TABLE I

DIPOLE MOMENT DATA

N_2	d_{12}	ϵ_{12}
Coprostan-3-one		
0.00000000	0.873090	2.2731
0.00052308	0.873384	2.2798
0.00074663	[a]	2.2829
0.00104392	0.873591	2.2871
0.00198058	0.874071	2.2998
$\alpha = 13.523$, $\beta = 0.490$, $(P_e + P_a) = 130.60$, $\epsilon_1 = 2.2729$, $d_1 = 0.87310$, $M_R = 118.73$, $P_{2\infty} = 315.8$, $\mu = 3.01$ D		
4-Fluorocoprostan-3-one		
0.000000000	0.873050	2.2718
0.000288442	0.873281	2.2792
0.000493620	0.873510	2.2850
0.000940493	0.873813	2.2966
0.00136424	0.874025	2.3076
$\alpha = 26.228$, $\beta = 0.734$, $(P_e + P_a) = 130.36$, $\epsilon_1 = 2.2719$, $d_1 = 0.87308$, $M_R = 118.51$, $P_{2\infty} = 501.3$, $\mu = 4.26$ D		
Cyclohexyl Fluoride		
0.00000000	0.873172	2.2713
0.00146111	0.873235	2.2783
0.00298955	0.873326	2 2863
0.00462863	0.873481	2.2946
0.00591418	0.873550	2.3012
$\alpha = 5.074$, $\beta = 0.0680$, $(P_e + P_a) = 30.25$, $\epsilon_1 = 2.2711$, $d_1 = 0.87315$, $M_R = 27.51$, $P_{2\infty} = 107.4$, $\mu = 1.94$		

[a] This point was discarded by the computer.

From the bond moments and the angles between the dipoles, the moments for the two epimeric fluoroketones were calculated. The methods and numerical values are those used earlier,[5] except that a new value for the C—F dipole was obtained from cyclohexyl fluoride. The latter compound had a moment of 1.94 D (in benzene solution at 25°). The moment of coprostan-3-one was also measured and found to be 3.01 D. A value of 3.01 D was consequently used for the C—O dipole when the fluorine was axial, and 2.84 D was used when the fluorine was equatorial (taking into account the moment induced by the neighboring equatorial C—F dipole as described previously.[5] The calculated values are as follows, 4α-fluorocoprostanone (axial fluorine) 2.97 D; 4β-fluorocoprostanone (equatorial fluorine), 4.32 D.

The moment of 4-fluorocoprostan-3-one was measured in benzene solution and found to be 4.26 D, and the configuration at C-4 is thus unequivocally established as β (equatorial).

EXPERIMENTAL

Coprostan-3-one Δ^4-Cholestene-3-one was prepared from cholesterol in the usual manner *via* an Oppenhauer oxidation.[7] Coprostan-3-one was prepared from Δ^4-cholesten-3-one by hydrogenation in ether with pallatium catalyst according to the procedure of Grosshof.[8] M.p. 62–62.5° (reported m.p. 63°[9]) from acetone.

Cyclohexyl fluoride. The addition of anhydrous hydrofluoric acid to cyclohexene (in a polyethylene bottle) was carried out following essentially the literature procedure.[10] The product had b.p. 64.5° (237 mm.), lit.[10] b.p. 71.2° (300 mm.).

4-Fluorocoprostan-3-one. Used directly as received, m.p. 154.5–155° after drying 12 hr.

Measurements of dipole moments. The dipole moment apparatus used has been previously described.[5] The dipole moments were measured in benzene solution, and the calculations were carried out by essentially the method of Halverstadt and Kumler[11] utilizing an IBM 650 computer programmed as described earlier.[12] As the coprostanone derivatives are of such high molecular weight, the usual neglect of atomic polarization may introduce some error.[13] Unfortunately, there is no good simple method for determining the atomic polarization. What has been done in the present case is to set it equal to10% of the molar refractivity, for coprostanone, 4-fluorocoprostanone, and fluorocyclohexane. The effect of taking the atomic polarization into account was to lower the experimental moments slightly, of coprostanone from 3.10 to 3.01 D. and of cyclohexyl-fluoride from 1.98 to 1.94 D. These changes are not of great significance as the experimental error is about .03 D. The data are summarized in Table I.

Acknowledgment. The authors are indebted to Dr. E. V. Jensen, of the University of Chicago, for furnishing the sample of 4-fluorocoprostan-3-one used in this work, and to the Public Health Service for financial support.

