillips Gloeilampenfabrieken, Eindhoven, Holland, has called my attention to the fact that an error was made in determining the equation of the straight line plot of log p against $1/T$ from the data given in my article. The corrected equation is

$$\log p = 13.652 - \frac{5276}{T}$$

but the heat of vaporization remains unchanged since it was determined from the slope of the line from the graph."—Arthur A. Vernon.

Nicholas T. Farinacci and Louis P. Hammett. Water Catalysis in Alcoholysis of Benzhydryl Chloride.

Page 2543. In column 1, line 3 from the end, for "$k_1 + k_2$" read "$k_1 + k_2c_w$." In Table I, the items in the last column should be "0.0, 27.7, 46.0."—Louis P. Hammett.

1938, Vol. 60

Herbert N. McCoy. Biography of Julius Stieglitz.

Page 15 (*Obit.*). In column 1, line 30, omit the words "popular" and "("aspirin")."—Herbert N. McCoy.

J. Allen Wheat, II, and A. W. Browne. The Chlorinates. II. Temperature–Concentration Equilibria in the System Alpha-Carbon Tetrachloride–Chlorine. The Carbon Perchlorides.

Page 372. In column 1, line 9 from the end, for "2-$(CCl_4)_2 \cdot Cl_2$" read "$(CCl_4)_2 \cdot Cl_2$."

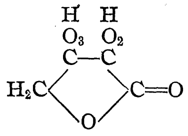
F. F. Blicke and E. L. Cataline. Tertiary Arsines and Arsine Oxides.

Page 422. In Table II, in the column of compound names, "Oxide" should be inserted as a heading between lines 7 and 8.—F. F. Blicke.

W. D. Kumler. The Dissociation Constants of Some Enols Related to *l*-Ascorbic Acid. Tetronic Acid, α-Chlorotetronic Acid, α-Bromotetronic Acid, α-Iodotetronic Acid, α-Hydroxytetronic Acid and Ethyl α-Iodoacetoacetate.

Page 861. In footnote (1a), the next to the last word should be "lactone" instead of "lactose."

In column 2, the structural formula numbering should be as indicated:



W. D. Kumler.

A. H. Blatt. The Alkylation of Oxymethylene Desoxybenzoin.

Page 1165. In column 2, line 22, for "esterification" read "etherification."—A. H. Blatt.

George Scatchard and C. L. Raymond. Vapor–Liquid Equilibrium. II. Chloroform–Ethanol Mixtures at 35, 45 and 55°.

Page 1278. The temperatures are in error due to an error in the calibration of the potentiometer. The mixtures were studied at 34.97_0, 44.97_9 and 54.97_6°. To replace Table I, the vapor pressures of the components may be represented by the following equations for the common logarithm of the pressure in mm. of mercury, which were determined by least squares ($T = 273.16 + t$)

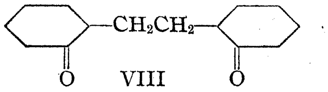
Ethanol, 35–75°: (S. D., 1.6×10^{-4}) $\log p = 7.80335 - 1343.010/T - 136050/T^2$

Chloroform, 35–60°: (S. D., 6.5×10^{-4}) $\log p = 6.24266 - 674.551/T - 150306/T^2$

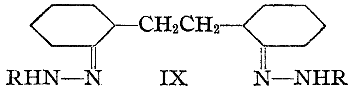
The average deviation of our published results from these equations is −0.1%; so the comparison with the measurements of others is scarcely affected. These equations yield as normal boiling points 78.30_6° for ethanol and 61.20_4° for chloroform.—GEORGE SCATCHARD.

John R. Durland and Homer Adkins. Hydrophenanthrenes.

Page 1502. In column 2 the second and third formulas should be:



VIII



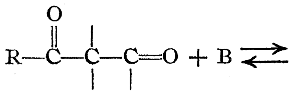
IX

Louis F. Fieser and E. B. Hershberg. Substitution Reactions and Meso Derivatives of 1,2-Benzanthracene.

Page 1895. In column 2, line 18 from the end, for "3-acetoxy-10-methyl-" read "3-methoxy-10-acetoxy-."—LOUIS F. FIESER.

Charles R. Hauser. Condensations Brought about by Bases. III. The General Course of the Claisen Type of Condensation.

Page 1957. In column 1, the last equation should read:



$$R-\overset{\overset{\displaystyle O}{\|}}{C}-\underset{|}{\overset{|}{C}}-\underset{|}{C}{=}O + B \rightleftarrows$$

(enolate anion of 1,3-diketo compound)$^-$ + BH$^+$

M. S. Kharasch, William Goldberg and Frank R. Mayo. The Catalytic Condensation of Grignard Reagents with Hydrocarbons.

Page 2004. In column 1, line 17 from the end, for "turnings" read "powder."—M. S. KHARASCH.

Albert Dorfman, Stewart A. Koser and Felix Saunders. The Activity of Certain Nicotinic Acid Derivatives as Growth Essential for the Dysentery Bacillus.

Page 2005. In column 1, line 1, for "Pyridine-2-sulfonic" read "Pyridine-3-sulfonic."—FELIX SAUNDERS.

D. M. Wrinch. The Structure of the Insulin Molecule.

Page 2006. In column 1, lines 4–5, for "with six slits whose centers give an octahedron," read "which by parallel displacement of faces through ± $a/2$ becomes an octahedron with the same distance ($16a$) between parallel faces and consequently".

In column 2, line 12, for "6°" read "66°."—D. M. WRINCH.

Roger Adams and T. A. Geissman. Structure of Gossypol. VII. Gossypol Dimethyl Ether.

Page 2163. In column 2, the second formula should be:

$$\left[C_{14}H_{11}(OH)(OCH_3)\left(\begin{matrix}OCH_3\\CHO\end{matrix}\right)\right]_2$$

—ROGER ADAMS.

Roger Adams, R. C. Morris and E. C. Kirkpatrick. Structure of Gossypol. IX. Oxidation and Degradation of Gossypol Hexamethyl Ether; Gossic Acid.

Page 2172. In column 2, line 30, for "315–317°" read "327–328° (corr.)."—ROGER ADAMS.

Roger Adams, R. C. Morris, D. J. Butterbaugh and E. C. Kirkpatrick. Structure of Gossypol. XIV. Apogossypolic Acid.

Page 2191. In column 2, line 6 from the end, for "Formula V" read "Formula VI."

Page 2192. In column 1, line 5, for "Formula V" read "Formula II."—ROGER ADAMS.

J. L. Crenshaw, Arthur C. Cope, Norma Finkelstein and Ruth Rogan. The Dioxanates of the Mercuric Halides.

Page 2310. In Table I, the transition points of Solid HgI_2 Dioxanate (87.7°) and Solid $HgBr_2$ Dioxanate (173.1°) are interchanged.

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Subject Index to Volume LX, 1938