DEPARTMENT OF CHEMISTRY
WAYNE STATE UNIVERSITY
DETROIT 2, MICH.

(7) R. V. Oppenlauer, *Org. Syntheses*, Coll. Vol. III, 207 (1955).

(8) H. Grosshof, *Z. physiol.*, **223**, 249 (1934); **225**, 197 (1934).

(9) L. F. Fieser and M. Fieser, *Steroids*, Reinhold, 1959, p. 29.

(10) A. V. Grosse and C. B. Linn, *J. Org. Chem.*, **3**, 26 (1938).

(11) I. F. Halverstadt and W. D. Kumler, *J. Am. Chem. Soc.*, **64**, 1988 (1942).

(12) N. L. Allinger and J. Allinger, *J. Org. Chem.*, **24**, 1613 (1959).

(13) L. E. Sutton in E. A. Braude and F. C. Nachod's *Determination of Organic Structures by Physical Methods*, Academic Press, Inc., New York, 1955, p. 378.

Bromination of Naphthalene in 60% Aqueous Acetic Acid[1]

ERNST BERLINER AND BARBARA J. LANDRY[2]

Received September 18, 1961

In glacial acetic acid and other nonpolar solvents the bromination of aromatic compounds is usually second-, and sometimes third-, order in bromine,[3]

(1) Kinetics of Aromatic Halogenation. IX.

(2) Taken from the M.A. thesis of Barbara J. Landry, May 1960.

(3) P. W. Robertson, P. B. D. de la Mare, and W. T. G. Johnston, *J. Chem. Soc.*, 276 (1943); P. W. Robertson, *Science Progress*, 418 (1955); P. B. D. de la Mare and J. H. Ridd, *Aromatic Substitution*, Butterworth's Scientific Publications, London, 1959, Chap. 9; R. M. Keefer, A. Ottenberg, and L. J. Andrews, *J. Am. Chem. Soc.*, **78**, 255 (1956).

but in 50% aqueous acetic acid and in the presence of a large amount of bromide ion, the reaction of naphthalene and a few other hydrocarbons has been shown to be of the second order over-all, first-order in both hydrocarbon and bromine.[4] The interest in extending the latter reaction from 50% to 60% acetic acid was two-fold: one was to find out where, on a gradual increase of acetic acid in the solvent, a change-over from low-order to high-order bromination occurs and what kinetic form this change-over might take; the other was to make available a solvent of greater solvent power than 50% aqueous acetic acid, so that other and less soluble compounds might be studied for comparative purposes under well defined kinetic conditions.

The kinetics of bromination of naphthalene in 60% aqueous acetic acid was studied exactly in the same manner as the reaction in the 50% mixture,[4] and the same kinetic criteria were applied. The results for bromination in 60% acid—except for a slight and expected reduction in rate—were found to be completely analogous to bromination in the 50% acid, and the conclusions are the same. It will therefore suffice to summarize the kinetic results and to refer for particulars to previous publications.[4]

Within one kinetic run, second-order rate constants are obtained, and the reaction is first-order in naphthalene and in bromine, because rate constants remain the same when the concentrations of reactants are varied by factors of 4.5, and 6, respectively (Table I, A). The rate constants decrease when the bromide ion concentration is increased at a constant salt concentration (Table I, B). When the observed rate constants are plotted against the expression $K/(K + Br^-)$, where K is the dissociation constant of the tribromide ion,[5] a straight line is obtained, whose least-square slope has the value 0.108 ± 0.0004 l. mole^{-1} sec.$^{-1}$ at 25.0°.[6] As was shown before,[4] the relation $k_{obs} = kK/(K + Br^-)$ should hold if free bromine is the sole brominating agent, and the slope, k, is equal to the rate constant for bromination by free bromine, which is therefore identified as the brominating species.[6] The rate increases almost linearly with an increase in ionic strength (Table I, C). The observed activation energy, obtained from measurements of rate constants at five temperatures (Table I, D) is 16.6 ± 0.07 kcal., log A is 9.87 ± 0.05 and $\Delta S^{\ddagger}$ is −15.3 e.u.

TABLE I

BROMINATION OF NAPHTHALENE IN 60% AQUEOUS ACETIC ACID[a]

A. The dependence of rate on initial concentration of reactants[b] NaBr 0.20M, T 25.0°

Naphthalene Moles/L.	Br_2 Moles/L.	$k_{obs} \times 10^3$
0.007191	0.0008511	5.26
0.007191	0.001715	5.63
0.007500	0.001829	5.12
0.01200	0.001840	5.34
0.01200	0.003659	5.20
0.01647	0.001773	5.16
0.01960	0.002793	5.27
0.01960	0.004368	5.08
0.02257	0.005273	5.37
0.03435	0.004359	5.22

B. The effect of bromide ions.[c] T 25.0°

NaBr Moles/L.	$NaClO_4$ Moles/L.	$k_{obs} \times 10^3$
0.10	0.40	13.72
0.15	0.35	9.64
0.20	0.30	7.56
0.25	0.25	6.25
0.30	0.20	5.31
0.35	0.15	4.57
0.40	0.10	4.14
0.45	0.05	3.69
0.50	—	3.32

C. The effect of ionic strength.[c] NaBr 0.20M, T 25.0°

$NaClO_4$ Moles/L.	Total Salt Concentration Moles/L.	$k_{obs} \times 10^3$
0.00	0.20	5.08
0.10	0.30	5.83
0.20	0.40	6.64
0.30	0.50	7.56
0.40	0.60	8.36
0.50	0.70	9.21
0.60	0.80	10.09

D. The effect of temperature.[c] NaBr 0.30M, $NaClO_4$ 0.20M

T	$k_{obs} \times 10^3$
20.00	3.23
25.04	5.31
30.03	8.24
35.03	12.97
40.04	20.05

[a] All rate constants are in l. mole^{-1} sec.$^{-1}$. [b] The average value of 39 determinations for k_{obs} is (5.30 ± 0.22) × 10^{-3} l. mole^{-1} sec.$^{-1}$. [c] Naphthalene 0.0120M, $Br_2 \simeq 0.003$ M.

At an identical bromide ion concentration the reaction in 50% acetic acid is 3.60 times faster than in 60% acetic acid. Part of this decrease is due to a decrease in K, *i.e.*, less free bromine is available in the less aqueous solvent. When the observed rate constants are corrected for reaction by free

(4) E. Berliner and M. C. Beckett, *J. Am. Chem. Soc.*, 79, 1425 (1957); E. Berliner and J. C. Powers, *J. Am. Chem. Soc.*, 83, 905 (1961).

(5) A value of 0.0140 mole/l. was obtained for K in 60% aqueous acetic acid at room temperature by interpolation from the smooth curve drawn through points representing literature values of K in 0, 25, 50, 70, 75, and 80% aqueous acetic acid. Data from W. J. Jones, *J. Chem. Soc.*, 99, 392 (1911), E. Grovenstein, Jr., and U. V. Henderson, Jr., *J. Am. Chem. Soc.*, 78, 569 (1956) and ref. 4.

(6) The intercept should go through the origin, and the very small positive intercept here obtained (4.5 × 10^{-4} l. mole^{-1} sec.$^{-1}$) may indicate a very small amount of bromination by the tribromide ion, or, more likely, may be kinetically insignificant.

bromine, the actual ratio of reactivities becomes 3.11. If comparison is made directly through the slopes of the aforementioned plots—which represent bromination by free bromine—the ratio of rate constants becomes similarly 3.16. This is the factor by which the rate is reduced in the less polar solvent. Subject to the uncertainty in ΔH and ΔS for K,[7] this slowdown in rate is caused entirely by a lowering of the activation entropy, because in 50% acetic acid at the same concentrations of sodium bromide and sodium perchlorate the activation energy is 16.8 kcal. and $\Delta S^{\ddagger}$ is -12.1 e.u. That the activation entropy should be responsible for lowering the rate on going from a more to a less aqueous solvent is not unreasonable for a reaction in which ions are formed from neutral molecules.[8]

EXPERIMENTAL

All inorganic materials and the glacial acetic acid were as described before.[4] The naphthalene (Baker Analyzed Reagent) melted at 80.4–80.7°, after three crystallizations from ethanol. The 60% (by volume) aqueous acetic acid was prepared by mixing three volumes of glacial acetic acid with two volumes of distilled water, both of which had been thermostatted at 25.0°. The kinetic data were not affected when different batches of solvent mixture were used. Stock solutions of reagents were prepared at temperatures at which kinetic runs were carried out. The procedures for the kinetic runs and the determination of rate constants have been described.[4] Because runs were relatively fast, blanks due to volatility of bromine were small and within the experimental errors and were discarded. The rate constants recorded in the Table (except for those under A) are average values of at least duplicate runs, which usually agreed to within better than 2%. Data for one kinetic run follow.

A KINETIC RUN IN THE BROMINATION OF NAPHTHALENE IN 60% AQUEOUS ACETIC ACID

Naphthalene 0.01222 M, Br_2 0.003215 M, NaBr 0.20 M, $NaClO_4$ 0.30 M, T 25.0°

Time, Min.	0.01969N Thiosulfate, Ml.	$k_{obs} \times 10^3$, l. mole^{-1} sec.$^{-1}$
0	3.266	—
10	3.094	7.45
25	2.848	7.59
40	2.620	7.71
60	2.360	7.67
85	2.084	7.61
110	1.850	7.52
140	1.606	7.49

Acknowledgment. This work was supported by the National Science Foundation Grant G-4474, which is gratefully acknowledged.

DEPARTMENT OF CHEMISTRY
BRYN MAWR COLLEGE
BRYN MAWR, PA.

(7) It is assumed that these values are not very different in 50% and 60% aqueous acetic acid.

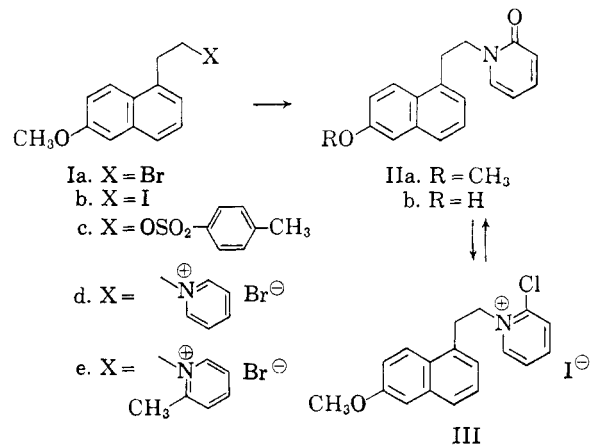
(8) A. A. Frost and R. G. Pearson, *Kinetics and Mechanism*, second ed., John Wiley and Sons, Inc., New York, N. Y., 1961, p. 137 *ff*.

The Synthesis of 1-(β-1-Naphthylethyl)-2(1*H*)-pyridones

LEO A. PAQUETTE[1] AND NORMAN A. NELSON[1]

Received September 18, 1961

In connection with studies on the anti-inflammatory activity of nitrogen-containing steroid analogs, it became of interest to undertake the synthesis of 1-(β-1-naphthylethyl)-2(1*H*)-pyridones. The preparation of related 6-(1,2,3,4-tetrahydro-2-naphthyl)-2(1*H*)-pyridones has already been reported.[2]



III

Our initial approaches to the system IIa were uniformly unsuccessful; included were attempts to alkylate β-(6-methoxy-1-naphthyl)ethyl bromide (Ia),[3] iodide (Ib),[4] and tosylate (Ic) with 2-pyridone salts,[5] to oxidize the pyridinium bromide (Id) with alkaline potassium ferricyanide,[6] to condense Id with 2-pyridone salts,[7] and to submit the picolinium salt (Ie) to the conditions of the King reaction.[8–10]

A successful synthesis of IIa was achieved when the bromide Ia was treated with 2-ethoxypyridine at 110–130° for twenty four hours in the absence of solvent. The reaction of 2-ethoxypyridine with

(1) Department of Chemistry, The Upjohn Company, Kalamazoo, Mich.

(2) N. A. Nelson and L. A. Paquette, *J. Org. Chem.*, **27**, 964 (1962).

(3) W. E. Bachmann, W. Cole, and A. L. Wilds, *J. Am. Chem. Soc.*, **62**, 824 (1940).

(4) W. E. Bachmann and R. E. Holmen, *J. Am. Chem. Soc.*, **73**, 3660 (1951).

(5) *Cf. inter alia*, M. Barash and J. M. Osbond, *Chem. & Ind.*, 490 (1958).

(6) *Cf. inter alia*, E. E. van Tamelen and J. S. Baran, *J. Am. Chem. Soc.*, **80**, 4659 (1958), and references cited therein.

(7) These conditions would be analogous to those developed for the Kröhnke reaction, *cf.* F. Kröhnke, *Ber.*, **71**, 2583 (1938).

(8) J. A. Berson and T. Cohen, *J. Am. Chem. Soc.*, **78**, 416 (1956).

(9) F. Kröhnke and K. F. Gross, *Ber.*, **92**, 22 (1959).

(10) J. A. Berson and J. S. Walia, *J. Org. Chem.*, **24**, 756 (1959).